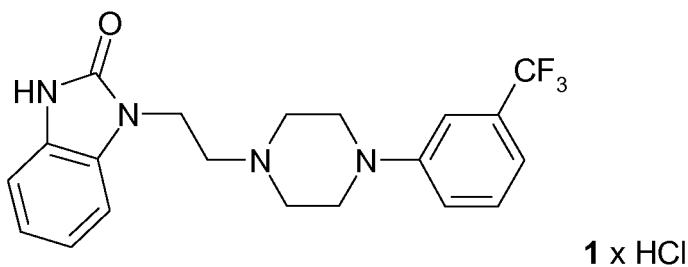


Treatment of vasomotor symptoms

The present invention relates to methods for the treatment of vasomotor symptoms associated with the menopause 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.

Women transitioning through the menopausal frequently experience a variety of symptoms which have been attributed to estrogen deprivation due to ovarian failure. Menopause is defined as the cessation of menstruation in women. The timing of the menopause is determined with hindsight and is established after twelve months of amenorrhoea. Most women experience menopause between the ages of 40 and 55. Menopausal transition is characterized by hot flashes, headaches, night sweats, atrophic vaginitis, frequent urinary tract infections, cold hands and feet, forgetfulness and an inability to concentrate. Emotional indicators of menopause transitioning include anxiety, distress, irritability, mood swings, depression and decreased sex drive. There are many undesirable symptoms too numerous to articulate which are attributed to changes in the female body as she transitions through the menopause.

Some of the symptoms, e.g., vulvar and vaginal atrophy can be clearly attributed to estrogen deficiency; however, hot flashes are likely to arise as a result of an alteration in the CNS thermoregulatory set-point located in the anterior portion of the hypothalamus. Hot flashes, also known as “vasomotor flushes” or “hot flushes” are very common in peri- and postmenopausal women. The dilation of peripheral blood vessels results in reddening and warming of the skin during a hot flash. Further symptoms such as increased heart rate, night sweats, headaches, dizziness, weight gain, fatigue and insomnia may be associated with a hot flash. Hot flashes may appear prior to the cessation of the menses and may be the first sign that menopause is approaching. During the perimenopausal period, appr. 75% of women complain of hot flashes. In most of these women the symptoms will last appr. 1 year. About one-third of postmenopausal women will report symptoms that last up to 5 years after natural menopause, and hot flashes can persist for up to 15 years in 20% or more of women. Menopause induced by surgery is associated with about a 90% probability of hot flashes during the first year, and hot flashes associated with surgical menopause are often more abrupt and severe and can last longer than those associated with a non-surgical menopause.

The US Bureau of Census estimates that currently 49 million American women are over the age of 50 years. Thus, over 32 million women in the USA today might have had hot flashes, and up to 6 million might have reported severe symptoms.

Now, experimental results from studies performed in patients with major Depressive Disorder have shown that flibanserin may be useful for the treatment of vasomotor symptoms (e.g, hot flashes, night sweats, moodswings and irritability).

Accordingly, the instant invention relates to a method for the treatment of vasomotor symptoms comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof.

In an further aspect, the instant invention relates to a method for the treatment of vasomotor symptoms associated with the menopausal transition comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or
5 optionally in form of the hydrates and/or solvates thereof.

As vasomotors symptoms do not only occur due to naturally occurring menopause but may also be also due to surgically (e.g., hysterectomy and bilateral ovariectomy) induced menopause or by the use of medications (e.g. by selective estrogen
10 receptor modulators, GnRH analogues and Aromatase inhibitors), or induced by radioation and chemotherapeutic agents, the present invention relates to a method for the treatment or prevention of vasomotor symptoms associated with iatrogenic induced menopause, comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the free base, the pharmacologically
15 acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof.

In another embodiment the present invention refers to a method for the treatment of hot flashes, night sweats, moodswings and irritability comprising the administration
20 of a therapeutically effective amount of flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof.

Another aspect of the present invention relates to the use of flibanserin for the
25 treatment of moderate to severe vasomotor symptoms associated with a natural or iatrogenic hypogonadal state in men.

Still further aspect of the present invention relates to use of flibanserin for treatment of hot flushes in men, preferably in hypogonadal men, men on androgen deprivation
30 treatment or those who underwent castration.

Another embodiment of the invention relates to the use of flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof for the preparation of a medicament for the treatment of any one of the above mentioned conditions.

- 5 As already mentioned above, Flibanserin may be used in form of the free base, optionally in form of its pharmaceutically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof. 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, 10 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. If Flibanserin is used in form of the free base, it is preferably used in form of Flibanserin polymorph A as disclosed in WO 15 03/014079.

- Flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates, may be incorporated into the conventional pharmaceutical preparation in solid, liquid or 20 spray form. The composition may, for example, be presented in a form suitable for oral, rectal, parenteral administration or for nasal inhalation: preferred forms includes for example, capsules, tablets, coated tablets, ampoules, suppositories and nasal spray.

- 25 The active ingredient may be incorporated in excipients or carriers conventionally 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 30 formulated in dosage units, each dosage unit being adapted to supply a single dose of the active ingredient. The dose 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.

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 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 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 of 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 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.

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

Examples

10 Clinical Trial

In twelve Phase II clinical studies performed in patients diagnosed with Major Depressive Disorder, more then 1500 male and female subjects aged between 18 and 65 years received one or more doses of flibanserin ranging from 2 mg to 100 mg b.i.d. A preliminary analysis of safety database in these subjects showed that flibanserin was associated with virtually no AEs coded as hot flushes/flushing as compared to placebo (1.25%) or selective serotonin reuptake inhibitors (2.1%). (see table 1).

Treatment	Placebo	Flibanserin in mg							Paroxetine in mg	Fluoxetine in mg
		20 bid	50 bid	100 bid	20 qd	50 qd	100 qd	2 bid		
N	718	225	521	154	63	64	63	120	275	145
flushing	5	2	0	0	1	0	0	1	2	2
Hot flush	4	2	1	0	0	0	0	1	3	2

20 Table 1:

In Table 1 it is shown that 9 patients of 718 receiving placebo (1.25 %), 5 patients of 275 (1.8 %) or 4 of 145 (2.75 %) receiving Paroxetine or Fluoxetine respectively suffered form flushing or hot flushes. In stark contrast, in the group receiving 50 to 200 mg/day Flibanserin only one out of 802 patients suffered from flushing. These data suggest that flibanserin is useful for the treatment of vasomotor symptoms like hot flushes in menopausal women.

Examples of pharmaceutical formulations

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

15 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
25		lactose	55 mg
		microcrystalline cellulose	35 mg
		polyvinylpyrrolidone	15 mg
		sodium-carboxymethyl starch	23 mg
		magnesium stearate	<u>2 mg</u>
30			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.

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

15 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
20 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.

25

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

30

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.

E) Ampoule solution

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

10 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.

15 F) Suppositories

flibanserin hydrochloride	50 mg
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.

25 In a particular preferred embodiment of the instsnt 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).

30 G) Film coated tablet

Core

<u>Constituents</u>	mg/tablet
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Flibanserin	25.000
Lactose monohydrate	71.720
Microcrystalline cellulose	23.905
HPMC (Methocel E5)	1.250
Carboxymethylcellulose sodium	2.500
Magnesium stearate	0.625

Coating

<u>Constituents</u>	mg/ tablet
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>	mg/tablet
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>	mg/ tablet
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

5 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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10 J) Film coated tablet

Core

<u>Constituents</u>	mg/tablet
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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

Coating

<u>Constituents</u>	mg/ tablet
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	133.000
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5 K) Film coated tabletCore

<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 tablet

5 Core

<u>Constituents</u>	mg/tablet
Flibanserin	20.000
Lactose monohydrate	130.000
Microcrystalline cellulose	43.100
Hydroxypropyl Cellulose (e.g. Klucel LF)	1.900
Sodium Starch Glycolate	4.000
Magnesium stearate	1.000

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	205.000
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Patent Claims

- 1) A method for the treatment of vasomotor symptoms comprising the administration of a therapeutically effective amount of flibanserin, optionally in form of the free base, the pharmacologically acceptable acid addition salts and/or
5 optionally in form of the hydrates and/or solvates thereof.
- 2) A method according to claim 1, characterized in that the vasomotor symptoms are vasomotor symptoms associated with the menopause.
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- 3) A method according to claim 1, characterized in that the vasomotor symptoms are vasomotor symptoms associated with surgically induced menopause.
- 4) A method according to claim 1, characterized in that the vasomotor symptoms are vasomotor symptoms associated with iatrogenic induced menopause.
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- 5) A method according to claim 1 or 4, characterized in that the vasomotor symptoms are vasomotor symptoms associated with the use of medication, radiation or chemotherapeutic agents.
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- 6) A method according to claim 1, characterized in that the vasomotor symptoms are selected from the group consisting of hot flashes, night sweats, moodswings and irritability.
- 25 7) A method according to claim 1, characterized in that the vasomotor symptoms are selected from the group of moderate to severe vasomotor symptoms associated with a natural or iatrogenic hypogonadal state in men.
- 8) A method according to claim 7, characterized in that the vasomotor symptoms are vasomotor symptoms associated with the use of medication, radiation or
30 chemotherapeutic agents.

9) A method according to claim 7 or 8, characterized in that the vasomotor symptoms are hot flashes in men.

10) A method according to any one of the claims 1 to 9, characterized in that
5 flibanserin is applied in form of a pharmaceutically acceptable acid addition salt selected from the salts formed by 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, citric acid, and mixtures thereof.

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11) A method according to any one of the claims 1 to 9, characterized in that flibanserin is applied in form of flibanserin polymorph A.

12) A method according to any one of the claims 1 to 9, characterized in that
15 flibanserin is applied in a dosis range between 0.1 to 400 mg per day.

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