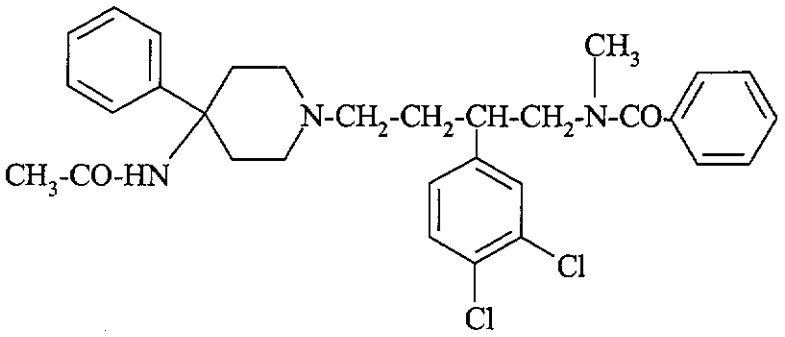
PHARMACEUTICAL COMPOSITION COMPRISING, IN COMBINATION, SAREDUTANT AND A SELECTIVE SEROTONIN REUPTAKE INHIBITOR OR A SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITOR

A subject-matter of the present invention is pharmaceutical compositions comprising, in combination, (S)-(-)-N-[4-(4-acetamido-4-phenylpiperidin-1-yl)-2-(3,4-dichlorophenyl)butyl]-N-methylbenzamide or one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor or with a serotonin/norepinephrine reuptake inhibitor.

(S)-(-)-N-[4-(4-Acetamido-4-phenylpiperidin-1-yl)-2-(3,4-dichlorophenyl)butyl]-N-methylbenzamide, the international nonproprietary name of which is saredutant, of formula:



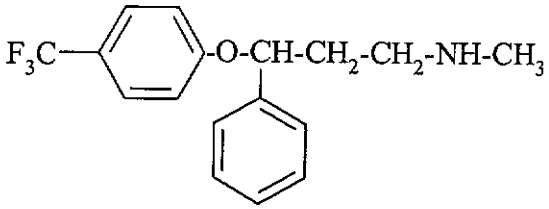
(I)

hereinafter referred to as compound A, and its pharmaceutically acceptable salts have been described as powerful and selective nonpeptide antagonists of the NK_2 receptors of neurokinin A (Life Sciences, 1992, 50(15), PL101-PL106) and can be prepared according to Patents EP 0 474 561 or US 5 236 921.

The salts are the salts with conventional pharmaceutically acceptable inorganic or organic acids, such as the hydrochloride, the hydrobromide, the sulphate, the hydrogensulphate, the dihydrogenphosphate, the methanesulphonate, the methyl sulphate, the acetate, the oxalate, the maleate, the fumarate, the succinate, the naphthalene-2-sulphonate, the glyconate, the gluconate, the citrate, the isethionate, the benzenesulphonate or the para-toluenesulphonate.

The term "selective serotonin reuptake inhibitor" (SSRI) is understood to mean a compound such as, for example:

- (±)-N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine, the international nonproprietary name of which is fluoxetine, of formula:



(II)

hereafter referred to as compound B, and its pharmaceutically acceptable salts, which can be prepared according to Patent US 4 314 081;

- 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile, the international nonproprietary name of which is citalopram, and its pharmaceutically acceptable salts, which can be prepared according to Patent US 4 136 193;
- S-(+)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-5-carbonitrile, the international nonproprietary name of which is escitalopram, and its pharmaceutically acceptable salts, which can be prepared according to Patent EP 0 347 066 or US 4 943 590;
- trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, the international nonproprietary name of which is paroxetine, and its pharmaceutically acceptable salts, which can be prepared according to Patents US 3 912 743 and US 4 007 196;
- (1S)-cis-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthaleneamine, the international nonproprietary name of which is sertraline, and its pharmaceutically acceptable salts, which can be prepared according to Patent US 4 536 518;
- 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone O-(2-aminoethyl)oxime, the international nonproprietary name of which is fluvoxamine, and its pharmaceutically acceptable salts, which can be prepared according to Patent US 4 085 225;

The term "serotonin/norepinephrine reuptake inhibitor" (SNRI) is understood to mean a compound such as, for example:

- 1-[2-dimethylamino-1-(4-methoxyphenyl)ethyl]cyclohexan-1-ol, the international nonproprietary name of which is venlafaxine, and its pharmaceutically acceptable salts, which can be prepared according to Patent EP 0 112 669;
- (+)-(S)-N-methyl-3-(1-naphthyloxy)-3-(thiophen-2-yl)propan-1-amine, the international nonproprietary name of which is duloxetine, and its pharmaceutically acceptable salts, which can be prepared according to Patent EP 0 273 658;
- (1R,2R)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropane-1-carboxamide, the

international nonproprietary name of which is milnacipran, and its pharmaceutically acceptable salts, which can be prepared according to Patent US 4 478 836;

It has now been found, surprisingly, that the combination of saredutant with a selective serotonin reuptake inhibitor or with a serotonin/norepinephrine reuptake inhibitor significantly enhances the pharmacological effects of each of the compounds used alone, in particular the antidepressant effects.

Thus, the pharmaceutical compositions comprising such combinations can be of use in the manufacture of medicaments intended for the prevention and treatment of mood disorders chosen from major depressive disorder, resistant depressive disorder, dysthymic disorder, depressive disorder not otherwise specified, bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, mood disorder induced by a substance, mood disorder not otherwise specified; anxiety disorders chosen from panic attack, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress condition, acute stress condition, generalized anxiety disorder or anxiety disorder induced by a substance.

In particular, the pharmaceutical compositions comprising such combinations can be of use in the manufacture of medicaments intended for the prevention and treatment of a major depressive disorder.

In particular again, the pharmaceutical compositions comprising such combinations can be of use in the manufacture of medicaments intended for the treatment of sexual dysfunctions associated with a major depressive disorder.

The term "sexual dysfunctions" is understood to mean any pathology as defined by the American Psychiatric Association – DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised text (Washington DC, 2000), pages 617-654, and which includes disorders of sexual desire (that is to say, the disorder: fall in sexual desire, and the disorder: sexual aversion), disorders of sexual arousal (that is to say, female sexual arousal disorder and male erectile disorder), orgasmic disorders (that is to say, female orgasmic disorder, male orgasmic disorder and premature ejaculation), painful sexual disorders (that is say, dyspareunia and vaginismus), sexual dysfunction due to a general medial condition, sexual dysfunction induced by a substance and sexual dysfunctions not otherwise specified.

Thus, according to one of its aspects, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor or with

a serotonin/norepinephrine reuptake inhibitor, and also at least one pharmaceutically acceptable excipient.

In particular, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor chosen from fluoxetine, citalopram, escitalopram, paroxetine, sertraline and fluvoxamine or one of their pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with fluoxetine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with citalopram or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with escitalopram or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with paroxetine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with sertraline or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with fluvoxamine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a serotonin/norepinephrine reuptake inhibitor, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a serotonin/norepinephrine reuptake inhibitor chosen from venlafaxine, duloxetine and milnacipran or one of their pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with venlafaxine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with duloxetine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

In particular again, a subject-matter of the present invention is pharmaceutical compositions comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with milnacipran or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

According to another of its aspects, a subject-matter of the present invention is the combination of saredutant or of one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor or with a serotonin/norepinephrine reuptake inhibitor.

In particular, a subject-matter of the present invention is the combination of saredutant or of one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor chosen from fluoxetine, citalopram, escitalopram, paroxetine, sertraline and fluvoxamine or one of their pharmaceutically acceptable salts.

In particular again, a subject-matter of the present invention is the combination of saredutant or of one of its pharmaceutically acceptable salts with a serotonin/norepinephrine reuptake inhibitor chosen from venlafaxine, duloxetine and milnacipran or one of their pharmaceutically acceptable salts.

According to another of its aspects, a subject-matter of the present invention is the use of a pharmaceutical composition comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a selective serotonin reuptake

inhibitor or with a serotonin/norepinephrine reuptake inhibitor or one of their pharmaceutically acceptable salts in the manufacture of medicaments intended for the prevention and treatment of mood disorders chosen from major depressive disorder, resistant depressive disorder, dysthymic disorder, depressive disorder not otherwise specified, bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, mood disorder induced by a substance, mood disorder not otherwise specified; anxiety disorders chosen from panic attack, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress condition, acute stress condition, generalized anxiety disorder or anxiety disorder induced by a substance.

In particular, a subject-matter of the present invention is the use of a pharmaceutical composition comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor or with a serotonin/norepinephrine reuptake inhibitor or one of their pharmaceutically acceptable salts in the manufacture of medicaments intended for the prevention and treatment of a major depressive disorder.

In particular again, a subject-matter of the present invention is the use of a pharmaceutical composition comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor or with a serotonin/norepinephrine reuptake inhibitor or one of their pharmaceutically acceptable salts in the manufacture of medicaments intended for the treatment of sexual dysfunctions associated with a major depressive disorder.

In particular again, a subject-matter of the present invention is the use of a pharmaceutical composition comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with escitolopram or one of its pharmaceutically acceptable salts in the manufacture of medicaments intended for the prevention and treatment of mood disorders chosen from major depressive disorder, resistant depressive disorder, dysthymic disorder, depressive disorder not otherwise specified, bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, mood disorder induced by a substance, mood disorder not otherwise specified; anxiety disorders chosen from panic attack, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress condition, acute stress condition, generalized anxiety disorder or anxiety disorder induced by a substance.

In particular again, a subject-matter of the present invention is the use of a pharmaceutical composition comprising, in combination, saredutant or one of its

pharmaceutically acceptable salts with escitolopram or one of its pharmaceutically acceptable salts in the manufacture of medicaments intended for the prevention and treatment of a major depressive disorder.

In particular again, a subject-matter of the present invention is the use of a pharmaceutical composition comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with escitolopram or one of its pharmaceutically acceptable salts in the manufacture of medicaments intended for the treatment of sexual dysfunctions associated with a major depressive disorder.

In particular again, a subject-matter of the present invention is the use of a pharmaceutical composition comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with paroxetine or one of its pharmaceutically acceptable salts in the manufacture of medicaments intended for the prevention and treatment of mood disorders chosen from major depressive disorder, resistant depressive disorder, dysthymic disorder, depressive disorder not otherwise specified, bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, mood disorder induced by a substance, mood disorder not otherwise specified; anxiety disorders chosen from panic attack, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress condition, acute stress condition, generalized anxiety disorder or anxiety disorder induced by a substance.

In particular again, a subject-matter of the present invention is the use of a pharmaceutical composition comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with paroxetine or one of its pharmaceutically acceptable salts in the manufacture of medicaments intended for the prevention and treatment of a major depressive disorder.

In particular again, a subject-matter of the present invention is the use of a pharmaceutical composition comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with paroxetine or one of its pharmaceutically acceptable salts in the manufacture of medicaments intended for the treatment of sexual dysfunctions associated with a major depressive disorder.

According to another of its aspects, a subject-matter of the present invention is the use of the combination of saredutant or of one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor or with a serotonin/norepinephrine inhibitor or one of their pharmaceutically acceptable salts in the manufacture of medicaments intended for the prevention and treatment of mood disorders chosen from major depressive disorder, resistant depressive disorder, dysthymic disorder,

depressive disorder not otherwise specified, bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, mood disorder induced by a substance, mood disorder not otherwise specified; anxiety disorders chosen from panic attack, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress condition, acute stress condition, generalized anxiety disorder or anxiety disorder induced by a substance.

The excipients are chosen, according to the pharmaceutical form and the method of administration desired, from the usual excipients which are known to a person skilled in the art.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intratracheal, intranasal, transdermal or rectal administration, the active principles can be administered in unit administration form, as a mixture with conventional pharmaceutical excipients, to animals and human beings for the prevention or treatment of the above disorders or diseases.

The appropriate unit administration forms comprise oral forms, such as tablets, soft or hard gelatin capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intraocular or intranasal administration forms, forms for administration by inhalation, topical, transdermal, subcutaneous, intramuscular or intravenous administration forms, rectal administration forms and implants. For topical application, the compounds according to the invention can be used in creams, gels, ointments or lotions.

In the pharmaceutical compositions of the present invention, the active principle or the active principles are generally formulated as dosage units. The dosage unit comprises from 2.5 to 500 mg, advantageously from 10 to 250 mg, preferably from 10 to 150 mg per dosage unit, for daily administrations, one or more times per day. Although these dosages are examples of average situations, there may be specific cases where higher or lower dosages are appropriate; such dosages also come within the invention. According to the standard practice, the dosage appropriate to each patient is determined by the physician according to the method of administration and the age, weight and the response of the said patient.

According to another aspect of the invention, the compound A and the other active principle according to the invention can be administered simultaneously, separately or spread out over time.

The term "simultaneous use" is understood to mean the administration of the compounds of the composition according to the invention comprise within one and the

same pharmaceutical form.

The term "separate use" is understood to mean the administration, at the same time, of the two compounds of the composition according to the invention, each comprised within a separate pharmaceutical form.

The term "use spread out over time" is understood to mean the successive administration of the first compound of the composition according to the invention, comprised within a pharmaceutical form, and then of the second compound of the composition according to the invention, comprised within a separate pharmaceutical form.

In the case of this "use spread out over time", the period of time elapsed between the administration of the first compound of the composition according to the invention and the administration of the second compound of the same composition according to the invention generally does not exceed 24 hours.

The unit pharmaceutical forms comprising either just one of the constituent compounds of the composition according to the invention or the combination of the 2 compounds which can be employed in the various types of use described above may, for example, be appropriate for oral, nasal, parenteral or transdermal administration.

Consequently, in the case of a "separate use" and of a "use spread out over time", two separate pharmaceutical forms may be intended for the same route of administration or for a different route of administration (oral and transdermal or oral and nasal or parenteral and transdermal, and the like).

The invention thus also relates to a kit comprising the compound A and the other active principle according to the invention in which the said compound A and the other active principle according to the invention are in separate compartments and in similar or different packagings and are intended to be administered simultaneously, separately or spread out over time.

Specifically and without implied limitation, the enhancement in the pharmacological effects of a combination according to the invention of the compound A and of fluoxetine (compound B) have been demonstrated in animals.

Specifically again, the effects of a combination according to the invention of the compound A and of a selective serotonin reuptake inhibitor are studied during clinical studies.

EXAMPLE 1

The in-vivo rat test DRL-72 s (Differential Reinforcement of Low-rate-72 seconds) is used according to the technique described by C. Louis et al., Neuropsychopharmacology, 2006, 1-8.

Effects compared with regard to the percentage of rewards obtained (reinforced presses) with respect to the total number of presses by the rat after intraperitoneal administration of the compound A alone, of the compound B alone and of the compound A + compound B combination versus the control (solvent alone).

Beforehand, the minimum active doses of the compound A alone and of the compound B alone in the DRL-72 s test were determined, namely:

- compound A: 10 mg/kg intraperitoneally;
- compound B: 5 mg/kg intraperitoneally.

For the present study, a weakly active dose of compound A alone and an inactive dose of compound B alone and of compound A + compound B were selected.

The compound A alone at the dose of 3 mg/kg and the compound B alone at the dose of 2.5 mg/kg were dissolved in a 0.9% (weight/volume) aqueous sodium chloride solution comprising 0.1% (v/v) Tween 80® and administered intraperitoneally at a final volume of 1 ml/kg .

The combination was administered intraperitoneally by two simultaneous administrations of the compound A (3 mg/kg) and then of the compound B (2.5 mg/kg).

The doses of the compounds are expressed in the free basis form.

For the requirements of the test, the effect of the compound A alone, the effect of the compound B alone and the effect of the compound A + compound B combination, compared with the effect of the solvent (control), are measured for each animal.

Each rat (n=8) thus receives four injections spread out over time, namely the solvent (control), the compound A alone, the compound B alone and the compound A + compound B combination.

The results obtained are collated in Table I and are expressed as a percentage of rewards obtained with respect to the total number of presses over the duration of the test (1 hour), in the mean ± SEM (standard error of the mean) form.

TABLE I

	% reinforced presses/total number of presses (n = 8 rats)
Solvent control	3.07 ± 0.48%
Compound A, 3 mg/kg	6.41 ± 1.73%
Compound B, 2.5 mg/kg	3.82 ± 0.76%
Compound, A 3 mg/kg + Compound B, 2.5 mg/kg	11.01 ± 2.6% *

* $p < 0.05$ versus control

The results obtained show that:

- the compound A, administered alone at the dose of 3 mg/kg, only slightly modifies the percentage number of rewards obtained with respect to the control; furthermore, this increase is not statistically significant;

- the compound B, administered alone at the dose of 2.5 mg/kg, does not modify the percentage number of rewards obtained with respect to the control;

- the combination of the compound A and the compound B markedly increases the percentage number of rewards obtained with respect to the control and this increase is statistically significant.

Thus, the combination of the compound A and the compound B according to the invention unexpectedly shows its positive effects on the behaviour of the animals in this test, making it possible to confirm the antidepressant potential of the combination for a therapeutic application.

EXAMPLE 2

The effects of a combination according to the invention of saredutant with escitalopram are evaluated during multicentric randomized double-blind clinical studies lasting eight weeks in which a group receiving a fixed dose of saredutant once daily in combination with a fixed dose of escitalopram once daily is compared with a group receiving saredutant placebo in combination with a fixed dose of escitalopram and with another group receiving saredutant placebo in combination with escitalopram placebo.

These clinical studies are carried out on adult male or female patients exhibiting a major depressive disorder as defined by the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised text (DSM-IV-TR), and confirmed by the criteria of the Mini International Neuropsychiatric Interview (MINI), Lecrubier Y. et al., Eur. Psychiatr., 1997, 12, 224-231.

The change in the total score on the Hamilton Depression Rating Scale comprising 17 items (HAM-D) between the final visit (expected on the 56th day) and the first visit (before the beginning of the treatment) is measured with respect to the placebo group. The Hamilton Depression Rating Scale is defined by Hamilton M., J. Neurol. Neurosurg. Psychiatry, 1960, 23, 56-62.

The change in the total score of the CSFQ comprising 14 items (Changes in Sexual Functioning Questionnaire) between the final visit (expected on the 56th day) and the first visit (before the beginning of the treatment) is also measured with respect to the placebo group. The CSFQ is defined by Clayton AH et al., Psychopharmacol.

Bull., 1997, 33, 731-745.

EXAMPLE 3

The effects of a combination according to the invention of saredutant with paroxetine are evaluated during multicentric randomized double-blind clinical studies lasting eight weeks in which a group receiving a fixed dose of saredutant once daily in combination with a fixed dose of paroxetine once daily is compared with a group receiving saredutant placebo in combination with a fixed dose of paroxetine and with another group receiving saredutant placebo in combination with paroxetine placebo.

These clinical studies are carried out on adult male or female patients exhibiting a major depressive disorder as defined by the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised text (DSM-IV-TR), and confirmed by the criteria of the Mini International Neuropsychiatric Interview (MINI), Lecrubier Y. et al., Eur. Psychiatr., 1997, 12, 224-231.

The change in the total score on the Hamilton Depression Rating Scale comprising 17 items (HAM-D) between the final visit (expected on the 56th day) and the first visit (before the beginning of the treatment) is measured with respect to the placebo group. The Hamilton Depression Rating Scale is defined by Hamilton M., J. Neurol. Neurosurg. Psychiatry, 1960, 23, 56-62.

The change in the total score of the CSFQ comprising 14 items (Changes in Sexual Functioning Questionnaire) between the final visit (expected on the 56th day) and the first visit (before the beginning of the treatment) is also measured with respect to the placebo group. The CSFQ is defined by Clayton AH et al., Psychopharmacol. Bull., 1997, 33, 731-745.

EXAMPLE 4: Hard gelatin capsule comprising 30 mg of saredutant

Saredutant (expressed as base)	30.0 mg
Lactose monohydrate (200 mesh)	q.s. 400.0 mg
Croscarmellose sodium	8.0 mg
Magnesium stearate	4.0 mg
Purified water*	q.s.
For an opaque hard gelatin capsule of size 0, filled to	400.0 mg

* evaporated in the drying after the wet granulation.

EXAMPLE 5: Hard gelatin capsule comprising 100 mg of saredutant

Saredutant (expressed as base)	100.0 mg
Lactose monohydrate (200 mesh)	q.s. 400.0 mg
Croscarmellose sodium	8.0 mg
Magnesium stearate	4.0 mg

Purified water*	q.s.
For an opaque hard gelatin capsule of size 0, filled to	400.0 mg

* evaporated in the drying after the wet granulation.

CLAIMS

1. Pharmaceutical composition comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor or with a serotonin/norepinephrine reuptake inhibitor, and also at least one pharmaceutically acceptable excipient.
2. Pharmaceutical composition according to Claim 1, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor, and also at least one pharmaceutically acceptable excipient.
3. Pharmaceutical composition according to Claim 1 or Claim 2, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor chosen from fluoxetine, citalopram, escitalopram, paroxetine, sertraline and fluvoxamine or one of their pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.
4. Pharmaceutical composition according to Claim 3, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with fluoxetine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.
5. Pharmaceutical composition according to Claim 3, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with citalopram or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.
6. Pharmaceutical composition according to Claim 3, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with escitalopram or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.
7. Pharmaceutical composition according to Claim 3, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with paroxetine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.
8. Pharmaceutical composition according to Claim 3, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with sertraline or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically

acceptable excipient.

9. Pharmaceutical composition according to Claim 3, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with fluvoxamine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

10. Pharmaceutical composition according to Claim 1, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a serotonin/norepinephrine reuptake inhibitor, and also at least one pharmaceutically acceptable excipient.

11. Pharmaceutical composition according to Claim 1 or Claim 10, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with a serotonin/norepinephrine reuptake inhibitor chosen from venlafaxine, duloxetine and milnacipran or one of their pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

12. Pharmaceutical composition according to Claim 11, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with venlafaxine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

13. Pharmaceutical composition according to Claim 11, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with duloxetine or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

14. Pharmaceutical composition according to Claim 11, comprising, in combination, saredutant or one of its pharmaceutically acceptable salts with milnacipran or one of its pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

15. Combination of saredutant or of one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor or with a serotonin/norepinephrine reuptake inhibitor.

16. Combination of saredutant according to Claim 15 or of one of its pharmaceutically acceptable salts with a selective serotonin reuptake inhibitor chosen from fluoxetine, citalopram, escitalopram, paroxetine, sertraline and fluvoxamine or one of their pharmaceutically acceptable salts.

17. Combination of saredutant according to Claim 15 or of one of its pharmaceutically acceptable salts with a serotonin/norepinephrine reuptake inhibitor chosen from venlafaxine, duloxetine and milnacipran or one of their

pharmaceutically acceptable salts.

18. Use of a pharmaceutical composition according to any one of Claims 1 to 14 in the manufacture of medicaments intended for the prevention and treatment of mood disorders chosen from major depressive disorder, resistant depressive disorder, dysthymic disorder, depressive disorder not otherwise specified, bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, mood disorder induced by a substance, mood disorder not otherwise specified; anxiety disorders chosen from panic attack, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress condition, acute stress condition, generalized anxiety disorder or anxiety disorder induced by a substance.
19. Use according to Claim 18 for the prevention and treatment of a major depressive disorder.
20. Use according to Claim 19 for the treatment of sexual dysfunctions associated with a major depressive disorder.
21. Use of a pharmaceutical composition according to Claim 6 in the manufacture of medicaments intended for the prevention and treatment of mood disorders chosen from major depressive disorder, resistant depressive disorder, dysthymic disorder, depressive disorder not otherwise specified, bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, mood disorder induced by a substance, mood disorder not otherwise specified; anxiety disorders chosen from panic attack, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress condition, acute stress condition, generalized anxiety disorder or anxiety disorder induced by a substance.
22. Use according to Claim 21 for the prevention and treatment of a major depressive disorder.
23. Use according to Claim 22 for the treatment of sexual dysfunctions associated with a major depressive disorder.
24. Use of a pharmaceutical composition according to Claim 7 in the manufacture of medicaments intended for the prevention and treatment of mood disorders chosen from major depressive disorder, resistant depressive disorder, dysthymic disorder, depressive disorder not otherwise specified, bipolar I disorder, bipolar II disorder, cyclothymic disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, mood disorder induced by a substance, mood disorder not otherwise specified; anxiety disorders chosen from panic attack,

agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress condition, acute stress condition, generalized anxiety disorder or anxiety disorder induced by a substance.

25. Use according to Claim 24 for the treatment and prevention of a major depressive disorder.

26. Use according to Claim 25 for the treatment of sexual dysfunctions associated with a major depressive disorder.