

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 June 2009 (04.06.2009)

PCT

(10) International Publication Number
WO 2009/069014 A1

(51) International Patent Classification:

C07D 411/04 (2006.01) **A61K 31/39** (2006.01)
A61P 31/12 (2006.01)

(21) International Application Number:

PCT/IB2008/051694

(22) International Filing Date: 30 April 2008 (30.04.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

2504/DEL/2007 29 November 2007 (29.11.2007) IN

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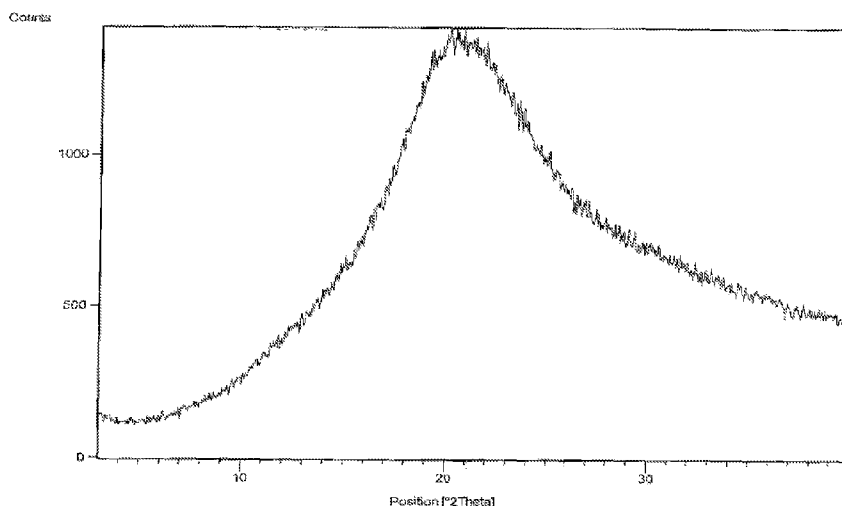
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: AMORPHOUS LAMIVUDINE AND ITS PREPARATION

FIGURE 1



(57) Abstract: The present invention relates to amorphous lamivudine. The present invention further relates to a process for the preparation of amorphous lamivudine by spray drying.

WO 2009/069014 A1



Published:

— *with international search report*

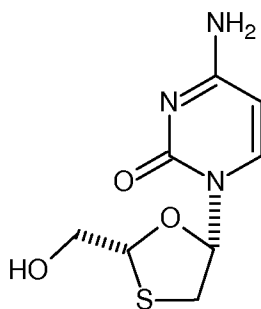
AMORPHOUS LAMIVUDINE AND ITS PREPARATION

Field of the Invention

The present invention relates to amorphous lamivudine. The present invention further relates to a process for the preparation of amorphous lamivudine by spray drying.

Background of the Invention

Lamivudine is a substituted 1,3-oxathiolane and it is presently available in the market as an antiretroviral agent. Lamivudine is a cis-(-)-isomer and it is chemically (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one of Formula I (A) having the structure as depicted below.



FORMULA I

Several processes for the preparation of different polymorphs of lamivudine have been reported. U.S. Patent No. 5,905,082 provides a process for preparing lamivudine by enzymatic separation of (±)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidine-2-one. However, according to US '082 patent, lamivudine so obtained has an enantiomeric excess of only about 90%. The process described is tedious and time-consuming and involves an unstirrable mass that needs manual breaking up followed by multiple washings. The product obtained is referred as Form I which has handling and stability problems. US '082 patent also provides a process of converting Form I to Form II in industrial methylated spirit by seeding.

J. Pharm. Sci., (1996), 85 (2): 193-199 and *J. Chem. Soc., Perkin Trans.*, (1997), 2:2653-2659 provide characterization methods of Form I and Form II by XRPD, DSC, Scanning Electron Micrographs and single crystal analysis.

U.S. Patent No. 6,329,522 provides a process for the purification of lamivudine through the formation of salicylate salt and a crystallization method for lamivudine from isopropyl acetate. However, both the preparation of lamivudine salicylate and crystallization of lamivudine involve seeding, and US '522 patent does not disclose any method to obtain the seed crystals of lamivudine salicylate as well as lamivudine. WO 03/027106 provides a process for preparing Form II of lamivudine from lamivudine salicylate using ethyl acetate and acetonitrile as solvents and triethylamine as a base. However, WO '106 application does not disclose any specific method to obtain lamivudine salicylate.

WO 2007/119248 provides a process for the preparation of Form III of lamivudine. Form III is prepared by dissolving Form II in water by heating to 45°C and subsequent cooling to 30°C. However, the time involved for reducing the temperature from 45°C to 30°C varies from 15 minutes to 1 hour 40 minutes. The mixture so obtained is further stirred at 10°C for 1 hour, filtered and dried in vacuum at 45°C for 24 hours to obtain Form III. The process also involves optional washing with ethanol or industrial methylated spirit. Form III is also prepared by dissolving Form I in water by heating to 45°C and subsequent cooling to 10°C. However, the time involved for reducing the temperature from 45°C to 10°C is 10 minutes. The mixture so obtained is stirred at 10°C for 1 hour, filtered and dried in vacuum at 45°C for 24 h to obtain Form III. Form III is also prepared by stirring a suspension of Form I or Form II in water at 25°C for 24 hours or 48 hours. The mixture is further stirred at 10°C for 1 hour, filtered and dried in vacuum at 45°C for 24 hours to obtain Form III.

WO 2007/119248 application also provides processes for preparing Form I and Form II of lamivudine. Form I is prepared by dissolving lamivudine in water by heating to 45°C and subsequent cooling to 30°C in 0.5 minute. The solid product crystallized as unstirrable mass is broken up, stirred at 10°C, filtered and washed with industrial methylated spirit. The washed material is dried in vacuum at 45°C for 24 hours to obtain Form I. Form I is also prepared in a similar way from a mixture of water and denaturated spirit. However, in this process, the time involved for reducing the temperature from 45°C to 30°C is 12 minutes and it also involves seeding with Form I crystals. The washing at the final step is also carried out with a mixture of water and denaturated spirit. Form II is

prepared refluxing lamivudine in ethanol and partially removing the solvent by distillation. The concentrated solution is cooled to 15°C in 35 minutes, stirred at 15°C for 1 hour, filtered and washed with ethanol. The washed product is dried in vacuum at 50°C for 12 hours to obtain Form II. However, WO '248 application does not disclose any method to
5 obtain starting lamivudine for preparing Form I or Form II.

All reported crystalline forms and processes suffer from one or the other deficiency, especially from a scalability and stability point of view, thus rendering them unsuitable for commercial use.

Summary of the Invention

10 We have found that lamivudine can be prepared in amorphous form. Such amorphous form can be without the contamination of any crystalline form. We have also developed a simple process for the preparation of amorphous lamivudine by spray drying. By employing present process, lamivudine existing in any crystalline form can be converted into amorphous form. The amorphous lamivudine of the present invention is
15 suitable for preparing pharmaceutical compositions comprising lamivudine.

Brief Description of the Figure

Figure 1 is an X-ray powder diffractogram (XRPD) pattern of amorphous lamivudine.

Detailed Description of the Invention

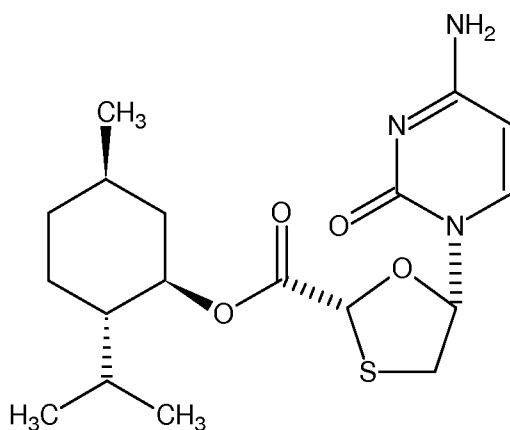
20 In one aspect, amorphous lamivudine is provided. The amorphous lamivudine has an XRPD pattern substantially as provided in Figure 1.

In another aspect, a process for the preparation of amorphous lamivudine is provided,

wherein the process comprises,

- 25 a) dissolving lamivudine in water or an organic solvent, or a mixture thereof,
to obtain a solution, and
- b) removing the solvent from the solution obtained in step a) by spray drying
to obtain amorphous lamivudine.

The lamivudine used as the starting material has a chemical purity of about 98% or above and a chiral purity of about 99% or above. The pure lamivudine used as the starting material can be in any crystalline form and can be prepared by reducing (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (2*R*,5*S*)-5-(4-amino-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylate of Formula II,

**FORMULA II**

The compound of Formula II can be prepared according to the method provided in U.S. Patent No. 5,905,082. The compound of Formula II is reduced in the presence of water or an organic solvent or a mixture thereof, to obtain lamivudine. The organic solvent is preferably selected from the group consisting of alkanols, ethers and esters. The organic solvent is more preferably selected from the group consisting of methanol, ethanol, tetrahydrofuran, dioxane, isopropyl acetate and ethyl acetate. The reduction is carried out by using a reducing agent. The reducing agent is preferably sodium borohydride, lithium aluminium hydride, lithium borohydride, lithium-tri-ethyl borohydride or lithium-tri-sec-butyl borohydride. The reducing agent is more preferably sodium borohydride. The reduction is preferably carried out in the presence of a phosphate or borate buffer. The buffer is preferably dipotassium hydrogen phosphate. The lamivudine is further treated with salicylic acid. The lamivudine salicylate is isolated from the reaction mixture without the addition of seed lamivudine salicylate. The isolation of lamivudine salicylate is carried out by stirring the reaction mixture in a temperature range from about 10°C to about 25°C. The stirring is preferably carried out initially at about 25°C to about 30°C and subsequently at about 10°C to about 15°C. The stirring can be carried out from about 10 minutes to about 100 hours. The lamivudine salicylate so obtained is treated with a base in the presence of an organic solvent, or a mixture of water and an organic solvent.

Preferably a mixture of water and an organic solvent is used as a solvent medium while treating lamivudine salicylate with a base. The organic solvent is preferably selected from the group consisting of alkanols, ethers and esters. The organic solvent is more preferably selected from the group consisting of methanol, ethanol, tetrahydrofuran, dioxane, isopropyl acetate and ethyl acetate. The base is preferably an amine, more preferably a tertiary amine. The treatment of lamivudine salicylate with the base is carried out at a temperature of 55°C or below, preferably at about 40°C to about 50°C. The process is accompanied by stirring to facilitate the liberation of lamivudine as a free base. The lamivudine is isolated from the reaction mixture without adding any seed. The isolation is carried out by stirring the reaction mixture at a temperature of about 0°C to about 35°C, preferably at about 15°C to about 30°C, followed by filtration, distillation and/or concentration. A washing of lamivudine with an organic solvent can optionally be employed after isolation. The lamivudine so obtained can be further purified by treating with activated charcoal in the presence of an organic solvent. The lamivudine so obtained has a chemical purity of about 98% or above and a chiral purity of about 99% or above.

The lamivudine so obtained is dissolved in water or an organic solvent, or a mixture thereof. The organic solvent is selected from the group consisting of alcohols, ketones, esters, ethers and nitriles. The organic solvent is preferably selected from the group consisting of methanol, ethanol, n-propanol, 2-propanol, n-butanol, sec-butanol, ethyl acetate, acetone, acetonitrile and tetrahydrofuran. The lamivudine is preferably dissolved in a mixture of water and an organic solvent. The ratio of water and the organic solvent can be 1:1 to 1:100. The dissolution process can be accompanied by heating the reaction mixture to ensure complete dissolution. The heating may be carried out to attain a temperature of about 35°C to about reflux temperature. The solvent is removed from the solution so obtained by spray drying in a spray drier. The solution may optionally be filtered prior to spray drying. . The inlet and outlet temperatures, feed rate, and atomizer type of the spray drier can be adjusted to optimize output and particle size. The air inlet temperature is preferably controlled from about 75°C to about 95°C. The outlet temperature is preferably controlled from about 50°C to about 70°C. An inert gas such as nitrogen can also be used as a carrier gas. After the spray drying process, the amorphous product is collected from the spray dryer and optionally further dried under vacuum to obtain amorphous lamivudine.

In still another aspect, a pharmaceutical composition comprising amorphous lamivudine is provided which optionally contains one or more excipients.

In yet a further aspect, a method of treating HIV or HBV infections is provided which comprises administering to a human in need thereof a therapeutically effective
5 amount of amorphous lamivudine.

Powder XRD of the samples were determined by using Panalytical X'Pert Pro X-Ray Powder Diffractometer in the range 3-40 degree 2 theta and under tube voltage and current of 45 Kv and 40 mA respectively. Copper radiation of wavelength 1.54 angstrom and Xceleor detector was used.

10 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 Crystalline Form II of Lamivudine

15 a) Preparation of lamivudine salicylate:

Dipotassium hydrogen orthophosphate (205.5 g) was added to deionised water (423 mL) and stirred at 25° to 30°C to obtain a solution. The solution was cooled to 17° to 22°C, followed by the addition of denaturated spirit (900 mL) at the same temperature and stirred for 5 minutes. (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (2*R*,5*S*)-5-(4-amino-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylate (150 g) was added to the mixture
20 at 17° to 22°C and stirred for 30 minutes at 18° to 20°C. Sodium borohydride solution was added slowly to the reaction mixture over a period of 2 to 3 hours at 18° to 20°C.

(Preparation of sodium borohydride solution: Sodium hydroxide (0.75 g) was dissolved in deionised water (143 mL). Sodium borohydride (30 g) was added to the solution at 20° to
25 35°C, stirred at 20° to 35°C to obtain a solution and cooled to 17° to 22°C). The reaction mixture was stirred for 6 hours at 18° to 22°C and the reaction mixture was allowed to settle at 18° to 25°C. The organic layer was separated and denaturated spirit (150 mL) was added to the aqueous layer at 18° to 25°C. The reaction mixture was stirred for 15 minutes at the same temperature and allowed to settle. The organic layer was separated and
30 combined with the previously obtained organic layer. The pH of the combined organic

layer was adjusted to 6.0 to 6.5 with dilute hydrochloric acid (20 mL; prepared by mixing 10 mL of concentrated hydrochloric acid with 10 mL of deionised water) at 18° to 25°C, followed by stirring for 10 minutes at the same temperature. The pH of the reaction mixture was adjusted to 8.0 to 8.5 with aqueous sodium hydroxide solution (28 mL; prepared by dissolving 2.1 g of sodium hydroxide in 27 mL of deionised water) at 18° to 25°C. The reaction mixture was concentrated under vacuum at about 55°C till the residual volume was about 375 mL. Deionised water (300 mL) was added to the concentrated reaction mixture at 25° to 30°C and stirred for 10 minutes. The reaction mixture was washed with toluene (2 X 150 mL) at 25° to 30°C and the toluene layer was extracted with deionised water (150 mL) at 25° to 30°C. The aqueous layers were combined and salicylic acid (57 g) was added at 25° to 30°C. Deionised water (150 mL) was added to the reaction mixture and heated to 78° to 82°C to get a clear solution. The reaction mixture was cooled to 25° to 30°C over a period of 2 hours and stirred at the same temperature for 4 hours. The reaction mixture was further cooled to 10° to 15°C and stirred for 2 hours at 10° to 15°C. The solid was filtered, washed with deionised water (150 mL) and dried by suction. The solid so obtained was washed with methanol (90 mL, pre-cooled to 5° to 10°C) and dried at 45° to 50°C in hot air oven to obtain the title compound.

Yield: 132 g

b) Preparation of crystalline Form II of lamivudine:

Lamivudine salicylate (120 g) was added to a mixture of ethyl acetate (720 mL) and water (6 mL) at 25° to 35°C. The reaction mixture was heated to 45° to 50°C, followed by the addition of triethylamine (104.76 g) over 30 minutes at 45° to 50°C. The reaction mixture was stirred for 4 hours at the same temperature and cooled to 25° to 30°C. The reaction mixture was stirred for further 30 minutes at 25° to 30°C, filtered and dried by suction. The solid obtained was washed with ethyl acetate. Ethyl acetate (600 mL) was added to the washed solid and heated to 50° to 55°C. The mixture was stirred at 50° to 55°C for 15 minutes, cooled to 25° to 30°C and stirred for further 30 minutes. The solid was filtered at 25° to 30°C, washed with ethyl acetate (60 mL) and dried under vacuum at 45° to 50°C to obtain lamivudine. Lamivudine (60 g) so obtained was added to absolute alcohol (1.2 L) at 25° to 35°C. The reaction mixture was heated to 75° to 78°C and stirred to obtain a solution. Activated carbon (6 g) was added to the solution so obtained at 75° to 78°C,

stirred for 30 minutes at the same temperature and filtered through Celite bed at the same temperature. The carbon bed was washed with absolute alcohol (60 mL; preheated to 75° to 76°C) and the reaction mixture was concentrated under vacuum to obtain a volume of about 300 mL. The concentrated reaction mixture was heated to 74° to 76°C, stirred for 15
5 minutes and cooled to 20° to 25°C in 1 hour time. The reaction mixture was further cooled to 5° to 10°C in 1 hour time and stirred for 30 minutes. The solid was filtered, washed with absolute alcohol (30 mL, pre-cooled to 5° to 10°C) and dried under vacuum at 50° to 55°C to obtain the title compound.

Yield: 53 g

10 HPLC Purity: 99.0%

Chiral Purity: 99.8%

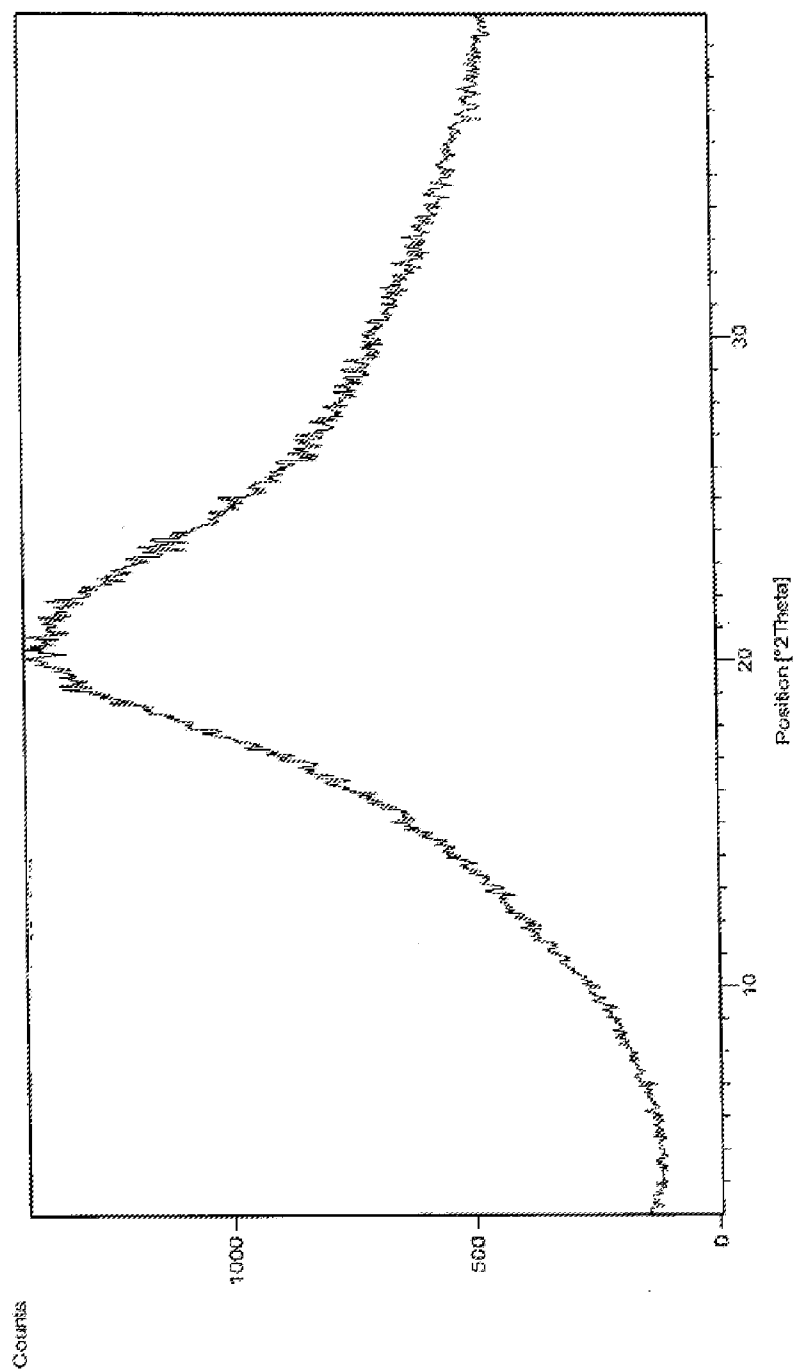
Example 2: Preparation of Amorphous Lamivudine

Crystalline Form II of lamivudine (30 g) as prepared in Example 1 was dissolved in a mixture of methanol (210 mL) and water (90 mL) at 45° to 50°C. The resultant solution
15 was spray dried (Inlet temperature: 85° to 90°C; Outlet temperature: 60° to 65°C). The amorphous powder so obtained was dried at 45° to 50°C under vacuum for 3 to 4 hours to obtain the title compound having an XRPD pattern as depicted in Figure 1.

Yield: 25 g

We Claim:

- 1 1. Amorphous lamivudine.
- 1 2. Amorphous lamivudine according to claim 1 having an XRPD pattern substantially
2 as depicted in Figure 1.
- 1 3. A process for the preparation of amorphous lamivudine, comprising:
 - 2 a) dissolving lamivudine in water or an organic solvent, or a mixture thereof,
3 to obtain a solution, and
 - 4 b) removing the solvent from the solution obtained in step a) by spray drying
5 to obtain amorphous lamivudine.
- 1 4. A process according to claim 3, wherein the lamivudine used in step a) has a
2 chemical purity of about 98% or above and a chiral purity of about 99% or above.
- 1 5. A process according to claim 3, wherein the organic solvent is selected from the
2 group consisting of alcohols, ketones, esters, ethers and nitriles.
- 1 6. A process according to claim 5, wherein the organic solvent is selected from the
2 group consisting of methanol, ethanol, n-propanol, 2-propanol, n-butanol, sec-butanol,
3 ethyl acetate, acetone, acetonitrile and tetrahydrofuran.
- 1 7. A process according to claim 3, wherein step a) is accompanied by heating.
- 1 8. A process according to claim 3, wherein step a) further comprises filtering of the
2 solution.
- 1 9. A pharmaceutical composition comprising amorphous lamivudine.
- 1 10. A method of treating HIV or HBV infections, which comprises of administering to
2 a human in need thereof a therapeutically effective amount of amorphous lamivudine.

FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2008/051694

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D411/04 A61P31/12 A61K31/39

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 A61P A61K

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, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 395 300 B1 (STRAUB JULIE [US] ET AL) 28 May 2002 (2002-05-28) column 7, line 33; claim 4 column 12, paragraph 2 - paragraph 3 -----	1-10
Y	WO 2007/119248 A (LUPIN LTD [IN]; SINGH GIRIJ PAL [IN]; SRIVASTAVA DHANANJAI [IN]; SAINI) 25 October 2007 (2007-10-25) cited in the application page 4, paragraph 3 page 1 - page 3 -----	1-10
Y	US 2003/004130 A1 (ROSS MALCOLM [IL] ET AL) 2 January 2003 (2003-01-02) paragraph [0035] ----- -/--	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

16 October 2008

Date of mailing of the international search report

29/10/2008

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2008/051694

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages.	Relevant to claim No.
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A	ANSHUMAN A AMBIKE ET AL: "Spray-Dried Amorphous Solid Dispersions of Simvastatin, a Low Tg Drug: In Vitro and in Vivo Evaluations" PHARMACEUTICAL RESEARCH, KLUWER ACADEMIC PUBLISHERS-PLENUM PUBLISHERS, NE, vol. 22, no. 6, 1 June 2005 (2005-06-01), pages 990-998, XP019370876 ISSN: 1573-904X page 990	1-10
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2008/051694

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