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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2012 (27.12.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/176140 A1

(51) **International Patent Classification**:
C07D 401/12 (2006.01) *A61P 1/04* (2006.01)
A61K 31/4439 (2006.01)

(21) **International Application Number**:
PCT/IB2012/053123

(22) **International Filing Date**:
20 June 2012 (20.06.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
1744/DEL/2011 21 June 2011 (21.06.2011) IN

(71) **Applicant** *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Head Office: 12th Floor, Devika Tower, 06 Nehru Place, New Delhi, Delhi 110019 (IN).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **RAY, Anmol, Kumar** [IN/IN]; s/o Sri Shaleshwar RAY, c/o R. P. Srivastava, (I.P.S. Retd.), 194-A, Girnar Colony, Gandhi Path, Queen's Road, Jaipur, Rajasthan 302021 (IN). **MITTAL, Anu** [IN/IN]; 34/5A, B.N. Colony, Pipli, Kurukshetra, Haryana 136131 (IN). **GOTTUMUKKALA, Nagaraju** [IN/IN]; H. No. 6-124, Chinaamiram, Bhimavaram, West Godavari, Andhra Pradesh 534204 (IN). **KHANNA, Mahavir, Singh** [IN/IN]; C-36A, Jitar Nagar, Parwana Road, New Delhi, Delhi 110051 (IN). **THAPER, Rajesh, Kumar** [IN/IN]; Quarter Number 67-68, Roulki Bakshi Nagar, Jammu, Jammu and Kashmir 180001 (IN). **PRASAD, Mohan** [IN/IN]; D-50, Greenwoods City, Sector 46, Gurgaon, Haryana 122003 (IN). **ARORA, Sudershan, Kumar** [IN/IN]; A-3/803, Sahara Grace, M.G. Road, Gurgaon, Haryana 122001 (IN).

(74) **Common Representative**: **RANBAXY LABORATORIES LIMITED**; c/o Dr. B. Vijayaraghavan, Intellectual Property Dept., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2012/176140 A1

(54) **Title**: PROCESS FOR THE PREPARATION OF DEXLANSOPRAZOLE

(57) **Abstract**: The present invention relates to a process for the preparation of dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1, using dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50.

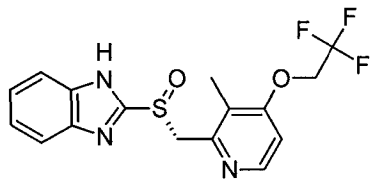
PROCESS FOR THE PREPARATION OF DEXLANSOPRAZOLE

Field of the Invention

The present invention relates to a process for the preparation of dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1.

Background of the Invention

Dexlansoprazole is chemically 2-[(R)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole as represented by Formula I.



FORMULA I

U.S. Patent Nos. 6,462,058, and 7,285,668 and US Patent Application No. 2007/0004779 describe processes for preparing crystalline forms of dexlansoprazole and its hydrates. PCT Publication No. WO 2009/117489 describes a process for the preparation of amorphous dexlansoprazole.

U.S. Patent No. 7,271,182 describes sodium salt, magnesium salt, lithium salt, potassium salt, calcium salt, or barium salt of dexlansoprazole and their preparation method.

U.S. Patent No. 7,169,799 describes processes for preparing crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole·n′H_2O (wherein n′ is about 0 to about 0.1) or a salt thereof by crystallization from an organic solvent solution or suspension in which (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole·nH_2O (wherein n is about 0.1 to about 1.0) or a salt thereof has been dissolved or suspended.

Summary of the Invention

The present inventors have found that the dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50 can be converted into dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1. By employing the present invention, dexlansoprazole.xH_2O, wherein x is

about 0.0 to about 0.1, can also be obtained as chirally and chemically pure material in a consistent manner. Thus, the present invention provides a simple, efficient and industrially preferable process for the preparation of dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1.

Detailed Description of the Invention

One aspect of the present invention provides a process for the preparation of dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50, which comprises:

a) treating a salt of dexlansoprazole with an agent capable of liberating dexlansoprazole as a free base in the presence of a solvent;

b) treating the dexlansoprazole obtained in step a) with water and a solvent selected from the group consisting of halogenated hydrocarbon, ketone, C_{1-3} alkanol, ether and a mixture thereof; and

c) isolating dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50 from the mixture thereof.

The salt of dexlansoprazole used as a starting material may be in any solid form and prepared according to the methods described in U.S. Patent No. 7,271,182. The salt may be, for example, sodium salt of dexlansoprazole. The salt of dexlansoprazole is treated with an agent capable of liberating dexlansoprazole as a free base in the presence of a solvent. The agent capable of liberating dexlansoprazole as a free base may be an acid, for example, hydrochloric acid, amine salt, for example, ammonium halide, or a hydrogen sulfate, for example, sodium or potassium hydrogen sulfate. The solvent used in step a) or step b) may be water, water-miscible solvent, for example, acetone, C_{1-3} alkanol, dioxane, tetrahydrofuran, dimethylformamide, acetonitrile, dimethylsulfoxide or water immiscible solvent, for example, halogenated hydrocarbon, dichloromethane, or a mixture thereof.

The reaction mixture obtained in step a) or step b) may preferably be treated with water, dichloromethane, acetone, or a mixture thereof. The liberation of dexlansoprazole as a free base may be effected by stirring the reaction mixture. The reaction mixture may be treated with ammonia, for example, aqueous ammonia or an alkyl amine, for example, diisopropylethylamine in the presence of a ketone solvent, for example, acetone. The

dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50 obtained as a free base may optionally be isolated by solvent removal.

Another aspect of the present invention provides a process for the preparation of dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1, which comprises:

a) treating a salt of dexlansoprazole with an agent capable of liberating dexlansoprazole as a free base in the presence of a solvent;

b) treating the dexlansoprazole obtained in step a) with water and a solvent selected from the group consisting of C_{4-8} hydrocarbon, halogenated hydrocarbon, ketone, C_{1-3} alkanol, ether and a mixture thereof;

c) isolating dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50 from the mixture thereof; and

d) isolating dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1 by crystallization from solvent, solution or suspensions in which dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50, has been dissolved or suspended.

The salt of dexlansoprazole used as a starting material may be in any solid form and prepared according to the methods described in U.S. Patent No. 7,271,182. The salt may be, for example, sodium salt of dexlansoprazole. The salt of dexlansoprazole is treated with an agent capable of liberating dexlansoprazole as a free base in the presence of a solvent. The agent capable of liberating dexlansoprazole as a free base may be an acid, for example, hydrochloric acid, amine salt, for example, ammonium halide, or a hydrogen sulfate, for example, sodium or potassium hydrogen sulfate. The solvent used in step a) or step b) may be water, water miscible solvent, for example, acetone, C_{1-3} alkanol, dioxane, tetrahydrofuran, dimethylformamide, acetonitrile, dimethylsulfoxide or water immiscible solvent, for example, halogenated hydrocarbon, dichloromethane, or a mixture thereof.

The reaction mixture obtained in step a) or step b) may preferably be treated with water, dichloromethane, acetone or a mixture thereof. The liberation of dexlansoprazole as a free base may be effected by stirring the reaction mixture. The reaction mixture may be treated with ammonia, for example, aqueous ammonia or an alkyl amine, for example,

diisopropylethylamine in the presence of a ketone solvent, for example, acetone. The dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50 obtained as a free base may optionally be isolated by solvent removal.

The dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50 isolated in step c) may be treated with a solvent. The solvent used in step d) may be selected from the group consisting of water, C_{1-7} alkanol, halogenated hydrocarbon, ketone, aliphatic hydrocarbon, cyclic aliphatic hydrocarbon, ether and a mixture thereof. The solvent may be, for example, n-butanol, tertiary-butanol, cyclohexane, dichloromethane, acetone, heptane, methanol, methyl t-butyl ether, diisopropyl ether or a mixture thereof. The treatment with the solvent may be carried out at a temperature of about -30°C to about 60°C, for example, about 15°C to about 45°C. The dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1, may be isolated by filtration, distillation, decantation, vacuum drying, evaporation, or a combination thereof.

Another aspect of the present invention provides a process for the preparation of dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1, which comprises:

a) treating dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50, with a solvent selected from the group consisting of water, C_{1-7} alkanol, aliphatic hydrocarbon, cyclic aliphatic hydrocarbon, halogenated hydrocarbon, ketone, ether and a mixture thereof; and

b) isolating dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1 from the mixture thereof.

The dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50, is treated with a solvent selected from the group consisting of water, C_{1-7} alkanol, halogenated hydrocarbon, ketone, aliphatic hydrocarbon, cyclic aliphatic hydrocarbon, ketone, ether, and a mixture thereof. The solvent may be, for example, n-butanol, tertiary-butanol, cyclohexane, dichloromethane, acetone, heptane, methanol, methyl t-butyl ether, diisopropyl ether, or a mixture thereof. The treatment with the solvent may be carried out at a temperature of about -30°C to about 60°C, for example, about 15°C to about 45°C. The dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1 may be isolated by filtration, distillation, decantation, vacuum drying, evaporation, or a combination thereof.

Another aspect of present invention provides dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1: Preparation of Dexlansoprazole.xH_2O, wherein x is about 27

Dexlansoprazole sodium (300 g) was dissolved in de-ionized water (15 L) at 26°C to 30°C and the pH of the reaction mixture was adjusted to 12.4 to 12.6 using sodium hydroxide (100 g). The reaction mixture was heated to 45°C to 50°C, stirred for 30 minutes and filtered through Celite-bed and filtrate was cooled to 35°C to 38°C. The filtrate was extracted with dichloromethane (2×1200 mL). The pH of the aqueous reaction mixture was adjusted to 7.4 to 7.8 with dropwise addition of 2N hydrochloric acid (1485 mL). The reaction mixture was filtered, washed with water (1500 mL) and added to acetone (900 mL). De-ionized water (300 mL) and aqueous ammonia (22.8 mL) were added to this reaction mixture and heated to 35°C to 38°C. De-ionized water (4.8 L) was added dropwise over a period of 45 minutes to 60 minutes. The reaction mixture was stirred for 3 hours to 4 hours at 35°C to 38°C and the precipitate obtained was filtered and washed with water (600 mL). The precipitate was again added to acetone (900 mL) followed by addition of de-ionized water (300 mL) and aqueous ammonia (22.8 mL). The reaction mixture was heated to 35°C to 38°C. De-ionized water (4.8 L) was added to the reaction mixture drop-wise over a period of 45 minutes to 60 minutes. The reaction mixture was stirred for 3 hours to 4 hours at 35°C to 38°C and the precipitate obtained was filtered and washed with water (600 mL) to obtain the title product.

Yield: 402 g

Moisture: 57.0%

Example 2: Preparation of Dexlansoprazole. xH_2O, wherein x is about 0.0 to about 0.1

Dexlansoprazole (402 g) prepared according to Example 1 was dissolved in dichloromethane (1500 mL) and washed with 5% aqueous sodium chloride solution (1800 mL). Layers obtained were separated and washed with de-ionized water (1800 mL).

Organic layer was separated and filtered through Celite bed followed by washing with dichloromethane (300 mL). Diisopropylethylamine (0.3 g) was added to the combined dichloromethane layer (1800 mL). n-Butanol (360 mL) and activated carbon were added to the reaction mixture and stirred for 30 minutes. The reaction mixture was filtered through celite and a bed of molecular sieve (120 g) to get moisture of organic layer not more than 0.25% w/w. Solvents were recovered completely under vacuum at less than 35°C to get the residue. Cyclohexane (2 x 360 mL) was added to the residue. The cyclohexane was recovered completely from the reaction mixture under vacuum at less than 35°C to get the residue. Cyclohexane (4300 mL) was added to the residue dropwise and the solution was stirred for 4 hours at 25°C to 30°C. The reaction mixture was filtered. Cyclohexane (600 mL) was added to the solid material and the reaction mixture was stirred for 30 minutes at 25°C to 30°C, filtered under nitrogen atmosphere and dried under vacuum at 35°C to 38°C for 10 hours to 12 hours to obtain the title compound.

Yield: 138 g

Moisture: 0.14%

WE CLAIM

1. A process for the preparation of dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50, which comprises:

a) treating a salt of dexlansoprazole with an agent capable of liberating dexlansoprazole as a free base in the presence of a solvent;

b) treating the dexlansoprazole obtained in step a) with water and a solvent selected from the group consisting of halogenated hydrocarbon, ketone, C_{1-3} alkanol, ether and a mixture thereof; and

c) isolating dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50 from the mixture thereof.

2. A process for the preparation of dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1, which comprises:

a) treating a salt of dexlansoprazole with an agent capable of liberating dexlansoprazole as a free base in the presence of a solvent;

b) treating the dexlansoprazole obtained in step a) with water and a solvent selected from the group consisting of C_{4-8} hydrocarbon, halogenated hydrocarbon, ketone, C_{1-3} alkanol, ether and a mixture thereof;

c) isolating dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50 from the mixture thereof; and

d) isolating dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1 by crystallization from solvent, solution or suspensions in which dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50, has been dissolved or suspended.

3. A process according to claim 1 or claim 2, wherein the salt of dexlansoprazole is sodium salt.

4. A process according to claim 1 or claim 2, wherein the agent capable of liberating dexlansoprazole as a free base is an acid, amine salt or hydrogen sulfate.

5. A process according to claim 4, wherein the agent capable of liberating dexlansoprazole is hydrochloric acid.

6. A process according to claim 1 or claim 2, wherein the solvent used in step a) is water, halogenated hydrocarbon, or a mixture thereof.

7. A process according to claim 6, wherein the halogenated hydrocarbon is dichloromethane.

8. A process according to claim 1 or claim 2, wherein the halogenated hydrocarbon used in step b) is dichloromethane.

9. A process according to claim 1 or claim 2, wherein the ketone used in step b) is acetone.

10. A process according to claim 1 or claim 2, wherein the ether used in step b) is tetrahydrofuran.

11. A process according to claim 2, wherein the solvent used in step d) is selected from the group consisting of water, C_{1-7} alkanol, halogenated hydrocarbon, ketone, aliphatic hydrocarbon, cyclic aliphatic hydrocarbon, ether, and a mixture thereof.

12. A process according to claim 11, wherein the solvent used in step d) is n-butanol, tertiary-butanol, cyclohexane, dichloromethane, acetone, heptane, methanol, methyl t-butyl ether, diisopropyl ether, or a mixture thereof.

13. A process for the preparation of dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1, which comprises:

a) treating dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50, with solvent selected from the group consisting of C_{1-7} alkanol, aliphatic hydrocarbon, cyclic aliphatic hydrocarbon, halogenated hydrocarbon, ketone, ether, and a mixture thereof; and

b) isolating dexlansoprazole.xH_2O, wherein x is about 0.0 to about 0.1 from the mixture thereof.

14. A process according to claim 13, wherein the solvent is n-butanol, tertiary-butanol, cyclohexane, dichloromethane, acetone, heptane, methanol, methyl t-butyl ether, diisopropyl ether, or a mixture thereof.

15. Dexlansoprazole.xH_2O, wherein x is about 2.6 to about 50.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053123

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/4439 A61P1/04
ADD.

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)
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 practicable, 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	WO 2009/088857 A1 (TAKEDA PHARMACEUTICAL [JP]; URAKAMI KOJI [JP]; LORIMER KEITH [US]; MEY) 16 July 2009 (2009-07-16)	1,3-10, 15
Y	Dexlansoprazole (H2O)5 :; page 4, line 17 Process for preparation of Dexlansoprazole hydrate comprising the steps b) treating dexlansoprazole free base with water and an organic solvent and c) isolationg dexlansoprazole from the mixture; examples 1, 4-5, 8, 9	1,3-10

-/--

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

[X] See patent family 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 application or patent 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
26 November 2012	04/12/2012

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, Fax: (+31-70) 340-3016	Lange, Tim

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053123

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	CN 102 234 265 A (TIANJIN HANKANG PHARMACEUTICAL BIOTECHNOLOGY CO LTD) 9 November 2011 (2011-11-09) Dexlansoprazole (H2O)2.5 : method for preparation of Dexlansoprazole (H2O)2.5 comprising the steps of b) dissolving Dexlansoprazole in iPrOH, HOAc, H2O, then heat and cool and c) isolating the crystals obtained by filtration; abstract & DATABASE CAPLUS, [Online] 1 January 2011 (2011-01-01), YAN JIE ET AL: "Dexlansoprazole compound used for preparing drugs for treating non-erosive gastroesophageal reflux caused pyrosis and erosive esophagitisns", XP007921005, retrieved from CAPLUS Database accession no. 2011-1451056 abstract	1,3-10, 15
X,P	& DATABASE WPI [Online] THOMSON SCIENTIFIC, LONDON, GB; 9 November 2011 (2011-11-09), Jie Yan, Xin Huang: "Lansoprazole Compound", XP002683198, Database accession no. 2011-Q06061 abstract	1,3-10

X	EP 1 552 833 A1 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 13 July 2005 (2005-07-13) Dexlansoprazole (H2O)0.5 and Dexlansoprazole (H2O)1.5 :; page 14 - page 15; examples 1-2 process for preparation of Dexlansoprazole hydrates comprising steps b) dissolving Dexlansoprazole in acetone/ water and c) isolating the precipitated hydrate; page 14 - page 15	1,3-10

X	WO 2004/018454 A1 (TEVA PHARMA [IL]; TEVA PHARMA [US]; SINGER CLAUDE [IL]; LIBERMAN ANITA) 4 March 2004 (2004-03-04) Process for preparation of Dexlansoprazole with <0.1% water comprising the step d) redissolving "wet" Dexlansoprazole in hot acetone, cool and then isolate Dexlansoprazole with very low water content :; examples 2, 9-16	2-15

	-/--	

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053123

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/095144 A2 (MSN LAB LTD [IN]; SATYANARAYANA REDDY MANNE [IN]; ESWARAIAH SAJJA [IN]) 26 August 2010 (2010-08-26) Process for preparation of Dexlansoprazole hydrates comprising the step: a) treating Dexlansoprazole with an agent (NH3) capable of liberating the free base in presence of solvent (acetone) b) add acetone and aqueous ammonia c) isolating Dexlansoprazole as polyhydrate d) after drying obtain the sesquihydrate; page 26; example 18 Process for preparation of anhydrous Dexlansoprazole comprising the steps: a) dissolving the hydrated form of Dexlansoprazole in solvent mixture of acetone and heptane b) isolating the anhydrous form therefrom; example 17	1-14

Y	"Isolation and Purification Techniques 2.18 General Considerations ED - Vogel A I; Tatchell A R; Furnis B S; Hannaford A J; Smith P W G", 1 January 1996 (1996-01-01), VOGEL'S TEXTBOOK OF PRACTICAL ORGANIC CHEMISTRY, PRENTICE HALL, PAGE(S) 131 - 133, XP002672724, ISBN: 0-582-46236-3 "If the crude solid product contains the required product in the form of a salt..... acidification of the aqeuous solution (or basidification in the case of amine salts) liberates the free acid (or base), which may be recovered by....solvent extraction.."; page 132, paragraph 4th	1,3-10

X	WO 00/78745 A2 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 28 December 2000 (2000-12-28) (Dexlansoprazole)(H2O)5 :; page 2, line 35	15

X,P	WO 2011/121548 A1 (RANBAXY LAB LTD [IN]; MITTAL ANU [IN]; RAY ANMOL KUMAR [IN]; KHANNA MA) 6 October 2011 (2011-10-06) Process for preparation of crystalline Dexlansoprazole with moisture content of 0.1% :; examples 2-3	2-4,6-14

	-/--	

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053123

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2012/104805 A1 (RANBAXY LAB LTD [IN]; RAY ANMOL KUMAR [IN]; MITTAL ANU [IN]; GOTTUMUKK) 9 August 2012 (2012-08-09) Process for preparation of crystalline Dexlansoprazole with moisture content of 0.09% :; example 3 Process for preparation of crystalline Dexlansoprazole with moisture content of ranging from 0.08% tp 0.14% :; examples 4-8	2-14
X	WO 2011/004387 A2 (MATRIX LAB LTD [IN]; JETTI RAMAKOTESWARA RAO; BHAGAVATULA NEELIMA; LAH) 13 January 2011 (2011-01-13) Process for converstion of Dexlansoprazole (H2O)1.5 to Dexlansoprazole (H2O)0.5, the process comprising the step of recrystallization in solvent such as hexane, ether etc. :; claims 15-16	2-14
X,P	WO 2011/092665 A1 (RANBAXY LAB LTD [IN]; RAY ANMOL KUMAR [IN]; KHANNA MAHAVIR SINGH [IN];) 4 August 2011 (2011-08-04) Process for the preparation of anhydrous Dexlansoprazole with moisture content of 0.13% involving recrystallization in antisolvents such as (iPr)2O ether and n-hexane :; example 6	2-4,6-14
X	WO 2010/056059 A2 (HANMI PHARM IND CO LTD [KR]; JANG SUN YOUNG [KR]; KIM TAI WON [KR]; KI) 20 May 2010 (2010-05-20) Reference example 1 produces anhydrous Lansoprazole crystals with 0.4% water content according to example 2 of WO2000/78745, which obtains the anhydrous crystals through recrystalization in antisolvents such as diisopropylether, acetone mixture :; page 11, line 6 - line 14	2-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/053123

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1(completely); 3-10(partially)

   Process for the preparation of Dexlansoprazole-(H2O)x, wherein X is about 2.6-50

   ---

2. claims: 2, 11-14(completely); 3-10(partially)

   Process for the preparation of Dexlansoprazole-(H2O)x, wherein X is about 0-0.1

   ---

3. claim: 15

   Dexlansoprazole-(H2O)x, wherein X is about 2.6-50

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/053123

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009088857 A1	16-07-2009	CA 2676477 A1	16-07-2009
		CA 2738458 A1	16-07-2009
		EP 2227462 A1	15-09-2010
		EP 2292612 A2	09-03-2011
		JP 2011507977 A	10-03-2011
		US 2010286400 A1	11-11-2010
		WO 2009088857 A1	16-07-2009
CN 102234265 A	09-11-2011	NONE	
EP 1552833 A1	13-07-2005	AU 2003273000 A1	04-05-2004
		CA 2502219 A1	29-04-2004
		CA 2771725 A1	29-04-2004
		EP 1552833 A1	13-07-2005
		JP 2010180225 A	19-08-2010
		US 2006057195 A1	16-03-2006
		US 2011020410 A1	27-01-2011
		WO 2004035052 A1	29-04-2004
WO 2004018454 A1	04-03-2004	AT 375338 T	15-10-2007
		AU 2003258335 A1	11-03-2004
		DE 60316791 T2	24-07-2008
		EP 1501824 A1	02-02-2005
		ES 2294358 T3	01-04-2008
		IL 166985 A	15-04-2010
		JP 2006500380 A	05-01-2006
		JP 2010083897 A	15-04-2010
		PT 1501824 E	28-11-2007
		US 2004192923 A1	30-09-2004
		US 2005165059 A1	28-07-2005
		US 2005165060 A1	28-07-2005
		US 2005165061 A1	28-07-2005
		WO 2004018454 A1	04-03-2004
WO 2010095144 A2	26-08-2010	NONE	
WO 0078745 A2	28-12-2000	AR 031069 A1	10-09-2003
		AR 079473 A2	25-01-2012
		AT 391126 T	15-04-2008
		AU 778820 B2	23-12-2004
		AU 5247800 A	09-01-2001
		BR 0011674 A	19-03-2002
		CA 2375201 A1	28-12-2000
		CN 1355798 A	26-06-2002
		DE 60038481 T2	09-04-2009
		DK 1129088 T3	09-06-2008
		EP 1129088 A2	05-09-2001
		EP 1977751 A1	08-10-2008
		EP 2343289 A1	13-07-2011
		ES 2300265 T3	16-06-2008
		HK 1038227 A1	20-06-2008
		HU 0201659 A2	28-11-2002
		IL 145996 A	08-07-2008
		MX PA01012642 A	22-07-2002
		NO 20016087 A	13-12-2001
		NZ 515702 A	25-07-2003
		PL 352193 A1	11-08-2003
		PT 1129088 E	05-05-2008

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/053123

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		SI 1129088 T1	31-08-2008
		TW I275587 B	11-03-2007
		TW I289557 B	11-11-2007
		US 6462058 B1	08-10-2002
		US 2003045724 A1	06-03-2003
		US 2004048898 A1	11-03-2004
		US 2005228026 A1	13-10-2005
		US 2008132547 A1	05-06-2008
		US 2009163553 A1	25-06-2009
		US 2010222391 A1	02-09-2010
		US 2011319450 A1	29-12-2011
		WO 0078745 A2	28-12-2000
		WO 2004083200 A1	30-09-2004
		ZA 200108331 A	10-10-2002
WO 2011121548 A1	06-10-2011	AU 2011234003 A1	01-11-2012
		WO 2011121548 A1	06-10-2011
WO 2012104805 A1	09-08-2012	NONE	
WO 2011004387 A2	13-01-2011	NONE	
WO 2011092665 A1	04-08-2011	AU 2011210328 A1	16-08-2012
		CA 2788147 A1	04-08-2011
		EP 2528912 A1	05-12-2012
		WO 2011092665 A1	04-08-2011
WO 2010056059 A2	20-05-2010	KR 20110086607 A	28-07-2011
		WO 2010056059 A2	20-05-2010