



(86) Date de dépôt PCT/PCT Filing Date: 2005/04/18
 (87) Date publication PCT/PCT Publication Date: 2005/11/03
 (45) Date de délivrance/Issue Date: 2013/04/02
 (85) Entrée phase nationale/National Entry: 2006/10/05
 (86) N° demande PCT/PCT Application No.: EP 2005/004086
 (87) N° publication PCT/PCT Publication No.: 2005/102343
 (30) Priorité/Priority: 2004/04/22 (US60/564,660)

(51) Cl.Int./Int.Cl. *A61K 31/496* (2006.01),
A61P 15/00 (2006.01), *C07D 235/26* (2006.01)
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(54) Titre : UTILISATION DE FLIBANSERINE DANS LE TRAITEMENT DE TROUBLES PREMENSTRUELS ET
D'AUTRES TROUBLES SEXUELS CHEZ LA FEMME
 (54) Title: USE OF FLIBANSERIN IN THE TREATMENT OF PREMENSTRUAL AND OTHER FEMALE SEXUAL
DISORDERS

(57) **Abrégé/Abstract:**

The invention relates to a method for the treatment of premenstrual and other female sexual disorders comprising the administration of a therapeutically effective amount of flibanserin.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
3 November 2005 (03.11.2005)

PCT

(10) International Publication Number
WO 2005/102343 A1

- (51) International Patent Classification⁷: **A61K 31/496**, A61P 15/00
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- (21) International Application Number: PCT/EP2005/004086
- (22) International Filing Date: 18 April 2005 (18.04.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/564,660 22 April 2004 (22.04.2004) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



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(54) Title: USE OF FLIBANSERIN IN THE TREATMENT OF PREMENSTRUAL AND OTHER FEMALE SEXUAL DISORDERS

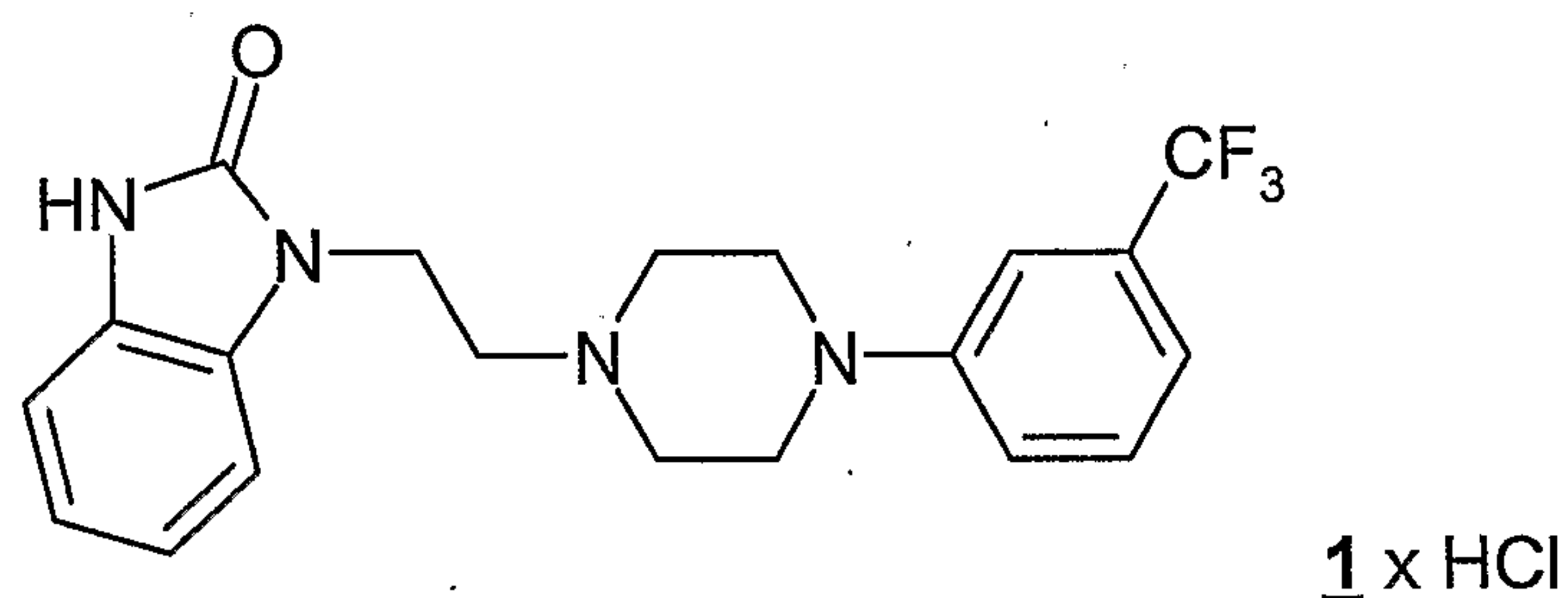
(57) Abstract: The invention relates to a method for the treatment of premenstrual and other female sexual disorders comprising the administration of a therapeutically effective amount of flibanserin.

USE OF FLIBANSERIN IN THE TREATMENT OF PREMENSTRUAL AND OTHER FEMALE SEXUAL DISORDERS

The invention relates to a method for the treatment of premenstrual and other female sexual disorders comprising the administration of a therapeutically effective amount of flibanserin.

Description of the invention

The compound 1-[2-(4-(3-trifluoromethyl-phenyl)piperazin-1-yl)ethyl]-2,3-dihydro-1H-benzimidazol-2-one (flibanserin) is disclosed in form of its hydrochloride in European Patent Application EP-A-526434 and has the following chemical structure:



Flibanserin shows affinity for the 5-HT_{1A} and 5-HT₂-receptor. It is therefore a promising therapeutic agent for the treatment of a variety of diseases, for instance depression, schizophrenia, and anxiety.

In studies of female patients suffering from sexual dysfunction it has been found that flibanserin optionally in form of the pharmacologically acceptable acid addition salts thereof proved to be effective in the treatment of premenstrual disorders. Accordingly, the instant invention relates to a method for the treatment of premenstrual disorders comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof.

In a preferred embodiment the invention relates to a method for the treatment of premenstrual disorders selected from the group consisting of premenstrual dysphoria, premenstrual syndrome, premenstrual dysphoric disorder, comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof.

In another preferred embodiment the invention relates to a method for the treatment of sexual aversion disorder in females comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof.

In another preferred embodiment the invention relates to a method for the treatment of sexual arousal disorder in females comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof.

In another preferred embodiment the invention relates to a method for the treatment of orgasmic disorder in females comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof.

In another preferred embodiment the invention relates to a method for the treatment of sexual pain disorders in females comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof.

In a particular preferred embodiment the invention relates to a method for the treatment sexual pain disorders selected from the group consisting of dyspareunia, vaginismus, noncoital sexual pain disorder, sexual dysfunction due to a general medical condition and substance-induced sexual dysfunction comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof.

Another embodiment of the invention relates to the use of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of the aforementioned disorders.

The beneficial effects of flibanserin can be observed regardless of whether the disturbance existed lifelong or was acquired, and independent of etiologic origin (organic - both, physically and drug induced-, psychogen, a combination of organic - both, physically and drug induced-, and psychogen, or unknown).

Flibanserin can optionally used in form of its pharmaceutically acceptable acid addition salts. Suitable acid addition salts include for example those of the acids selected from, succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid and citric acid. Mixtures of the abovementioned acid addition salts may also be used. From the aforementioned acid addition salts the hydrochloride and the hydrobromide, particularly the hydrochloride, are preferred.

Flibanserin, optionally used in form of its pharmaceutically acceptable acid addition salts, may be incorporated into the conventional pharmaceutical preparation in solid, liquid or spray form. The composition may, for example, be presented in a form
5 suitable for oral, rectal, parenteral administration or for nasal inhalation: preferred forms includes for example, capsules, tablets, coated tablets, ampoules, suppositories and nasal spray.

The active ingredient may be incorporated in excipients or carriers conventionally
10 used in pharmaceutical compositions such as, for example, talc, arabic gum, lactose, gelatine, magnesium stearate, corn starch, aqueous or non aqueous vehicles, polyvinyl pyrrolidone, semisynthetic glycerides of fatty acids, benzalconium chloride, sodium phosphate, EDTA, polysorbate 80. The compositions are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose
15 of the active ingredient. The dosis range applicable per day is between 0.1 to 400, preferably between 1.0 to 300, more preferably between 2 to 200 mg. Each dosage unit may conveniently contain from 0,01 mg to 100 mg, preferably from 0,1 to 50 mg.

20 Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or
25 polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example
30 collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according
35 to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. of a flavouring such as vanilline or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation

products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection are prepared in the usual way, e.g. of. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, and transferred into injection vials or ampoules.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

The Examples which follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

20	A)	<u>Tablets</u>	<u>per tablet</u>
		flibanserin hydrochloride	100 mg
		lactose	240 mg
		corn starch	340 mg
25		polyvinylpyrrolidone	45 mg
		magnesium stearate	15 mg
			<hr/> <hr/> 740 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

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B)	<u>Tablets</u>	<u>per tablet</u>
	flibanserin hydrochloride	80 mg
	corn starch	190 mg

		5	
	lactose	55 mg	
	microcrystalline cellulose	35 mg	
	polyvinylpyrrolidone	15 mg	
	sodium-carboxymethyl starch	23 mg	
5	magnesium stearate	<u>2 mg</u>	
		400 mg	

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size:

	C)	<u>Coated tablets</u>	<u>per coated tablet</u>
15		flibanserin hydrochloride	5 mg
		corn starch	41.5 mg
		lactose	30 mg
		polyvinylpyrrolidone	3 mg
20		magnesium stearate	<u>0.5 mg</u>
			80 mg

The active substance, corn starch, lactose and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45°C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores with a diameter of 6 mm are compressed in a tablet-making machine. The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax.

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	D)	<u>Capsules</u>	<u>per capsule</u>
		flibanserin hydrochloride	1 50 mg
35		Corn starch	268.5 mg
		Magnesium stearate	<u>1.5 mg</u>
			420 mg

The substance and corn starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

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E) Ampoule solution

	flibanserin hydrochloride	50 mg
	sodium chloride	50 mg
10	water for inj.	5 ml

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The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion.

F) Suppositories

	flibanserin hydrochloride	50 mg
20	solid fat	<u>1650 mg</u>
		1700 mg

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The hard fat is melted. At 40°C the ground active substance is homogeneously dispersed. It is cooled to 38°C and poured into slightly chilled suppository moulds.

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In a particular preferred embodiment of the instant invention, flibanserin is administered in form of specific film coated tablets. Examples of these preferred formulations are listed below. The film coated tablets listed below can be manufactured according to procedures known in the art (see hereto WO 03/097058).

G) Film coated tablet

Core

<u>Constituents</u>	<u>mg/tablet</u>
Flibanserin	25.000
Lactose monohydrate	71.720
Microcrystalline cellulose	23.905
HPMC (Methocel E5)	1.250

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Carboxymethylcellulose sodium	2.500
Magnesium stearate	0.625

Coating

<u>Constituents</u>	<u>mg/ tablet</u>
HPMC (Methocel E5)	1.440
Polyethylene Glycol 6000	0.420
Titanium dioxide	0.600
Talc	0.514
Iron oxide red	0.026
Total Film coated tablet	128.000

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H) Film coated tabletCore

<u>Constituents</u>	<u>mg/tablet</u>
Flibanserin	50.000
Lactose monohydrate	143.440
Microcrystalline cellulose	47.810
HPMC (e.g. Pharmacoat 606)	2.500
Carboxymethylcellulose sodium	5.000
Magnesium stearate	1.250

Coating

<u>Constituents</u>	<u>mg/ tablet</u>
HPMC (e.g. Pharmacoat 606)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.000
Talc	0.857
Iron oxide red	0.043
Total Film coated tablet	255.000

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I) Film coated tablet

Core

<u>Constituents</u>	mg/tablet
Flibanserin	100.000
Lactose monohydrate	171.080
Microcrystalline cellulose	57.020
HPMC (e.g. Methocel E5)	3.400
Carboxymethylcellulose sodium	6.800
Magnesium stearate	1.700

Coating

<u>Constituents</u>	mg/ tablet
HPMC (e.g. Methocel E5)	3.360
Polyethylene Glycol 6000	0.980
Titanium dioxide	1.400
Talc	1.200
Iron oxide red	0.060
Total Film coated tablet	347.000

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J) Film coated tabletCore

<u>Constituents</u>	mg/tablet
Flibanserin	2.000
Dibasic Calciumphosphate, anhydrous	61.010
Microcrystalline cellulose	61.010
HPMC (Methocel E5)	1.950
Carboxymethylcellulose sodium	2.600
Colloidal silicon dioxide	0.650
Magnesium stearate	0.780

10 Coating

<u>Constituents</u>	mg/ tablet
HPMC (Methocel E5)	1.440
Polyethylene Glycol 6000	0.420

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Titanium dioxide	0.600
Talc	0.514
Iron oxide red	0.026
Total Film coated tablet	133.000

K) Film coated tablet

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Core

<u>Constituents</u>	mg/tablet
Flibanserin	100.000
Dibasic Calciumphosphate, anhydrous	69.750
Microcrystalline cellulose	69.750
HPMC (e.g. Methocel E5)	2.750
Carboxymethylcellulose sodium	5.000
Colloidal silicon dioxide	1.250
Magnesium stearate	1.500

Coating

<u>Constituents</u>	mg/ tablet
HPMC (e.g. Methocel E5)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.043
Talc	0.857
Total Film coated tablet	255.000

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L) Film coated tabletCore

<u>Constituents</u>	mg/tablet
Flibanserin	20.000
Lactose monohydrate	130.000
Microcrystalline cellulose	43.100

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Hydroxypropyl Cellulose (e.g. Klucel LF)	1.900
Sodium Starch Glycolate	4.000
Magnesium stearate	1.000

Coating

Constituents	mg/ tablet
HPMC (e.g. Methocel E5)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.043
Talc	0.857

Total Film coated tablet	205.000
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CLAIMS:

1. A use of flibanserin or a pharmaceutically acceptable salt thereof in preparation of a pharmaceutical composition for treatment of a premenstrual disorder in a female.
- 5 2. A use according to claim 1, wherein the flibanserin or the pharmaceutically acceptable salt thereof is in an amount for provision of the female with 0.1 to 400mg of the flibanserin or the pharmaceutically acceptable salt thereof per day.
- 10 3. A use according to claim 1 or 2, wherein the flibanserin or the pharmaceutically acceptable salt thereof is in the form of a pharmaceutically acceptable acid addition salt, wherein the salt is formed by an acid selected from the group consisting of succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid, citric acid, and mixtures thereof.
- 15 4. A use according to any one of claims 1 to 3, wherein the premenstrual disorder is selected from the group consisting of premenstrual dysphoria, premenstrual syndrome and premenstrual dysphoric disorder.
5. A use of flibanserin or a pharmaceutically acceptable salt thereof for treatment of a premenstrual disorder in a female.
- 20 6. A use according to claim 5, wherein the flibanserin or the pharmaceutically acceptable salt thereof is in an amount for provision of the female with 0.1 to 400mg of the flibanserin or the pharmaceutically acceptable salt thereof per day.
- 25 7. A use according to claim 5 or 6, wherein the flibanserin or the pharmaceutically acceptable salt thereof is in the form of a pharmaceutically acceptable acid addition salt wherein the salt is formed by an acid selected from the

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group consisting of succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid, citric acid, and mixtures thereof.

8. A use according to any one of claims 5 to 7, wherein the premenstrual disorder is selected from the group consisting of premenstrual dysphoria, premenstrual syndrome and premenstrual dysphoric disorder.
9. Flibanserin or a pharmaceutically acceptable salt thereof for treatment of a premenstrual disorder in a female.
10. Flibanserin or a pharmaceutically acceptable salt thereof according to claim 9, in an amount for provision of the female with 0.1 to 400mg of the flibanserin or the pharmaceutically acceptable salt thereof per day.
11. Flibanserin or a pharmaceutically acceptable salt thereof according to claim 9 or 10, in the form of a pharmaceutically acceptable acid addition salt wherein the salt is formed by an acid selected from the group consisting of succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid, citric acid, and mixtures thereof.
12. Flibanserin or a pharmaceutically acceptable salt thereof according to any one of claims 9 to 11, wherein the premenstrual disorder is selected from the group consisting of premenstrual dysphoria, premenstrual syndrome and premenstrual dysphoric disorder.
13. A pharmaceutical composition comprising flibanserin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent for treatment of a premenstrual disorder in a female.
14. A pharmaceutical composition according to claim 13, wherein the flibanserin or the pharmaceutically acceptable salt thereof is in an amount for

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provision of the female with 0.1 to 400mg of the flibanserin or the pharmaceutically acceptable salt thereof per day.

15. A pharmaceutical composition according to claim 13 or 14, wherein the flibanserin or the pharmaceutically acceptable salt thereof is in the form of a pharmaceutically acceptable acid addition salt wherein the salt is formed by an acid selected from the group consisting of succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid, citric acid, and mixtures thereof.
16. A pharmaceutical composition according to any one of claims 13 to 15, wherein the premenstrual disorder is selected from the group consisting of premenstrual dysphoria, premenstrual syndrome and premenstrual dysphoric disorder.