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2	S LICITANTE (71)		
Nombre: BIDACHEM S. P. A. sociedad constituida y existente bajo las leyes de Italia Dirección: Strada Statale 11 (Pandana Sup.) N. 8 I-24040 Formovo s Giovanni Bergamo Italia Domicilio: Formovo s Giovanni Bergamo, Italia		IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____	
3	REPRESENTANTE O APODERADO		
Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 38 11 Fax: 217 92 11 E-mail: clientes@camyo.com. Domicilio: Bogotá, Colombia.		IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 438.019 T.P 31.929	
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7	Clasificación Internacional (51) CO7D 40/360, A61K 31/495, A61P 25/00		

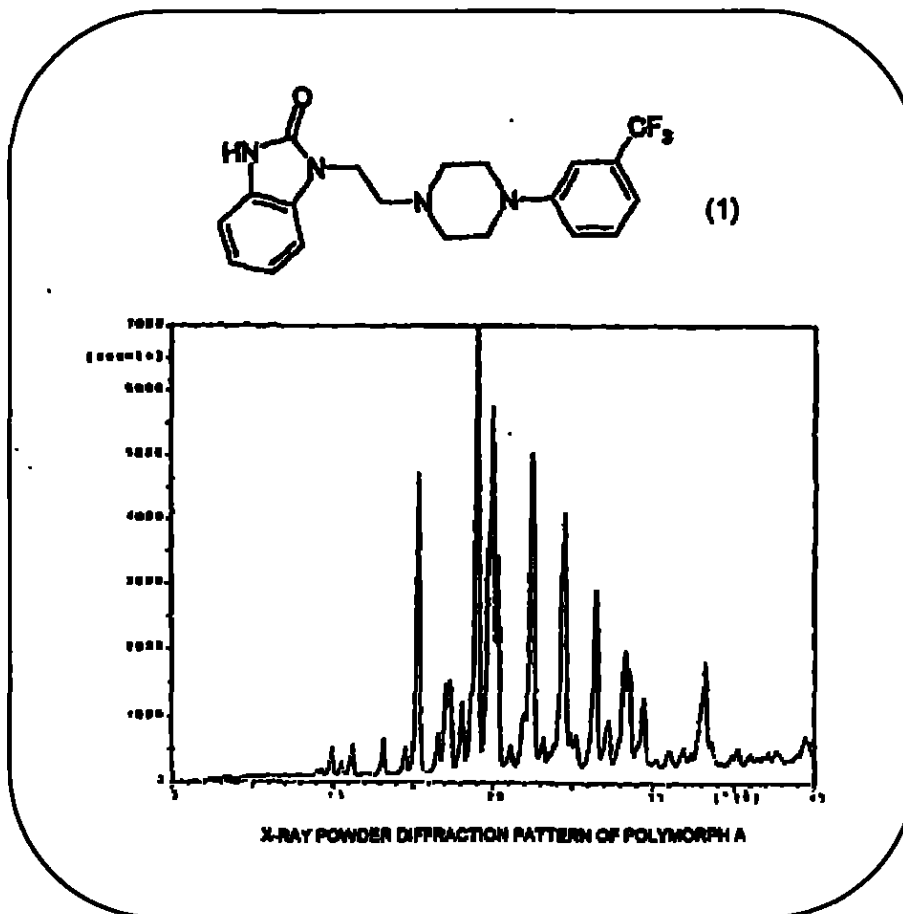
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10	Anexos:
☒	Comprobante de pago de la tasa de presentación de la solicitud por \$ 422.000.00.
☐	Comprobante de pago por reivindicación de prioridad.
☐	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
☐	Poderes, si fuere el caso.
☐	Documento de cesión del inventor al solicitante o a su causante.
☐	Declaraciones.
☒	Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
☒	Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
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☒	Arte final 12x12
☐	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
☒	Otros
	FORMA PCT/IB/306 NOTIFICACIÓN DEL REGISTRO DE UN CAMBIO (NOTIFICATION OF THE RECORDING OF A CHANGE): CAMBIO DE NOMBRE DEL SOLICITANTE Y CAMBIO DE DOMICILIO DE INVENTOR

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente,

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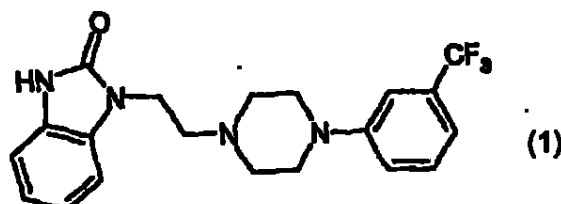
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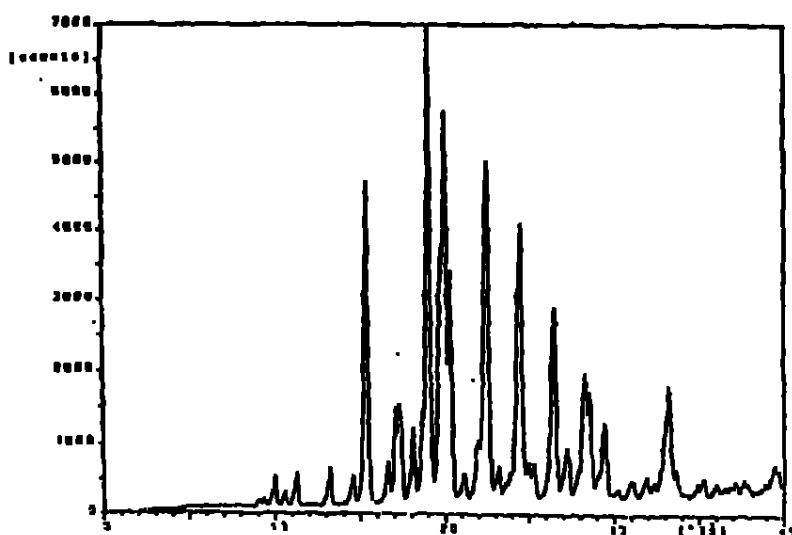
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[Continued on next page]

(54) Title: STABLE POLYMORPH OF FLIBANSERIN, TECHNICAL PROCESS FOR ITS PREPARATION AND THE USE THEREOF FOR PREPARING MEDICAMENTS



(57) Abstract: This invention relates to the polymorph A of flibanserin (1), to a technical process for the preparation thereof, as well as to the use thereof for preparing medicaments.



X-RAY POWDER DIFFRACTION PATTERN OF POLYMORPH A

WO 03/014079 A1

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WO 03/014079 A1



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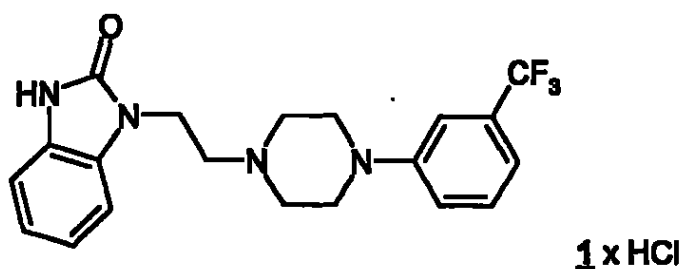
— *with international search report*

Stable polymorph of filbanserin, technical process for its preparation and the use thereof for preparing medicaments

The invention relates to the polymorph A of filbanserin, to a technical process for the preparation thereof, as well as to the use thereof for preparing medicaments.

Background of the Invention

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



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

Another problem which may arise in the grinding process for preparing the desired pharmaceutical formulation is the input of energy caused by this process and the stress on the surface of the crystals. This may in certain circumstances lead to polymorphous changes, to a change in the amorphous configuration or to a change in the crystal lattice. Since the pharmaceutical quality of a pharmaceutical formulation requires that the active substance should always have the same crystalline morphology, the stability and properties of the crystalline active substance are subject to stringent requirements from this point of view as well.

The stability of a pharmaceutically active substance is also important in pharmaceutical compositions for determining the shelf life of the particular medicament; the shelf life is the length of time during which the medicament can be administered without any risk. High stability of a medicament in the abovementioned pharmaceutical compositions under various storage conditions is therefore an additional advantage for both the patient and the manufacturer.

Apart from the requirements indicated above, it should be generally borne in mind that any change to the solid state of a pharmaceutical composition which is capable of improving its physical and chemical stability gives a significant advantage over less stable forms of the same medicament.

The aim of the invention is thus to provide a new, stable crystalline form of the compound filbanserin which meets the stringent requirements imposed on pharmaceutically active substances as mentioned above.

Detailed description of the invention

Surprisingly, it has been found that the free base of filbanserin in a specific polymorphic form fulfils the requirements mentioned hereinbefore.

Moreover it has been found that, depending on the choice of conditions which can be applied during the synthesis of filbanserin the free base occurs in different crystalline modifications, polymorphs A and B.

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It has been found that these different modifications can be deliberately produced by a suitable choice of the process conditions used in the manufacturing process.

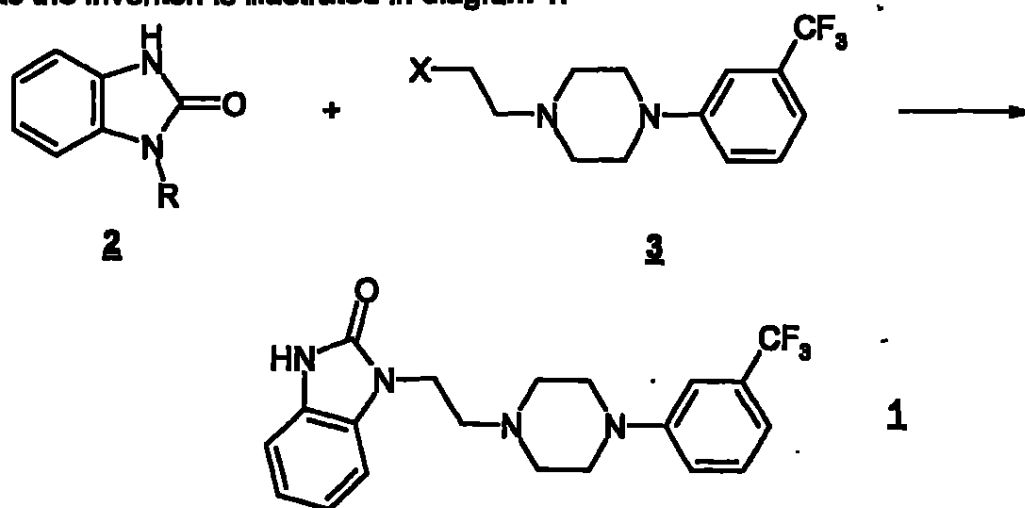
Surprisingly, it has been found that polymorph A, which can be obtained in crystalline form by choosing specific reaction conditions, meets the stringent requirements mentioned above and thus solves the problem on which the present invention is based. Accordingly the present invention relates to polymorph A of filbanserin. Polymorph A of filbanserin is characterised by a melting point of about 161°C (determined via DSC; heating rate 10 K/min).

15

Polymorph B, the less stable modification of filbanserin displays a melting point of about 120°C (determined via DSC; heating rate 10 K/min). Whereas polymorph B shows little stability under the effects of for instance mechanical stress produced by grinding, polymorph A turned out to fulfill the aforementioned stability requirements.

20

According to another aspect, the present invention relates to a process for the manufacture of polymorph A of filbanserin in technical scale. The process according to the invention is illustrated in diagram 1.



25 Diagram 1:

The benzimidazolone **2** is reacted with the piperazine-derivative **3** under basic reaction conditions in a suitable solvent to lead to **1**. In **2** the group R denotes an amino protecting group. The protecting group used may be any of the groups

commonly used to protect the amino function. Examples include groups selected from alkyl, substituted alkyl, heterosubstituted alkyl, unsaturated alkyl, alkyl substituted heteroatoms, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, alkyloxycarbonyl groups and aryloxycarbonyl groups. Preferred protecting groups are selected from butyl, 1,1-diphenylmethyl, methoxymethyl, benzyloxymethyl, trichloroethoxymethyl, pyrrolidinomethyl, cyanomethyl, pivaloyloxymethyl, allyl, 2-propenyl, t-butyldimethylsilyl, methoxy, thiomethyl, 4-methoxyphenyl, benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 2-nitrobenzyl, t-butoxycarbonyl, benzyloxycarbonyl, phenoxy carbonyl, 4-chloro-phenoxy carbonyl, 4-nitro-phenoxy carbonyl, methoxycarbonyl and ethoxycarbonyl. Among them the preferred protecting groups are selected from t-butoxycarbonyl, ethoxycarbonyl, methoxycarbonyl, benzyloxycarbonyl, phenoxy carbonyl and 2-propenyl, the latter being most preferred. X in 3 represents a leaving group selected from chlorine, bromine, iodine, methanesulphonate, trifluoromethanesulphonate or para-toluenesulphonate. Preferably X denotes chlorine, bromine or iodine, chlorine being most preferred. Suitable solvents are selected from water, alcohols and mixtures of water with alcohols, polar aprotic solvents and mixtures thereof with water. Preferred solvents are selected from the group consisting of dimethylformamide, dimethylsulfoxide, acetonitrile, tetrahydrofuran, dioxane, methanol, ethanol, isopropanol and mixtures of one or several of the aforementioned solvents with water. Preferred solvents are those being readily miscible with water. Preferably, a mixture of water with one of the alcohols methanol, ethanol or isopropanol is used as the solvent. In a preferred embodiment a mixture of water and isopropanol is used as the solvent. The base used may be an alkali metal- or alkaline earth metal carbonate of lithium, sodium, potassium, calcium such as sodium carbonate, lithium carbonate, potassium carbonate, calcium carbonate and preferably potassium carbonate. It is also possible to use the hydrogen carbonates of lithium, sodium and potassium. Preferably, the alkali metal- or alkaline earth metal hydroxides of lithium, sodium, potassium, magnesium, calcium, but preferably sodium hydroxide, potassium hydroxide, lithium hydroxide and calcium hydroxide in alcohols or water may also be used. Most preferred base is sodium hydroxide. The base is preferably added in form of its aqueous solution, preferably in form of concentrated aqueous solutions, for example in concentrations between 30 - 50% weight/volume. In a preferred embodiment aqueous sodium hydroxide solution in a concentration of about 45% weight/volume is used.

The compounds 2 and 3 are introduced into the reaction in a molar ratio of between 1:1 to 1:2, preferably in a molar ratio of between 1:1.1 to 1:1.5.

As mentioned hereinbefore a mixture of water and isopropanol is used as a preferred solvent mixture for the conduction of the process according to the invention. In this solvent mixture the weight-ratio of water to isopropanol in the preferred solvent mixture is between 10:1 and 1:1, more preferred between 8:1 and 3:1, particular
5 preferred between 7:1 and 5:1. Per mol of compound 2 about 2 - 10 kg, preferably 3 - 8 kg, more preferred 4 - 7 kg of the aforementioned solvent mixture are used. In a preferred embodiment the reaction is conducted using aqueous sodium hydroxide solution in a concentration of about 45% weight/volume as the base. Per mol of 2 about 0.1 - 1.5 kg, preferably 0.2 - 1.0 kg, particularly preferred 0.3 - 0.6 kg of the
10 aforementioned sodium hydroxide solution are used. The reaction mixture containing 2, 3 and the base in the aforementioned suitable solvent is preferably heated to at least 50°C. In a preferred embodiment the reaction temperature is in a range of between 60°C to the boiling point of the solvent. Particularly preferred is a temperature between 70 - 90°C. The reaction mixture is heated at the aforementioned
15 temperature for about 10 minutes to about 12 hours, preferably for about 15 minutes to about 6 hours, more preferably for about 30 minutes to about 3 hours. The reaction mixture is preferably heated at the aforementioned temperature for about 45 to 60 minutes.

20 Subsequently the protective group R is cleaved. The cleaving conditions depend on the choice of group R. If R denotes for instance benzyl, cleavage is conducted via hydrogenation in acetic acid in the presence of an appropriate catalyst (e.g. Pd on charcoal) or it can be cleaved in aqueous HBr. In case R is methoxycarbonyl, ethoxycarbonyl, phenoxy carbonyl, 4-nitrophenoxy carbonyl it can be cleaved for
25 example by using aqueous alkaline solutions such as NaOH (aq) or KOH(aq). In case R is t-butoxycarbonyl it can be cleaved for instance in aqueous HCl or HBr. In case R denotes 2-propenyl, the particularly preferred protective group according to the invention, cleavage of R is effected via acidic reaction conditions. In a particularly preferred process according to the invention the 2-propenyl group is cleaved by
30 using a strong mineral acid, preferably an acid selected from the group consisting of hydrobromic acid, hydrochloric acid and sulfuric acid, more preferably hydrochloric acid. Hydrochloric acid can be added in gaseous form or in form of its aqueous solutions, the addition of aqueous solutions being preferred. Particularly preferred is the addition of hydrochloric acid in form of its concentrated solution (about 36%
35 weight/volume). Per mol 2 at least one mol of hydrochloric acid is to be added. Preferably the amount of added concentrated hydrochloric acid (36% weight/volume) per mol 2 is between 50 - 500g, more preferred between 80 - 250g. Particularly preferred about 120 - 160 g of concentrated (36% w/v) aqueous hydrochloric acid are added per mol 2 used. Additional water can be optionally added. At a

temperature of about 70 - 90°C about 30 - 70%, preferably about 35 - 60% of the solvent is removed via distillation. At a temperature of about 60 - 80°C the pH of the remaining residue is adjusted to about 5 - 9, preferably to about 6 - 8 by addition of aqueous sodium hydroxide (45% w/v). At a temperature of about 40 - 55°C the pH is
5 adjusted to about 8 - 9 by addition of aqueous sodium hydroxide (45% w/v). Subsequently the mixture is cooled to about 20-40°C, preferably about 30-35°C and centrifuged. The residue thus obtained is washed with about 100 to 750 ml water per mol introduced 2, preferably with about 200 to 500, particularly preferred with about 300 to 400 ml water per mol introduced 2 and isopropanol (about 50 to 250 g per mol
10 2, preferably about 100 to 200 g per mol 2) and then with water until chlorides elimination. Optionally the product thus obtained can be subjected to another purification step. Preferably, said purification is conducted via crystallization of 1 from for instance acetone.

15 One aspect of the present invention relates to filbanserin polymorph A obtainable via the method described above.

The following example of synthesis serves to illustrate a method of preparing polymorph A of filbanserin. It is to be regarded only as a possible method described
20 by way of example, without restricting the invention to its contents.

Example:

375 kg of 1-[(3-trifluoromethyl)phenyl]-4-(2-chloroethyl)piperazine are charged in a reactor with 2500 kg of water and 200 kg of aqueous Sodium Hydroxide 45%.
25 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
30 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
35 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 filbanserin 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 filbanserin polymorph A.

5

As mentioned hereinbefore filbanserin 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
10 was 10 K/min.

The filbanserin 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.

20

Setting parameters:

X-ray

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

25

Start angle [2θ]: 2.000
End angle [2θ]: 60.000
Step size [2θ]: 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

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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:

5

Angle [°2 θ]	d-value α 1 [Å]	d-value α 2 [Å]	Peak width [°2 θ]	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

14

WO 03/014079

PCT/EP02/08466

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28.325	3.1482	3.1580	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	2.8028	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	2.5785	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
48.510	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	1.6585	1.6606	0.320	130	328	1.8	1.72
56.220	1.6348	1.6389	0.320	121	331	1.7	0.87
58.770	1.6203	1.6243	0.240	142	335	1.9	1.59
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

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

A further aspect of the present invention relates to the use of flibanserin polymorph A for preparing a pharmaceutical composition for treating diseases in which the use of compounds displaying affinity for the 5-HT_{1A} and 5-HT₂-receptor may have a therapeutic benefit.

A further aspect of the present invention relates to the use of flibanserin polymorph A for preparing a pharmaceutical composition 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 flibanserin polymorph A for the preparation of a medicament for the treatment of disorders of sexual desire.

In a preferred embodiment the invention relates to the use of flibanserin polymorph A for the preparation of a medicament 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 flibanserin polymorph A for the preparation of a medicament 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 flibanserin polymorph A for the preparation of a medicament for the treatment of disorders selected from the group of Hypoactive Sexual Desire Disorder and loss of sexual desire.

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

The beneficial effects of flibanserin polymorph A 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

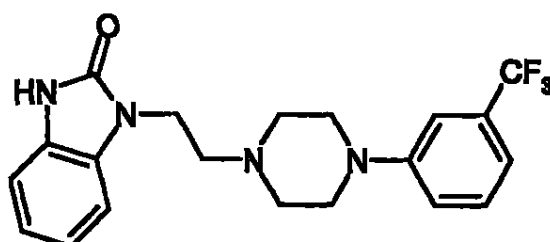
combination of organic - both, physically and drug induced-, and psychogen, or unknown).

As a further feature of the present invention there are provided pharmaceutical compositions comprising as an active ingredient filbanserin polymorph A in addition with one or more pharmaceutical carrier, diluents or excipients. For pharmaceutical administration filbanserin polymorph A may be incorporated into the conventional pharmaceutical preparation in solid, liquid or spray form. The composition may, for example, be presented in a form suitable for oral, rectal, parenteral administration or for nasal inhalation: preferred forms includes for example, capsules, tablets, coated tablets, ampoules, suppositories and nasal spray.

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

Patent Claims

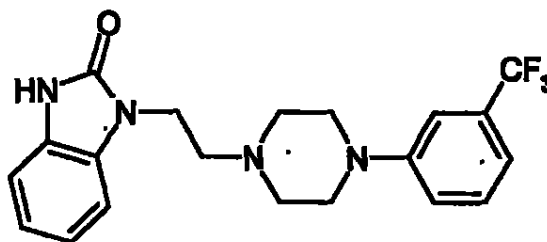
- 1) Crystalline polymorph A (form A) of flibanserin 1,

1

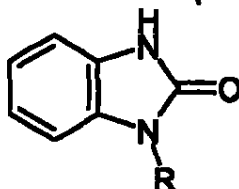
having an endothermic maximum at 161°C which occurs during thermal analysis using DSC.

- 2) Flibanserin 1 comprising form A according to claim 1.

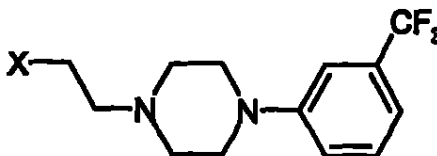
- 3) Process for the technical preparation of flibanserin 1 according to claim 1 or 2,

1

characterized in that in a first reaction step a benzimidazolone 2

2

wherein R denotes a suitable amino protecting group is reacted with a piperazine 3

3

wherein X is a leaving group selected from chlorine, bromine, iodine, methanesulphonate, trifluoromethanesulphonate and para-toluenesulphonate.

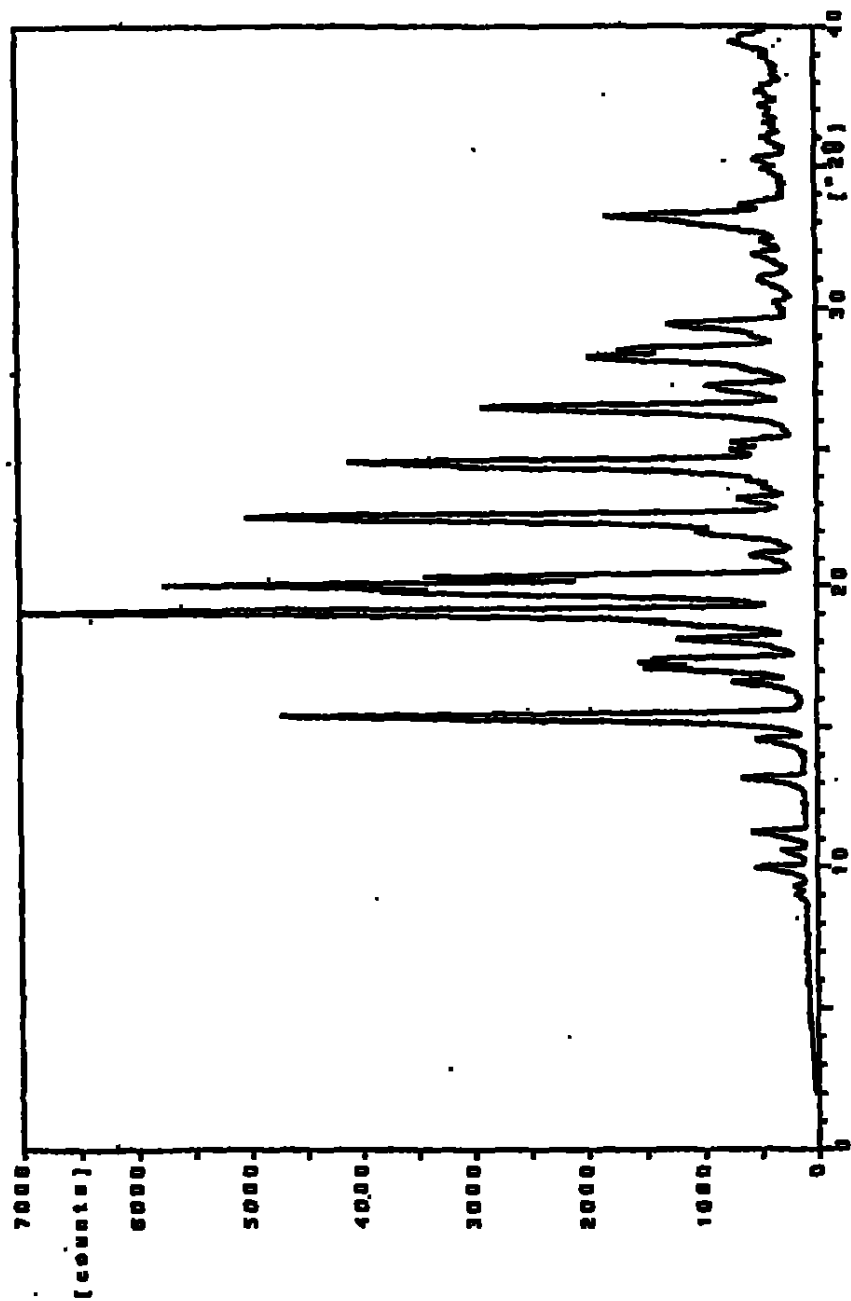
in a suitable solvent selected from water, alcohols, mixtures of water with alcohols, polar aprotic solvents and mixtures thereof with water in presence of a suitable base and that in a second reaction step the amino protecting group R is cleaved under suitable cleaving conditions.

5

- 4) Process according to claim 3, characterized in that the reaction of 2 with 3 is conducted at a temperature of at least 50°C.
- 5) Process according to claim 4, characterized in that heating is conducted for about 10 minutes to about 12 hours.
- 6) Polymorph A of fibanserin 1 obtainable according to one of claims 3 to 5.
- 7) Polymorph A of fibanserin 1 according to one of claims 1, 2 or 6 for use as a medicament.
- 8) Use of polymorph A of fibanserin 1 according to one of claims 1, 2 or 6 for preparing a medicament for treating diseases in which the use of therapeutic effective amounts of compounds displaying affinity for the 5-HT_{1A} and 5-HT₂ receptor display a therapeutic benefit.
- 9) Use of polymorph A of fibanserin 1 according to one of claims 1, 2 or 6 for preparing a medicament for treating a disease selected from depression, schizophrenia, Parkinson, anxiety, sleep disturbances, sexual and mental disorders and age associated memory impairment.
- 10) Pharmaceutical compositions comprising as an active ingredient polymorph A of fibanserin 1 according to one of claims 1, 2 or 6 optionally in admixture with one or more pharmaceutical carriers, diluents or excipients.

30

19.



Figur 1: X-ray powder diffraction pattern of polymorph A

INTERNATIONAL SEARCH REP RT

International Application No

PCT/EP 02/08466

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/06 A61K31/495 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 526 434 A (BOEHRINGER INGELHEIM ITALIA) 3 February 1993 (1993-02-03) " 1-'2-(4-(3-trifluoromethyl-phenyl) piperazin-1-yl)ethyl-2,3-dihydro-1H-benzimidazol-2-one " page 17; example 3	1-10
A	BORSINI F ET AL: "BIMT 17, A 5-HT _{2A} RECEPTOR ANTAGONIST AND 5-HT _{1A} RECEPTOR FULL AGONIST IN RAT CEREBRAL CORTEX" NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 352, no. 3, September 1995 (1995-09), pages 276-282, XP001057819 ISSN: 0028-1298 figure 1 -/-	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document relating to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

6 November 2002

Date of mailing of the international search report

21/11/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5318 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Baston, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08466

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GIRON ET AL: "Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates" THERMOCHIMICA ACTA, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 248, 1995, pages 1-59, XP002101808 ISSN: 0040-6031 the whole document	1-10
A	BERNSTEIN, J. ET AL.: "Concomitant Polymorphs" ANGEWANDTE CHEMIE, INT. ED., 1999, pages 3441-3461, XP002219563 the whole document	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/08466

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0526434	A	03-02-1993	IT 1251144 B 04-05-1995
			AT 191910 T 15-05-2000
			AU 665366 B2 04-01-1996
			AU 2427592 A 02-03-1993
			CA 2114542 A1 18-02-1993
			CZ 281511 B6 16-10-1996
			CZ 9400170 A3 18-05-1994
			DE 69230926 D1 25-05-2000
			DE 69230926 T2 05-10-2000
			DK 526434 T3 17-07-2000
			EE 3070 B1 16-02-1998
			EP 0526434 A1 03-02-1993
			ES 2144412 T3 16-06-2000
			FI 940420 A 28-01-1994
			GR 3033947 T3 30-11-2000
			HK 1010725 A1 12-01-2001
			HU 70195 A2 28-09-1995
			HU 9500292 A3 28-09-1995
			IE 922464 A1 10-02-1993
			IL 102665 A 31-10-1996
			WO 9303016 A1 18-02-1993
			JP 6509575 T 27-10-1994
			KR 263495 B1 01-11-2000
			MX 9204139 A1 01-01-1993
			NO 940306 A 14-03-1994
			NZ 243777 A 27-04-1995
			PL 302163 A1 11-07-1994
			PT 526434 T 31-08-2000
			RU 2096411 C1 20-11-1997
			SG 52407 A1 28-09-1998
			SK 10194 A3 07-12-1994
			US 5576318 A 19-11-1996
			ZA 9205682 A 31-01-1994

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 82bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:		
BOEHRINGER INGELHEIM INTERNATIONAL GMBH Binger Strasse 173 55218 Ingelheim Germany		
Eingang CD Patents 28. Juli 2003		
SB	gesehen	erledigt
<i>[Signature]</i>	<i>[Signature]</i>	

Date of mailing (day/month/year) 18 July 2003 (18.07.03)	ERFASST	Applicant's or agent's file reference 1-1232.PCT
International application No. PCT/EP02/08466		IMPORTANT NOTIFICATION
		International filing date (day/month/year) 30 July 2002 (30.07.02)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address BOEHRINGER INGELHEIM INTERNATIONAL GMBH Binger Strasse 173 55218 INGELHEIM Germany	State of Nationality DE	State of Residence DE
	Telephone No. 06132/77-2483	
	Facsimile No. 06132/77-4377	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☒ the name ☒ the address ☒ the nationality ☒ the residence

Name and Address BIDACHEM S.P.A. Strada Statale 11 (Padana Sup.) N.8 I-24040 Fornovo s. Giovanni Bergamo Italy	State of Nationality IT	State of Residence IT
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Change of applicant:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 28, Switzerland Facsimile No. (41-22) 338 8970	Authorized officer: Frédéric SONTAG (Fax 338 8970) Telephone No. (41-22) 338 8971
---	--

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
Binger Strasse 173
55218-INGELHEIM
Germany

Date of mailing (day/month/year) 18 July 2003 (18.07.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 1-1232-PCT	
International application No. PCT/EP02/08466	International filing date (day/month/year) 30 July 2002 (30.07.02)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Telexprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

State of Nationality

State of Residence

WEYMANN, Markus
BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Binger Strasse 173
55218 Ingelheim
Germany

DE

DE

Telephone No.

08132/77-2463

Facsimile No.

08132/77-4377

Telexprinter No.

3. Further observations, if necessary:

The Person identified in Box 2 should be added to the record as new agent.

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Office concerned
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Frédéric SONTAG (Fax 338 8970)

Facsimile No. (41 22) 338 89 70

Telephone No. (41 22) 338 83 01

Form PCT/IB/308 (March 1994)

005752838

Eingang CD Patents		
17 April 2003		
SB	gesehen	erledigt
WU		
		PCT

PCT/EP02/08468

PATENT COOPERATION TREATY

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
Binger Strasse 173
55216 INGELHEIM
Germany

Date of mailing (day/month/year) 04 April 2003 (04.04.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 1-1232-PCT	
International application No. PCT/EP02/08468	International filing date (day/month/year) 30 July 2002 (30.07.02)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

DUBINI, Enrica
Via Ludovico Muratori, 54
I-ZIP 20136 MILANO
Italy

State of Nationality
IT

State of Residence
IT

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

DUBINI, Enrica
Via Ludovico Muratori, 54
I-20136 Milano
Italy

State of Nationality
IT

State of Residence
IT

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.88.70	Authorized officer Elisabeth KÖNIG (Fax 338 8970) Telephone No. (41-22) 338 8748
--	--

26

PATENT COOPERATION TREATY

PCT/EP02/008466

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

To:

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Binger Strasse 173
55216 INGELHEIM
ALLEMAGNE

(PCT Rule 47.1(c), first sentence) Eingang CD Patents

ERFASST

Date of mailing(day/month/year)
20 February 2003 (20.02.03)

05. März 2003

Applicant's or agent's file reference
1-1232-PCT

SB	gesehen	erledigt
WJ		

IMPORTANT NOTICE

International application No.
PCT/EP02/008466

International filing date(day/month/year)
30 July 2002 (30.07.02)

Priority date(day/month/year)
02 August 2001 (02.08.01)

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL GMBH

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 20 February 2003 (20.02.03) under No. WO 03/014079.

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, (October and November 2001) and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Judith Zahra

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

Eingang CD Patents
13. März 2003
SB gesehen erledigt

PATENT COOPERATION TREATY

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION
(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
Binger Strasse 173
55216 INGELHEIM
Germany

Date of mailing (day/month/year) 01 March 2003 (01.03.03)		IMPORTANT INFORMATION	
Applicant's or agent's file reference 1-1232-PCT			
International application No. PCT/EP02/08486	International filing date (day/month/year) 30 July 2002 (30.07.02)	Priority date (day/month/year) 02 August 2001 (02.08.01)	
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al			

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:
EP : AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,SK,TR
National : AU,BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:
AP : GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
EA : AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
OA : BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National : AE,AG,AL,AM,AT,AZ,BA,BB,BR,BY,BZ,CH,CO,CR,CU,CZ,DK,DM,DZ,EC,EE,ES,FI,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MW,MX,MZ,NZ,OM,PH,PT,SD,SE,SG,SI,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZM,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 38(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: Leslie BARRIOS
Facsimile No. (41-22) 338.88.70	Telephone No. (41-22) 338 8715

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION Applicant's or agent's file reference Case 1/1232-PCT	
International application No. PCT/EP02/08468	International filing date (day/month/year) 30 July 2002 (30.07.02) (Earliest) Priority date (day/month/year) 02 August 2001 (02.08.01)
Title of invention Stable polymorph of fibanaserin, technical process for its preparation and the use thereof for preparing medicaments	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Boehringer Ingelheim International GmbH Binger Strasse 173 D-55216 Ingelheim am Rhein DE	Telephone No. 06132/77-2463 Facsimile No. 06132/77-4377 Teleprinter No. Applicant's registration No. with the Office
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BOMBARDA, Carlo 12912 Nightingale CT. Chester, VA 23836 USA	
State (that is, country) of nationality: IT	State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) DUBINI, Enrica Via Ludovico Muratori 54 ZIP 20135 Milano ITALIEN	
State (that is, country) of nationality: IT	State (that is, country) of residence: IT
☒ Further applicants are indicated on a continuation sheet.	

79
29

Sheet No. 2.

International application No.
PCT/EP02/08466

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
EZHAYA, Antoine
Via Ogliari, 6
ZIP 20141 Milano
ITALIEN

State (that is, country) of nationality:
IT

State (that is, country) of residence:
IT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 3.

International application No.
PCT/EP02/08466

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☐ agent ☐ common representative
and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	Telephone No.
	Facsimile No.
	Teleprinter No.
	Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments*

1. The applicant wishes the international preliminary examination to start on the basis of:

☐ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Sheet No. 4.

International application No.
PCT/EP02/08466

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|---|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☐ copy of general power of attorney;
reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Boehringer Ingelheim International GmbH

I.V.

Dr. Kompter

Dr. Weymann

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due
to CORRECTIONS under Rule 60.1(b):

- | | |
|--|---|
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | ☐ The applicant has been informed accordingly. |
| 4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5. | |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | |

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/EP02/08466	For International Preliminary Examining Authority use only								
Applicant's or agent's file reference Case 1/1232-PCT	Date stamp of the IPEA								
Applicant									
CALCULATION OF PRESCRIBED FEES									
1. Preliminary examination fee	1.530 P								
2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)	159 H								
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	1.689 € TOTAL								
MODE OF PAYMENT									
<table style="width: 100%;"> <tr> <td>☒ authorization to charge deposit account with the IPEA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT <i>(This mode of payment may not be available at all IPEAs)</i>									
☒ Authorization to charge the total fees indicated above. ☒ <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.</i>	IPEA/ <u>EP</u> Deposit Account No.: <u>2800.0140</u> Date: <u>January 14, 2003</u> Name: <u>Boehringer Ingelheim GmbH</u> Signature: <u>Dr. Kompter</u> <u>Dr. V. Mann</u>								

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1-1232-PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 02/08466	International filing date (day/month/year) 30/07/2002	(Earliest) Priority Date (day/month/year) 02/08/2001
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 05 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 29.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

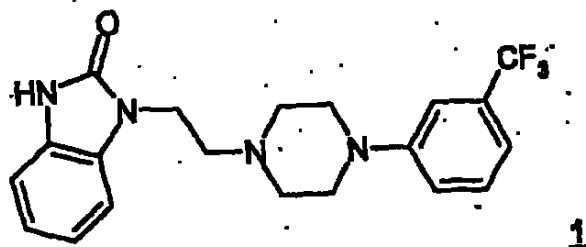
INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 02/08466

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

This invention relates to the polymorph A of flibanserin (1), to a technical process for the preparation thereof, as well as to the use thereof for preparing medicaments.



35

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08466

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/06 A61K31/495 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 526 434 A (BOEHRINGER INGELHEIM ITALIA) 3 February 1993 (1993-02-03) " 1-'2-(4-(3-trifluoromethyl-phenyl) piperazin-1-yl)ethyl-2,3-dihydro-1H-benzimidazol-2-one " page 17; example 3	1-10
A	BORSINI F ET AL: "BIMT 17, A 5-HT2A RECEPTOR ANTAGONIST AND 5-HT1A RECEPTOR FULL AGONIST IN RAT CEREBRAL CORTEX" NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 352, no. 3, September 1995 (1995-09), pages 276-282, XP001057819 ISSN: 0028-1298 figure 1	1-10
-/-		

☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"O" document referring to an oral disclosure, use, exhibition or other means	"Z" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 6 November 2002	Date of mailing of the international search report 21/11/2002
--	--

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentkan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3018	Authorized officer Baston, E
---	-------------------------------------

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08466

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GIRON ET AL: "Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates" THERMOCHIMICA ACTA, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 248, 1995, pages 1-59, XP002101808 ISSN: 0040-6031 the whole document	1-10
A	BERNSTEIN, J. ET AL.: "Concomitant Polymorphs" ANGEWANDTE CHEMIE, INT. ED., 1999, pages 3441-3461, XP002219563 the whole document	1-10

Ø RW

EXT A 507

1/4

PCT REQUEST

Original (for SUBMISSION) - printed on 29.07.2002 03:23:26 PM

1-1232-PCT

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.06.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	1-1232-PCT
I	Title of invention	STABLE POLYMORPH OF FLIBANSERIN, TECHNICAL PROCESS FOR ITS PREPARATION AND THE USE THEREOF FOR PREPARING MEDICAMENTS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BOEHRINGER INGELHEIM INTERNATIONAL GMBH
II-5	Address:	Binger Strasse 173 D-55216 INGELHEIM Germany
II-6	State of nationality	DE
II-7	State of residence	DE
II-8	Telephone No.	06132/77-2463
II-9	Facsimile No.	06132/77-4377
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	BOMBARDA, Carlo
III-1-5	Address:	12912 Nightingale CT. CHESTER, VA 23836 United States of America
III-1-6	State of nationality	IT
III-1-7	State of residence	US

PCT REQUEST

1-1232-PCT

Original (for SUBMISSION) - printed on 29.07.2002 03:23:28 PM

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	DUBINI, Enrica
III-2-5	Address:	Via Ludovico Muraton, 54 I-ZIP 20135 MILANO Italy
III-2-6	State of nationality	IT
III-2-7	State of residence	IT
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	EZHAYA, Antoine
III-3-5	Address:	Via Ogliari, 6 I-ZIP 20141 MILANO Italy
III-3-6	State of nationality	IT
III-3-7	State of residence	IT
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI 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 MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

PCT REQUEST

1-1232-PCT

Original (for SUBMISSION) - printed on 29.07.2002 03:23:28 PM

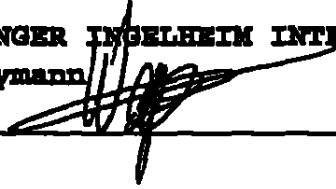
V-5	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4.8(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 18 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier regional application		
VI-1-1	Filing date	02 August 2001 (02.08.2001)	
VI-1-2	Number	01118593.1	
VI-1-3	Regional Office	EP	
VI-2	Priority claim of earlier regional application		
VI-2-1	Filing date	19 December 2001 (19.12.2001)	
VI-2-2	Number	01130180.1	
VI-2-3	Regional Office	EP	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	4	-
IX-2	Description	11	-
IX-3	Claims	2	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	1	-
IX-7	TOTAL	19	

40

PCT REQUEST

1-1232-PCT

Original (for SUBMISSION) - printed on 29.07.2002 03:23:28 PM

	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-13	Priority document(s)	Item(s) VI-1, VI-2	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	
X-1-2	Name of signatory	Dr. Weymann	
X-1-3	Capacity	i.V. 	
X-2	Signature of applicant, agent or common representative		
X-2-1	Name	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	
X-2-2	Name of signatory	Dr. Fuchs	
X-2-3	Capacity	i.V. 	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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41

PCT (ANNEX - FEE CALCULATION SHEET)

1-1232-PCT

Original (for SUBMISSION) - printed on 29.07.2002 03:23:28 PM

(This sheet is not part of and does not count as a sheet of the international application)

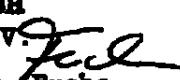
0	For receiving Office use only			
0-1	International Application No.			
0-2	Date stamp of the receiving Office			
0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.06.2002)		
0-8	Applicant's or agent's file reference	1-1232-PCT		
2	Applicant	BOEHRINGER INGELHEIM INTERNATIONAL GMBH, et al.		
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (EUR)	
12-1	Transmittal fee T	⇒	100	
12-2-1	Search fee S	⇒	945	
12-2-2	International search to be carried out by	EP		
12-3	International fee			
	Basic fee			
	(first 30 sheets) b1	444		
12-4	Remaining sheets	0		
12-5	Additional amount (A)	10		
12-6	Total additional amount b2	0		
12-7	b1 + b2 = B	444		
12-8	Designation fees			
	Number of designations contained in international application	93		
12-9	Number of designation fees payable (maximum 5)	5		
12-10	Amount of designation fee (A)	96		
12-11	Total designation fees D	480		
12-12	PCT-EASY fee reduction R	-137		
12-13	Total international fee (B+D-R) I	⇒	787	
12-17	TOTAL FEES PAYABLE (T+S+H+P)	⇒	1.832	
12-18	Mode of payment	authorization to charge deposit account		
12-20	Deposit account instructions			
	The receiving Office:	European Patent Office (EPO) (RO/EP)		
12-20-1	Authorization to charge the total fees indicated above.	✓		
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓		
12-21	Deposit account No.	2800.0140		
12-22	Date	29 July 2002 (29.07.2002)		

12

PCT (ANNEX - FEE CALCULATION SHEET)

1-1232-PCT

Original (for SUBMISSION) - printed on 29.07.2002 09:23:28 PM

12-23	Name and signature	BOEHRINGER INGELHEIM GMBH i.v.  Dr. Fuchs Dr. Meymann
-------	--------------------	---

VALIDATION LOG AND REMARKS

13-2-1	Validation messages Request	Green? The title of the invention shall be short and precise. Please verify.
13-2-7	Validation messages Contents	Green? Figure of the drawings which should accompany the abstract not specified. Please verify.
13-2-8	Validation messages Fees	Green? Please confirm that fee schedule utilized is the latest available
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

BOEHRINGER INGELHEIM INTERNATIONAL
GMBH
Binger Strasse 173
55216 INGELHEIM
Germany

Date of mailing (day/month/year) 07 November 2002 (07.11.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 1-1232-PCT	
International application No. PCT/EP02/08466	International filing date (day/month/year) 30 July 2002 (30.07.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 02 August 2001 (02.08.01)
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
02 Augu 2001 (02.08.01)	01118593.1	EP	04 Octo 2002 (04.10.02)
19 Deco 2001 (19.12.01)	01130180.1	EP	04 Octo 2002 (04.10.02)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer R. Grenier (Fax 338 8970) Telephone No. (41-22) 338.83.38
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Boehringer
Ingelheim

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European Patent Office
D-80298 Munich

Boehringer Ingelheim
International GmbH

CD Patents

14 April 2003

International Patent Application PCT/EP02/08466
Applicant: **Boehringer Ingelheim International GmbH**
Our ref.: **Case 1/1232-PCT**

Concerning the written opinion (PCT rule 66) dated March 10, 2003:

The novelty (Art. 33(2) PCT) of the pending claims has been acknowledged by the Examining Division. However, the Examining Division raised objections concerning the inventive step (Art. 33(3) PCT) of the instant application.

The Examining Division holds that Flibanserin is known from D1. However, as an introductory remark the applicant would like to emphasise that D1 only discloses Flibanserin in form of its hydrochloride salt, whereas the instant application is directed to polymorph A of the free base of Flibanserin.

Under item 3 of the written opinion the Examining Division mentioned D3/D4 as allegedly relevant for the assessment of inventive step of the pending claims. However, in view of the foregoing D3/D4 which are directed to different polymorphs of the same molecule (i.e. same salt forms), cannot be considered relevant for the instant invention.

For the assessment of inventive step (PCT Art. 33(3)) it needs to be determined, whether Flibanserin^{BasePA} (= free base of Flibanserin in polymorph A form) is obvious for a person skilled in the art in view of D1. As Flibanserin^{BasePA} shows superior properties over Flibanserin*HCl (= Flibanserin hydrochloride salt according to D1) which were neither taught by nor deducible from the prior art, the applicant trusts that the instant application satisfies with the criteria of inventiveness. This finding is supported by the following experimental results.

- a) Flibanserin*HCl (according to D1) absorbs moisture (hygroscopicity).
Contrary to the hydrochloride Flibanserin^{BasePA} shows no hygroscopicity

Our reference
wy/s

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Deutsche Bank AG
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Swift: DEUTDE33

at different temperature ranges for different relative humidity values. Annex 1 presents said behaviour of the compounds against moisture. Whereas Flibanserin^{BasePA} at room temperature for 53%, 75% and 94% R.H. does not absorb any moisture (Annex 1, figure left), Flibanserin*HCl stored at 93% R.H. picks up moisture without any limitation at least as far as the observation period is concerned (Annex 1 figure right).

In other terms, Flibanserin^{BasePA} can easily be used in drug product preparation, whereas Flibanserin*HCl is definitely problematic for pharmaceutical development as capsule or tablet. Most important hereby is the lack of weight control or the change in physico-chemical properties. This advantageous and for a medical product important property of Flibanserin^{BasePA} was neither taught nor rendered obvious by D1 and, therefore, proves its unexpected superiority over the prior art.

- b) According to its thermal behaviour prior art Flibanserin*HCl may give rise to many polymorpha. This polymorphism may be problematic in terms of stability.

Annex 2 shows the thermal behaviour of Flibanserin*HCl in a DSC analysis. The graph shows several events taking place at different temperatures. Whereas events at 107 and 135°C are related to water and solvent desorption, events at 153 and 190-194°C are suggestive of transitions into a different physical state, 226°C is the melting point.

Annexes 3 to 5 show a DSC obtained for prior art Flibanserin*HCl after storage at 40°C and 75% relative humidity, and 70°C / 75% R.H., respectively, or RT / 90% R.H.. The DSC plots show the different thermal behaviour of the salt as a function of storage conditions, suggesting relevant changes in physico-chemical properties.

Annex 6 shows the thermal behaviour of Flibanserin^{BasePA}, wherein only one single event, the melting at 161°C, can be found. The same behaviour is unchanged when the compound is stored at 40°C and 75% relative humidity, respectively 70°C / 75% R.H. or RT / 90% R.H..

This advantageous and for a medical product important property of Flibanserin^{BasePA} was neither taught nor rendered obvious by D1 and, therefore, proves its unexpected superiority over the prior art.

- c) A qualitative evaluation of the solubility according to *European Pharmacopoeia* led to the finding that both Flibanserin^{BasePA} and Flibanserin*HCl are equally insoluble in water. The unexpected finding that the free base polymorph A according to the invention shows an equal solubility if compared with the prior art hydrochloride must be

astonishing for a person skilled in the art who would normally expect that the acid addition salt is superior in this respect.

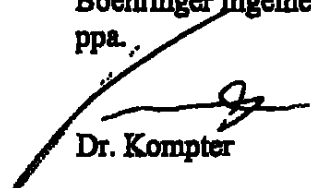
Again, this was totally unexpected by a person skilled in the art.

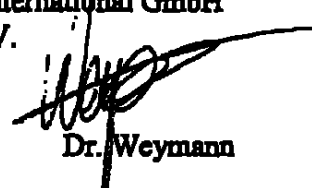
- d) Finally, despite of an equal solubility-behaviour of Flibanserin^{BasePA} and the prior art hydrochloride in water, it is remarkable that Flibanserin*HCl proved to be absolutely unsuitable to form homogeneous suspensions, whereas Flibanserin^{BasePA} is suitable. The practical consequence is that even though it is impossible to prepare suspensions of the hydrochloride for oral use, Flibanserin^{BasePA} is applicable in these kinds of formulations as well.

In view of the foregoing applicant is of the opinion that Flibanserin^{BasePA} according to the invention shows a superiority over the prior art hydrochloride that was neither taught nor rendered obvious for a person of ordinary skill in the art by the cited documents. Consequently, the claimed invention complies with the requirements of Art. 33(3) PCT.

Examination should be continued in light of the arguments and technical data presented herewith. Applicant requests the objection under Art. 33(3) PCT to be withdrawn.

Boehringer Ingelheim International GmbH
ppa. i.V.

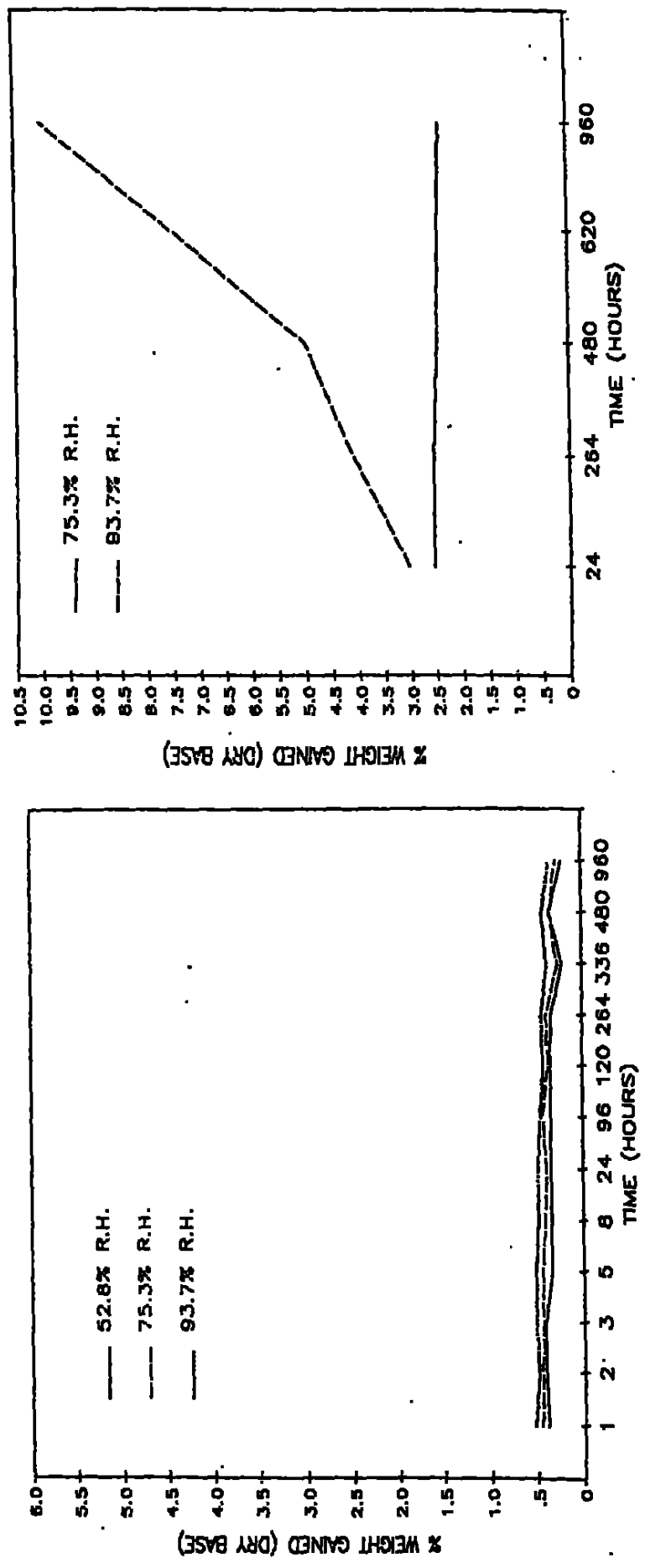

Dr. Kompter


Dr. Weymann

Encl.: Annexes 1-6

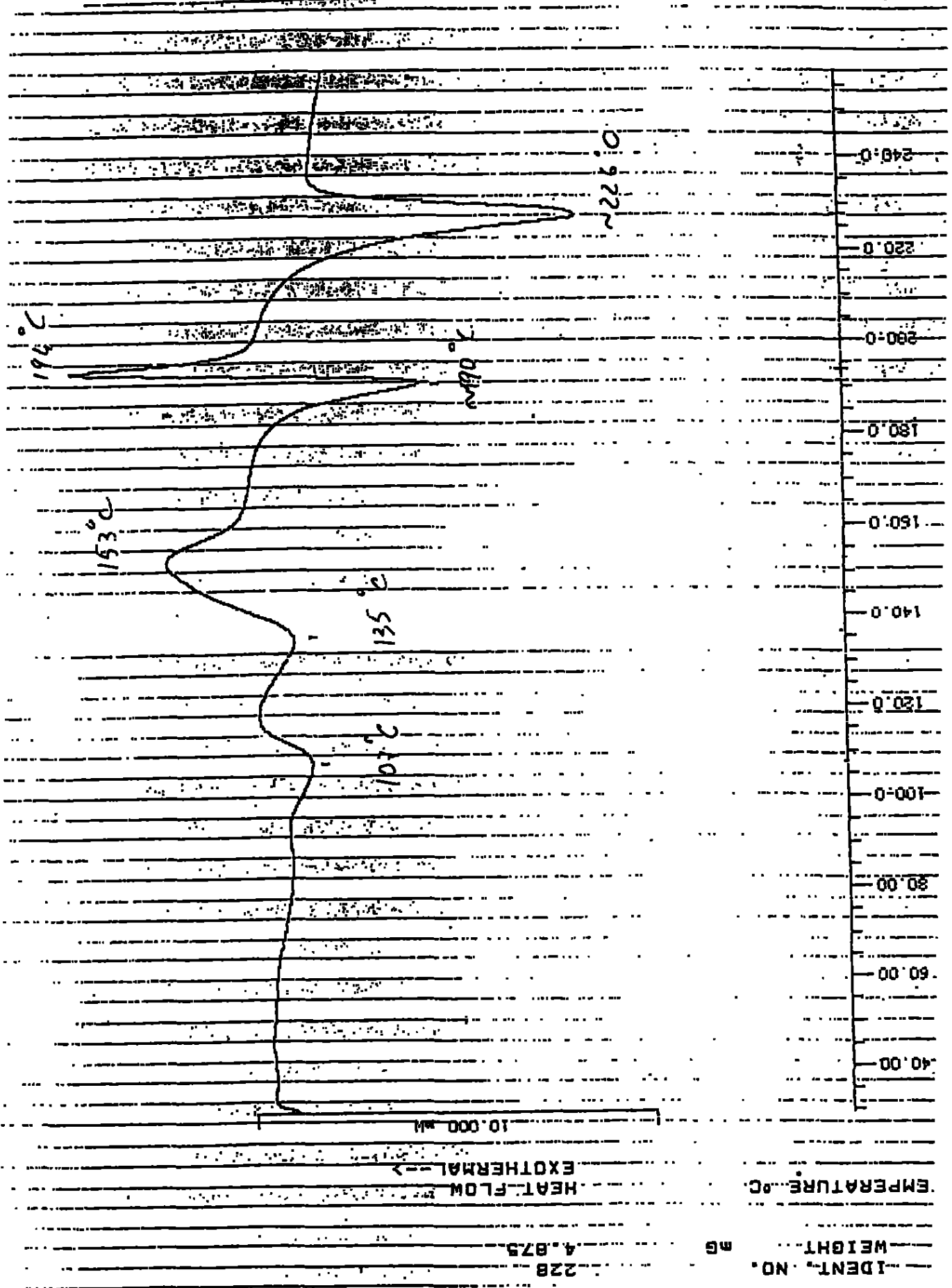
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Base vs Hydrochloride: Comparative Hygroscopicity Studies



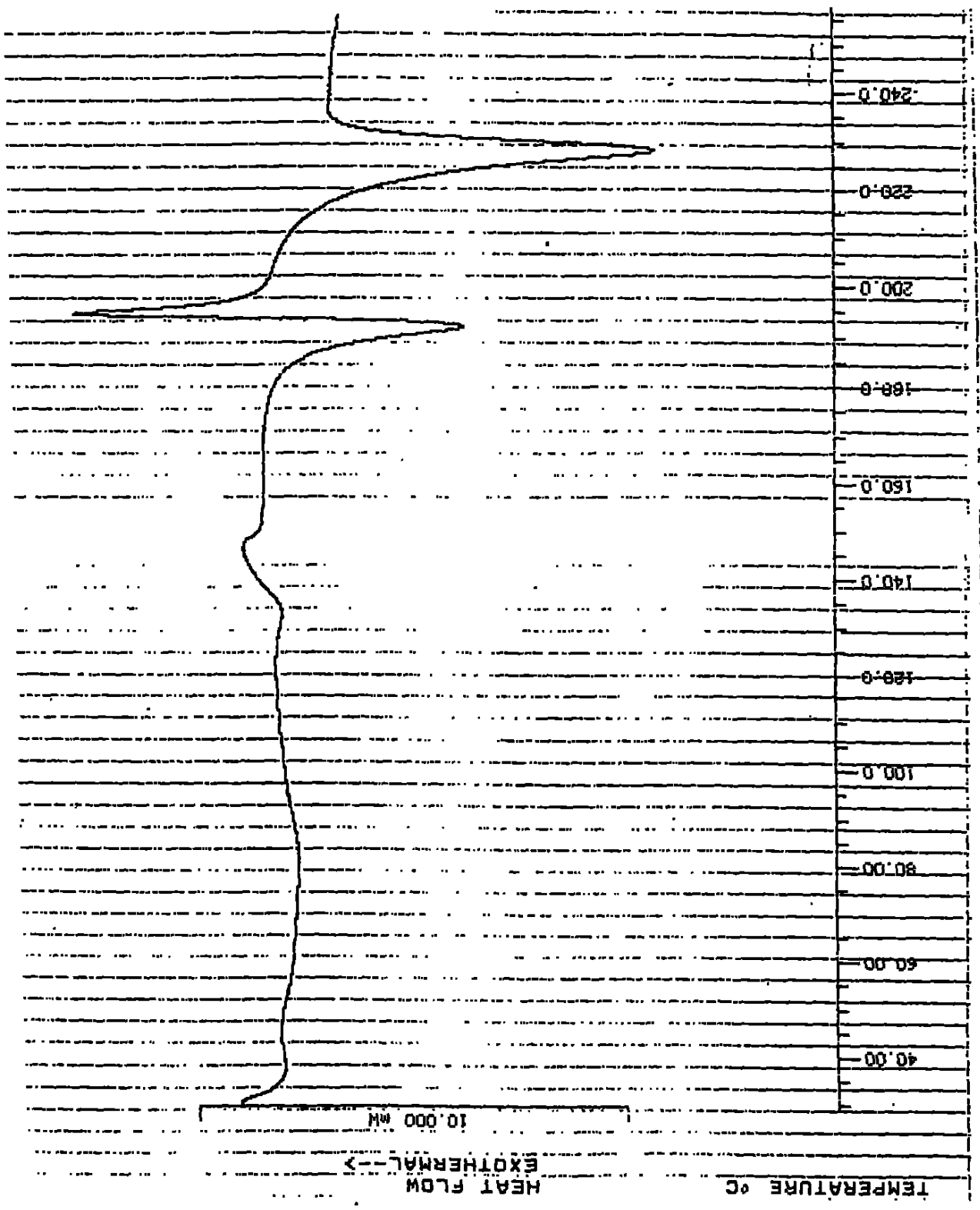
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Annex 2: DSC-Thermogram of Filbanserin*HCl

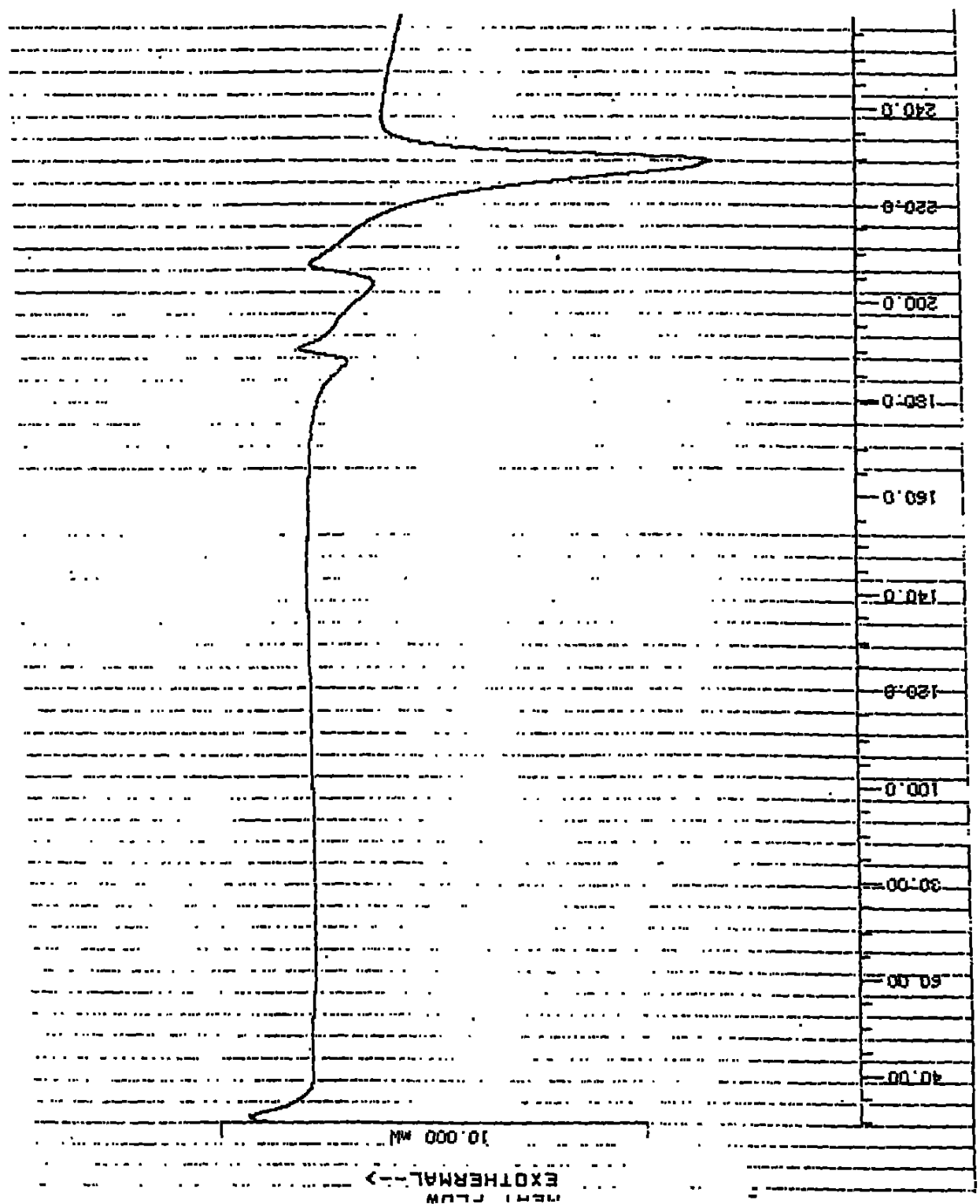


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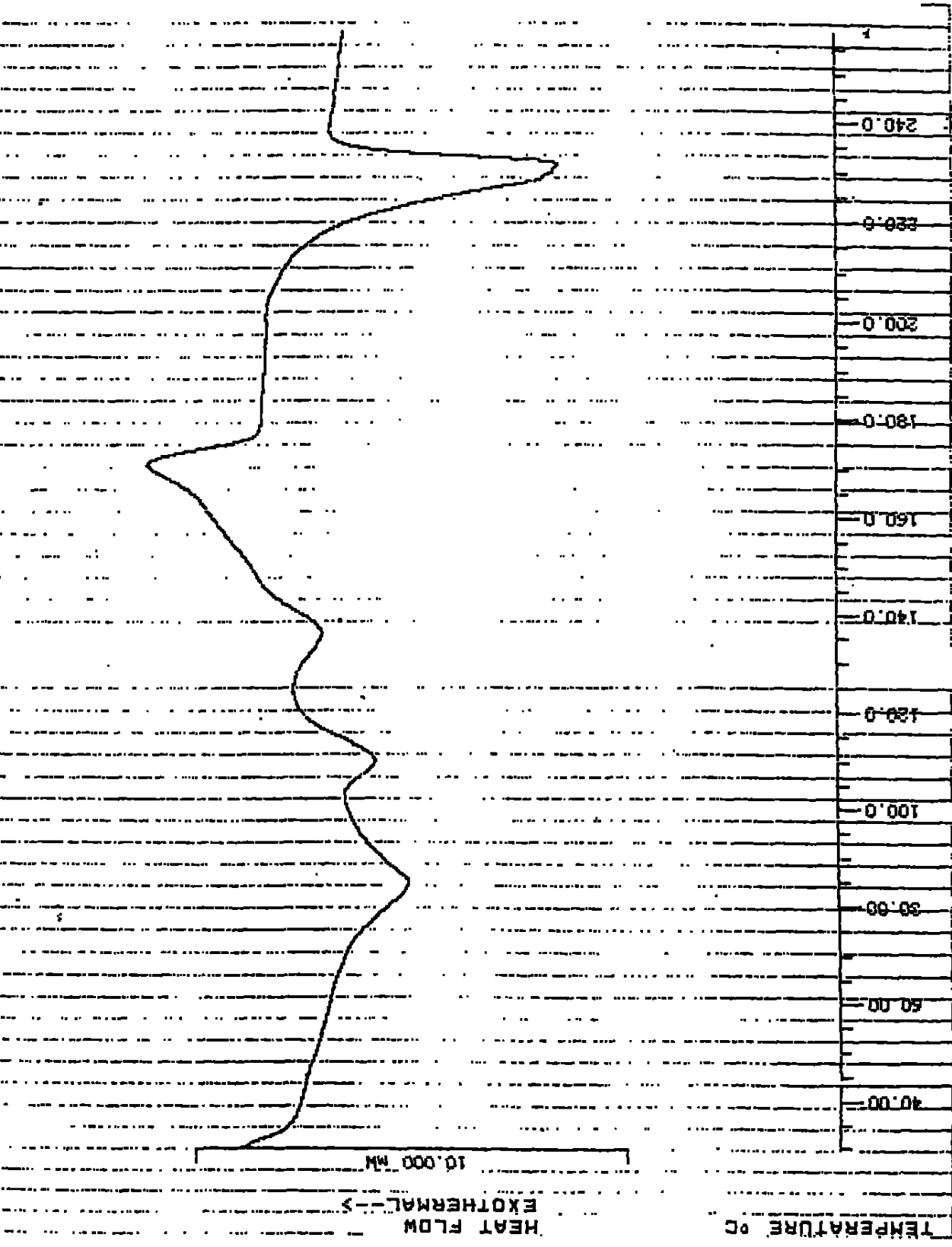
Annex 3: DSC-Thermogram of Filibanserlin*HCl after storage at 40°C / 75% relative humidity



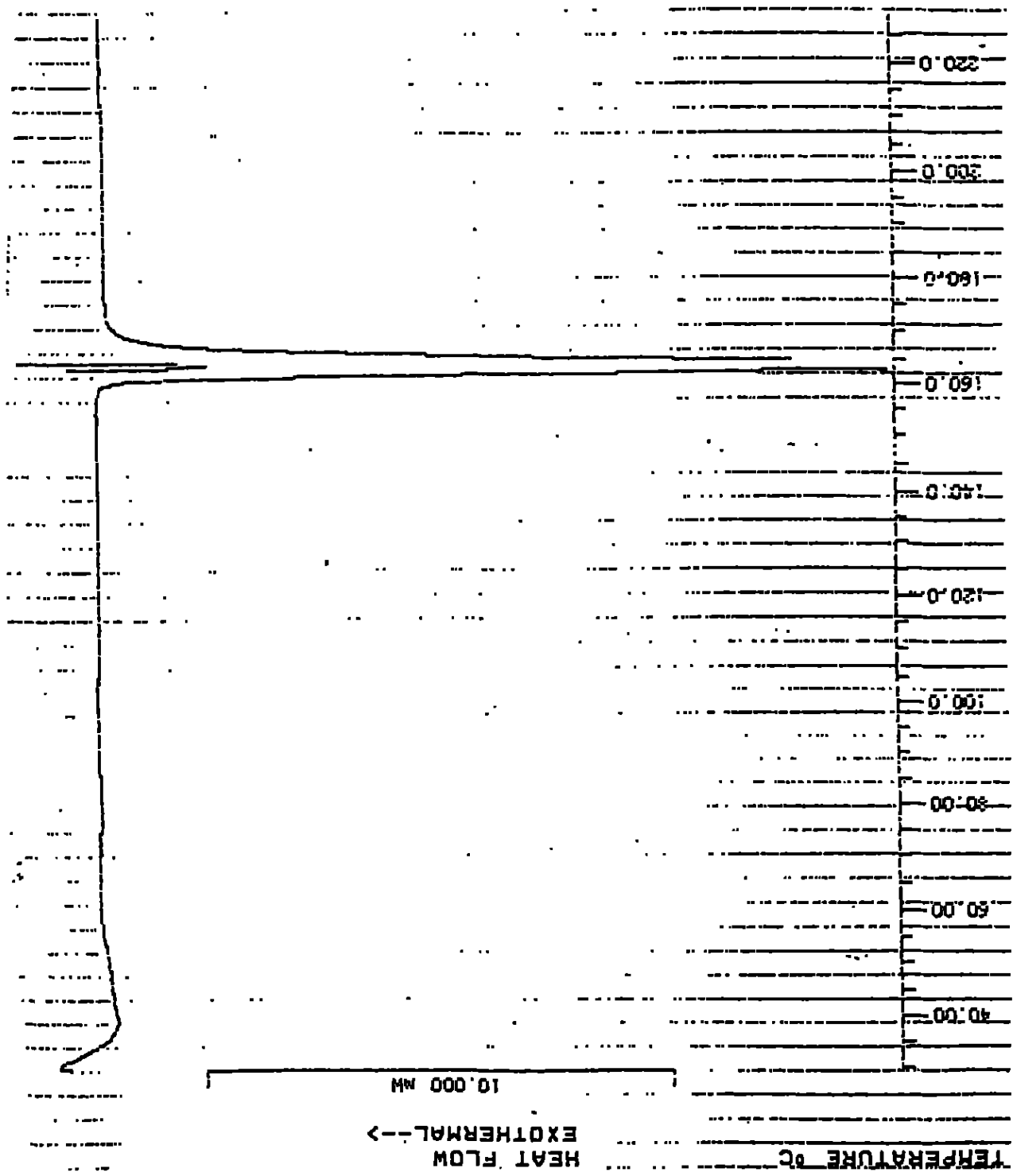
Annex 4: DSC-Thermogram of Filbanserin*HCl after storage at 70°C / 75% relative humidity



Annex 5: DSC-Thermogram of Filbanserin*HCl after storage at RT / 90% relative humidity



Annex 6: DSC-Thermogram of Filbanserin^{Base}PA



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To: BOEHRINGER INGELHEIM INTERNATIONAL GMBH Binger Strasse 173 D-55216 Ingelheim am Rhein ALLEMAGNE		Eingang CD Patents 04. Feb. 2003 SB gelesen erledigt	
		NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY (PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))	
		Date of mailing (day/month/year) 03-02-2003	
Applicant's or agent's file reference Case 1/1-1232-PCT		IMPORTANT NOTIFICATION	
International application No. PCT/EP 02/ 08466	International filing date (day/month/year) 30/07/2002	Priority date (day/month/year) 02/08/2001	
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al.			

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

16/01/2003

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide, Volume II*.

- ☐ (*If applicable*) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/

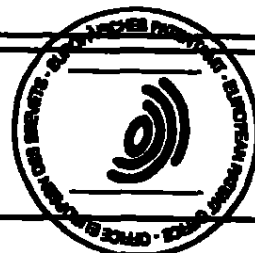


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54

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

To: BOEHRINGER INGELHEIM INTERNATIONAL GMBH Binger Strasse 173 D-55216 Ingelheim am Rhein ALLEMAGNE		Eingang CD Patents 14. Mai 2003		Date of mailing (day/month/year) 13.05.2003	
Applicant's or agent's file reference Case 1/1-1232-PCT		IMPORTANT NOTIFICATION			
International application No. PCT/EP02/08486		International filing date (day/month/year) 30/07/2002		Priority date (day/month/year) 02/08/2001	
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al.					
1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application. 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices. 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices. 4. REMINDER The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301). Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned. For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide. For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.					
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. +49 89 2369 - 0 Tlx 523858 epmu d Fax +49 89 2369 - 4485			Authorized officer Brell, S Tel. +49 89 2369-7271		

45
55

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Case 1/1-1232-PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP02/08486	International filing date (day/month/year) 30/07/2002	Priority date (day/month/year) 02/08/2001	
International Patent Classification (IPC) or national classification and IPC C07D403/06			
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al.			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.			
3. This report contains indications relating to the following items: - I ☒ Basis of the report - II ☐ Priority - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability - IV ☐ Lack of unity of invention - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement - VI ☐ Certain documents cited - VII ☐ Certain defects in the international application - VIII ☐ Certain observations on the international application			
Date of submission of the demand 16/01/2003		Date of completion of this report 13.05.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80296 Munich Tel. +49 89 2369 - 0 Tlx 623656 epmu d Fax: +49 89 2369 - 4465		Authorized officer Baston, E Telephone No. +49 89 2369 8229 	

42
56

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP02/08466

L. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-11 as originally filed

Claims, No.:

1-10 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

27
57

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP02/08466

- ☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-10
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-10
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-10
	No:	Claims

**2. Citations and explanations
see separate sheet**

1/8
50

INTERNATIONAL PRELIMINARY

International application No. PCT/EP02/08466

EXAMINATION REPORT - SEPARATE SHEET

To section V

The following documents were cited in the search report and were considered for the examination of the present application:

- D1: EP-A-0 526 434 (BOEHRINGER INGELHEIM ITALIA) 3 February 1993
D2: BORSINI F ET AL: 'BIMT 17, A 5-HT_{2A} RECEPTOR ANTAGONIST AND 5-HT_{1A} RECEPTOR FULL AGONIST IN RAT CEREBRAL CORTEX' NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 352, no. 3, September 1995, pages 276-282,
D3: GIRON ET AL: 'Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates' THERMOCHIMICA ACTA, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 248, 1995, pages 1-59,
D4: BERNSTEIN, J. ET AL.: 'Concomitant Polymorphs' ANGEWANDTE CHEMIE, INT. ED., 1999, pages 3441-3461.

(1) The present application relates to a stable polymorph of 1-[2-(4-(3-trifluoromethyl-phenyl) piperazin-1-yl)ethyl]-2,3-dihydro-1H-benzimidazol-2-one (flibanserin), which has affinity for the 5-HT_{1A} and 5-HT₂-receptor. This activity is considered to be useful for the treatment of e.g. depression, Parkinson or anxiety.

(2) Flibanserin is known from document D1 (compare page 17, example 3) and D2 (figure 1). D1 discloses a crystalline form of this compound with a specified melting point of 230-231 °C. The presently claimed polymorph has a melting point of 161 °C and is thus clearly to be distinguished from the disclosure of document D1 (Art. 33(2) PCT). Moreover the applicant considers the fact important that D1 discloses the hydrochloride salt of the structure, whereas the present application relates to a polymorph of a "free compound".

(3) In view of documents D3 and D4 it is acknowledged that polymorphs might reveal distinctive physico-chemical or pharmacokinetic properties. The applicant provided arguments and data which reveal that the presently claimed compound would absorb to a much lesser extent moisture in contrast to the hydrochloride known from D1. It was thus concluded that the newly developed polymorph is advantageous for the purpose of drug product formulation (weight control). The involvement of an inventive step is

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INTERNATIONAL PRELIMINARY

International application No. PCT/EP02/08466

EXAMINATION REPORT - SEPARATE SHEET

acknowledged (Art. 33(3) PCT).

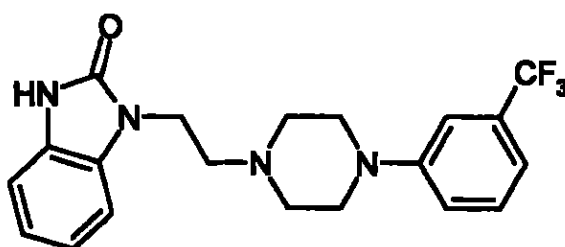
- 1 -

Compuesto polimorfo estable de flibanserina, procedimiento industrial para su preparación, y uso del mismo para preparar medicamentos

El invento se refiere al compuesto polimorfo A de flibanserina, a un procedimiento industrial para la preparación del mismo y también al uso del mismo para preparar medicamentos.

Fundamento del invento

El compuesto 1-[2-(4-(3-trifluorometil-fenil)piperazin-1-il)etil]-2,3-dihidro-1H-benzolimidazol-2-ona (flibanserina) es descrito, en forma de su hidrocloreto, en la Solicitud de Patente Europea EP-A-526434 y tiene la estructura química siguiente:



1 x HCl

La flibanserina muestra afinidad por los receptores 5-HT_{1A} y 5-HT₂. Por lo tanto, es un agente terapéutico prometedor para el tratamiento de una diversidad de enfermedades, tales como, por ejemplo, depresión, esquizofrenia, enfermedad de Parkinson, ansiedad, alteraciones del sueño, trastornos sexuales y mentales, y deterioro de la memoria asociado con la edad.

Por supuesto, una cierta actividad farmacéutica es el requisito previo básico que ha de satisfacer un agente farmacéuticamente activo antes de que el mismo sea aprobado como un medicamento para el mercado. Sin embargo, hay una diversidad de requisitos adicionales que un agente farmacéuticamente activo ha de cumplir. Estos requisitos se basan en diversos parámetros que están relacionados con la naturaleza de la propia sustancia activa. Sin ser restrictivos, son ejemplos de estos parámetros la estabilidad del agente activo bajo diversas condiciones ambientales, su estabilidad durante la producción de la formulación farmacéutica y la estabilidad del agente activo en las composiciones medicinales finales. La sustancia farmacéuticamente activa usada para preparar las composiciones farmacéuticas debe ser lo más pura posible, y su estabilidad en almacenamiento de larga duración debe estar

garantizada bajo diversas condiciones ambientales. Esto es absolutamente esencial para evitar el uso de composiciones farmacéuticas que contengan, además de la propia sustancia activa, por ejemplo, productos de descomposición de la misma. En tales casos, el contenido de sustancia activa en el medicamento podría ser inferior al especificado.

La distribución uniforme del medicamento en la formulación es un factor crítico, particularmente cuando el medicamento ha de ser administrado en dosis pequeñas. Para asegurar una distribución uniforme, el tamaño de las partículas de la sustancia activa puede ser reducido hasta un nivel adecuado mediante, por ejemplo, trituration. Puesto que en la medida de lo posible ha de evitarse la descomposición de la sustancia farmacéuticamente activa como un efecto secundario de la trituration (o micronización), a pesar de las duras condiciones requeridas durante el proceso, es absolutamente esencial que la sustancia activa sea muy estable a lo largo del proceso de trituration. Solamente si la sustancia activa es suficientemente estable durante el proceso de trituration es posible producir una formulación farmacéutica homogénea que siempre contenga la cantidad especificada de sustancia activa de un modo reproducible.

Otro problema que puede surgir en el proceso de trituration para preparar la formulación farmacéutica deseada es la entrada de energía causada por este proceso y la tensión sobre la superficie de los cristales. En ciertas circunstancias, esto puede conducir a cambios polimorfos, a un cambio en la configuración amorfa o a un cambio en la red cristalina. Puesto que la calidad farmacéutica de una formulación farmacéutica requiere que la sustancia activa tenga siempre la misma morfología cristalina, la estabilidad y las propiedades de la sustancia cristalina activa están también sujetas a requisitos estrictos desde este punto de vista.

La estabilidad de una sustancia farmacéuticamente activa es también importante en las composiciones farmacéuticas para determinar el tiempo de conservación del medicamento concreto; el tiempo de conservación es el período de tiempo durante el cual el medicamento puede ser administrado sin riesgo alguno. Por lo tanto, una elevada estabilidad de un medicamento en las susodichas composiciones farmacéuticas bajo diversas condiciones de almacenamiento es una ventaja adicional tanto para el paciente como para el fabricante.

Al margen de los requisitos anteriormente indicados, ha de tenerse generalmente presente que cualquier cambio relativo al estado sólido de una composición farmacéutica, que sea capaz de mejorar sus estabilidades física y química proporciona una ventaja significativa con respecto a formas menos estables del mismo medicamento.

De este modo, el fin del invento es proporcionar una nueva forma cristalina y estable del compuesto flibanserina que satisfaga los estrictos requisitos impuestos a sustancias farmacéuticamente activas, como los anteriormente mencionados.

10

Descripción detallada del invento

Sorprendentemente, se ha hallado que la base libre de flibanserina en una forma polimórfica específica satisface los requisitos anteriormente mencionados.

15

Se ha hallado además que, dependiendo de la elección de las condiciones que pueden aplicarse durante la síntesis de flibanserina, la base libre se presenta en diferentes modificaciones cristalinas, los compuestos polimorfos A y B.

Se ha hallado que estas diferentes modificaciones pueden ser deliberadamente producidas mediante una adecuada elección de las condiciones de procesamiento usadas en el proceso de fabricación.

Sorprendentemente, se ha hallado que el compuesto polimorfo A, que puede ser obtenido en forma cristalina al elegir unas condiciones de reacción específicas, satisface los estrictos requisitos anteriormente mencionados y, por lo tanto, resuelve el problema en que se basa el presente invento. En consecuencia, el presente invento se refiere al compuesto polimorfo A de flibanserina. El compuesto polimorfo A de flibanserina se caracteriza por un punto de fusión de aproximadamente 161°C [determinado por calorimetría diferencial de barrido (DSC; del inglés, differential scanning calorimetry); velocidad de calentamiento de 10°K/min].

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El compuesto polimorfo B, la modificación menos estable de la flibanserina, presenta un punto de fusión de aproximadamente 120°C (determinado por DSC; velocidad de calentamiento de 10°K/min). Mientras que el compuesto polimorfo B muestra poca estabilidad bajo los efectos de, por ejemplo, la tensión mecánica producida por la trituración, el compuesto poli-

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- 4 -

morfo A llega a satisfacer los requisitos de estabilidad anteriormente mencionados.

De acuerdo con otro aspecto, el presente invento se refiere a un procedimiento para la fabricación del compuesto polimorfo A de filbanserina a escala industrial. El procedimiento de acuerdo con el invento se ilustra en el diagrama 1.

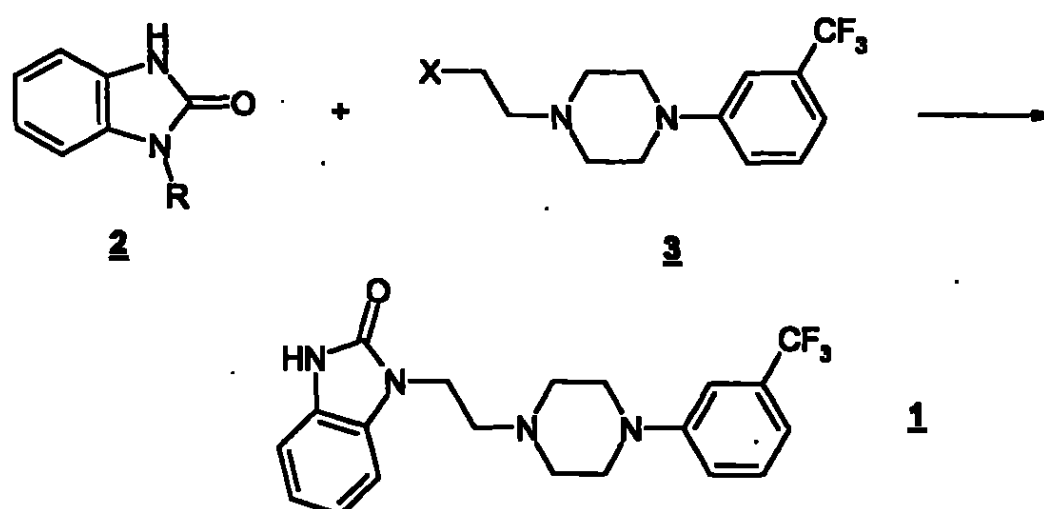


Diagrama 1

La benzimidazolona **2** es hecha reaccionar con el derivado **3** de piperazina bajo condiciones de reacción básicas en un disolvente adecuado para llegar a **1**. En **2**, el grupo R representa un grupo protector de aminas. El grupo protector usado puede ser cualquiera de los grupos comúnmente utilizados para proteger la función amina. Los ejemplos incluyen grupos seleccionados entre alquilo, alquilo sustituido, alquilo heterosustituido, alquilo insaturado, heteroátomos sustituidos con alquilo, fenilo sustituido o no sustituido, bencilo sustituido o no sustituido, grupos alquilo oxycarbonilo y grupos arilo oxycarbonilo. Los grupos protectores preferidos son seleccionados entre butilo, 1,1-difenilmetilo, metoximetilo, benciloximetilo, tricloroetoximetilo, pirrolidinometilo, clonometilo, pivaloiloximetilo, alilo, 2-propenilo, t-butilidimetilsililo, metoxilo, tiometilo, 4-metoxifenilo, bencilo, 4-metoxibencilo, 2,4-dimetoxibencilo, 2-nitrobencilo, t-butoxicarbonilo, benciloxicarbonilo, fenoxicarbonilo, 4-cloro-fenoxicarbonilo, 4-nitro-fenoxicarbonilo, metoxicarbonilo y etoxicarbonilo. Entre estos, los grupos protectores preferidos son seleccionados entre t-butoxicarbonilo, etoxicarbonilo, metoxicarbonilo, benciloxicarbonilo, fenoxicarbonilo y 2-

propenilo, siendo muy preferido el último. En 3, X representa un grupo lábil seleccionado entre cloro, bromo, yodo, metanosulfonato, trifluorometanosulfonato y para-toluenosulfonato. X representa preferiblemente cloro, bromo o yodo, siendo muy preferido el cloro. Los disolventes adecuados son seleccionados entre agua, alcoholes y mezclas de agua con alcoholes, disolventes apróticos polares y mezclas de los mismos con agua. Los disolventes preferidos son seleccionados del grupo que consiste en dimetilformamida, dimetilsulfóxido, acetonitrilo, tetrahidrofurano, dioxano, metanol, etanol, isopropanol y mezclas de uno o varios de los susodichos disolventes con agua. Los disolventes preferidos son aquellos que son fácilmente miscibles con agua. Como disolvente se usa preferiblemente una mezcla de agua con uno de los alcoholes metanol, etanol e isopropanol. En una realización preferida, se usa como disolvente una mezcla de agua e isopropanol. La base usada puede ser un carbonato alcalino o alcalinotérreo de litio, sodio, potasio o calcio, tal como carbonato de sodio, carbonato de litio, carbonato de potasio o carbonato de calcio, y preferiblemente carbonato de potasio. También es posible usar los hidrogenocarbonatos de litio, sodio y potasio. Preferiblemente, pueden usarse también los hidróxidos alcalinos o alcalinotérreos de litio, sodio, potasio, magnesio y calcio, pero preferiblemente hidróxido de sodio, hidróxido de potasio, hidróxido de litio e hidróxido de calcio en alcoholes o agua. La base más preferida es el hidróxido de sodio. La base es preferiblemente añadida en forma de su disolución acuosa, preferiblemente en forma de disoluciones acuosas concentradas, tal como, por ejemplo, en concentraciones de entre 30 y 50 % en peso/volumen. En una realización preferida, se usa una disolución acuosa de hidróxido de sodio en una concentración de aproximadamente 45 % en peso/volumen.

Los compuestos 2 y 3 son introducidos en la mezcla de reacción en una relación molar de entre 1:1 y 1:2, preferiblemente en una relación molar de entre 1:1,1 y 1:1,5. Como se mencionó anteriormente, se usa una mezcla de agua e isopropanol como una mezcla disolvente preferida para la conducción del procedimiento de acuerdo con el invento. En esta mezcla disolvente, la relación ponderal de agua a isopropanol en la mezcla disolvente preferida es entre 10:1 y 1:1, más preferida es entre 8:1 y 3:1, particularmente preferida es entre 7:1 y 5:1. Por mol de compuesto 2 se usan aproximadamente 2-10 kg, preferiblemente 3-8 kg, más preferiblemente 4-7 kg de la mezcla disolvente anteriormente mencionada. En una realización preferida, la reacción es llevada cabo usando como base una disolución acuosa de hidróxido de sodio en una

concentración de aproximadamente 45 % en peso/volumen. Por mol de 2 se usan aproximadamente 0,1-1,5 kg, preferiblemente 0,2-1,0 kg, de forma particularmente preferida 0,3-0,6 kg de la disolución de hidróxido de sodio anteriormente mencionada. La mezcla de reacción que contiene 2, 3 y la base
5 en el adecuado disolvente anteriormente mencionado es preferiblemente calentada a al menos 50°C. En una realización preferida, la temperatura de reacción está en el intervalo de entre 60°C y el punto de ebullición del disolvente. Se prefiere particularmente una temperatura de entre 70 y 90°C. La mezcla de reacción es calentada a la susodicha temperatura durante un periodo
10 de aproximadamente 10 minutos a aproximadamente 12 horas, preferiblemente de aproximadamente 15 minutos a aproximadamente 6 horas, más preferiblemente de aproximadamente 30 minutos a aproximadamente 3 horas. La mezcla de reacción es preferiblemente calentada a la susodicha temperatura durante un periodo de aproximadamente 45 a 60 minutos.

15 El grupo protector R es posteriormente escindido. Las condiciones de escisión dependen de la elección del grupo R. Si R representa, por ejemplo, bencilo, la escisión es llevada a cabo por medio de hidrogenación en ácido acético en presencia de un catalizador apropiado (por ejemplo, Pd sobre carbón vegetal) o R puede ser escindido en HBr acuoso. En el caso de que R sea
20 metoxycarbonilo, etoxycarbonilo, fenoxycarbonilo o 4-nitrofenoxycarbonilo, puede ser escindido, por ejemplo, usando disoluciones acuosas alcalinas tales como NaOH (acuoso) o KOH (acuoso). En el caso de que R sea t-butoxycarbonilo, puede ser escindido, por ejemplo, en HCl o HBr acuosos. En el caso de que R represente 2-propenilo, el grupo protector particularmente preferido de acuerdo
25 con el invento, la escisión de R es efectuada por medio de condiciones de reacción ácidas. En un procedimiento particularmente preferido de acuerdo con el invento, el grupo 2-propenilo es escindido usando un ácido mineral fuerte, preferiblemente un ácido seleccionado del grupo que consiste en ácido bromhídrico, ácido clorhídrico y ácido sulfúrico, más preferiblemente ácido clorhídrico. El ácido clorhídrico puede ser añadido en forma gaseosa o en forma
30 de sus disoluciones acuosas, prefiriéndose la adición de disoluciones acuosas. Se prefiere particularmente la adición de ácido clorhídrico en forma de su disolución concentrada (aproximadamente al 36 % en peso/volumen). Ha de añadirse al menos un mol de ácido clorhídrico por mol de 2. Preferiblemente, la
35 cantidad de ácido clorhídrico concentrado añadido (al 36 % en peso/volumen) por mol de 2 es entre 50 y 500 g, más preferiblemente entre 80 y 250 g. De

forma particularmente preferida, se añaden aproximadamente 120-160 g de ácido clorhídrico acuoso concentrado (al 36 % en peso/volumen) por mol de **2** usado. Puede añadirse opcionalmente agua adicional. A una temperatura de aproximadamente 70-90°C, se elimina aproximadamente el 30-70 %, preferiblemente aproximadamente el 35-60 %, del disolvente por medio de destilación. A una temperatura de aproximadamente 60-80°C, el pH del residuo restante es ajustado a aproximadamente 5-9, preferiblemente a aproximadamente 6-8, mediante la adición de hidróxido sódico acuoso (al 45 % en peso/volumen). A una temperatura de aproximadamente 40-55°C, el pH es ajustado a aproximadamente 8-9 mediante la adición de hidróxido sódico acuoso (al 45 % en peso/volumen). Posteriormente, la mezcla es enfriada a aproximadamente 20-40°C, preferiblemente a aproximadamente 30-35°C, y es centrifugada. El residuo así obtenido es lavado con aproximadamente de 100 a 750 ml de agua por mol de **2** introducido, preferiblemente con aproximadamente de 200 a 500, de forma particularmente preferida con aproximadamente de 300 a 400, ml de agua por mol de **2** introducido e isopropanol (aproximadamente de 50 a 250 g por mol de **2**, preferiblemente de aproximadamente 100 a 200 g por mol de **2**), y luego con agua hasta la eliminación de los cloruros. Opcionalmente, el producto así obtenido puede ser sometido a otra operación de purificación. Dicha purificación es llevada preferiblemente a cabo por medio de la cristalización de **1** en, por ejemplo, acetona.

Un aspecto del presente invento se refiere al compuesto polimorfo A de filbanserina, obtenible por medio del método anteriormente descrito.

El siguiente ejemplo de síntesis sirve para ilustrar un método para preparar el compuesto polimorfo A de filbanserina. Ha de ser considerado sólo como un posible método descrito a modo de ejemplo, sin que limite el invento en cuanto a sus contenidos.

Ejemplo

Se cargan 375 kg de 1-[(3-trifluorometil)fenil]-4-(2-cloroetil)piperazina en un reactor con 2.500 kg de agua y 200 kg de hidróxido sódico acuoso al 45 %. Bajo agitación, se añaden 169,2 kg de 1-(2-propenil)-1,3-dihidro-benzimidazol-2H-ona, 780 kg de isopropanol, 2.000 kg de agua y 220 kg de hidróxido de sodio acuoso al 45 %. Se calienta la mezcla de reacción a 75-85°C y se añaden 160 kg de ácido clorhídrico concentrado y 200 kg de agua. Se agita la mezcla de reacción a temperatura constante durante aproxi-

madamente 45 minutos. Después de la destilación de una mezcla de agua e isopropanol (aproximadamente 3.000 kg), se enfría el residuo restante a aproximadamente 65-75°C y se ajusta el pH a 6,5-7,5 mediante la adición de 125 kg de hidróxido sódico acuoso al 45 %. Tras enfriamiento a una temperatura de 45-50°C, se ajusta el valor de pH a 8-9 mediante la adición de aproximadamente 4 kg de hidróxido sódico acuoso al 45 %. La mezcla es posteriormente enfriada a 30-35°C y es centrifugada. El residuo así obtenido es lavado con 340 l de agua y 126 l de isopropanol y luego con agua hasta la eliminación de los cloruros. El producto húmedo es secado bajo vacío a una temperatura de aproximadamente 45-55°C, lo que conduce a 358 kg de compuesto polimorfo A de filbanserina crudo. El producto crudo así obtenido es cargado en un reactor con 1.750 kg de acetona, y la mezcla resultante es calentada bajo agitación hasta reflujo. La disolución obtenida es filtrada, y el producto de filtración es concentrado por destilación. La temperatura es mantenida a 0-5°C durante aproximadamente 1 hora, y el sólido precipitado es luego aislado por filtración y es secado a 55°C durante al menos 12 horas. La producción final es 280 kg de compuesto polimorfo A de filbanserina puro.

Como se mencionó anteriormente, el compuesto polimorfo A de filbanserina fue caracterizado por DSC. La temperatura máxima determinada para el compuesto polimorfo A es aproximadamente 161°C. Para la caracterización por medio de DSC se aplicó un sistema Mettler TA 3000 provisto de un procesador TC 10-A y una célula DSC 20. La velocidad de calentamiento fue 10°K/min.

El compuesto polimorfo A de filbanserina fue adicionalmente caracterizado por difracción de rayos X sobre polvo. El diagrama de difracción de rayos X sobre polvo del compuesto polimorfo A fue obtenido de acuerdo con las condiciones siguientes:

30	<u>Equipo:</u>	Difractómetro Philips PW 1800/10 provisto de un Microvax 2000 digital	
	<u>Parámetros de ajuste:</u>	<u>Rayos X</u>	
35		Tipo de tubo:	Cu (foco fino largo)
		Longitudes de onda (λ):	$K_{\alpha 1} = 0,154060 \text{ nm}$
			$K_{\alpha 2} = 0,154439 \text{ nm}$
		Relación de Intensidades (α_2/α_1):	0,500

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Ángulo Inicial [°2θ]: 2,000
Ángulo final [°2θ]: 60,000
Tamaño de paso [°2θ]: 0,020
Intensidad(es) máxima(s): 7.310,250
Tipo de barrido: continuo
Anchura mínima en la punta del pico: 0,00
Anchura máxima en la punta del pico: 1,00
Anchura en la base del pico: 2,00
Significación mínima: 0,75
Número de picos: 69

Generador: Tensión elevada: 50 kV
Corriente del tubo: 30 mA

En la Figura 1 se ilustra el diagrama de difracción de rayos X sobre polvo, obtenido para el compuesto polimorfo A. En la Tabla 1 se reúnen los valores apropiados.

Tabla 1

Ángulo [°2θ]	Valor d α1 [nm]	Valor d α2 [nm]	Anchura de pico [°2θ]	Intens. de pico [cuentas]	Intens. de fondo [cuentas]	Intens. relat. [%]	Signif.
5,195	1,69967	1,70390	0,960	8	69	0,1	1,05
9,045	0,97689	0,97931	0,100	92	96	1,3	0,97
9,335	0,94660	0,94896	0,080	114	98	1,6	0,88
10,025	0,88160	0,88379	0,140	400	100	5,5	7,18
10,595	0,83430	0,83637	0,140	204	102	2,8	3,46
11,290	0,78309	0,78503	0,140	467	104	6,4	6,91
13,225	0,66891	0,67058	0,180	548	112	7,5	13,10
14,595	0,60642	0,60793	0,180	404	121	5,5	9,17
15,460	0,57268	0,57410	0,140	4.186	125	57,3	23,20
16,655	0,53185	0,53317	0,200	515	130	7,0	12,38
17,085	0,51856	0,51985	0,100	1.347	132	18,4	2,78

- 10 -

17,285	0,51260	0,51388	0,060	1.399	135	19,1	2,26
17,420	0,50866	0,50992	0,100	1.204	135	16,5	4,71
18,140	0,48863	0,48984	0,180	1.043	139	14,3	13,14
18,650	0,47538	0,47656	0,120	1.063	142	14,5	0,91
19,140	0,46332	0,46447	0,140	7.310	144	100,0	32,77
19,820	0,44757	0,44869	0,160	3.624	146	49,6	9,02
20,080	0,44184	0,44294	0,140	5.402	149	73,9	21,06
20,385	0,43530	0,43638	0,160	2.652	149	36,3	23,25
21,215	0,41845	0,41949	0,160	369	154	5,0	5,78
21,890	0,40570	0,40670	0,200	773	156	10,6	3,09
22,630	0,39259	0,39357	0,280	4.277	161	58,5	74,66
23,210	0,38291	0,38386	0,120	484	164	6,6	3,33
24,355	0,36516	0,36607	0,060	2.725	169	37,3	1,16
24,610	0,36144	0,36234	0,140	3.540	172	48,4	17,08
24,995	0,35596	0,35684	0,100	529	174	7,2	1,01
25,260	0,35228	0,35316	0,120	557	174	7,6	3,02
26,575	0,33514	0,33597	0,240	2.421	182	33,1	42,58
27,155	0,32811	0,32893	0,140	676	185	9,2	1,32
27,310	0,32629	0,32710	0,100	767	185	10,5	2,75
27,865	0,31991	0,32071	0,120	420	188	5,7	1,08
28,210	0,31608	0,31686	0,100	1.467	190	20,1	0,79
28,325	0,31482	0,31560	0,140	1.789	190	24,5	4,41
28,650	0,31132	0,31210	0,180	1.204	190	16,5	11,65
29,520	0,30234	0,30309	0,220	1.011	196	13,8	15,74
30,250	0,29521	0,29594	0,120	159	199	2,2	1,22
31,105	0,28729	0,28800	0,360	282	204	3,9	8,14
31,905	0,28026	0,28096	0,100	339	207	4,6	0,96
32,350	0,27651	0,27720	0,120	237	210	3,2	3,01
33,300	0,26884	0,26950	0,180	1.347	216	18,4	14,06
33,640	0,26620	0,26686	0,100	404	216	5,5	1,45

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34,880	0,25701	0,25765	0,200	202	222	2,8	1,04
35,275	0,25422	0,25486	0,240	299	225	4,1	4,84
36,055	0,24890	0,24952	0,280	202	228	2,8	3,78
36,910	0,24333	0,24393	0,320	169	234	2,3	0,90
37,160	0,24175	0,24235	0,120	216	234	3,0	2,14
37,680	0,23853	0,23912	0,240	240	237	3,3	1,58
39,435	0,22831	0,22888	0,280	449	246	6,1	2,67
39,675	0,22698	0,22755	0,080	396	246	5,4	0,82
40,325	0,22347	0,22403	0,160	520	250	7,1	0,95
40,930	0,22031	0,22086	0,120	480	253	6,6	2,66
41,445	0,21769	0,21823	0,240	372	256	5,1	2,65
41,990	0,21499	0,21552	0,120	538	259	7,4	1,31
42,670	0,21172	0,21225	0,160	428	262	5,9	1,45
43,145	0,20950	0,21002	0,120	433	266	5,9	1,50
44,190	0,20478	0,20529	0,160	376	269	5,1	0,89
46,095	0,19675	0,19724	0,160	279	279	3,8	0,86
46,510	0,19509	0,19558	0,240	310	282	4,2	0,87
48,305	0,18826	0,18872	0,200	506	292	6,9	2,06
48,900	0,18610	0,18657	0,240	615	296	8,4	1,67
50,330	0,18115	0,18160	0,160	437	303	6,0	1,73
51,035	0,17881	0,17925	0,080	416	306	5,7	0,93
53,550	0,17099	0,17141	0,480	177	317	2,4	2,84
54,500	0,16823	0,16865	0,400	130	324	1,8	1,37
55,420	0,16565	0,16606	0,320	130	328	1,8	1,72
56,220	0,16348	0,16389	0,320	121	331	1,7	0,87
56,770	0,16203	0,16243	0,240	142	335	1,9	1,59
57,405	0,16039	0,16079	0,240	112	339	1,5	1,19
58,500	0,15764	0,15804	0,240	67	342	0,9	1,57

A la luz de la eficacia farmacéutica de la flibanserina, el presente invento se refiere además al uso del compuesto polimorfo A de flibanserina como un medicamento.

5 Un aspecto más del presente invento se refiere al uso del compuesto polimorfo A de flibanserina para preparar una composición farmacéutica para tratar enfermedades en que el uso de compuestos que presentan afinidad por los receptores 5-HT_{1A} y 5-HT₂ puede tener un beneficio terapéutico.

10 Un aspecto más del presente invento se refiere al uso del compuesto polimorfo A de flibanserina para preparar una composición farmacéutica para tratar una enfermedad seleccionada entre depresión, esquizofrenia, enfermedad de Parkinson, ansiedad, alteraciones del sueño, trastornos sexuales y mentales, y deterioro de la memoria asociado con la edad.

15 En particular, el presente invento se refiere al uso del compuesto polimorfo A de flibanserina para la preparación de un medicamento para el tratamiento de trastornos del deseo sexual.

20 En una realización preferida, el invento se refiere al uso del compuesto polimorfo A de flibanserina para la preparación de un medicamento para el tratamiento de trastornos seleccionados del grupo que consiste en trastorno de deseo sexual hipoactivo, pérdida de deseo sexual, carencia de deseo sexual, deseo sexual disminuido, deseo sexual inhibido, pérdida de libido, alteración de la libido, y frigidez.

25 De acuerdo con el invento, es particularmente preferido el uso del compuesto polimorfo A de flibanserina para la preparación de un medicamento para el tratamiento de trastornos seleccionados del grupo que consiste en trastorno de deseo sexual hipoactivo, pérdida de deseo sexual, carencia de deseo sexual, deseo sexual disminuido y deseo sexual inhibido.

30 En una realización particularmente preferida, el invento se refiere al uso del compuesto polimorfo A de flibanserina para la preparación de un medicamento para el tratamiento de trastornos seleccionados del grupo que consiste en trastorno de deseo sexual hipoactivo y pérdida de deseo sexual.

35 Los susodichos efectos terapéuticos del compuesto polimorfo A de flibanserina pueden alcanzarse en hombres y mujeres. Sin embargo, de acuerdo con un aspecto más del invento, se prefiere el uso del compuesto

polimorfo A de flibanserina para la preparación de un medicamento para el tratamiento de una disfunción sexual femenina.

Los efectos beneficiosos del compuesto polimorfo A de flibanserina pueden ser observados independientemente de si la alteración existía desde siempre o era adquirida, e independientemente del origen etiológico (orgánico -tanto físicamente provocado como provocado por fármacos-, sicógeno, una combinación de orgánico -tanto físicamente provocado como provocado por fármacos- y sicógeno, o desconocido).

Como una característica más del presente invento, se proporcionan composiciones farmacéuticas que comprenden, como un ingrediente activo, el compuesto polimorfo A de flibanserina junto con uno o más vehículos, agentes diluyentes o excipientes farmacéuticos. Para administración farmacéutica, el compuesto polimorfo A de flibanserina puede ser incorporado a la preparación farmacéutica convencional en forma sólida, líquida o pulverizable. La composición puede presentarse, por ejemplo, en una forma adecuada para administración oral, rectal o parenteral o para inhalación nasal; las formas preferidas incluyen, por ejemplo, cápsulas, tabletas, tabletas revestidas, ampollas, supositorios y formas para pulverización nasal.

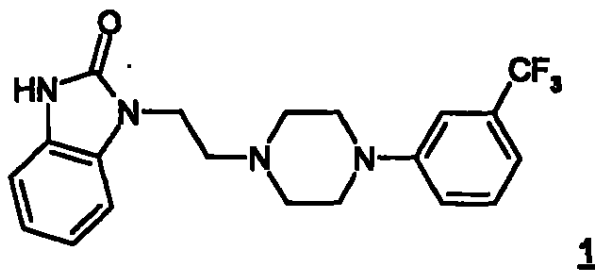
El ingrediente activo puede ser incorporado a excipientes o vehículos convencionalmente usados en composiciones farmacéuticas, tales como, por ejemplo, talco, goma arábiga, lactosa, gelatina, estearato de magnesio, almidón de maíz, vehículos acuosos o no acuosos, polivinilpirrolidona, glicéridos semisintéticos de ácidos grasos, cloruro de benzalconio, fosfato de sodio, EDTA y polisorbato 80. Las composiciones son ventajosamente formuladas en unidades de dosificación, estando cada unidad de dosificación adaptada para proporcionar una sola dosis del ingrediente activo. Cada unidad de dosificación puede contener convenientemente de 0,01 mg a 100 mg, preferiblemente de 0,1 a 50 mg.

30

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Reivindicaciones

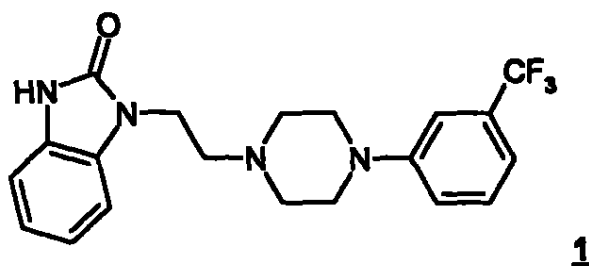
1) El compuesto polimorfo A cristalino (forma A) de filbanserina 1,



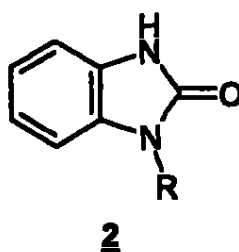
que tiene un máximo endotérmico a 161°C que se produce durante un análisis térmico usando DSC.

5 2) La filbanserina 1 que comprende la forma A de acuerdo con la reivindicación 1.

3) Un procedimiento para la preparación industrial de filbanserina 1 de acuerdo con la reivindicación 1 ó 2,

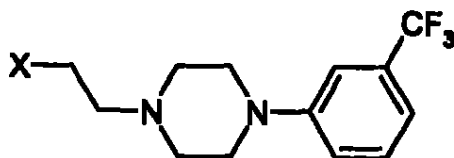


10 caracterizado porque, en una primera operación de reacción, una benzolimidazolona 2



en la que R representa un grupo protector de aminas adecuado, es hecha reaccionar con una piperazina 3

74



3

en la que X es un grupo lábil seleccionado entre cloro, bromo, yodo, metano-
sulfonato, trifluorometanosulfonato y para-toluenosulfonato, en un disolvente
adecuado seleccionado entre agua, alcoholes, mezclas de agua con alcoholes,
5 disolventes apróticos polares y mezclas de los mismos con agua, en presencia
de una base adecuada, y porque, en una segunda operación de reacción, el
grupo protector R de aminas es escindido bajo unas condiciones de escisión
adecuadas.

4) Un procedimiento de acuerdo con la reivindicación 3, caracteri-
10 zado porque la reacción de **2** con **3** es llevada a cabo a una temperatura de al
menos 50°C.

5) Un procedimiento de acuerdo con la reivindicación 4, caracteri-
zado porque el calentamiento es llevado a cabo durante un periodo de aproxi-
madamente 10 minutos a aproximadamente 12 horas.

15 6) El compuesto polimorfo A de flibanserina **1** obtenible de acuer-
do con una de las reivindicaciones 3 a 5.

7) El compuesto polimorfo A de flibanserina **1** de acuerdo con una
de las reivindicaciones 1, 2 y 6, para uso como un medicamento.

8) Uso del compuesto polimorfo A de flibanserina **1** de acuerdo con
20 una de las reivindicaciones 1, 2 y 6 para preparar un medicamento para tratar
enfermedades en que el uso de cantidades terapéuticas eficaces de compuestos
que presentan afinidad por los receptores 5-HT_{1A} y 5-HT₂ presenta un beneficio
terapéutico.

9) Uso del compuesto polimorfo A de flibanserina **1** de acuerdo con
25 una de las reivindicaciones 1, 2 y 6, para preparar un medicamento para tratar
una enfermedad seleccionada entre depresión, esquizofrenia, enfermedad de
Parkinson, ansiedad, alteraciones del sueño, trastornos sexuales y mentales, y
deterioro de la memoria asociado con la edad.

25

- 16 -

10) Composiciones farmacéuticas que comprenden un compuesto polimorfo A de flibanserina de acuerdo con una de las reivindicaciones 1, 2 y 6, como un ingrediente activo, opcionalmente en mezcla con uno o más vehículos, agentes diluyentes o excipientes farmacéuticos.

Traducción

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)

76

Referencia del expediente del agente o solicitante CASE 1/1-1232-PCT	PARA ACTUACIONES ADICIONALES	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)
Solicitud internacional No. PCT/EP02/08466	Fecha de presentación internacional (día/mes/año) 30/07/2002	Fecha de prioridad (día/mes/año) 02/08/2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07D 403/06		
Solicitante BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al.		

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.

2. Este INFORME consta de una total de 5 hojas, incluyendo la portada

☐ Este informe también se acompaña de ANEXOS, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

Estos anexos constan de un total de _____ hojas.

3. Este informe contiene indicaciones relativas a los siguientes aspectos:

I ☒ Fundamentos del informe

II ☐ Prioridad

III ☐ No se establece concepto relativo a la novedad, nivel inventivo y aplicación industrial

IV ☐ Carencia de unidad de la invención

V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración

VI ☐ Ciertos documentos citados

VII ☐ Ciertos defectos de la solicitud internacional

VIII ☐ Ciertas observaciones respecto a la solicitud internacional

Fecha de presentación de la demanda 16/01/2003	Fecha de terminación de este reporte 13.05.2003
Nombre y dirección de correo de la autoridad encargada del examen preliminar  Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tlx 523836 epmu d Fax: +49 89 2399 - 4465	Funcionario Autorizado Baston, E Teléfono No. +49 89 2399-2792

Formato PCT/IPEA409 (portada) (julio 1998)

77

I. Base del Informe

1. Respecto a los elementos de la solicitud internacional *(Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se refieren en este informe como "originalmente presentadas" y no se anexan a este informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17))*:

La descripción:

páginas 1-11, como se presentaron originalmente

Las reivindicaciones:

Números 1-10, como se presentaron originalmente

Los Dibujos:

Páginas 1/1, como se presentaron originalmente

2. Respecto al lenguaje, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje _____ el cual es:

- ☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).
☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).
☐ el lenguaje de la traducción entregada con propósitos del examen preliminar Internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier secuencia de nucleótido y/o amino ácidos divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

- ☐ contenido en la solicitud internacional en forma escrita
☐ presentado junto con la solicitud internacional en forma legible por computador
☐ entregado posteriormente a esta Administración en forma legible por computador
☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.
☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. ☐ Las modificaciones han dado como resultado la cancelación de:

- ☐ la descripción, páginas _____,
☐ las reivindicaciones, Nos. _____,
☐ los dibujos, página _____.

5. ☐ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)).

(Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este informe)

78

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

Novedad (N)	SI	Reivindicaciones	1-10
	NO	Reivindicaciones	
Nivel Inventivo (NI)	SI	Reivindicaciones	1-10
	NO	Reivindicaciones	
Aplicación Industrial (AI)	SI	Reivindicaciones	1-10
	NO	Reivindicaciones	

2. Citas y explicaciones

Ver Hoja Separada

Sección V

Los siguientes documentos fueron citados en el reporte de búsqueda y fueron considerados para el examen de la presente solicitud:

- D1: EP-A-0 526 434 (BOEHRINGER INGELHEIM MSTER) 3 de Febrero de 1993.
- D2: BORSINI F ET AL: 'BIMT 17, UN ANTAGONISTA DEL RECEPTOR 5-HT_{2A} Y MSTERDAM AGONISTA DEL RECEPTOR 5-HT_{1A} EN LA CORTEZA MSTERDA DE RATA' NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 532, no, Septiembre de 1995, páginas 276-282,
- D3: GIRON ET AL; 'Análisis térmico y métodos calorimétricos en la caracterización de polimorfos y solvatos' THERMOCHIMICA ACTA, ELSEVIER SCIENCE PUBLISHERS, MSTERDAM, nl, vol. 248, 1995, páginas 1-59,
- D4: BERNSTEIN, J. ET AL.: 'Polimorfos concomitantes' ANGEWANDTE CEIME, INT. ED., 1999, páginas 3441-3461.

1. La presente solicitud se relaciona con un polimorfo estable de 1-[2-(4-(3-fluorometil-fenil)piperazin-1-il)etil]-2,3-dihidro-1H-benzimidazol-2-ona (flibanserina), el cual tiene afinidad por los receptores 5-HT_{1A} y 5-HT₂. Esta actividad es considerada útil en el tratamiento de por ejemplo: la depresión, Parkinson o la ansiedad.

2. La flibanserina es conocida a partir del documento D1 (comparar página 17, ejemplo 3) y D2 (figura 1). D1 divulga una forma cristalina de este compuesto con un punto de fusión específico de 230-231°C. El polimorfo reivindicado aquí tiene un punto de fusión de 161°C y así puede distinguirse claramente de lo divulgado por D1 (Art. 33(2)PCT). Además, el solicitante considera importante que D1 divulga el clorhidrato de la estructura, mientras la presente solicitud se relaciona con un polimorfo de el "compuesto libre".

3. En relación con los documentos D3 y D4, se reconoce que los polimorfos pueden revelar propiedades fisicoquímicas o farmacocinéticas distintivas. El solicitante

proporcionó argumentos y datos que revelan que el compuesto reivindicado puede absorber una cantidad mucho menor de humedad en contraste con el clorhidrato conocido de D1. Se concluye así que el polimorfo nuevamente desarrollado es ventajoso para los propósitos de formulación de medicamentos (control de peso). Se reconoce el alcance del nivel inventivo (Art. 33(3)PCT).



FORMATO DE DIGITALIZACION
RELACION DE ANEXOS



Royal
Technologies S.A.
Imágenes, Gráficos, Fotografías y más

81

Expediente No		0496766.	No de Folio
Item		No de unidades	
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA	1	
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:

Arte final

82 82

NIT : 800176089-2

SUPERINTENDENCIA Y COORDINACION
Radicación : 80016766 00000000 Folios: 62
Fecha (Año): 2004-02-23 17:23:23
Trámite : 011 PCT-PATENTE 379 FASE NULI 411 Presente
Dependencia: 3620 DIVISION DE MARCAS COMERCIALES

RECIBO OFICIAL DE CAJA : 04 - 13,874
FECHA : FEBRERO 23 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	20338545	23/02/2004	17,945,800.00

***** C O N C E P T O *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	\$ 422,000.00

SOM: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____ 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

06014058-841-001-3

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	(/)
MÓDELO DE UTILIDAD	()	(/)
- Indicación de que se solicita la concesión de una patente.	()	(/)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	(/)
- Descripción de la invención.	()	(/)
- Dibujos de ser estos pertinentes.	()	(/)
- Comprobante de Pago de las tasas establecidas.	()	(/)
COMPLETA ()		INCOMPLETA ()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()		INCOMPLETA ()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()		INCOMPLETA ()

Firma Responsable: *Claudia M. Neiva*

Fecha:

25 84

**Industria y Comercio**

SUPERINTENDENCIA

Radicación 04-016766

Fecha 25-02-2004



04 016766 00

PETITORIO

SUPERINDUSTRIA Y COMERCIO

Radicación : 04016766 00000000

Folios 02 3n

Fecha (AÑO): 2004-02-25 17:23:25

Trámite : 011 PCT-PATENT 379 FASE NAC 411 PRESENTAR

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE**PCT**

Fecha

ENTRADA EN FASE NACIONAL**SOLICITUD DE:**

1

☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☐ Capítulo I.☒ Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: **BIDACHEM S. P. A.**
sociedad constituida y existente bajo las
leyes de Italia
Dirección: Strada Statale 11
(Pandana Sup.) N. 8
I-24040 Formovo s Giovanni
Bergamo
Italia
Domicilio: Formovo s Giovanni
Bergamo, Italia

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

3

**REPRESENTANTE
O APODERADO**

Nombre: **EMILIO FERRERO**
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 38 11
Fax: 217 92 11
E-mail: clientes@camyo.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número 438.019 T.P 31.929

4

**INVENTOR (ES)
(72)**

1. **Carlo BOMBARDA**
12912 Nightingale CT,
Chester, Virginia 23836,
Estados Unidos de América

2. **Enrica DUBINI**
Via Ludovico Muratori, 54
I-20135 Milano
Italia

3. **Antoine EZHAYA**
Via Oglia, 6
I-ZIP 20141
Italia

5

PCT (86)Solicitud Internacional No. PCT/EP02/08466Fecha: 30 de Julio de 2002Publicación Internacional No. WO 03/014079 A1Fecha : 20 de Febrero de 2003

6

Título (54)

COMPUESTO POLIMORFO ESTABLE DE FLIBANSERINA, PROCEDIMIENTO
INDUSTRIAL PARA SU PREPARACIÓN, Y USO DEL MISMO PARA PREPARAR
MEDICAMENTOS

7

Clasificación Internacional (51)C07D 40/360, A61K 31/495, A61P 25/00

8685

8	Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	SI ☒ NO ☐	EP	2 de Agosto de 2001	01118593.1
		EP	19 de Diciembre de 2001	01130180.1

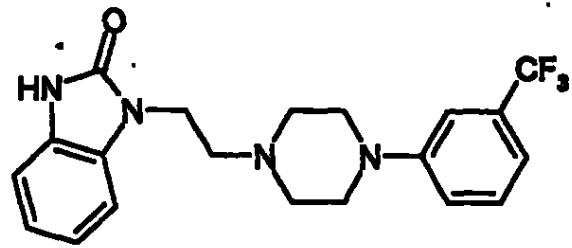
9	Comprobante de pago No.: 04 - 13.874 Fecha: Febrero 23 de 2004
----------	--

10	Anexos:
☒	Comprobante de pago de la tasa de presentación de la solicitud por \$ 422.000.00.
☐	Comprobante de pago por reivindicación de prioridad.
☐	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
☐	Poderes, si fuere el caso.
☐	Documento de cesión del inventor al solicitante o a su causante.
☐	Declaraciones.
☒	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
☒	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
☒	Copia del examen preliminar efectuado por la IPEA.
☒	Traducción del examen preliminar efectuado por la IPEA.
☐	De ser el caso, copia del contrato de acceso.
☐	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
☐	De ser el caso, certificado de depósito del material biológico.
☒	Arte final 12x12
☐	De ser el caso, Información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
☒	Otros
	FORMA PCT/IB/306 NOTIFICACIÓN DEL REGISTRO DE UN CAMBIO (NOTIFICATION OF THE RECORDING OF A CHANGE): CAMBIO DE NOMBRE DEL SOLICITANTE Y CAMBIO DE DOMICILIO DE INVENTOR

86

Reivindicaciones

1) El compuesto polimorfo A cristalino (forma A) de filbanserina **1**,

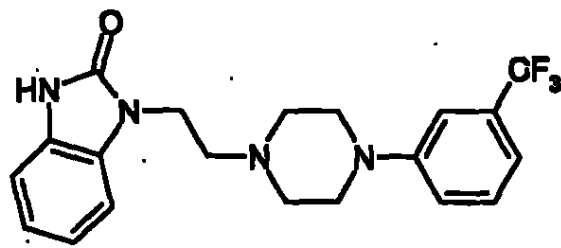


1

que tiene un máximo endotérmico a 161°C que se produce durante un análisis térmico usando DSC.

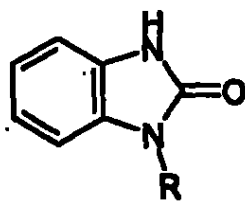
5 2) La filbanserina **1** que comprende la forma A de acuerdo con la reivindicación 1.

3) Un procedimiento para la preparación industrial de filbanserina **1** de acuerdo con la reivindicación 1 ó 2,



1

10 caracterizado porque, en una primera operación de reacción, una benzimidazolona **2**



2

en la que R representa un grupo protector de aminos adecuado, es hecha reaccionar con una piperazina **3**



48
8

2020
Bogotá, D.C.,

Doctor:
EMILIO FERRERO
Apoderado
BIDACHEM S.P.A

Oficio N°03494

ASUNTO:	Radicación N°	04-16788
	Solicitud Internacional	PCT/EP02/08488
	Fecha inicio fase nacional	02/03/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ❑ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 28-k) Decisión 486).
- ❑ La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.
- ❑ El solicitante referido en la solicitud internacional es diferente al referido en la solicitud nacional. Anexar documentos para aclarar.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 8-2-ABR-2004