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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2005 (17.11.2005)

PCT

(10) International Publication Number
WO 2005/108395 A1

(51) International Patent Classification[7]: C07D 417/12, A61K 31/496

(21) International Application Number: PCT/EP2005/052091

(22) International Filing Date: 10 May 2005 (10.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2004A000944 11 May 2004 (11.05.2004) IT

(71) Applicants *(for all designated States except US)*: **DIPHARMA S.p.A.** [IT/IT]; Via XXIV Maggio 40, I-33036 MERETO DI TOMBA (IT). **LUNDBECK PHARMACEUTICALS ITALY S.P.A.** [IT/IT]; Via Quarta Strada 2, I-35129 PADOVA (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VENTIMIGLIA, Gianpiero** [IT/IT]; Via Pirandello 1/A, I-20092 CINISELLO BALSAMO (IT). **ALLEGRINI, Pietro** [IT/IT]; Via Gorizia 1, I-20097 SAN DONATO MILANESE (IT). **CASTALDI, Graziano** [IT/IT]; Via Martiri della Libertà 22/A, I-28072 BRIONA (IT).

(74) Agents: **APPOLONI, Romano** et al.; Notarbartolo & Gervasi S.p.a., Corso di Porta Vittoria 9, I-20122 Milan (IT).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ZIPRASIDONE HYDROCHLORIDE POLYMORPH AND PROCESS FOR ITS PREPARATION

(57) Abstract: New crystalline form of ziprasidone hydrochloride hemihydrate, process for its preparation, its use for the purification of ziprasidone, its pharmaceutical compositions and their use in therapy.

WO 2005/108395 A1

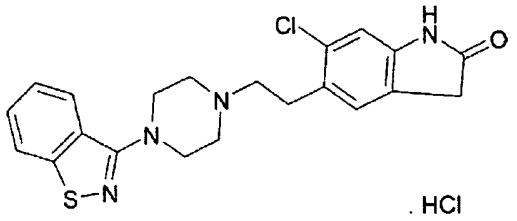
ZIPRASIDONE HYDROCHLORIDE POLYMORPH AND PROCESS FOR ITS PREPARATION

Field of the invention

The present invention relates to a new polymorphic form of ziprasidone hydrochloride, in particular its approximately hemihydrate crystalline form, a process for its preparation, its pharmaceutical composition and its use in therapy. The invention also provides a method for purifying a crystalline form of ziprasidone hydrochloride monohydrate, hemihydrate or anhydrate using said new approximately hemihydrate crystalline form.

Prior art

Ziprasidone hydrochloride, 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride, having the following formula,



is known from US 4,831,031 and is used in medicine as an antipsychotic drug.

Ziprasidone hydrochloride, as referred to in US 5,312,925, is known to exist in three different crystalline forms: the first is a monohydrate form having a water content equal to 3.97% by weight and characterised by the X-ray powder diffraction spectrum, XRPD, shown in figure 1 of the accompanying drawing; the second is a hemihydrate form, characterised by a water content equal to 2.55% by weight and by the X-ray powder diffraction spectrum shown in figure 2 of the accompanying drawings; the third is a substantially anhydrous crystalline form, indicated here as "crystalline anhydrate" for brevity, with a water content equal to 0.13% by weight characterised by the X-ray powder diffraction spectrum shown in figure 3 of the accompanying drawings.

Summary of the invention

In accordance with the present invention, it has now been found that ziprasidone

hydrochloride can also exist, in addition to said known crystalline monohydrate, hemihydrate and anhydrate forms, in a new approximately hemihydrate polymorphic form being stable at ambient temperature. A first aspect of the invention is therefore a new approximately hemihydrate crystalline form of ziprasidone hydrochloride, characterised by having a XRPD spectrum wherein the most intense diffraction peaks are found at 7.44; 12.60; 13.89; 17.88; 20.94 and 25.98 in 2θ.

An aspect of the invention described herein is also a process for preparing said approximately hemihydrate form of ziprasidone hydrochloride.

A further aspect of the invention is the use of the new approximately hemihydrate crystalline form of ziprasidone hydrochloride as intermediate in a method for purifying ziprasidone hydrochloride to obtain crystalline ziprasidone hydrochloride monohydrate, hemihydrate and anhydrate of a quality suitable for therapeutic use.

As a final aspect the invention also provides a pharmaceutical composition comprising at least one diluent and/or carrier and, as active principle, said new approximately hemihydrate crystalline form of ziprasidone hydrochloride and optionally at least one of the other known crystalline forms, and its use in therapy.

X-ray powder diffraction, XRPD, was also used to characterise the new crystalline form of the invention. Moreover, the water content of the compound under examination was determined by titration with the known Karl-Fischer method and the chloride content of the product was titrated potentiometrically. The X-ray diffraction spectra (XRPD) were gathered with a θ/θ automated powder and liquid diffractometer, an APD–2000 from the Ital-Structures company, under the following operative conditions: CuKα radiation (λ = 1.5418 Å), scanning with angular step size of 0.03° for a 1 second period.

Brief description of the figures

The figures of the accompanying illustrations show:

Figure 1. XRPD spectrum of ziprasidone hydrochloride monohydrate known from US 5,312,925.

Figure 2. XRPD spectrum of ziprasidone hydrochloride hemihydrate known from US 5,312,925 wherein the most intense diffraction peaks are found at 11.28;

18.09; 19.47; 23.67 and 26.16 in 2θ.

Figure 3. XRPD spectrum of ziprasidone hydrochloride anhydrate known from US 5,312,925.

Figure 4. XRPD spectrum of the new polymorphic approximately hemihydrate form of ziprasidone hydrochloride of the invention wherein the most intense diffraction peaks are found at 7.44; 12.60; 13.89; 17.88; 20.94 and 25.98 in 2θ.

Detailed description of the invention

Therefore, a first aspect of the present invention is the new approximately hemihydrate crystalline form of ziprasidone hydrochloride, having a XRPD spectrum as shown in said in figure 4, wherein the most intense diffraction peaks are found at 7.44; 12.60; 13.89; 17.88; 20.94 and 25.98 in 2θ.

In accordance with the present invention, the term "approximately hemihydrate" means that the crystalline solid has a water content of about 0.4 to 0.6 moles per mole of ziprasidone hydrochloride, preferably between about 0.45 and 0.55 moles.

A further aspect of the present invention is a process for preparing said approximately hemihydrate crystalline form of ziprasidone hydrochloride, comprising the preparation of a solution or suspension of ziprasidone free base in an organic solvent in the presence of water and the subsequent precipitation of said approximately hemihydrate crystalline form of ziprasidone hydrochloride by the addition of hydrochloric acid. Ziprasidone free base can be dissolved or suspended in the organic solvent in the presence of water; or it can be prepared directly in situ, for example by synthesising it in the same solvent according to one of the known preparation methods. Preferably ziprasidone free base is dissolved or suspended in a suitable organic solvent or in a mixture of organic solvents in the presence of water before adding the hydrochloric acid. Examples of organic solvent are ethers, such as diisopropyl ether, diethyl ether, tetrahydrofuran, dioxane, methyl t-butyl ether. Examples of preferred solvents are tetrahydrofuran and dioxane.

The percentage of water with respect to organic solvent is between about 0.05 and 95% v/v, preferably between about 0.1 and 5% v/v. The concentration of

ziprasidone free base in the starting solution can be between about 1 and 70% w/w, preferably between 5 and 40%. From the solution or from the resultant suspension the approximately hemihydrate ziprasidone hydrochloride can be obtained by adding hydrochloric acid in gaseous form or as a solution in water or an organic solvent. After cooling the solution or the resultant suspension, the approximately hemihydrate ziprasidone hydrochloride of the present invention is recovered by filtering, washing with the same solvent as used in the reaction and drying under vacuum until constant weight is achieved. The drying temperature of the product obtained depends on the solvent used in the process and is between 0°C and the boiling point of the solvent used, preferably between 20 and 70°C.

Approximately hemihydrate ziprasidone hydrochloride can be used for the treatment of pathologies in which ziprasidone hydrochloride is used, for example as described in US 4,831,031.

The invention also provides a pharmaceutical composition comprising ziprasidone hydrochloride in an approximately hemihydrate crystalline form, optionally at least one of ziprasidone hydrochloride, ziprasidone hydrochloride monohydrate, ziprasidone hydrochloride hemihydrate and ziprasidone hydrochloride anhydrate as active principle, and at least one excipient and/or carrier.

A pharmaceutical composition in accordance with the invention can be formulated with known methods in any pharmaceutical form known for administering to mammals, including humans.

The dosage of the active ingredient for instance in the capsules, tablets, sugar coated tablets or other pharmaceutical forms for unitary oral administration may range from about 15 to about 80 mg.

A further aspect of the present invention comprises a method for purifying known crystalline forms of ziprasidone hydrochloride monohydrate, hemihydrate and anhydrate, comprising converting said forms into the new approximately hemihydrate crystalline form and reconverting this latter into ziprasidone hydrochloride monohydrate, hemihydrate and anhydrate, respectively.

In accordance with this process, the known ziprasidone hydrochloride monohydrate, hemihydrate and anhydrate are used as the starting materials for

preparing a solution or a suspension of ziprasidone hydrochloride free base from which the new approximately hemihydrate crystalline form is obtained. A solution of this latter is in turn the starting material for obtaining the known ziprasidone hydrochloride monohydrate, hemihydrate or anhydrate, in accordance with known methods, for example from US 5,312,926. The process used for preparing the new approximately hemihydrate crystalline form in fact enables the product to be purified from the impurities formed during the course of the synthesis process due to parasitic reactions and degradation of the product itself. Ziprasidone hydrochloride monohydrate, hemihydrate and anhydrate are therefore obtained at good yields and with a high degree of purity, being at least higher than 99.5%, thus satisfying the usual requirement established by the regulations governing the preparation of galenic formulations.

Interest in the new crystalline form therefore appears at the moment to lie, for example but not limited thereto, in a useful application in pharmaceutical technology.

The following non limiting example illustrates the invention.

EXAMPLE - Preparation of the approximately hemihydrate form of ziprasidone hydrochloride

3g ziprasidone free base (7.3 mmoles; water content according to Karl-Fischer method: 1.21%) and 50 ml of tetrahydrofuran are introduced into a 100 ml flask, equipped with a magnetic stirrer and dropping funnel and the suspension is heated to a temperature of 35°C. Then gaseous HCl, obtained by adding 96% H_2SO_4 into 37% HCl drop-wise, are bubbled into the suspension for 15 minutes. At the end of the acid addition, the suspension is left to cool to ambient temperature and filtered through a Buckner, finally drying the product under vacuum in an oven at a temperature of 50°C. 2.8 g of product are obtained (yield: 84.7%). M.p..:>290°C (dec.) Chloride content (by potentiometric titration): 7.35%. Water content (by Karl-Fischer method):2.07%.

CLAIMS

1. Approximately hemihydrate crystalline form of ziprasidone hydrochloride characterised by having an XRPD spectrum wherein the most intense diffraction peaks are found at 7.44; 12.60; 13.89; 17.88; 20.94 and 25.98 in 2θ.

2. Crystalline form as claimed in claim 1 having an XPRD spectrum as shown in figure 4 of the accompanying drawings.

3. Crystalline form as claimed in claim 1 wherein the water content is within the range 0.4 – 0.6 moles per mole of ziprasidone hydrochloride.

4. Process for preparing the crystalline form of ziprasidone hydrochloride as claimed in claim 1, comprising the preparation of a solution or suspension of ziprasidone free base in an organic solvent in the presence of water and the subsequent precipitation of said approximately hemihydrate crystalline form by the addition of hydrochloric acid.

5. Process as claimed in claim 4, wherein the quantity of water compared to said organic solvent is between 0.05% and 95% v/v.

6. Process as claimed in claim 4, wherein the concentration of ziprasidone free base in the starting solution or suspension is between 1 and 70% w/w.

7. Pharmaceutical composition comprising as active principle ziprasidone hydrochloride in an approximately hemihydrate crystalline form as claimed in claim 1, and optionally at least one of ziprasidone hydrochloride, ziprasidone hydrochloride monohydrate, hemihydrate or anhydrate, and at least one excipient and/or carrier.

8. Purification method of a crystalline form of ziprasidone hydrochloride monohydrate, hemihydrate or anhydrate, comprising converting said form into the approximately hemihydrate crystalline form as claimed in claim 1 or 2, and reconverting this latter into ziprasidone hydrochloride monohydrate, hemihydrate or anhydrate, respectively.

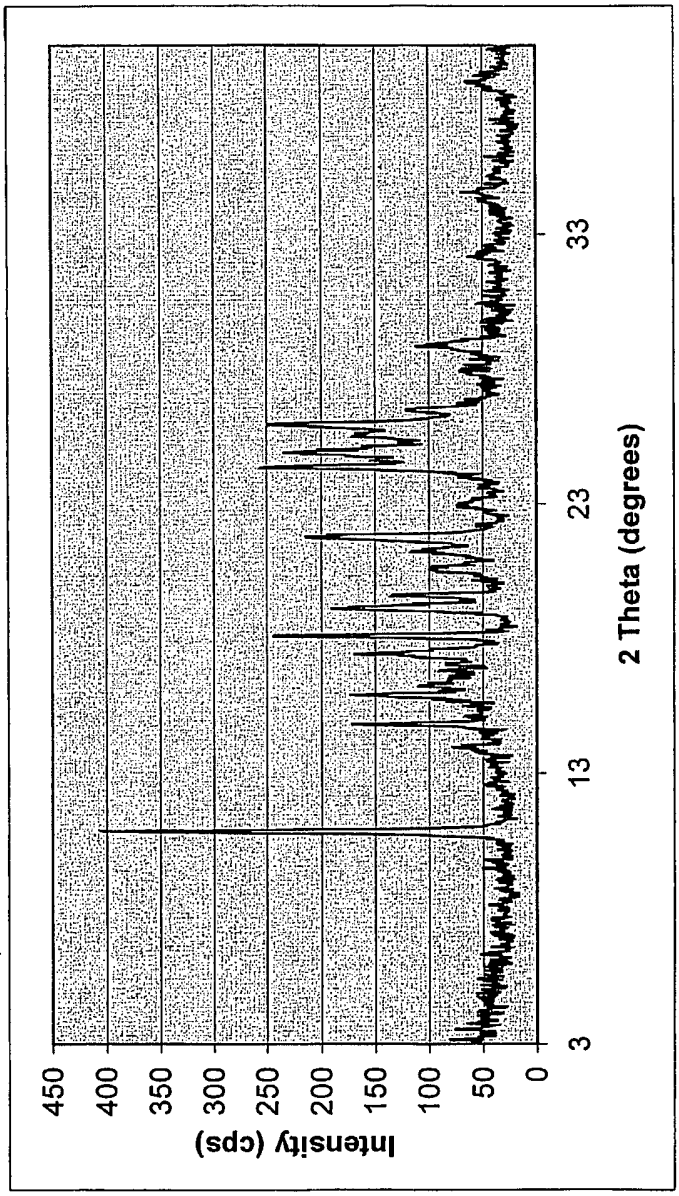

Intensity (cps)
450
400
350
300
250
200
150
100
50
0
3
13
23
33
2 Theta (degrees)

Figure 1

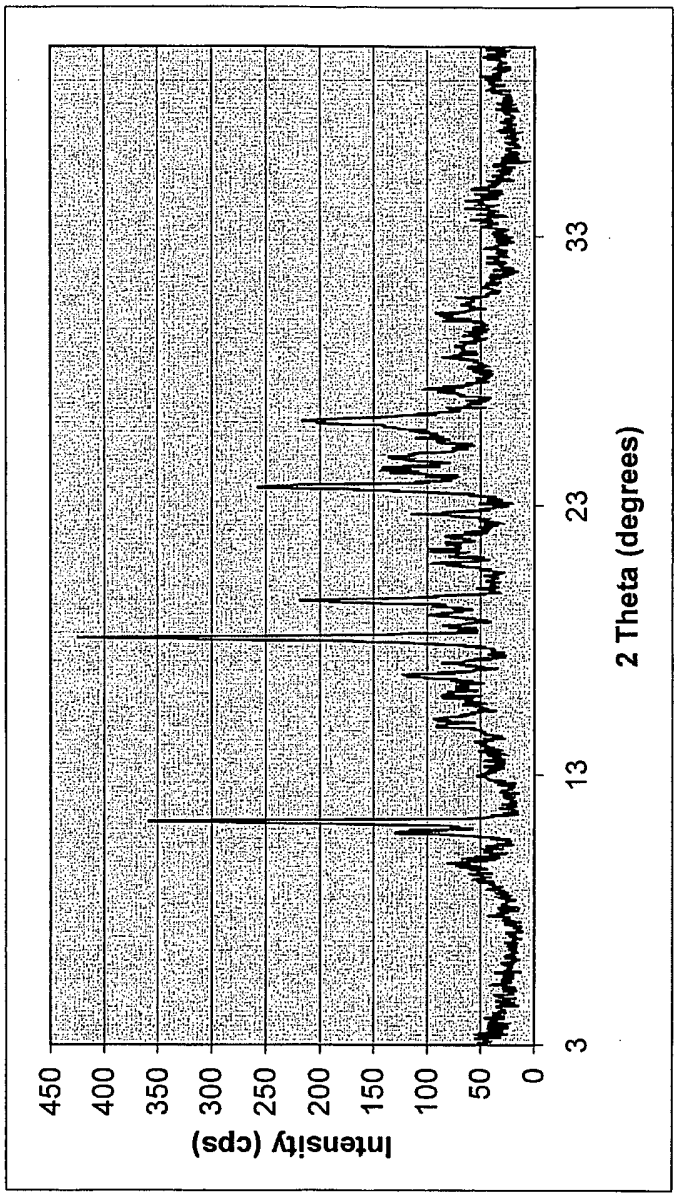

Intensity (cps)
450
400
350
300
250
200
150
100
50
0
3
13
23
33
2 Theta (degrees)

Figure 2

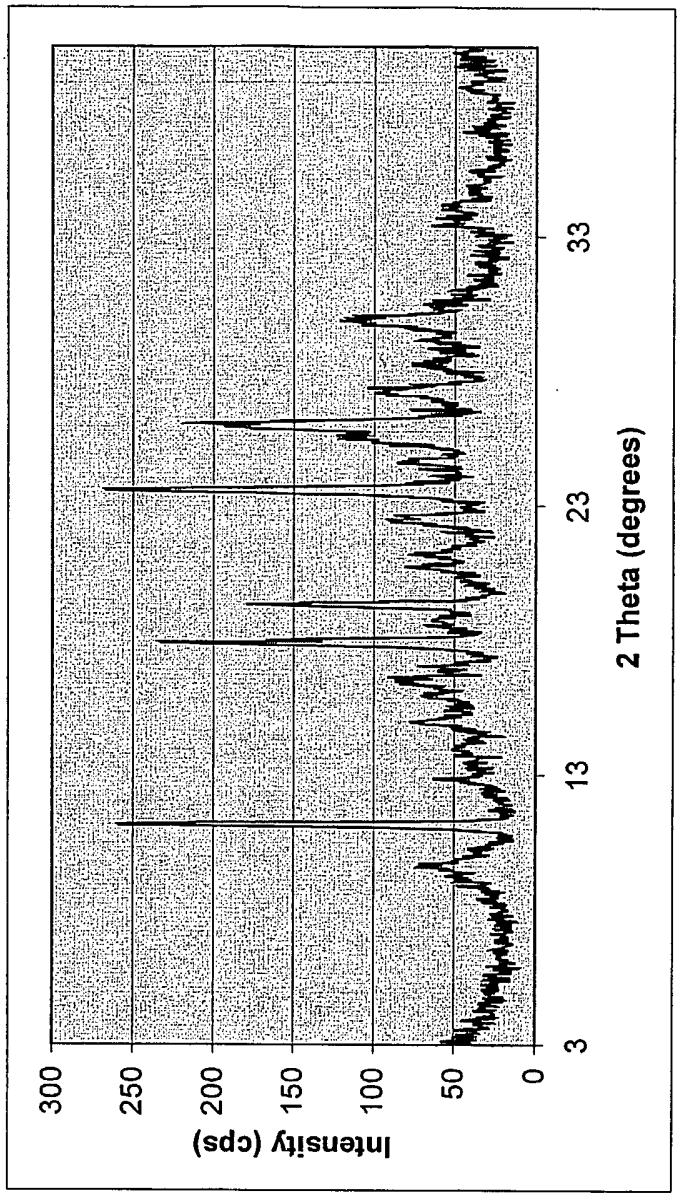

Intensity (cps)
300
250
200
150
100
50
0
3
13
23
33
2 Theta (degrees)

Figure 3

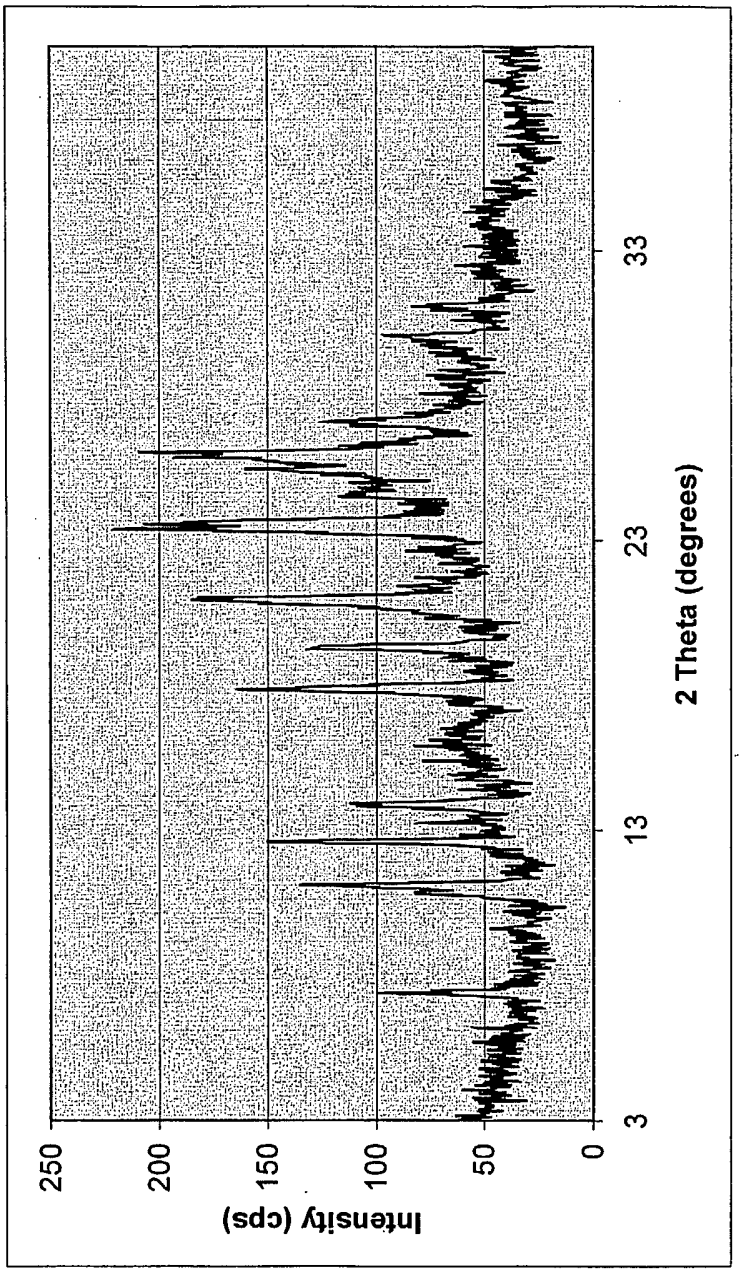


Figure 4

INTERNATIONAL SEARCH REPORT

PCT/EP2005/052091

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61K31/496

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 312 925 A (ALLEN ET AL) 17 May 1994 (1994-05-17) cited in the application claims; examples 1-3	1,4,7
A	US 4 831 031 A (J. A. LOWE, III ET AL) 16 May 1989 (1989-05-16) cited in the application column 12, line 21 - line 39 column 13, line 13 - line 17 claims 1,4,5,8,9	1,7
A	EP 0 584 903 A (PFIZER INC) 2 March 1994 (1994-03-02) example 1	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] 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 referring 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2005	07/09/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

INTERNATIONAL SEARCH REPORT

PCT/EP2005/052091

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/089948 A (HETERO DRUGS LIMITED; PARTHASARADHI, REDDY, BANDI; RATHNAKAR, REDDY, K) 21 October 2004 (2004-10-21) examples 1-4	4
A,P	WO 2005/016325 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; MEN) 24 February 2005 (2005-02-24) claims; examples	1,7

INTERNATIONAL SEARCH REPORT

PCT/EP2005/052091

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5312925 A	17-05-1994	AU 657231 B2	02-03-1995
		AU 4600493 A	16-06-1994
		BR 9303014 A	15-03-1994
		CA 2095587 A1	27-02-1994
		CA 2105114 A1	02-03-1994
		CN 1089607 A ,C	20-07-1994
		CZ 9301789 A3	13-04-1994
		DE 9312903 U1	05-01-1994
		EG 20251 A	31-05-1998
		EP 0586191 A1	09-03-1994
		FI 933804 A	02-03-1994
		HU 67023 A2	30-01-1995
		IL 106777 A	15-04-1997
		JP 2742372 B2	22-04-1998
		JP 6157521 A	03-06-1994
		MX 9305277 A1	31-03-1994
		NO 933093 A	02-03-1994
		NZ 248543 A	26-07-1995
		PL 300235 A1	05-04-1994
		PL 174396 B1	31-07-1998
		RU 2081116 C1	10-06-1997
		TW 422845 B	21-02-2001
		US 5338846 A	16-08-1994
		ZA 9306394 A	28-02-1995
US 4831031 A	16-05-1989	US 4883795 A	28-11-1989
EP 0584903 A	02-03-1994	US 5206366 A	27-04-1993
		AT 273976 T	15-09-2004
		AT 206422 T	15-10-2001
		AU 642836 B1	28-10-1993
		BR 9302065 A	26-07-1994
		CA 2095587 A1	27-02-1994
		CN 1083061 A ,C	02-03-1994
		CZ 9300877 A3	13-04-1994
		DE 69330853 D1	08-11-2001
		DE 69330853 T2	02-05-2002
		DE 69333597 D1	23-09-2004
		DK 584903 T3	03-12-2001
		EG 20214 A	30-11-1997
		EP 1029861 A1	23-08-2000
		EP 0584903 A1	02-03-1994
		ES 2225015 T3	16-03-2005
		ES 2161703 T3	16-12-2001
		FI 932012 A	27-02-1994
		HU 65750 A2	28-07-1994
		IL 105622 A	15-06-1998
		JP 2742370 B2	22-04-1998
		JP 6184143 A	05-07-1994
		KR 123441 B1	24-11-1997
		MX 9302813 A1	28-02-1994
		NO 931656 A	28-02-1994
		NZ 247539 A	26-09-1995
		PL 299002 A1	21-03-1994
		PT 1029861 T	30-11-2004
		PT 584903 T	28-02-2002
		RU 2061695 C1	10-06-1996
		SI 9300287 A	31-03-1994

INTERNATIONAL SEARCH REPORT

PCT/EP2005/052091

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0584903 A		SK 48593 A3	06-04-1994
		US 5338846 A	16-08-1994
		ZA 9306225 A	27-02-1995
WO 2004089948 A	21-10-2004	WO 2004089948 A1	21-10-2004
		AU 2003245027 A1	01-11-2004
		US 2005143396 A1	30-06-2005
WO 2005016325 A	24-02-2005	EP 1530570 A2	18-05-2005
		EP 1546146 A1	29-06-2005
		US 2005059680 A1	17-03-2005
		US 2005043324 A1	24-02-2005
		WO 2005016325 A2	24-02-2005
		WO 2005035531 A1	21-04-2005