



No. 08-046700- -00003-0000

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Act. 400 OPOSIOBSERVTER Folios: 37

**FORMULARIO ÚNICO DE OPOSICIÓN**

①

**OPOSICIÓN A**

- |                                                                       |                                                 |
|-----------------------------------------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> Patente de Invención.             | <input type="checkbox"/> Marca Colectiva        |
| <input type="checkbox"/> Patente de Modelo de Utilidad                | <input type="checkbox"/> Marca de Certificación |
| <input type="checkbox"/> Diseño Industrial                            | <input type="checkbox"/> Lema Comercial         |
| <input type="checkbox"/> Esquema de Trazado para Circuitos Integrados |                                                 |
| <input type="checkbox"/> Marcas de Productos o Servicios              |                                                 |

②

Número del expediente: 08 046 700

Solicitante: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

**SOLICITUD  
PUBLICADA**

Apoderado: EMILIO FERRERO

Título de la nueva creación o denominación del signo: USO DE FLIBANSERINA

PARA EL TRATAMIENTO DE TRASTORNOS DEL DESEO SEXUAL PREMENOPAUSICOS

Gaceta: 606

③ **OPOSICIÓN PRESENTADA POR:**

|                                      |                                                              |                                          |                                         |
|--------------------------------------|--------------------------------------------------------------|------------------------------------------|-----------------------------------------|
| <b>SOLICITANTE</b>                   | Nombre: <u>GYNOPHARM S.A.</u>                                | <b>IDENTIFICACIÓN</b>                    |                                         |
|                                      | Dirección: <u>Carrera 14 N° 94-44 Piso 7 Torre b</u>         | C.C. <input type="checkbox"/>            | NIT <input checked="" type="checkbox"/> |
|                                      | Nacionalidad o Domicilio: <u>COLOMBIA</u>                    | C.E. <input type="checkbox"/>            | Otro <input type="checkbox"/>           |
|                                      | Lugar de Constitución: <u>BARRANQUILLA</u>                   | Cual <u>                    </u>         |                                         |
|                                      | Teléfono: <u>2 36 84 95</u> Fax: <u>                    </u> | Número <u>802.006.279-4</u>              |                                         |
|                                      | E-mail: <u>                    </u>                          |                                          |                                         |
| <b>REPRESENTANTE<br/>O APODERADO</b> | Nombre: <u>CIELO ANGELA PEÑA<br/>RODRIGUEZ</u>               | <b>IDENTIFICACIÓN</b>                    |                                         |
|                                      | Dirección: <u>CARRERA 13 No. 119-95</u>                      | C.C. <input checked="" type="checkbox"/> | NIT <input type="checkbox"/>            |
|                                      | Teléfono: <u>(571)213 12 13</u> Fax: <u>(571)612 19 79</u>   | C.E. <input type="checkbox"/>            | Otro <input type="checkbox"/>           |
|                                      | E-mail: <u>negocios@optimum-co.com</u>                       | Cual <u>                    </u>         |                                         |
|                                      |                                                              | Número <u>51.940.252</u> TP <u>82701</u> |                                         |

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:                     

Justificación:

Ea presente solicitud no cumple con los requisitos de patentabilidad dado que lo  
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la  
misma tal y como se demostrara en el capítulo "Fundamento de Hechos"

⑤ Comprobante de pago No. \_\_\_\_\_

Fecha \_\_\_\_\_

## ⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZFIRMA: 

C.C. 51.940.252

TP. 82701

Señora Jefe,  
DIVISIÓN DE NUEVAS CREACIONES  
Superintendencia de Industria y Comercio  
E. S. D.

Referencia : Expediente N° 08 46700  
Asunto : Oposición a la solicitud de patente de Invención titulada  
"USO DE FLIBANSERINA PARA EL TRATAMIENTO DE  
TRASTORNOS DEL DESEO SEXUAL  
PREMENOPAUSICO"  
Solicitante : BOEHRINGER INGELHEIM INTERNATIONAL GMBH  
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial  
N° 606 del 31 de julio de 2009

Yo, CIELO ANGELA PEÑA RODRIGUEZ, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del Consejo Superior de la Judicatura, en calidad de Agente Oficioso de la sociedad GYNOPHARM S.A. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "USO DE FLIBANSERINA PARA EL TRATAMIENTO DE TRASTORNOS DEL DESEO SEXUAL PREMENOPAUSICO", cuyo titular es BOEHRINGER INGELHEIM

INTERNATIONAL GMBH., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

## 1. INTERÉS PARA ACTUAR ✓

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular FLIBANSERINA. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

## 2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 8 de mayo de 2008 reivindicando prioridad bajo la solicitud US20050734405P del 2005-11-08; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 605 del 30 de junio de 2009, cuya publicación internacional corresponde a la WO2007/054476 del 2007-05-18.
- 2.2. La solicitud colombiana 08 46700 objeto de la presente oposición, se refiere a uso de flibanserina, opcionalmente en forma de la base libre, las sales de adición de ácido farmacológicamente aceptables y/u opcionalmente en forma de los hidratos

y/o los solvatos de la misma, para la preparación de un medicamento para el tratamiento de Trastornos del Deseo Sexual premenopáusicos en mujeres; donde el Trastorno del Deseo Sexual premenopáusico se selecciona del grupo que consiste en: Trastorno del Deseo Sexual Hipoactivo premenopáusico, Trastorno de la Excitación Sexual premenopáusico, pérdida de deseo sexual premenopáusica, ausencia de deseo sexual premenopáusica, deseo sexual disminuido premenopáusico, deseo sexual inhibido premenopáusico, pérdida de la libido premenopáusica, trastorno de la libido premenopáusico y frigidez premenopáusica; Trastorno del Deseo Sexual Hipoactivo premenopáusico, Trastorno de la Excitación Sexual premenopáusico, pérdida de deseo sexual premenopáusica, ausencia de deseo sexual premenopáusica, deseo sexual disminuido premenopáusico, deseo sexual inhibido premenopáusico.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. Así las cosas, las invenciones



objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: WO03097058 publicada el 27 de noviembre de 2003.

2.5. Adicionalmente, además que la presente se refiere a un uso no patentable en Colombia, la materia tampoco cumple con el requisito de novedad. Efectivamente, la anterioridad D1, se anticipa al uso aquí planteado, de manera que el documento D1, particularmente en la descripción, define el uso composiciones orales farmacéuticas que contienen un polimorfo A de flibanserina para el tratamiento de trastornos hipoaffectivos de deseo sexual (HSSD). Particularmente, el documento D1 en la página 7, párrafos 6 a página 9 párrafo 4, revela su uso en el tratamiento de pérdida de deseo sexual, falta o pérdida decrecida de deseo sexual, deseo sexual inhibido, el cual se producido a lo largo de la vida o es adquirido. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 46700 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que*

*haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida." A la fecha de prioridad, 8 de noviembre de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, el uso de flibanserina, opcionalmente en forma de la base libre, las sales de adición de ácido farmacológicamente aceptables y/u opcionalmente en forma de los hidratos y/o los solvatos de la misma, para la preparación de un medicamento para el tratamiento de Trastornos del Deseo Sexual premenopáusicos en mujeres, sobre el cual busca protección en el capítulo reivindicatorio.*

2.7.2. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*". La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la*



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

*tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.* La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada **USO DE FLIBANSERINA PARA EL TRATAMIENTO DE TRASTORNOS DEL DESEO SEXUAL PREMENOPAUSICO**, cuyo titular es **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 606 del 31 de julio de 2009.

### 3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO03097058 publicada el 27 de noviembre de 2003.

### 4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.



Derecho de la Competencia, Propiedad  
Industrial y Comercio Exterior

## 5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de GYNOPHARM S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- DI: WO03097058 publicada el 27 de noviembre de 2003.



Derecho de la Competencia, Propiedad  
Industrial y Comercio Exterior

## 6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

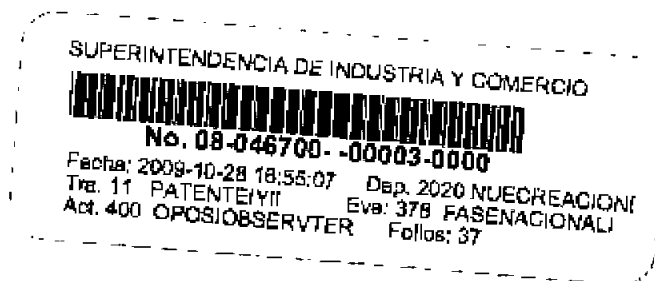
Señor Superintendente,

CIELO ANGELA PEÑA RODRIGUEZ  
C.C. 51'940.252 de Bogotá  
T.P.A. 82701 del C.S. de la J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800175089-2

RECIBO OFICIAL DE CAJA : 09 - 81,202  
FECHA : OCTUBRE 28 DE 2009



===== CONSIGNACION =====

| DEPOSITANTE   | TIPO PAGO      | BANCO | CUENTA | No. PAGO | FECHA PAGO | Vr. PAGO   |
|---------------|----------------|-------|--------|----------|------------|------------|
| GYNOFARM S.A. | RECIBO DE CAJA |       |        | 32048    | 29/04/2009 | 203,000.00 |
| GYNOFARM S.A. | RECIBO DE CAJA |       |        | 64132    | 31/02/2009 | 106,000.00 |
| GYNOFARM S.A. | RECIBO DE CAJA |       |        | 64133    | 31/03/2009 | 62,000.00  |

===== CONCEPTO =====

| CANT. ENTISTICO                             | CONCEPTO                     | TOTAL CONCEPTO |
|---------------------------------------------|------------------------------|----------------|
| 1 50005-01-04 PRESENTACION DE OBSERVACIONES | 12 MARCAS Y LEAS COMERCIALES | 267,000.00     |
|                                             | TOTAL :                      | \$ 237,000.00  |

SUM: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

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

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
27 November 2003 (27.11.2003)

PCT

(10) International Publication Number  
**WO 03/097058 A1**(51) International Patent Classification: **A61K 31/496**,  
9/30, A61P 25/16, 25/28, 15/00(21) International Application Number: **PCT/EP03/05226**(22) International Filing Date: **19 May 2003 (19.05.2003)**(25) Filing Language: **English**(26) Publication Language: **English**(30) Priority Data:  
02011224.9 **22 May 2002 (22.05.2002)** EP(71) Applicant (for all designated States except US):  
**BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG** [DE/DE]; Binger Strasse 173, 55216 Ingelheim (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FRIEDEL, Thomas** [DE/DE]; Dr. Hans-Liebherr-Strasse 48/4, 88416 OCHSENHAUSEN (DE). **RADTKE, Guido, Bernhard, Edmund** [DE/DE]; Weisshauptstrasse 9, 88400 BIBERACH (DE).(74) Common Representative: **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG**, Binger Strasse 173, 55216 Ingelheim (DE).(81) Designated States (national): **AB, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.**(84) Designated States (regional): **ARIPO** patent (GI, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), **Eurasian** patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), **European** patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, RO, SE, SI, SK, TR), **OAPI** patent (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.

**WO 03/097058 A1**(54) Title: **NEW PHARMACEUTICAL COMPOSITIONS CONTAINING FLIBANSERIN POLYMORPH A**

(57) Abstract: The invention relates to oral pharmaceutical compositions containing flibanserin polymorph A, methods for the preparation thereof and use thereof as a medicament.

## NEW PHARMACEUTICAL COMPOSITIONS CONTAINING FLIBANSERIN POLYMORPH A

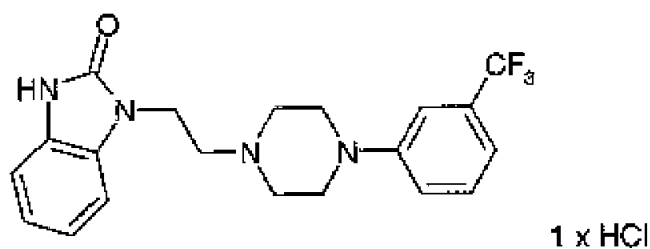
The invention relates to oral pharmaceutical compositions containing flibanserin, methods for the preparation thereof and use thereof as a medicament.

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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:

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Flibanserin shows affinity for the 5-HT<sub>1A</sub> and 5-HT<sub>2</sub>-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

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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.

10

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.

15 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

20 It has been found, surprisingly, that the free base of flibanserin in a specific polymorphic 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).

25

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.

30

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.

35

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  
5 and agglomerated lactose (Tabletose), 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  
10 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).

15 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,  
20 hydroxypropylcellulose, and mixtures thereof. Most preferably hydroxypropyl 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  
25 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  
30 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.

35 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.

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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, croscopovidone, croscarmellose sodium, sodium-carboxymethylcellulose, dried corn starch and mixtures thereof. Particularly preferably, within the scope of the present invention, sodium starch glycolate, croscopovidone, 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.%.
- 10 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
- 15 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.%.
- 20 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
- 25 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
- 30 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,

35 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.%. .

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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.

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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

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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  
5 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  
10 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  
15 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  
20 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<sub>1A</sub> and 5-HT<sub>2</sub>-receptor  
25 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,  
30 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.

35

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  
5 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. In a particularly preferred embodiment the invention relates to the use of the flibanserin polymorph A containing formulations according to the invention for the  
10 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<sub>1A</sub> and 5-HT<sub>2</sub>-receptor  
15 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,  
20 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  
25 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,  
30 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  
35 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 comprising the administration of a flibanserin polymorph A containing formulations according to the invention.

In a particularly 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.

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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  
10 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,  
15 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  
20 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-chloroethyl)piperazin are charged in a reactor with 2500 kg of water and 200 kg of aqueous Sodium Hydroxide 45%. Under  
25 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  
30 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  
35 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.

5 **Characterisation of flibanserin polymorph A:**

Flibanserin polymorph A was characterised by DSC (Differential 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.

10

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:

15 **Equipment:** Philips PW 1800/10 diffractometer equipped with a digital microvax 2000.

**Setting parameters:**

**X-ray**

20

Type tube: Cu (long fine focus)  
Wavelengths ( $\lambda$ ):  $K_{\alpha 1} = 1.54060 \text{ \AA}$   
 $K_{\alpha 2} = 1.54439 \text{ \AA}$   
Intensity ratio ( $\alpha 2/ \alpha 1$ ): 0.500

25

Start angle [ $^{\circ}2\theta$ ]: 2.000  
End angle [ $^{\circ}2\theta$ ]: 60.000  
Step size [ $^{\circ}2\theta$ ]: 0.020  
Maximum intensity[s]: 7310.250

30

Type of scan: continuous

35

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 appropriate values are collected in table 1.

Table 1:

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| Angle<br>[°2 $\theta$ ] | d-value<br>$\alpha$ 1 [Å] | d-value<br>$\alpha$ 2 [Å] | Peak width<br>[°2 $\theta$ ] | Peak int<br>[counts] | Back. int<br>[counts] | Rel. int<br>[%] | 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<br>[°2 $\theta$ ] | d-value<br>$\alpha$ 1 [Å] | d-value<br>$\alpha$ 2 [Å] | Peak width<br>[°2 $\theta$ ] | Peak int<br>[counts] | Back. int<br>[counts] | Rel. int<br>[%] | 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<br>[°2 $\theta$ ] | d-value<br>$\alpha$ 1 [Å] | d-value<br>$\alpha$ 2 [Å] | Peak width<br>[°2 $\theta$ ] | Peak int<br>[counts] | Back. int<br>[counts] | Rel. int<br>[%] | 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:**

5

**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

10 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);

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

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

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

**B) Process description:**

20 As a first step the granulation liquid for the wet granulation process is 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)

25 and stirred up before use. If necessary, any weight loss is compensated with purified water. The dry matter (solid content) of this granulation liquid is preferably 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.

35 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, preferably 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 %, preferably 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).

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

**Example N°1 - Composition**

**Core**

| <b><u>Constituents</u></b>    | <b>mg/tablet</b> |
|-------------------------------|------------------|
| 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            |

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**Coating**

| <b><u>Constituents</u></b> | <b>mg/ tablet</b> |
|----------------------------|-------------------|
| HPMC (Methocel E5)         | 1.440             |
| Polyethylene Glycol 6000   | 0.420             |
| Titanium dioxide           | 0.600             |
| Talc                       | 0.514             |
| Iron oxide red             | 0.026             |

|                                 |                |
|---------------------------------|----------------|
| <b>Total Film coated tablet</b> | <b>128.000</b> |
|---------------------------------|----------------|

**Example N°2 - Composition**Core

| <u>Constituents</u>           | 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

| <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      |

5

|                                 |                |
|---------------------------------|----------------|
| <b>Total Film coated tablet</b> | <b>255.000</b> |
|---------------------------------|----------------|

**Example N°3 - Composition**Core

| <u>Constituents</u>           | 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     |

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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      |

|                                 |                |
|---------------------------------|----------------|
| <b>Total Film coated tablet</b> | <b>347.000</b> |
|---------------------------------|----------------|

Example N°4 – Composition

5

Core

| <u>Constituents</u>                 | 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

| <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      |

|                                 |                |
|---------------------------------|----------------|
| <b>Total Film coated tablet</b> | <b>133.000</b> |
|---------------------------------|----------------|

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**Example N°5 – Composition**Core

| <u>Constituents</u>                 | 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     |

5 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      |

|                                 |                |
|---------------------------------|----------------|
| <b>Total Film coated tablet</b> | <b>255.000</b> |
|---------------------------------|----------------|

**Example N°6 – Composition**

10

Core

| <u>Constituents</u>                      | 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

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

|                                 |                |
|---------------------------------|----------------|
| <b>Total Film coated tablet</b> | <b>205.000</b> |
|---------------------------------|----------------|

## 20

## Claims

- 1) Pharmaceutical composition for oral administration comprising a tablet core,  
containing flibanserin polymorph A being characterized by an endothermic  
5 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  
10 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  
15 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  
20 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  
25 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  
30 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  
35 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<sub>1A</sub> and 5-HT<sub>2</sub>-receptor may have a therapeutic benefit.
- 10) Use according to claim 9, characterized in that the disease is selected from the group consisting of depression, schizophrenia, Parkinson, anxiety, sleep disturbances, sexual and mental disorders and age associated memory impairment.