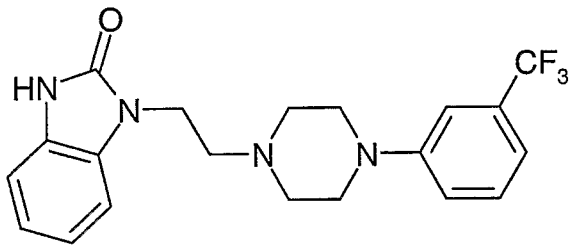
NEW PHARMACEUTICAL COMPOSITIONS CONTAINING FLIBANSERIN POLYMORPH A

The invention relates to oral pharmaceutical compositions containing flibanserin, methods for the preparation thereof and use thereof as a medicament.

Background 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 hydrochlorid 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, Parkinson, anxiety, sleep disturbances, sexual and mental disorders and age associated memory impairment.

A certain pharmaceutical activity is of course the basic prerequisite to be fulfilled by a pharmaceutically active agent before same is approved as a medicament on the market. However, there are a variety of additional requirements a pharmaceutically active agent has to comply with. These requirements are based on various parameters which are connected with the nature of the active substance itself. Without being restrictive, examples of these parameters are the stability of the active agent under various environmental conditions, its stability during production of the pharmaceutical formulation and the stability of the active agent in the final medicament compositions. The pharmaceutically active substance used for preparing the pharmaceutical compositions should be as pure as possible and its stability in long-term storage must be guaranteed under various environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the actual active substance, degradation products thereof, for example. In such cases the content of active substance in the medicament might be less than that specified.

Uniform distribution of the active substance in the formulation is a critical factor, particularly when the medicament has to be given in low doses. To ensure uniform

distribution, the particle size of the active substance can be reduced to a suitable level, e.g. by grinding. Since degradation and/or amorphization of the pharmaceutically active substance as a side effect of the grinding (or micronising) has to be avoided as far as possible, in spite of the hard conditions required during the process, it is absolutely essential that the active substance should be highly stable throughout the grinding process. Only if the active substance is sufficiently stable during the grinding process is it possible to produce a homogeneous pharmaceutical formulation which always contains the specified amount of active substance in reproducible manner.

Finally, the properties of the pharmaceutical composition as such decisively contribute to the bioavailability of the active agent and hence efficacy of the medicament in the intended medical use.

The aim of the invention is thus to provide a new formulation for oral administration containing flibanserin which meets the stringent requirements imposed on pharmaceutical compositions as mentioned above.

Description of the invention

It has been found, surprisingly, that the free base of flibanserin in a specific polymophic form best fulfils the requirements to be met within the formulation according to the invention. This specific polymorphic form (polymorph A) is obtainable by specific reaction conditions which are described in more detail hereinbelow. Among other features this polymorphic form is characterized by an endothermic maximum at 161°C which occurs during thermal analysis using DSC (Differential Scanning Calorimetry).

The pharmaceutical composition according to the invention is a tablet for oral administration comprising a core, containing flibanserin polymorph A being characterized by an endothermic maximum at 161°C determined by DSC in admixture with at least one pharmaceutically acceptable excipient and further comprising a film coating enveloping said core.

Based on the total mass of the core of the film-coated tablets according to the invention flibanserin polymorph A is present in amounts of 1 to 50 wt.%, preferably 5 to 45 wt.%, particularly preferably about 10 to 40 wt.%. Particularly preferably, the proportion of flibanserin polymorph A is between 15 and 35 wt.%, more preferably between 17 and 32 wt.% based on the total mass of the core.

The core of the pharmaceutical formulation according to the invention contains, in addition to flibanserin polymorph A, at least one excipient as filler/dry binder. Within the scope of the present invention typical fillers are for example lactose monohydrate, both fine milled material or modified lactose like spray-dried lactose and agglomerated lactose (Tablettose), anhydrous lactose,microcrystalline cellulose, dibasic calcium phosphate, cornstarch, sugar alcohols like e.g. mannitol and sorbitol and mixtures thereof. Preferably the filler within the formulation according to the invention is selected from the group consisting of lactose types, microcrystalline cellulose, cornstarch, sugar alcohols and mixtures thereof. More preferably the filler in the formulation according to the invention is selected from the group consisting of lactose types, microcrystalline cellulose, and mixtures thereof. If lactose is used as a filler it is preferably applied in form of the lactose monohydrate fine milled material (e.g. 200 mesh grade).

The core of the film-coated tablet according to the invention may also contain dry and/or wet binding agents, such as povidone (e.g. Kollidon K 25), copovidone (e.g. Kollidon VA 64), hydroxypropyl methylcellulose, hydroxypropylcellulose, corn starch and mixtures thereof. Preferably the binding agent is selected from the group of povidone, hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, hydroxypropylcellulose, and mixtures thereof. Most preferably hydroxyproypl methylcellulose is selected as binding agent. If hydroxypropyl methylcellulose (HPMC) is applied the HPMC polymers HPMC USP2910 and USP2208 like for instance Methocel E5, E4M, E15M, (K15M, and K100M) supplied for instance by the Dow Chemical Company are of special interest. In the aforementioned abbreviations the designation "E" refers to USP2910 whereas "K" refers to USP2208. The number designation refers to the viscosity in a 2% aqueous solution (e.g. 5 designates a viscosity of 5 cps; 15M designates a viscosity of 15000 cps).

Based on the total mass of the core of the film-coated tablets according to the invention the filler is preferably present in amounts of 50 to 99 wt.%, preferably 55 to 95 wt.%, particularly preferably about 60 to 90 wt.%. Particularly preferably, the proportion of the total amount of filler is between 65 and 85 wt.%, more preferably between 68 and 80 wt.% based on the total mass of the core.

Preferably the core of the tablet formulation according to the invention comprises flibanserin polymorph A in admixture with lactose monohydrate as the pharmaceutically acceptable excipient.
More preferably the core of the tablet formulation according to the invention comprises flibanserin polymorph A in admixture with lactose monohydrate and

microcrystalline cellulose as pharmaceutically acceptable excipients. In formulations according to the invention containing a mixture of lactose monohydrate and microcrystalline cellulose as filler components (or pharmaceutically acceptable excipients), the ratio of lactose monohydrate to microcrystalline cellulose is for example in the range of about 15:1 to about 1:5, preferably in a range of about 10:1 to about 1:3, more preferably in a range of about 6:1 to about 1:1.

In another preferred embodiment according to the invention tablet formulation comprises flibanserin polymorph A in admixture with lactose monohydrate, microcrystalline cellulose and HPMC as pharmaceutically acceptable excipients. In particular preferred formulations according to the invention containing a mixture of lactose monohydrate, microcrystalline cellulose and HPMC as filler/binder components (or pharmaceutically acceptable excipients), the amount of lactose monohydrate is for example in the range of 50 to 95 wt.%, preferably 60 to 90 wt.%, more preferably about 65 to 85 wt.% based on the total mass of the filler/binder used for the preparation of the core. In a particularly preferred embodiment these tablet formulations contain lactose monohydrate in an amount of about 70 to 80 wt.% based on the total mass of the filler/binder used for the preparation of the core. In the particular preferred formulations according to the invention containing a mixture of lactose monohydrate, microcrystalline cellulose and HPMC as filler/binder components (or pharmaceutically acceptable excipients), the amount of microcrystalline cellulose is for example in the range of 5 to 45 wt.%, preferably 15 to 35 wt.%, more preferably about 20 to 30 wt.% based on the total mass of the filler/binder used for the preparation of the core. In a particularly preferred embodiment these tablet formulations contain microcrystalline cellulose in an amount of about 22 to 28 wt.% based on the total mass of the filler/binder used for the preparation of the core. In the particularly preferred formulations according to the invention containing a mixture of lactose monohydrate, microcrystalline cellulose and HPMC as filler/binder components (or pharmaceutically acceptable excipients), the amount of HPMC is for example in the range of 0.5 to 5 wt.%, preferably 1.0 to 4.5 wt.% based on the total mass of the filler/binder used for the preparation of the core. In a particularly preferred embodiment these tablet formulations contain HPMC in an amount of about 1 to 3 wt.% based on the total mass of the filler/binder used for the preparation of the core.

The core of the film-coated tablet according to the invention may also contain disintegrants in addition to the ingredients mentioned above. Within the scope of the present invention these disintegrants may optionally also be known as breakdown agents. These are preferably selected according to the invention from among sodium

starch glycolate, crospovidone, croscarmellose sodium, sodium-carboxymethylcellulose, dried corn starch and mixtures thereof. Particularly preferably, within the scope of the present invention, sodium starch glycolate, crospovidone, sodium-carboxymethylcellulose and croscarmellose sodium, preferably croscarmellose sodium are used. If the abovementioned disintegrants are used, the amount by weight used based on the total mass of the core of the film-coated tablet according to the invention is for example in a range from about 0.1 - 10 wt.%, preferably about 0.5 - 5 wt.%, more preferably about 1 - 3 wt.%.

The core of the film-coated tablet according to the invention may also contain flow regulators as additional ingredients. Flow regulators within the scope of the present invention include, for example, silicon dioxide, talc, magnesium stearate and mixtures thereof. According to the invention silicon dioxide is preferably used, particularly preferably in colloidal, highly dispersed form.If the abovementioned flow regulators are used, the amount by weight thereof based on the total mass of the core of the film-coated tablet according to the invention is preferably in a range from about 0.1 - 5 wt.%, preferably about 0.3 - 2 wt.%, particularly preferably between 0.4 and 1.5 wt.%.

The core of the film-coated tablet according to the invention may also contain flow agents, lubricants and mould release or antiadhesive agents as further ingredients. These include, for example, within the scope of the present invention, stearic acid, magnesium stearate, calcium stearate, sodium stearyl fumarate, glycerol tribehenate, talc and mixtures thereof. According to the invention, stearic acid and magnesium stearate are preferably used. If one or several of the aforementioned ingredients is used the amount by weight thereof is preferably in a range from about 0.01 - 5 wt.%, preferably about 0.05 - 3 wt.%, particularly preferably about 0.1 - 2 wt.% based on the total mass of the core of the film-coated tablet. Preferably, especially in case of magnesium stearate the amount thereof is in the range of about 0.2 – 1.5 wt.% based on the total mass of the core of the film-coated tablet.

The film coating enveloping the core of the film-coated tablets according to the invention contains at least one or more film-forming agents selected from among hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and poly(ethylacrylate) methylmethacrylate, the latter in the form of Eudragit NE 30 D, for example. Alternatively, Eudragit RL 30 D or Eudragit E 12.5 may be used, for example. The above ingredients may optionally also be used in the form of mixtures thereof. Preferred film-forming agents are hydroxypropylmethylcellulose,

hydroxypropylcellulose, hydroxymethylcellulose and hydroxyethylcellulose, of which hydroxypropylmethylcellulose and hydroxypropylcellulose are particularly preferred as film-forming agents according to the invention. The abovementioned film-forming agents may be used on their own or in the form of the mixtures thereof. If only one of the abovementioned film-forming agents is used, hydroxypropylmethylcellulose is of particular importance in this context within the scope of the present invention. The amount by weight of film-forming agents based on the total mass of the film coating of the film-coated tablet according to the invention is preferably in a range from about 20 - 95 wt.%, preferably 30 - 90 wt.% .

The film coating enveloping the core may contain emulsifiers and/or plasticisers such as, for example, polyethyleneglycol, glycerol and propyleneglycol, optionally in the form of the mixtures thereof. Preferably, polyethyleneglycols are used as plasticisers. Without restricting the subject matter of the invention thereto, polyethyleneglycol 400 and polyethyleneglycol 6000 are examples of particularly preferred polyethyleneglycols. Within the description of the instant invention references to the term Macrogol are to be understood as references to the term polyethyleneglycol. The values 400 and 6000 mentioned hereinbefore indicate the average molecular weight of the polyethyleneglycol applied. The amount of plasticiser by weight based on the total mass of the film coating of the film-coated tablet according to the invention is preferably in a range from about 1 - 50 wt.%, preferably 5 - 40 wt.%, particularly preferably 10 - 30 wt.%. Preferably the amount of plasticiser is in a range of about 10 - 25 wt.%, more preferably in a range of about 12 - 18 wt.% based on the total mass of the film coating of the film-coated tablet.

The film coating of the film-coated tablet according to the invention may also contain coloured pigments and pigmenting excipients. Iron oxide, titanium dioxide, talc and mixtures thereof may be mentioned by way of example. In case talc is used the amount thereof is for example in a range from about 5 - 50 wt.%, preferably 10 - 40 wt.%, particularly preferably 15 - 30 wt.% based on the total mass of the film coating of the film-coated tablet. Preferably the amount of talc is in a range of about 15 - 20 wt.% based on the total mass of the film coating of the film-coated tablet. In case titanium dioxide is used the amount thereof is for example in a range from about 5 - 55 wt.%, preferably 10 - 40 wt.%, particularly preferably 15 - 35 wt.% based on the total mass of the film coating of the film-coated tablet. Preferably the amount of titanium dioxide is in a range of about 20 - 30 wt.% based on the total mass of the film coating of the film-coated tablet. In case iron oxide is used the amount thereof is for example in a range from about 0.1 - 5 wt.%, preferably about 0.25 - 3 wt.%, more

preferably about 0.5 – 1.5 wt.% based on the total mass of the film coating of the film-coated tablet.

In a particular preferred embodiment the film coat enveloping the core of the tablet according to the invention comprises hydroxypropyl methylcellulose, polyethyleneglycol and titanium dioxide. In another embodiment according to the invention the film coat enveloping the core of the tablet according to the invention comprises hydroxypropyl methylcellulose, polyethyleneglycol, titanium dioxide and talc. In yet another embodiment according to the invention the film coat enveloping the core of the tablet according to the invention comprises hydroxypropyl methylcellulose, polyethyleneglycol, titanium dioxide, talc and iron oxides, preferably iron oxide red.

The pharmaceutical composition according to the invention can be prepared according to the procedure outlined in detail in the experimental section of this patent application.

In the light of the pharmaceutical efficacy of flibanserin, the present invention furthermore relates to the use of the flibanserin polymorph A containing formulations according to the invention as a medicament.

A further aspect of the present invention relates to the use of the flibanserin polymorph A containing formulations according to the invention for treating diseases in which the use of compounds displaying affinity for the 5-HT_{1A} and 5-HT_2-receptor may have a therapeutic benefit.

A further aspect of the present invention relates to the use of the flibanserin polymorph A containing formulations according to the invention for treating a disease selected from depression, schizophrenia, Parkinson, anxiety, sleep disturbances, sexual and mental disorders and age associated memory impairment.

In particular, the instant invention relates to the use of the flibanserin polymorph A containing formulations according to the invention for the treatment of disorders of sexual desire.

In a preferred embodiment the invention relates to the use of the flibanserin polymorph A containing formulations according to the invention for the treatment of disorders selected from the group consisting of Hypoactive Sexual Desire Disorder,

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

Particular preferred according to the invention is the use of the flibanserin polymorph A containing formulations according to the invention for the treatment of disorders selected from the group consiting of Hypoactive Sexual Desire Disorder, loss of sexual desire, lack of sexual desire, decreased sexual desire, inhibited sexual desire. In a particularily preferred embodiment the invention relates to the use of the flibanserin polymorph A containing formulations according to the invention for the treatment of disorders selected from the group of Hypoactive Sexual Desire Disorder and loss of sexual desire.

Another aspect of the present invention relates to a method for treating diseases in which the use of compounds displaying affinity for the 5-HT_{1A} and 5-HT_2-receptor may have a therapeutic benefit comprising the administration of a flibanserin polymorph A containing formulations according to the invention.

A further aspect of the present invention relates to a method for treating a disease selected from depression, schizophrenia, Parkinson, anxiety, sleep disturbances, sexual and mental disorders and age associated memory impairment comprising the administration of a flibanserin polymorph A containing formulations according to the invention.

In particular, the instant invention relates to a method for the treatment of disorders of sexual desire comprising the administration of a flibanserin polymorph A containing formulations according to the invention.

In a preferred embodiment the invention relates to a method for the treatment of disorders selected from the group consisting of Hypoactive Sexual Desire Disorder, loss of sexual desire, lack of sexual desire, decreased sexual desire, inhibited sexual desire, loss of libido, libido disturbance, and frigidity, comprising the administration of a flibanserin polymorph A containing formulations according to the invention.

Particular preferred according to the invention is a method for the treatment of disorders selected from the group consiting of Hypoactive Sexual Desire Disorder, loss of sexual desire, lack of sexual desire, decreased sexual desire, inhibited sexual desire comprising the administration of a flibanserin polymorph A containing formulations according to the invention.

In a particularily preferred embodiment the invention relates to a method for the treatment of disorders selected from the group of Hypoactive Sexual Desire Disorder and loss of sexual desire, comprising the administration of a flibanserin polymorph A containing formulations according to the invention.

The aforementioned therapeutic effects of the flibanserin polymorph A containing formulations according to the invention can be achieved in men and women. However, according to a further aspect of the invention the use of the flibanserin polymorph A containing formulations according to the invention for the treatment of female sexual dysfunction is preferred.

The beneficial effects of the flibanserin polymorph A containing formulations according to the invention 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).

The invention will be further described by the following examples. These examples disclose certain preferred embodiments of the invention. Accordingly, it is intended that the invention be not limited to the following explicitly disclosed examples.

Synthesis of flibanserin polymorph A:

375 kg of 1-[(3-trifluoromethyl)phenyl]-4-(2-cloroethyl)piperazin are charged in a reactor with 2500 kg of water and 200 kg of aqueous Sodium Hydroxide 45%. Under stirring 169.2 kg of 1-(2-propenyl)-1,3-dihydro-benzimidazol-2H-one, 780 kg of isopropanol, 2000 kg of water and 220 kg of aqueous Sodium Hydroxide 45% are added. The reaction mixture is heated to 75-85°C and 160 kg of concentrated hydrochloric acid and 200 kg of water are added. The reaction mixture is stirred at constant temperature for about 45 minutes. After distillation of a mixture of water and Isopropanol (about 3000 kg) the remaining residue is cooled to about 65-75°C and the pH is adjusted to 6.5 – 7.5 by addition of 125 kg of aqueous Sodium Hydroxide 45%. After cooling to a temperature of 45-50°C, the pH value is adjusted to 8-9 by addition of about 4 kg of aqueous Sodium Hydroxide 45%.Subsequently the mixture is cooled to 30-35°C and centrifuged. The residue thus obtained is washed with 340 l of water and 126 l of isopropanol and then with water until chlorides elimination. The wet product is dried under vacuum at a temperature of about 45-55°C which leads to 358 kg of crude flibanserin polymorph A. The crude product thus obtained is loaded in a reactor with 1750 kg of Acetone and the resulting mixture is heated under stirring until reflux. The obtained solution is filtered and the filtrate is concentrated by

distillation. The temperature is maintained for about 1 hour 0-5°C, then the precipitate solid is isolated by filtration and dried at 55°C for at least 12 hours. The final yield is 280 kg of pure flibanserin polymorph A.

Characterisation of flibanserin polymorph A:

Flibanserin polymorph A was characterised by DSC (Differantial Scanning Calorimetry). The peak temperature determined for polymorph A is about 161°C. For the characterization via DSC a Mettler TA 3000 System equipped with TC 10-A processor and DSC 20 cell was applied. The heating rate was 10 K/min.

The flibanserin polymorph A was additionally characterised by powder x-ray diffractometry. The x-ray powder diffraction pattern for polymorph A was obtained according to the following conditions:

Equipment:	Philips PW 1800/10 diffractometer equipped with a digital microvax 2000.	
Setting parameters:	X-ray	
	Type tube:	Cu (long fine focus)
	Wavelenghts (λ):	$K_{\alpha 1}$ = 1.54060 Å
		$K_{\alpha 2}$ = 1.54439 Å
	Intensity ratio (α2/ α1):	0.500
	Start angle [°2Θ]:	2.000
	End angle [°2Θ]:	60.000
	Step size [°2Θ]:	0.020
	Maximum intensity[s]:	7310.250
	Type of scan:	continuous
	Minimum peak tip width:	0.00
	Maximum peak tip width:	1.00
	Peak base width:	2.00
	Minimum significance:	0.75
	Number of peaks:	69
Generator:	high voltage:	50 KV
	tube current:	30 mA

The powder x-ray diffraction pattern obtained for polymorph A is illustrated in figure 1. The appropiate values are collected in table 1.

Table 1:

Angle [°2Θ]	d-value α1 [Å]	d-value α 2 [Å]	Peak width [°2Θ]	Peak int [counts]	Back. int [counts]	Rel. int [%]	Signif.
5.195	16.9967	17.0390	0.960	8	69	0.1	1.05
9.045	9.7689	9.7931	0.100	92	96	1.3	0.97
9.335	9.4660	9.4896	0.080	114	98	1.6	0.88
10.025	8.8160	8.8379	0.140	400	100	5.5	7.18
10.595	8.3430	8.3637	0.140	204	102	2.8	3.46
11.290	7.8309	7.8503	0.140	467	104	6.4	6.91
13.225	6.6891	6.7058	0.180	548	112	7.5	13.10
14.595	6.0642	6.0793	0.180	404	121	5.5	9.17
15.460	5.7268	5.7410	0,140	4186	125	57.3	23.20
16.655	5.3185	5.3317	0.200	515	130	7.0	12.38
17.085	5.1856	5.1985	0.100	1347	132	18.4	2.78
17.285	5.1260	5.1388	0.060	1399	135	19.1	2.26
17.420	5.0866	5.0992	0.100	1204	135	16.5	4.71
18.140	4.8863	4.8984	0.180	1043	139	14.3	13.14
18.650	4.7538	4.7656	0.120	1063	142	14.5	0.91
19.140	4.6332	4.6447	0.140	7310	144	100.0	32.77
19.820	4.4757	4.4869	0.160	3624	146	49.6	9.02
20.080	4.4184	4.4294	0.140	5402	149	73.9	21.06
20.385	4.3530	4.3638	0.160	2652	149	36.3	23.25
21.215	4.1845	4.1949	0.160	369	154	5.0	5.78
21.890	4.0570	4.0670	0.200	773	156	10.6	3.09
22.630	3.9259	3.9357	0.280	4277	161	58.5	74.66
23.210	3.8291	3.8386	0.120	484	164	6.6	3.33
24.355	3.6516	3.6607	0.060	2725	169	37.3	1.16
24.610	3.6144	3.6234	0.140	3540	172	48.4	17.08
24.995	3.5596	3.5684	0.100	529	174	7.2	1.01
25.260	3.5228	3.5316	0.120	557	174	7.6	3.02
26.575	3.3514	3.3597	0.240	2421	182	33.1	42.58
27.155	3.2811	3.2893	0.140	676	185	9.2	1.32
27.310	3.2629	3.2710	0.100	767	185	10.5	2.75
27.865	3.1991	3.2071	0.120	420	188	5.7	1.08
28.210	3.1608	3.1686	0.100	1467	190	20.1	0.79

Table 1 (continued):

Angle [°2Θ]	d-value α1 [Å]	d-value α 2 [Å]	Peak width [°2Θ]	Peak int [counts]	Back. int [counts]	Rel. int [%]	Signif.
28.325	3.1482	3.1560	0.140	1789	190	24.5	4.41
28.650	3.1132	3.1210	0.180	1204	190	16.5	11.65
29.520	3.0234	3.0309	0.220	1011	196	13.8	15.74
30.250	2.9521	2.9594	0.120	159	199	2.2	1.22
31.105	2.8729	2.8800	0.360	282	204	3.9	8.14
31.905	2.8026	2.8096	0.100	339	207	4.6	0.96
32.350	2.7651	2.7720	0.120	237	210	3.2	3.01
33.300	2.6884	2.6950	0.180	1347	216	18.4	14.06
33.640	2.6620	2.6686	0.100	404	216	5.5	1.45
34.880	2.5701	2.5765	0.200	202	222	2.8	1.04
35.275	2.5422	2.5486	0.240	299	225	4.1	4.84
36.055	2.4890	2.4952	0.280	202	228	2.8	3.78
36.910	2.4333	2.4393	0.320	169	234	2.3	0.90
37.160	2.4175	2.4235	0.120	216	234	3.0	2.14
37.680	2.3853	2.3912	0.240	240	237	3.3	1.58
39.435	2.2831	2.2888	0.280	449	246	6.1	2.67
39.675	2.2698	2.2755	0.080	396	246	5.4	0.82
40.325	2.2347	2.2403	0.160	520	250	7.1	0.95
40.930	2.2031	2.2086	0.120	480	253	6.6	2.66
41.445	2.1769	2.1823	0.240	372	256	5.1	2.65
41.990	2.1499	2.1552	0.120	538	259	7.4	1.31
42.670	2.1172	2.1225	0.160	428	262	5.9	1.45
43.145	2.0950	2.1002	0.120	433	266	5.9	1.50
44.190	2.0478	2.0529	0.160	376	269	5.1	0.89
46.095	1.9675	1.9724	0.160	279	279	3.8	0.86
46.510	1.9509	1.9558	0.240	310	282	4.2	0.87
48.305	1.8826	1.8872	0.200	506	292	6.9	2.06
48.900	1.8610	1.8657	0.240	615	296	8.4	1.67
50.330	1.8115	1.8160	0.160	437	303	6.0	1.73
51.035	1.7881	1.7925	0.080	416	306	5.7	0.93
53.550	1.7099	1.7141	0.480	177	317	2.4	2.84
54.500	1.6823	1.6865	0.400	130	324	1.8	1.37
55.420	1.6565	1.6606	0.320	130	328	1.8	1.72
56.220	1.6348	1.6389	0.320	121	331	1.7	0.87
56.770	1.6203	1.6243	0.240	142	335	1.9	1.59

Table 1 (continued):

Angle [°2Θ]	d-value α1 [Å]	d-value α 2 [Å]	Peak width [°2Θ]	Peak int [counts]	Back. int [counts]	Rel. int [%]	Signif.
57.405	1.6039	1.6079	0.240	112	339	1.5	1.19
58.500	1.5764	1.5804	0.240	67	342	0.9	1.57

Manufacturing of flibanserin containing film-coated tablets:

A) Equipment used:

The following equipment was used in the method of preparation of the pharmaceutical composition according to the invention:

Mixing vessel with Ekato stirrer and Ultra Turrax for granulation liquid and film coating suspension;

high shear mixer/granulator (e.g. Diosna P 400);

wet screen machine (e.g. Alexanderwerk);

fluid bed dryer (e.g. Glatt WSG 15);

dry screen machine (e.g. Quadro Comil AS 197);

free fall blender (e.g. Servolift 120 l or container mixer);

rotary tablet press (e.g. Fette P 1200);

film coater (e.g. Glatt GC 1250);

B) Process description:

As a first step the granulation liquid for the wet granulation process ist prepared. Purified water is filled into a suitable mixing vessel and heated to about 80°C. Then Hypromellose (Methocel E5 Prem) and/or additional wet binding components are stirred in, and the dispersion is cooled down to room temperature. If necessary, the liquid is allowed to stand overnight (completeness of solution / reduction of frothing) and stirred up before use. If necessary, any weight loss is compensated with purified water. The dry matter (soldis content) of this granulation liquid is preferrably in the range of 4-6 %.

For the granulation process Lactose monohydrate, fine milled and sieved, the required quantity of Flibanserin polymorph A (depending on the dose strength), micronized quality, and Cellulose, microcrystalline (Avicel PH 101) are filled in in this order, mixed homogeneously for about 4 minutes using impeller and chopper blades. Next the granulation liquid is added either manually or by spray nozzles and the wet mass is granulated for about 2-3 minutes, again using impeller and chopper blades. After discharging of the high shear mixer/granulator the wet granules are wet-

screened through a 3.0 mm mesh size sieve to destroy large agglomerates. The wet-screened material is transferred to a conventional fluid bed drier (or alternatively to a tray drier) and dried at an inlet air temperature of approximately 100 °C until an exhaust air temperature (or alternatively product temperature) of approximately 50°C (45-55°C) is reached. The residual moisture of the granulate in terms of loss on drying should be in the range of 0.5-1.5 %. The dried granules are then dry screened with the help of a Comil screen machine using a 2 mm rasp screen. Finally, the screened granulate is filled into a suitable free-fall blender, e.g. a container mixer, the crosslinked Carboxymethylcellulose sodium (Croscarmellose sodium, brand name: Ac-Di-Sol) and Magnesium stearate are added, and the components are mixed for 10-20 minutes, preferrably 15 minutes, at a mixing speed of 10 rpm until homogeneous.

The final tableting mixture is compressed on a suitable tablets press (e.g. rotary press) to the respective target weight of the required dose strength of Flibanserin tablets using the appropriate tools (e.g. in case of 50 mg tablets: 9 mm round, biconvex, with bevelled edges; or in case of 100 mg tablets: 14x6.8 mm oblong shaped). Predetermined hardness specifications for the different tool dimensions have to be followed in order to achieve the intended drug dissolution profile and product characteristics.

Since the drug substance Flibanserin is of bitter taste and slightly light sensitive, a protecting film coat has to be applied to the tablet cores in order to achieve a stable and consumer friendly product. To this end a coating suspension is prepared by filling purified water into a suitable mixing vessel, and dissolving polyethyleneglycol 6000 and then hydroxypropylmethylcellulose with the help of a high intensity stirrer. In a next step an aqueous slurry of titanium dioxide, talc and iron oxide red (in case of coloured film tablets) is poured and stirred into the film-forming polymer solution. The dry matter of this coating suspension is in the range of 10-15 %, preferrably about 12-13 %.

The above prepared tablet cores are filled into a suitable film coater (e.g. an Accela Cota with a 36´´ pan, or a Glatt GC 1250 Coater with perforated pan, and top spray system), and preheated up to a temperature of approximately 50 °C. After this product temperature is reached the coating suspension is sprayed onto the cores with the help of one or more spray nozzles at a spray pressure of about 2 bar, a spray rate of about 4 kg/h (in case of Accela Cota), an inlet air temperature of about 60-85°C. It is important to control and maintain the product temperature during spraying at a level of between 48-52° C to achieve a high quality film-coat. After the spraying is finished the film-coated tablets are cooled down to approx. 30°C before the equipment is discharged. The total process time for the film-coating is in the range of 2-3 hours.

After all in-process and quality controls have been performed the bulk film-coated tablets are now ready for primary packaging into the respective marketing presentations (e.g. PVC/PVDC blister packs or HDPE bottles).

The following film-coated tablets were obtained in analogy to the method of preparation described hereinbefore.

Example N°1 - Composition

Core

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

Coating

Constituents	**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**

Example N°2 - Composition

Core

Constituents	**mg/tablet**
Flibanserin polymorph A	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

Constituents	**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**

Example N°3 - Composition

Core

Constituents	**mg/tablet**
Flibanserin polymorph A	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

Constituents	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**

Example N°4 – Composition

Core

Constituents	mg/tablet
Flibanserin polymorph A	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

Constituents	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**

Example N°5 – Composition

Core

Constituents	**mg/tablet**
Flibanserin polymorph A	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

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	**255.000**

Example N°6 – Composition

Core

Constituents	**mg/tablet**
Flibanserin polymorph A	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

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**

Claims

1) Pharmaceutical composition for oral administration comprising a tablet core, containing flibanserin polymorph A being characterized by an endothermic maximum at 161°C determined by DSC in admixture with at least one pharmaceutically acceptable excipient and further comprising a film coating, enveloping said tablet core.

2) Pharmaceutical composition according to claim 1, characterized in that the pharmaceutically acceptable excipient is a filler selected from the group consisting of lactose monohydrate, both fine milled material or modified lactose like spray-dried lactose and agglomerated lactose (Tablettose), anhydrous lactose, microcrystalline cellulose, dibasic calcium phosphate, cornstarch, sugar alcohols and mixtures thereof.

3) Pharmaceutical composition according to claim 1 or 2, characterized in that flibanserin polymorph A is present in amounts of 1 to 50 wt.% based on the total mass of the core.

4) Pharmaceutical composition according to claim 1, 2 or 3, characterized in that the core contains filler in amounts of 50 to 99 wt.% based on the total mass of the core.

5) Pharmaceutical composition according to claims 1, 2, 3 or 4, characterized in that the core additionally contains a binding agent selected from the group consisting of povidone, copovidone, hydroxypropyl methylcellulose, hydroxypropylcellulose, corn starch and mixtures thereof.

6) Pharmaceutical composition according to one of claims 1 to 5, characterized in that the core additionally contains a disintegrant selected from among sodium starch glycolate, crospovidone, croscarmellose sodium, sodium-carboxymethylcellulose, dried corn starch and mixtures thereof.

7) Pharmaceutical composition according to one of claims 1 to 6, characterized in that the core additionally contains flow regulators, lubricants and mould release or antiadhesive agents selected from the group consisting of silicon dioxide, talc, magnesium stearate and mixtures thereof.

8) Pharmaceutical composition according to one of claims 1 to 7, characterized in that the film coating enveloping the core contains at least one film-forming agent selected from among hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and poly(ethylacrylate) methylmethacrylate.

9) Use of a flibanserin polymorph A containing formulation according to one of claims 1 to 8 for treating diseases in which the use of compounds displaying affinity for the 5-HT_{1A} and 5-HT_2-receptor may have a therapeutic benefit.

10) Use according to claim 9, characterized in that the disease is selected from the group consisiting of depression, schizophrenia, Parkinson, anxiety, sleep disturbances, sexual and mental disorders and age associated memory impairment.