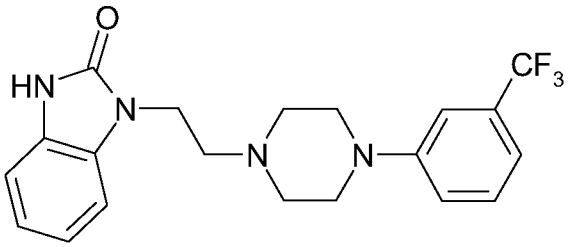
Use of flibanserin for the treatment of pre-menopausal Sexual Desire Disorders

The invention relates to the use of flibanserin for the preparation of a medicament for the treatment of pre-menopausal Sexual Desire Disorders.

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:



1 x HCl

Flibanserin shows affinity for the 5-HT_{1A} and 5-HT_2-receptor. It is therefore a promising therapeutic agent for the treatment of a variety of diseases, for instance depression, schizophrenia, and anxiety.

The generic term “Sexual Disorders” includes Sexual Desire Disorders, Sexual Arousal Disorders, Orgasmic Disorders, Sexual Pain Disorders, Sexual Dysfunction due to a General Medical Condition, Substance-Induced Sexual Dysfunction, and Sexual Dysfunction not otherwise specified (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision. Washington DC, American Psychiatric Association, 2000).

In studies of pre-menopausal female patients suffering from sexual dysfunction it has been found that 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 displays sexual desire enhancing properties. Accordingly, the instant 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 Sexual Desire Disorders in pre-menopausal women.

Within the present invention the terms “treatment of pre-menopausal Hypoactive Sexual Desire Disorder” etc. have the meaning of “treatment of Hypoactive Sexual Desire Disorders in pre-menopausal women” etc.

The beneficial effects of flibanserin can be observed regardless of whether the Sexual Desire Disorder existed lifelong or was acquired, is of the „generalized type“ or „situational type“and independent of etiologic origin (organic - both, physically and drug induced-, psychogen (due to psychological factors), a combination of organic - both, physically and drug induced-, and psychogen (due to combined factors), or unknown). The term “lifelong” refers to such Sexual Desire Disorders of the present invention, which have been present since the onset of sexual functioning. The term “acquired” refers to such Sexual Desire Disorders of the present invention which developed only after a period of normal sexual functioning. The „generalized type“ refers to such Sexual Disorders of the present invention wherein the disorder is not limited to certain types of stimulation, situations, or partners. The „situational type“ applies to such Sexual Disorders of the present invention wherein the disorder is limited to certain types of stimulation, situations, or partners. The subtype due to “psychological factors” applies when psychological factors are judged to have the major role in the onset, severity, exacerbation, or maintenance of the Sexual Disorder, and general medical conditions and substance play no role in the etiology of the Sexual Disorder. Finally the subtype due to “combined factors” applies when 1) psychological factors are judged to have a role in the onset, severity, exacerbation, or maintenance of the Sexual Disorder, and 2) a general medical condition or substance use is also judged to be contributory but is not sufficient to account for a Sexual Disorder (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision. Washington DC, American Psychiatric Association, 2000).

Therefore, e.g. the term “lifelong pre-menopausal Hypoactive Sexual Desire Disorder”refers to Hypoactive Sexual Desire Disorder in pre-menopausal women which has been present since the onset of sexual functioning and the term “acquired pre-menopausal Hypoactive Sexual Desire Disorder” refers to Hypoactive Sexual Desire Disorder in pre-menopausal women, which developed after a period of normal sexual functioning.

Accordingly, in a preferred embodiment 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 disorders selected from the group consisting of pre-menopausal Hypoactive Sexual Desire Disorder (HSDD), pre-menopausal Sexual Aversion Disorder, pre-menopausal loss of sexual desire, pre-

menopausal lack of sexual desire, pre-menopausal decreased sexual desire, pre-menopausal inhibited sexual desire, pre-menopausal loss of libido, pre-menopausal libido disturbance, and pre-menopausal frigidity.

Particular preferred according to the invention is 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 disorders selected from the group consiting of pre-menopausal Hypoactive Sexual Desire Disorder, pre-menopausal Sexual Aversion Disorder, pre-menopausal loss of sexual desire, pre-menopausal lack of sexual desire, pre-menopausal decreased sexual desire, and pre-menopausal inhibited sexual desire.

In a particularily preferred embodiment 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 disorders selected from the group of pre-menopausal Hypoactive Sexual Desire Disorder, pre-menopausal loss of sexual desire, pre-menopausal decreased sexual desire, and pre-menopausal inhibited sexual desire.

In a further preferred embodiment 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 disorders selected from the group consisting of lifelong pre-menopausal Hypoactive Sexual Desire Disorder, lifelong pre-menopausal Sexual Aversion Disorder, lifelong pre-menopausal loss of sexual desire, lifelong pre-menopausal lack of sexual desire, lifelong pre-menopausal decreased sexual desire, lifelong pre-menopausal inhibited sexual desire, lifelong pre-menopausal loss of libido, lifelong pre-menopausal libido disturbance, and lifelong pre-menopausal frigidity.

Particular preferred according to the invention is 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 disorders selected from the group consiting of lifelong pre-menopausal Hypoactive Sexual Desire Disorder, lifelong pre-

menopausal Sexual Aversion Disorder, lifelong pre-menopausal loss of sexual desire, lifelong pre-menopausal lack of sexual desire, lifelong pre-menopausal decreased sexual desire, and lifelong pre-menopausal inhibited sexual desire.

In a particularily preferred embodiment 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 disorders selected from the group of lifelong pre-menopausal Hypoactive Sexual Desire Disorder. lifelong pre-menopausal loss of sexual desire, lifelong pre-menopausal decreased sexual desire, and lifelong pre-menopausal inhibited sexual desire.

In a further preferred embodiment 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 disorders selected from the group consisting of acquired pre-menopausal Hypoactive Sexual Desire Disorder, acquired pre-menopausal Sexual Aversion Disorder, acquired pre-menopausal loss of sexual desire, acquired pre-menopausal lack of sexual desire, acquired pre-menopausal decreased sexual desire, acquired pre-menopausal inhibited sexual desire, acquired pre-menopausal loss of libido, acquired pre-menopausal libido disturbance, and acquired pre-menopausal frigidity.

Furthermore preferred according to the invention is 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 disorders selected from the group consiting of acquired pre-menopausal Hypoactive Sexual Desire Disorder, acquired pre-menopausal Sexual Aversion Disorder, acquired pre-menopausal loss of sexual desire, acquired pre-menopausal lack of sexual desire, acquired pre-menopausal decreased sexual desire, acquired pre-menopausal inhibited sexual desire.

In a particularily preferred embodiment 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 disorders selected from the group of acquired pre-menopausal Hypoactive Sexual Desire Disorder, acquired pre-

menopausal loss of sexual desire, acquired pre-menopausal decreased sexual desire and acquired pre-menopausal inhibited sexual desire.

Furthermore the present invention relates to the generalized or situational subtype of any of the above mentioned conditions and/or to such which are due to organic factors, psychological factors or due to combined factors.

Flibanserin can optionally used in form of the free base, 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, 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, particularily 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 03/014079.

Flibanserin, optionally used in form of the free base, the pharmacologically acceptable acid addition salts and/or optionally in form of the hydrates and/or solvates thereof, may be incorporated into the conventional pharmaceutical preparation in solid, liquid or 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.

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, acqueous or non acqueous vehicles, polyvynil pyrrolidone, semisynthetic glicerides 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 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.

The dosage units are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily consecutively over a period of time.

Preferably, the dose is administered to a patient in the morning and the evening, more preferably once in the morning (25 or 50 mg of flibanserin) and once in the evening (25 or 50 mg of flibanserin), most preferably once in the evening only (50 or 100 mg of flibanserin) consecutively over a period of time.

As a result side-effects such as sedation are of lesser significance.

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 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 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

A)	Tablets	per tablet
	flibanserin	100 mg
	lactose	240 mg
	corn starch	340 mg
	polyvinylpyrrolidone	45 mg
	magnesium stearate	15 mg
		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.

B)	Tablets	per tablet
	flibanserin	80 mg
	corn starch	190 mg
	lactose	55 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
	sodium-carboxymethyl starch	23 mg

magnesium stearate	2 mg
	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) Coated tablets

	per coated tablet
flibanserin	5 mg
corn starch	41.5 mg
lactose	30 mg
polyvinylpyrrolidone	3 mg
magnesium stearate	0.5 mg
	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.

D) Capsules

	per capsule
flibanserin	1 50 mg
Corn starch	268.5 mg
Magnesium stearate	1.5 mg
	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.

E) Ampoule solution

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

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	50 mg
solid fat	1650 mg
	1700 mg

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.

Results of Clinical Trials

In the following, experimental data of a clinical trial proving the effect of flibanserin in the treatment of Sexual Desire Disorders in pre-menopausal women are presented.

This trial was designed as a prospective, multi-center, twelve-week, randomized, double-blind, placebo-controlled, proof of concept, parallel-group trial comparing the effects of flibanserin (maximum total daily dose: 100 mg b.i.d.) to placebo in pre-menopausal female patients with HSDD. Seventy-five patients were to be randomized to each treatment group.

This proof of concept trial was designed to assess whether twelve weeks of flibanserin treatment produced a clinically meaningful therapeutic response in healthy female patients with HSDD (as determined by DSM-IV criteria). Efficacy for flibanserin was assessed versus a parallel placebo group.

After a Screening period (no treatment) of approximately twenty-eight days, eligible patients were randomized into the twelve week, double-blind portion of the trial during which they were to take study medication in the morning and in the evening about 12 hours apart.

Trial Periods	Screening	Baseline	Treatment		Final Visit
Visit	1	2	3	4	5
Day	-28 +/- 3	0	28 +/- 3	56 +/- 3	84 +/- 3
Week	-4	0	4	8	12

Patients must have been pre-menopausal females who were 18 to 45 years of age with the primary diagnosis of HSDD, acquired type, according to DSM-IV criteria. The current episode must have been at least 24 weeks in duration by the Baseline Visit.

The baseline severity criterion was from the Arizona Sexual Experiences Scale, requiring a score of 5 or 6 (very weak or no sex drive) on the sex drive item. (McGahuey CA. et al., Psychiatric Annals 1999; 29(1): 39-45; McGahuey CA. et al., J. Sex Marital Therapy 2000; 26: 25-44).

The assignment of doses was a simple random assignment with the possibility of a one-time up-titration at Week 8. The starting dosage was to be one tablet in the morning and one tablet in the evening.

Patients were instructed to take the blinded study medication as close to every twelve hours as possible. It was recommended that doses not be taken less than ten hours apart. If a dose was missed, the next regular dose was to be taken as scheduled. No double doses were to be taken. Patients were advised that each dose of study medication was to be taken with 150 millimeter (five ounces) of water.

If the patient was not showing meaningful improvement at Day 56 (Week 8) in the investigator's opinion and had no severe or intolerable adverse events, the number of tablets per day was to be doubled from one tablet each morning and evening, increasing the dose of flibanserin from 50 mg b.i.d. to 100 mg b.i.d, or doubling the number of placebo tablets from two per day to four per day for patients in the placebo group.

As one efficacy variable to prove efficacy of flibanserin in the treatment of HSDD in pre-menopausal women, the Interactive Voice Response-Female Sexual Behavior Questionnaire (IVR-FSBQ) was designed as a simple self-administered questionnaire to be completed using a telephone to measure sexual desire-related feelings and events. To facilitate compliance with its use, the FSBQ was to be used in this trial on a weekly basis via an IVR System developed and administered by Healthcare Technology Systems, Inc.

The IVR-FSBQ (as far as related to desire) is shown below.

1. How often did you engage in sexual thoughts such as thinking about having sex or sexual fantasies, this past week?

If not at all in the past week - Press 0
If on one day in the past week - Press 1
If on two days in the past week - Press 2
If on three days or more but not every day in the past week - Press 3
If everyday this past week - Press 4
If more than once per day in the past week - Press 5

Analyses of endpoints were performed on the FAS (Full Analysis Dataset). The LOCF method (Last Observation carried forward) of data estimation was used unless otherwise specified.

To meet the DSM-IV criteria for Hypoactive Sexual Desire Disorder, the severity requirement on lack of desire is “persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity.” Thus, IVR-FSBQ question 1, ““How often did you engage in sexual thoughts such as thinking about having sex or sexual fantasies, this past week?“ is of the essence in proving whether flibanserin treats Sexual Desire Disorders. One major result of this clinical trial was the difference on

this question, namely in the monthly mean change from baseline, between patients treated with flibanserin and placebo. A graph for IVR-FSBQ Monthly Mean Change from Baseline scores for Frequency of Sexual Thoughts is displayed in Fig. 1., which clearly demonstrates the efficacy of flibanserin in the treatment of Sexual Desire Disorders in pre-menopausal women.

Claims

1) 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 pre-menopausal Sexual Desire Disorders in women.

2) Use according to claim 1, characterized in that the pre-menopausal Sexual Desire Disorder is selected from the group consisting of pre-menopausal Hypoactive Sexual Desire Disorder, pre-menopausal Sexual Aversion Disorder, pre-menopausal loss of sexual desire, pre-menopausal lack of sexual desire, pre-menopausal decreased sexual desire, pre-menopausal inhibited sexual desire, pre-menopausal loss of libido, pre-menopausal libido disturbance, and pre-menopausal frigidity.

3) Use according to claim 1 or 2, characterized in that the pre-menopausal Sexual Desire Disorder is selected from the group consisting of pre-menopausal Hypoactive Sexual Desire Disorder, pre-menopausal Sexual Aversion Disorder, pre-menopausal loss of sexual desire, pre-menopausal lack of sexual desire, pre-menopausal decreased sexual desire, pre-menopausal inhibited sexual desire.

4) Use according to claim 1, 2 or 3 characterized in that the pre-menopausal Sexual Desire Disorders are of lifelong type.

5) Use according to claim 1, 2 or 3 characterized in that the pre-menopausal Sexual Desire Disorders are of acquired type.

6) Use according to one or more of the preceding claims, characterized in that the pre-menopusal Sexual Desire Disorders are of the generalized subtype.

7) Use according to one or more of the preceding claims, characterized in that the pre-menopusal Sexual Desire Disorders are of the situational subtype.

8) Use according to one or more of the preceding claims, characterized in that the pre-menopusal Sexual Desire Disorders are due to psychological factors.

9) Use according to one or more of the preceding claims, characterized in that the pre-menopusal Sexual Desire Disorders are due to organic factors.

10) Use according to one or more of the preceding claims, characterized in that the pre-menopusal Sexual Desire Disorders are due to combined factors.

11) Use according to one or more of the preceding claims characterized in that 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.

12) Use according to one or more of the preceding claims, characterized in that flibanserin is applied in form of its free base.

13) Use according to claim 12, characterized in that flibanserin is applied in form of a polymorph A of the free base, having a melting point of about 161 °C as measured using DSC

14) Use according to one or more of the preceding claims, characterized in that flibanserin is applied in a dosis range between 0.1 to 400 mg per day.

15) Use according to one or more of the preceding claims, characterized in that flibanserin is applied once or twice daily consecutively over a period of time.

16) Use according to one or more of the preceding claims, characterized in that flibanserin is applied in the morning and the evening, more preferably once in the morning (25 or 50 mg of flibanserin) and once in the evening (25 or 50 mg of flibanserin),

17) Use according to one or more of the preceding claims, characterized in that flibanserin is applied once in the evening only (50 or 100 mg of flibanserin) consecutively over a period of time.