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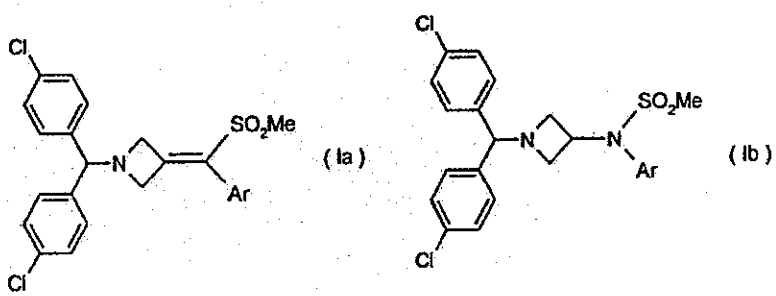
(54) Title: PHARMACEUTICAL COMPOSITIONS BASED ON AZETIDINE DERIVATIVES

(54) Titre : COMPOSITIONS PHARMACEUTIQUES A BASE DE DERIVES D'AZETIDINE



(57) Abstract: The invention concerns a stable pharmaceutical composition comprising at least an azetidine derivative of general formula (Ia) or (Ib), wherein: Ar is aromatic or heteroaromatic group optionally substituted by one or several C_1-C_4 alkyl, halogen, NO_2, CN, C_1-C_4 alkoxy or OH, optionally combined with another active principle capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib), in a system comprising not more than two main excipients selected among a non-ionic surfactant with hydrophilic character capable of solubilizing the azetidine derivative of general formula (Ia) or (Ib) and optionally the active principle potentiating the effects of the azetidine derivative, and capable of causing the formation of a colloidal system, optionally with addition of a second lipophilic excipient, stabilizing the formulation. The pharmaceutical compositions comprising azetidine derivatives of formulae (Ia) or (Ib) are particularly useful because of the high affinity of said derivatives for cannabinoid receptors.

(57) Abrégé : Composition pharmaceutique stable comprenant au moins un dérivé d'azétidine de formule générale (Ia) ou (Ib) dans laquelle Ar est un groupement aromatique ou hétéroaromatique éventuellement substitué par un ou plusieurs (C1-C4)alkyle, halogène, NO2, CN, (C1-C4)alkoxy ou OH, éventuellement en association avec un autre principe actif capable de potentialiser les effets du dérivé d'azétidine de formule générale (Ia) ou (Ib), dans un système comprenant au plus 2 excipients principaux choisis parmi un agent tensio-actif non-ionique à caractère hydrophile capable de solubiliser le dérivé d'azétidine de formule générale (Ia) ou (Ib) et le cas échéant le principe actif potentialisant les effets du dérivé d'azétidine, et capable de provoquer la formation d'un système colloïdal, additionné éventuellement d'un second excipient de nature lipophile, stabilisant la formulation.Les compositions pharmaceutiques comprenant des dérivés d'azétidine de formules (Ia) ou (Ib) sont particulièrement intéressantes du fait de la forte affinité de ces dérivés pour les récepteurs cannabinoïdes.

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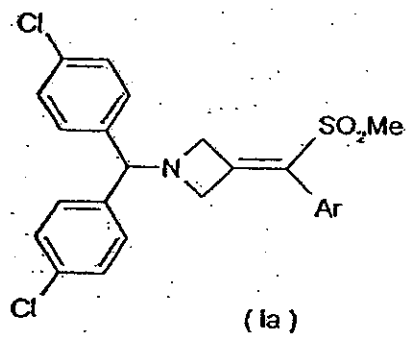
PHARMACEUTICAL COMPOSITIONS BASED ON AZETIDINE DERIVATIVES

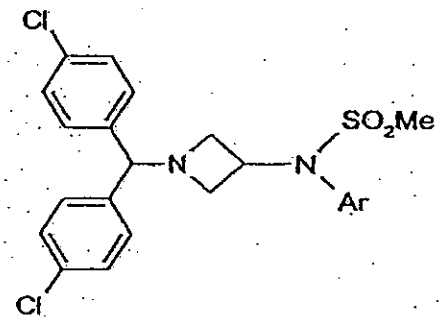
The present invention relates to stable formulations of azetidine derivatives.

An aspect of the present invention provides a stable pharmaceutical composition comprising at least one azetidine derivative of general formula:



(Ia)

or



(Ib)

in which Ar is an aromatic or heteroaromatic group optionally substituted with one or more (C1-C4)alkyl, halogen, NO_2, CN, (C1-C4)alkoxy or OH groups, optionally in combination with another active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib), in a system comprising at most 2 principal excipients chosen from a nonionic surfactant with a hydrophilic character capable of solubilizing the azetidine derivative of general

formula (Ia) or (Ib) and, where appropriate, the active ingredient potentiating the effects of the azetidine derivative, and capable of causing the formation of a colloidal system, optionally supplemented with a second excipient of a lipophilic nature, stabilizing the formulation.

WO 01/64633, WO 01/64634 and WO 99/01451, there have been described azetidine derivatives of general formula (Ia) or (Ib) and their applications. In particular, these azetidine derivatives are particularly advantageous for their high affinity for cannabinoid receptors and in particular CB1-type receptors.

Unfortunately, azetidine derivatives are products which are only very slightly water-soluble. Up until now, it was envisaged to administer the azetidine derivatives of general formula (Ia) or (Ib), in particular by the oral route, in the form of tablets in formulations comprising, inter alia, cellulose, lactose and other excipients. However, such formulations are not always sufficiently well suited to these sparingly water-soluble products because of an excessively low bioavailability.

Numerous documents describe systems suitable for solubilizing and/or enhancing the bioavailability of hydrophobic active ingredients. However, the systems tested have so far proved ineffective for the preparation of pharmaceutical compositions containing azetidine derivatives defined above which are stable and bioavailable and in which the azetidine derivative is solubilized at an effective concentration.

In particular, J. Pharm Sciences, 89(8), 967 (2000) and Pharmaceutical Technology Europe, p. 20, September 2000 mention the formulation of active

ingredients which are sparingly soluble in water, in medium-chain triglycerides. However, the trials carried out with formulations based on Miglyol® have given insufficient results from the point of view of their bioavailability.

Moreover, international application WO 95/24893 describes compositions comprising a digestible oil, a lipophilic surfactant and a hydrophilic surfactant which are intended for the formulation of hydrophobic active ingredients and for the enhancement of their bioavailability. Unfortunately, the above azetidine derivatives have proved too weakly bioavailable in this type of formulation. In particular, the formulation of such azetidine derivatives in a Miglyol®/Capryol®/Cremophor® system has also proved insufficient in vivo from the pharmacokinetic point of view.

It has now been found that it is possible to prepare chemically and physically stable pharmaceutical compositions comprising a derivative of general formula (Ia) or (Ib), optionally in combination with another active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib), in a system comprising at most 2 principal excipients chosen from a nonionic

surfactant with a hydrophilic character capable of solubilizing the azetidine derivative of general formula (Ia) or (Ib) and, where appropriate, the active ingredient potentiating the effects of the azetidine derivative, and of causing the formation of a colloidal system, optionally supplemented with a second excipient of a lipophilic nature, stabilizing the formulation.

According to the invention, preferred compositions comprise:

- at least one active ingredient of general formula (Ia) or (Ib),
- optionally another active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib),
- a nonionic surfactant with a hydrophilic character capable of solubilizing the azetidine derivative of general formula (Ia) or (Ib) and, where appropriate, the active ingredient potentiating the effects of the azetidine derivative, and capable of causing the formation of a colloidal system,
- optionally a surfactant with a lipophilic character having an HLB of less than 10, and stabilizing the composition,
- optionally additional additives chosen from stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or

agents which can modify, for example, the organoleptic properties.

The nonionic surfactant with a hydrophilic character capable of solubilizing the azetidine derivative of general formula (Ia) or (Ib) and, where appropriate, the active ingredient potentiating the effects of the azetidine derivative, and capable of causing the formation of a colloidal system, may be chosen from solid or semisolid agents, which melt at low temperature (T°C < 60°C), or from liquid agents, whose HLB is between 10 and 20, such as glycerides of polyethylene glycol and saturated fatty acids.

It is understood that, in the above definition, the saturated fatty acids may contain from 6 to 18 carbon atoms, and that the said glycerides of polyethylene glycol (PEG) and saturated fatty acids may be of natural or synthetic origin.

By way of example, the nonionic surfactant with a hydrophilic character may be chosen from agents such as Labrasol® [caprylcaproyl macrogol-8 glyceride] and the Gelucire® products: Gelucire 44/14, Gelucire 50/13, [lauroyl (or stearoyl, palmitoyl) macrogol-32 glyceride].

According to a preferred embodiment of the invention, the composition may also comprise an agent a surface-active agent with a lipophilic character having

an HLB of less than 10, and stabilizing the composition. This agent may be chosen from agents capable of enhancing the solubilization of the azetidine derivative of general formula (Ia) or (Ib) and, if necessary, of the associated active ingredient. According to the invention, this agent may be chosen from glycerides of polyethylene glycol and fatty acids, in particular unsaturated fatty acids, from esters of polyethylene glycol and fatty acids or from esters of fatty acids and sorbitol. It being understood that the above fatty acids may contain from 6 to 18 carbon atoms.

By way of example, the agent may be chosen from oleic acid, from the Labrafil® products [oleoyl (or lineoyl) macrogol-8 glycerides], for example Labrafil M1944CS, Capryol 90® (polyethylene glycol monocaprylate) or Span 20® (sorbitol monolaurate). The present list being given without limitation.

Among the excipients cited above, Labrasol®, Gelucire® or the Labrafil®/Labrasol® pair are especially more particularly preferred.

It has also been demonstrated (but not published by the filing date of the present application) that for certain treatments such as, for example, obesity, it may be advantageous to administer the azetidine derivatives of general formula (Ia) or (Ib) at the same time as sibutramine which causes a

synergistic effect in the reduction of food consumption.

Sibutramine and its effects have been described in the references below: WO 90/061110; D. H. RYAN et al., Obesity Research, 3 (4), 553 (1995); H. C. JACKSON et al., British Journal of Pharmacology, 121, 1758 (1997); G. FANGHANEL et al., Inter. J. Obes., 24 (2), 144 (2000); G. A. BRAY et al., Obes. Res., 7(2), 189 (1999).

Moreover, for other treatments such as schizophrenia or the treatment of neurological disorders such as Parkinson's disease, it may be advantageous to administer the azetidine derivatives of general formula (Ia) or (Ib) at the same time as one or more agents which activate dopaminergic neurotransmission in the brain. These combinations make it possible to potentiate the effects of a dopaminergic monotherapy (levodopa, dopaminergic agonists, and inhibitors of enzymes), and make it possible to reduce side effects, in particular dyskinesia.

Among the dopaminergic agonists, the following products may be mentioned in particular: bromocriptine (Novartis), cabergoline (Pharmacia Corp.) adrogolide (Abbott Laboratories), BAM-1110 (Maruko Seiyaku Co Ltd), Duodopa® (Neopharma), L-dopa, dopadose (Neopharma), CHF1512 (Chiesi), NeuroCell-PD (Diacrin Inc), PNU-95666 (Pharmacia & Upjohn) ropinirole

(GlaxoSmithKline Beecham), pramipexole (Boehringer Ingelheim) rotigotine (Discovery Therapeutics, Lohmann Therapie System), spheramine (Titan Pharmaceuticals), TV1203 (Teva pharmaceutical), uridine (Polifarma).

It is understood that the compositions comprising, in addition, an active ingredient other than the azetidine derivative of general formula (Ia) or (Ib) and capable of potentiating the effects thereof may contain a product as defined in the paragraphs above and that said compositions fall within the scope of the present invention.

According to the invention, the active ingredient of general formula (Ia) or (Ib) can represent from 0.01 to 70% by weight of the total composition. Preferably, it represents from 0.05 to 50% by weight and more particularly still from 0.1 to 20% by weight of the total composition.

It is understood that the dosage may vary according to the degree or the nature of the condition to be treated. Thus, the quantity of active product in a composition according to the invention will be determined such that a suitable dosage can be prescribed. As a result, the quantity of azetidine derivative of general formula (Ia) or (Ib) varies as a function of its solubility in the mixture and also as a function of the appropriate dosage for the treatment of patients.

In humans, the daily doses administered by the oral route can be generally between 0.1 and 100 mg of azetidine derivative of general formula (Ia) or (Ib). It is understood that, to choose the most appropriate dosage, there should be taken into account the weight of the patient, his general state of health, his age and all factors which may influence the efficacy of the treatment. Preferably, the compositions are prepared such that a unit dose contains from 0.1 to 50 mg of active product.

Among the azetidine derivatives of general formula (Ia) or (Ib), the following products are more particularly preferred:

- 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine);
- N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide
- N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide
- N-{1-[bis-(4-chlorophenyl)methyl]-azetidin-3-yl}-N-(6-chlorpyrid-2-yl)methylsulfonamide
- N-{1-[bis-(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-6-yl-methylsulfonamide.

It is understood that the compositions according to the invention, containing these products, are particularly preferred.

In the alternative, where a second active

ingredient is introduced, the compositions may comprise 0.2 to 15 mg in the case where the associated product is sibutramine. However, this quantity may optionally be lower and may vary from 0.2 to 10 mg.

In the case where the associated product is L-dopa, the compositions may comprise 100 to 300 mg of this second active ingredient, preferably 250 mg.

The nonionic surfactant, with a hydrophilic character capable of causing the formation of a colloidal system, may represent from 20 to 100% relative to the total weight of the excipients present in the composition, preferably from 40 to 100% and more particularly from 60 to 100%.

Where appropriate, when the composition also contains an agent of a lipophilic nature having an HLB of less than 10, the quantity of this agent with a low HLB may represent from 0.1 to 60% relative to the total weight of the excipients present in the composition, and more particularly from 1 to 40%.

When the composition further comprises certain additional additives, the latter may be stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or agents which can modify, for example, the organoleptic properties.

The stabilizing agents may be, for example, antioxidants chosen in particular from α-tocopherol, ascorbyl palmitate, BHT (butyl hydroxytoluene), BHA

(butyl hydroxyanisole), propyl gallate or malic acid for example;

The preservatives may, by way of example, be chosen from sodium metabisulfite, propylene glycol, ethanol or glycerin;

Among the agents capable of adjusting the viscosity, there may be mentioned, for example, lecithins, phospholipids, propylene glycol alginate, sodium alginate or glycerin;

The agents capable of modifying the organoleptic properties of the composition are, by way of example, malic acid, fumaric acid, glycerin, vanillin or menthol.

When such additives are used, the latter may constitute from 0.001% to 5% by weight of the total composition.

According to another aspect of the present invention, there is provided a process for preparing a composition as defined above wherein there is prepared, where appropriate, the mixture of principal excipients, after heating, if necessary, in the case of the solid or semisolid excipients, and then, if necessary, the mixture with the additional additives, and then the azetidine derivatives of general formula (Ia) or (Ib) and, where appropriate, the active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib), are added and stirring is maintained in order to obtain a homogeneous mixture.

The use of this process is described in greater detail below in the examples.

The compositions according to the invention may be provided in the liquid, solid or semipasty state.

They are particularly suitable for presentation in the form of hard gelatin capsules or soft gelatin capsules, or in the form of an oral solution.

The compositions according to the invention are particularly advantageous because of their good stability, both physically and chemically, and the enhancement of the bioavailablity which they offer upon oral administration of the azetidine derivatives of general formula (Ia) or (Ib).

Particularly preferred are the compositions comprising:

- at least one active ingredient of general formula (Ia) or (Ib),
- a nonionic surfactant with a hydrophilic character capable of solubilizing the azetidine derivative of general formula (Ia) or (Ib), and capable of causing the formation of a colloidal system,
- optionally a surfactant with a lipophilic character having an HLB of less than 10, and stabilizing the composition,

- optionally additional additives chosen from stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or agents which can modify, for example, the organoleptic properties.

A further aspect of the present invention provides a presentation kit containing a composition as defined above and a composition comprising an active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib).

According to another alternative of the invention, the preferred compositions as defined above, containing at least one active ingredient of general formula (Ia) or (Ib), may be administered before, simultaneously with or after the administration of an active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib).

It is understood that the presentation kits comprising, on the one hand, a preferred composition according to the invention as defined above and, on the other hand, a composition comprising the active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib) also fall within the scope of the present invention. It

is also understood that the presentation kits may contain, as composition capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib), compositions comprising sibutramine, or comprising an agent which activates dopaminergic neurotransmission in the brain.

The following examples, given without

limitation, illustrate compositions according to the present invention.

Example 1

The Labrasol/Labrafil M1944CS mixture, 60/40 (m/m) ratio, is prepared at room temperature (20°C), by magnetic stirring for 15 minutes of 14.4 g of Labrasol and 9.6 g of Labrafil M1944CS in a beaker. A very good miscibility is observed. 200 mg of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine are introduced into another beaker, and adjusted to 20 g with the Labrasol/Labrafil M1944CS 60/40 mixture in order to obtain a final concentration of 10 mg/g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine. The mixture of the 3 constituents is kept mechanically stirred (300 rpm) at room temperature for 2 hours in order to obtain complete dissolution of the 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine. The solution obtained is distributed in 1 g fractions into sealed glass vials and stored at 5°C.

A satisfactory chemical and physical stability was demonstrated for 1 month at 5°C.

An enhancement of the pharmacokinetic parameters by a factor of at least 2.5 was observed in comparison with a composition of 1-[bis(4-chloro-

phenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine in Miglyol 812®.

Example 2

By carrying out the procedure as above in example 1, but starting with 16.8 g of Labrasol and 7.2 g of Labrafil M1944CS in order to manufacture the Labrasol/Labrafil M1944CS mixture at the 70/30 (m/m) ratio, a composition is prepared containing 200 mg of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-(methylsulfonyl)methylene]azetidine adjusted to 20 g with the Labrasol/Labrafil M1944CS 70/30 mixture, in order to obtain a final concentration of 10 mg/g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine.

A satisfactory chemical and physical stability was demonstrated for 1 month at 5°C.

This composition was tested in an in vitro model, in comparison with the composition of example 1. 400 mg of the composition were incubated in 20 ml of medium simulating gastric fluid (reference USP). After an incubation of 2 hours at 37°C, an HPLC assay was carried out after filtration on a 2 :m filter, in order to determine the colloidal stability of the formulations.

The behavior of this composition is equivalent to the behavior of the composition of

example 1.

Example 3

By carrying out the procedure as above in example 1, but starting with 19.2 g of Labrasol and 4.8 g of Labrafil M1944CS in order to manufacture the Labrasol/Labrafil M1944CS mixture at the 80/20 (m/m) ratio, a composition is prepared containing 200 mg of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-(methylsulfonyl)methylene]azetidine adjusted to 20 g with the Labrasol/Labrafil M1944CS 80/20 mixture, in order to obtain a final concentration of 10 mg/g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-(methylsulfonyl)methylene]azetidine.

A satisfactory chemical and physical stability was demonstrated for 1 month at 5°C.

This composition was tested in an in vitro model, in comparison with the composition of example 1. 400 mg of the composition were incubated in 20 ml of medium simulating gastric fluid (reference USP). After an incubation of 2 hours at 37°C, an HPLC assay was carried out after filtration on a 2 :m filter, in order to determine the colloidal stability of the formulations.

The behavior of this composition is equivalent to the behavior of the composition of example 1.

Example 4

By carrying out the procedure as above in example 1, but starting with 21.6 g of Labrasol and 2.4 g of Labrafil M1944CS in order to manufacture the Labrasol/Labrafil M1944CS mixture at the 90/10 (m/m) ratio, a composition is prepared containing 200 mg of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-(methylsulfonyl)methylene]azetidine adjusted to 20 g with the Labrasol/Labrafil M1944CS 90/10 mixture, in order to obtain a final concentration of 10 mg/g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluoro-phenyl)(methylsulfonyl)methylene]azetidine.

A satisfactory chemical and physical stability was demonstrated for 1 month at 5°C.

This composition was tested in an in vitro model, in comparison with the composition of example 1. 400 mg of the composition were incubated in 20 ml of medium simulating gastric fluid (reference USP). After an incubation of 2 hours at 37°C, an HPLC assay was carried out after filtration on a 2 :m filter, in order to determine the colloidal stability of the formulations.

The behavior of this composition is equivalent to the behavior of the composition of example 1.

Example 5

By carrying out the procedure as above in example 1, but starting with 24 g of Labrasol only, a composition is prepared containing 200 mg of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine adjusted to 20 g with Labrasol, in order to obtain a final concentration of 10 mg/g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine.

A satisfactory chemical and physical stability was demonstrated for 1 month at 5°C.

This composition was tested in an in vitro model, in comparison with the composition of example 1. 400 mg of the composition were incubated in 20 ml of medium simulating gastric fluid (reference USP). After an incubation of 2 hours at 37°C, an HPLC assay was carried out after filtration on a 2 :m filter, in order to determine the colloidal stability of the formulations.

The behavior of this composition is equivalent to the behavior of the composition of example 1.

Example 6

By carrying out the procedure as above in example 1, but starting with 24 g of Gelucire 44/14 as a replacement for the Labrasol/Labrafil M1944CS

mixture. Gelucire 44/14 is molten beforehand in the region of 55°C. 200 mg of 1-[bis(4-chlorophenyl)-methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)-methylene]azetidine are introduced into a beaker, and adjusted to 20 g with Gelucire 44/14, in order to obtain a final concentration of 10 mg/g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methyl-sulfonyl)methylene]azetidine. The mixture of the 2 constituents is kept magnetically stirred (300 rpm) at 50-55°C for 1 hour in order to obtain complete dissolution of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine. The mass is distributed into hard gelatin capsules which are stored overnight in a freezer at -20°C. The envelope of the hard gelatin capsules is then separated from the solid mass contained inside using a cutter. The samples are stored in sealed glass vials at 5°C.

A satisfactory chemical and physical stability was demonstrated for 1 month at 5°C.

This composition was tested in an in vitro model, in comparison with the composition of example 1. 400 mg of the composition were incubated in 20 ml of medium simulating gastric fluid (reference USP). After an incubation of 2 hours at 37°C, an HPLC assay was carried out after filtration on a 2 :m filter, in order to determine the colloidal stability of the formulations.

The behavior of this composition is equivalent to the behavior of the composition of example 1.

Example 7

A Labrasol/Labrafil M1944CS mixture, 60/40 (m/m) ratio, is prepared at room temperature (20°C), by magnetic stirring for 15 minutes of 30 g of Labrasol and 20 g of Labrafil M1944CS in a beaker. A very good miscibility is observed. 20 mg of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine are introduced into a graduated flask of 10 ml. After having adjusted to 10 ml with the necessary quantity of Labrasol/Labrafil M1944CS 60/40 mixture, the mixture of the 3 constituents is kept magnetically stirred (500 rpm) at room temperature for 2 hours in order to obtain complete dissolution of the 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine. The solution obtained is distributed in 2.5 ml fractions into sealed glass vials and stored at 5°C.

This formulation, at the concentration of 2 mg/ml of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine, was used to carry out pharmacokinetic studies in monkeys after oral administration at a dose of 1 mg/kg. To do this, this solution was diluted to one tenth in apple

juice in order to facilitate administration to the animal. The emulsion obtained after dilution is physically and chemically stable for at least one hour.

Example 8

A Labrasol/Labrafil M1944CS mixture, 60/40 (m/m) ratio, is prepared at room temperature (20°C), by magnetic stirring for 15 minutes of 30 g of Labrasol and 20 g of Labrafil M1944CS in a beaker. A very good miscibility is observed. 20 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)-methylsulfonamide are introduced into a graduated flask of 10 ml. After having adjusted to 10 ml with the necessary quantity of Labrasol/Labrafil M1944CS 60/40 mixture, the mixture of the 3 constituents is kept magnetically stirred (500 rpm) at room temperature for 2 hours in order to obtain complete dissolution of the N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide. The solution obtained is distributed in 2.5 ml fractions into sealed glass vials and stored at 5°C.

This formulation, at the concentration of 2 mg/ml of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide, was used to carry out pharmacokinetic studies in monkeys after oral administration at a dose of 1 mg/kg. To do this, this solution was diluted one tenth in apple juice in

order to facilitate administration to the animal. The emulsion obtained after dilution is physically and chemically stable for at least one hour.

Example 9

A Labrasol/Labrafil M1944CS mixture, 60/40 (m/m) ratio, is prepared at room temperature (20°C), by magnetic stirring for 15 minutes of 30 g of Labrasol and 20 g of Labrafil M1944CS in a beaker. A very good miscibility is observed. 10 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide are introduced into a graduated flask of 10 ml. After having adjusted to 10 ml with the necessary quantity of Labrasol/Labrafil M1944CS 60/40 mixture, the mixture of the 3 constituents is kept magnetically stirred (500 rpm) at room temperature for 2 hours in order to obtain complete dissolution of the N-{1-[bis-(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-yl-methylsulfonamide. The solution obtained is distributed in 2.5 ml fractions into sealed glass vials and stored at 5°C.

This formulation, at the concentration of 1 mg/ml of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide was used to carry out pharmacological studies in rats after oral administration at a dose of 1 mg/kg.

Example 10

By carrying out the procedure as above in example 9, but starting with 30 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethyl-sulfonamide adjusted to 10 ml with the Labrasol/Labrafil M1944CS 60/40 mixture, a solution is prepared containing 3 mg/ml of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethyl-sulfonamide.

This formulation at the concentration of 3 mg/ml of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide was used to carry out pharmacological studies in rats after oral administration at a dose of 3 mg/kg.

Example 11

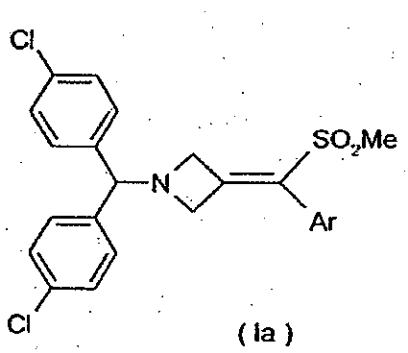
By carrying out the procedure as above in example 9, but starting with 50 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethyl-sulfonamide adjusted to 5 ml with the Labrasol/Labrafil M1944CS 60/40 mixture, a solution is prepared containing 10 mg/ml of N-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide.

This formulation at the concentration of 10 mg/ml of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide was used to carry out

pharmacological studies in rats after oral administration at a dose of 10 mg/kg.

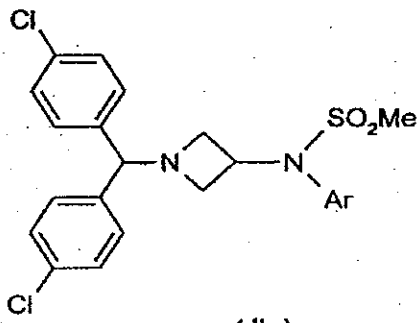
CLAIMS

1. A stable pharmaceutical composition comprising at least one azetidine derivative of general formula:



(Ia)

or



(Ib)

in which Ar is an aromatic or heteroaromatic group optionally substituted with one or more (C1-C4)alkyl, halogen, NO_2, CN, (C1-C4)alkoxy or OH groups, optionally in combination with another active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib), in a system comprising at most 2 principal excipients chosen from a nonionic surfactant with a hydrophilic character capable of solubilizing the azetidine derivative of general formula (Ia) or (Ib) and, where appropriate, the active ingredient potentiating the effects of the azetidine derivative, and capable of causing the formation of a colloidal system, optionally supplemented with a second

excipient of a lipophilic nature, stabilizing the formulation.

2. The pharmaceutical composition as claimed in claim 1, which comprises:

- at least one azetidine derivative of general formula (Ia) or (Ib), as claimed in claim 1,
- optionally another active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib),
- a nonionic surfactant with a hydrophilic character capable of solubilizing the azetidine derivative of general formula (Ia) or (Ib) and, where appropriate, the active ingredient potentiating the effects of the azetidine derivative, and capable of causing the formation of a colloidal system,
- optionally a surfactant with a lipophilic character having an HLB of less than 10, and stabilizing the composition,
- optionally additional additives chosen from stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or agents which can modify, for example, the organoleptic properties.

3. The pharmaceutical composition as claimed in claim 1 or 2, which comprises:

- at least one azetidine derivative of general formula (Ia) or (Ib), as claimed in claim 1,
- a nonionic surfactant with a hydrophilic character capable of solubilizing the azetidine derivative as claimed in claim 1, and capable of causing the formation of a colloidal system,
- optionally a surfactant with a lipophilic character having an HLB of less than 10, and stabilizing the composition,
- optionally additional additives chosen from stabilizing agents, preservatives, agents which make it possible to adjust the viscosity, or agents which can modify, for example, the organoleptic properties.

4. The pharmaceutical composition as claimed in one of claims 1 to 3, wherein the aromatic group of the azetidine derivative of general formula (Ia) or (Ib) is chosen from a phenyl or naphthyl group.

5. The pharmaceutical composition as claimed in one of claims 1 to 3, wherein the heteroaromatic group is chosen from a pyridyl, furyl, thienyl, thiazolyl, imidazolyl or oxazolyl group.

6. The pharmaceutical composition as claimed in one of claims 1 to 5, wherein the nonionic surfactant with a hydrophilic character capable of solubilizing the azetidine derivative of general formula (Ia) or (Ib) and, where appropriate, the active

ingredient potentiating the effects of the azetidine derivative, and capable of causing the formation of a colloidal system, is chosen from glycerides of polyethylene glycol and saturated fatty acids, whose HLB is between 10 and 20.

7. The pharmaceutical composition as claimed in claim 6, wherein the glycerides of polyethylene glycol and saturated fatty acids are glycerides of polyethylene glycol and saturated fatty acids containing from 6 to 18 carbon atoms.

8. The pharmaceutical composition as claimed in claim 6 or 7, wherein the glycerydes may be of natural or synthetic origin.

9. The pharmaceutical composition as claimed in one of claims 1 to 8, wherein the excipient with a lipophilic character, stabilizing the composition, is chosen from glycerides of polyethylene glycol and unsaturated fatty acids, from esters of polyethylene glycol and fatty acids or from esters of fatty acids and sorbitol, having an HLB of less than 10.

10. The pharmaceutical composition as claimed in one of claims 1 to 9, wherein the system comprising at most 2 excipients consists of Labrasol®, Gelucire® or the Labrafil®/Labrasol® pair.

11. The pharmaceutical composition as claimed in one of claims 1 to 10, wherein the an active

ingredient derived from azetidine, defined in claim 1, is present in an amount of 0.01 to 70% by weight of the total composition.

12. The pharmaceutical composition as claimed in one of claims 1 to 11, wherein the nonionic surfactant with a hydrophilic character capable of solubilizing the azetidine derivative according to claim 1, and capable of causing the formation of a colloidal system, is present in an amount of 20 to 100% relative to the total weight of the excipients in the composition.

13. The pharmaceutical composition as claimed in one of claims 1 to 12, wherein, where appropriate, agent with a lipophilic character, stabilizing the formulation, is present in an amount of 0.1 to 60% relative to the total weight of the excipients in the composition.

14. A process for preparing a composition as claimed in one of claims 1 to 13, wherein there is prepared, where appropriate, the mixture of principal excipients, after heating, if necessary, in the case of the solid or semisolid excipients, and then, if necessary, the mixture with the additional additives, and then the azetidine derivative as defined in claim 1 and, where appropriate, the active ingredient capable of potentiating the effects of the azetidine derivative of general formula (Ia) or (Ib), defined in claim 1 are

added and stirring is maintained in order to obtain a homogeneous mixture.

15. A presentation kit containing a composition as claimed in claim 3 and a composition comprising an active ingredient capable of potentiating the effects of the azetidine derivative defined in claim 1.

16. The presentation kit as claimed in claim 15, containing a composition as claimed in claim 3 and a composition comprising sibutramine.

17. The presentation kit as claimed in claim 15, containing a composition as claimed in claim 3 and a composition comprising an agent which activates dopaminergic neurotransmission in the brain.

18. The pharmaceutical composition as claimed in claim 1 wherein the azetidine derivative is N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl) methylsulfonamide.