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(71) **Applicant** *(for all designated States except US)*: **AUROBINDO PHARMA LIMITED** [IN/IN]; Plot No.2, Maitrivihar, Ameerpet, Hyderabad 500038, Andhra Pradesh (IN).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **NAWARE, Nishant Babanrao** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar, Ameerpet, Hyderabad 500038, Andhra Pradesh (IN). **PANCHAGNULA, Chandrasekhar** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar, Ameerpet, Hyderabad 500038, Andhra Pradesh (IN). **BHAMARE, Shailesh Suresh** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar, Ameerpet, Hyderabad 500038, Andhra Pradesh (IN). **DEO, Kishor Dattatray** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar, Ameerpet, Hyderabad 500038, Andhra Pradesh (IN). **MEENAKSHISUNDERAM, Sivakumaran** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar, Ameerpet, Hyderabad 500038, Andhra Pradesh (IN).

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(54) **Title**: STABLE DOSAGE FORMS OF LAMIVUDINE AND TENOFOVIR

(57) **Abstract**: The present invention relates to stable pharmaceutical dosage forms of combination of antiretroviral agents. More particularly, the present invention relates to stable dosage forms comprising lamivudine and tenofovir disoproxil fumarate prepared by wet granulation.

STABLE DOSAGE FORMS OF LAMIVUDINE AND TENOFOVIR

Field of the invention

The present invention relates to stable pharmaceutical dosage forms of combination of antiretroviral agents. More particularly, the present invention relates to stable dosage forms comprising lamivudine and tenofovir disoproxil fumarate prepared by wet granulation.

Background of the invention

The human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS). This disease is characterized by the destruction of the immune system, particularly of the CD4 and T-cell making the host susceptible to opportunistic infections. HIV is also associated with a precursor AIDS-related complex (ARC), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss.

Anti-retroviral drugs, such as reverse transcriptase inhibitors and viral protease inhibitors, have been used to treat HIV infection. These treatments can effectively suppress viral production when used in combinations known as HAART (Highly Active Anti-Retroviral Therapy).

Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. Chemically, tenofovir disoproxil fumarate (tenofovir DF) is 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate and is commercially available as tablets under the trade name Viread®. Tenofovir disoproxil fumarate was first disclosed in US patent No. 5,922,695.

Chemically, lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and is commercially available as tablets and oral solution under the trade name Epivir®. Lamivudine and method of treating HIV using lamivudine was first disclosed in US 5,047,407.

One substantial and persistent problem in the treatment of AIDS has been the ability of the HIV virus to develop resistance to the individual

therapeutic agents employed to treat the disease. Thus, a need remains for an efficacious and long lasting therapy for AIDS which lowers HIV viral levels of patients to undetectable levels and raises CD4 cell counts for prolonged periods of time without the development of resistance. Hence, there is a need to develop combination of drugs to treat AIDS called as fixed dose combinations (FDC).

The various advantages of FDCs when compared to the separate ARV regimens are ease of use, better adherences to the dosage schedules, reduced risk of drug resistance and increased affordability. Combination therapy reduces the daily dosages to be taken by patients and simplifies dosing schedule thereby increases patient compliance.

Following are few patents/publications, which disclose combinations of antiretrovirals.

US 5,627,186 disclose combination of lamivudine and zidovudine for treating HIV infections.

US 6,417,191 discloses combination of abacavir and lamivudine; abacavir, lamivudine and zidovudine for treating HIV infections.

US 2004/0224917 discloses therapeutic combinations of emtricitabine and tenofovir DF useful for treatment of HIV infections.

US 2007/0077295 discloses composition of tenofovir DF and emtricitabine prepared by dry granulation for treating HIV infections.

US 2007/099902 discloses a multi component unitary dosage form comprising tenofovir DF and emtricitabine in first component and efavirenz in second component useful for treatment of HIV infections.

ZA 2001/10500 discloses pharmaceutical composition of lamivudine, zidovudine and nevirapine and process, which comprises wet granulating lamivudine, zidovudine, nevirapine and diluent with water; drying, sizing and blending the granules with disintegrant; lubricating the granules; and compressing the lubricated granules into tablets.

WO 2004/089382 discloses combination of lamivudine, zidovudine and efavirenz for treating HIV infections.

WO 2004/089383 discloses combination of lamivudine, stavudine and efavirenz for treating HIV infections.

WO 2006/001029 discloses a process for preparing a composition of lamivudine, zidovudine and nevirapine and process which comprises granulating lamivudine, zidovudine, nevirapine, microcrystalline cellulose, starch, croscarmellose sodium with a solution of polyvinylpyrrolidone k-30 and drying the granules, blending the dried granules with magnesium stearate, croscarmellose sodium, colloidal anhydrous silica, crospovidone and compressing the blend into tablets.

WO 2006/086865 discloses a composition comprising lamivudine, zidovudine and nevirapine in a single coated tablet prepared by dry granulation.

WO 2006/114709 discloses a composition comprising lamivudine, zidovudine and nevirapine prepared by a granulation process comprising the steps of preparing granules of lamivudine plus zidovudine and granules of nevirapine separately, blending the obtained granules with excipients and finally compressing the granules into tablets.

WO 2007/026156 discloses a composition comprising lamivudine, stavudine and nevirapine for pediatric treatment of viral infections.

WO 2007/068934 discloses a bilayered formulation comprising lamivudine and tenofovir. It is disclosed in this publication that lamivudine and tenofovir DF when intimately mixed to form a single layered tablet showed undesirable properties in stability testing. The appearance of tablets changed to brown colour at controlled room temperature (25°C) and even at accelerated temperature (40°C). Inorder to avoid the discoloration, lamivudine and tenofovir DF are formulated as a bilayered tablet. This patent publication further discloses a kit comprising bilayered tablet of lamivudine and tenofovir as first formulation and efavirenz tablet as second formulation.

WO 2008/043829 discloses combination of emtricitabine, tenofovir and nevirapine for once a day administration.

WO 2008/096369 discloses a formulation comprising lamivudine and tenofovir DF prepared by granulating tenofovir DF seperately by dry

granulation and blending the granules with extragranular lamivudine and finally compressing into tablets. This publication further discloses monolithic tablets comprising emtricitabine/lamivudine, tenofovir DF and efavirenz.

The above prior art disclose compositions of various combinations of antiretroviral agents prepared as single and/or double layered tablets. However, still there is a need to develop stable single layer dosage form comprising lamivudine and tenofovir which avoids the common problems associated with bilayered tablets like layer seperation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield etc.

Thus, the inventors of the present invention during their continuous efforts to develop a stable composition of lamivudine and tenofovir disoproxil fumarate found that lamivudine and tenofovir can be prepared as single layer tablets which are stable. The inventors of the present invention have surprisingly found that when lamivudine and tenofovir were granulated separately and compressed into a single layered tablet resulted in a stable dosage form.

Objective of the invention

Accordingly, the main objective of the present invention is to provide stable dosage forms comprising lamivudine and tenofovir and process for preparing the dosage form.

Yet another objective of the present invention is to provide stable dosage form of lamivudine and tenofovir in such a way that it will comply with the reference products of each of these approved individual drugs in terms of *in vitro* parameters like dissolution, disintegration, etc and *in vivo* parameters like bioequivalence.

Summary of the invention

Accordingly, the present invention provides stable single layer tablet form comprising lamivudine and tenofovir disoproxil fumarate prepared by wet granulation process.

Detailed description of the invention

In another embodiment of the present invention, the dosage form further comprises one or more excipients selected from diluents, binders, disintegrants, surfactants, glidants and lubricants.

Suitable diluents of the present invention are selected from mannitol, lactose, microcrystalline cellulose, maltitol, sorbitol, maltodextrin, maltose, starch, calcium carbonate, calcium phosphate dibasic, calcium sulfate or a combination thereof. The diluent may be used in the range of 5-50% by weight of the tablet.

Suitable binders of the present invention are selected from hydroxy propyl cellulose, hydroxypropyl methylcellulose, gelatin, hydroxy ethyl cellulose, povidone, starch and methylcellulose or a combination thereof. The binder may be used in the range of 0.5-10% by weight of the tablet.

Suitable disintegrants of the present invention are selected from sodium starch glycolate, croscarmellose sodium, crospovidone, starch, hydroxypropyl cellulose, magnesium aluminum silicate, pregelatinized starch or a combination thereof. The disintegrant may be used in the range of 1-15% by weight of the tablet.

Suitable surfactants of the present invention are selected from sodium lauryl sulphate, polysorbate, sorbitan monolaurate, polyoxyethylene-polyoxypropylene block copolymer (poloxamer), polyethylene glycol derivatives, cetyl alcohol or a combination thereof. The surfactant may be used in the range of 0.01-1% by weight of the tablet.

Suitable glidants of the present invention are selected from magnesium trisilicate, talc, tribasic calcium phosphate, glyceryl monostearate, glyceryl stearate and silica dioxide or a combination thereof. The glidant may be used in the range of 0.1-2% by weight of the tablet.

Suitable lubricants of the present invention are selected from calcium stearate, magnesium stearate, hydrogenated vegetable oil, stearic acid, magnesium aluminum silicate, sodium stearyl fumarate, glyceryl behenate or a

combination thereof. The lubricant may be used in the range of 0.1-5% by weight of the tablet.

Tenofovir as used herein refers to tenofovir disoproxil fumarate. In another embodiment of the present invention, the stable dosage form comprises 50-500 mg of lamivudine and 50-500 mg of tenofovir.

In a preferred embodiment of the present invention, the stable tablet dosage form comprises compressed granules of

i) lamivudine granules comprising 10-50% by weight of diluent selected from microcrystalline cellulose, lactose and mannitol, 0.5-10% by weight of binder selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose and povidone, 1-15% by weight of disintegrant selected from croscarmellose sodium, sodium starch glycolate and crospovidone and

ii) tenofovir granules comprising 10-50% by weight of diluent selected from microcrystalline cellulose, lactose and mannitol, 0.5-10% by weight of binder selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose and povidone, 1-15% by weight of disintegrant selected from croscarmellose sodium, sodium starch glycolate and crospovidone prepared by wet granulation.

In a preferred embodiment of the present invention, the stable tablet dosage form comprises lamivudine, tenofovir, 10-50% by weight of diluent selected from microcrystalline cellulose, lactose and mannitol, 0.5-10% by weight of binder selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose and povidone, 1-15% by weight of disintegrant selected from croscarmellose sodium, sodium starch glycolate and crospovidone, 0.1-2% by weight of glidant selected from colloidal silicon dioxide and talc, 0.1-5% by weight of glidant selected from magnesium stearate and stearic acid of the total composition, wherein the tablets are prepared by wet granulation.

In another embodiment of the present invention, the stable tablet dosage form comprising lamivudine and tenofovir prepared by wet granulation process, comprises the steps of:

a) granulating lamivudine and tenofovir and one or more pharmaceutically acceptable excipients using solvent or with a binder solution,

b) drying the wet granules,

c) sieving the dried granules to obtain uniform granules of lamivudine and tenofovir,

d) blending the granules of step (c) with one or more extragranular excipients,

e) lubricating the granules and compressing into tablets.

In another embodiment of the present invention, there is provided an alternative process for the preparation of the stable tablet dosage form comprising lamivudine and tenofovir by wet granulation process, which comprises the steps of:

a) preparing granules comprising lamivudine and one or more pharmaceutically acceptable excipients,

b) preparing granules comprising tenofovir and one or more pharmaceutically acceptable excipients,

c) blending the granules of step (a) and (b), with pharmaceutically acceptable excipients,

d) blending the granules of step (c) with extragranular excipients,

e) lubricating the blended granules and finally compressing the blend into tablets.

In another embodiment, the solvents used for granulation process may be selected from water, isopropyl alcohol, acetone, ethanol, methylene chloride or combination thereof.

In another embodiment of the present invention, the tablets of the present invention may optionally be coated to prevent the degradation of lamivudine from light with coating polymers.

Suitable film forming polymers used according to the present invention are selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxy ethyl cellulose, xanthan gum and the like or a combination there of.

In another embodiment, the stable dosage form of the present invention is used for the treatment or prevention of symptoms of HIV infections in an infected individual.

The following examples further exemplify the invention and are not intended to limit the scope of the invention. It is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one known to the industry.

Example 1

S. No.	Ingredients	Quantity per unit (mg)
1.	Lamivudine	300.00
2.	Tenofovir Disoproxil Fumarate	300.00
3.	Microcrystalline Cellulose	180.00
4.	Croscarmellose sodium	55.00
5.	Purified water	Q.S.
Extragranular ingredients		
6.	Microcrystalline Cellulose	110.00
7.	Croscarmellose sodium	45.00
8.	Magnesium Stearate	10.00
Tablet Weight		**1000.00**
Film Coating		
9.	Opadry II blue	40.00

The processing steps involved in manufacturing stable tablets of lamivudine and tenofovir are given below:

a) preparation of granules of lamivudine plus tenofovir:

i) lamivudine and tenofovir were sifted and blended with microcrystalline cellulose and croscarmellose sodium,

ii) the blend of step (i) was granulated using water,

iii) the wet mass was dried and sized and blended with extragranular microcrystalline cellulose and croscarmellose sodium,

iv) lubricated the blend of step (iii) with magnesium stearate and compressed into tablets and

v) the tablets of step (iv) were coated with Opadry II blue.

Dissolution profile of lamivudine and tenofovir tablets prepared according to example 1 was carried out in 0.1 N HCl as dissolution medium using USP Apparatus II with 900 ml at 75 rpm speed. The release profile (% drug dissolved in min) is given in Table 1.

Table 1

Time (min)	% Drug dissolved	
	Lamivudine	Tenofovir
5	65	61
10	100	98
15	101	101
20	101	100
30	101	100
45	101	99

Example 2

S. No.	Ingredients	Quantity per unit (mg)
Granulation 1 (Lamivudine part)		
1.	Lamivudine	300.00
2.	Microcrystalline Cellulose	119.75
3.	Croscarmellose Sodium	40.00
4.	Hypromellose	9.00
5.	Purified Water	q.s
Granulation II (Tenofovir Disoproxil Fumarate part)		
6.	Tenofovir Disoproxil Fumarate	300.00
7.	Microcrystalline Cellulose	120.25

8.	Croscarmellose Sodium	40.00
9.	Hypromellose	12.00
10.	Purified Water	q.s.
	Lubrication for Tenofovir part	
11.	Magnesium Stearate	15.00
Extra Granular (Lamivudine + Tenofovir combined Part)		
12.	Croscarmellose Sodium	50.00
13.	Colloidal silicon dioxide	10.00
14.	Magnesium Stearate	20.00
Core Tablet weight		1035.00
15.	Opadry II blue	34.500
16.	Purified Water	q.s.
Coated tablet weight		1066.050

The processing steps involved in manufacturing stable tablets of lamivudine and tenofovir are given below:

a) preparation of granules of lamivudine:

i) lamivudine was sifted and blended with microcrystalline cellulose and croscarmellose sodium,

ii) binder solution was prepared by dissolving hypromellose in water,

iii) the blend of step (i) was granulated using binder solution of step ii),

iv) the wet mass was dried and sized,

b) preparation of granules of tenofovir:

i) tenofovir was sifted and blended with microcrystalline cellulose and croscarmellose sodium,

ii) binder solution was prepared by dissolving hypromellose in water,

iii) the blend of step (i) was granulated using binder solution of step ii),

iv) the wet mass was dried and sized,

v) the sized granules of step iv) were lubricated with magnesium stearate,

b) blending and lubrication of granules:

i) the granules obtained in step a) and step b) were blended together,

ii) the extragranular microcrystalline cellulose and croscarmellose sodium were sifted and blended and mixed with granules of step (i)

iii) the blend of step (ii) was lubricated with magnesium stearate and compressed into tablets and

iv) the tablets of step (iii) were coated with Opadry II blue.

Dissolution profile of lamivudine and tenofovir tablets prepared according to example 2 was carried out in 0.1 N HCl as dissolution medium using USP Apparatus II with 900 ml at 75 rpm speed. The release profile (% drug dissolved in min) is given in Table 1.

Table 2

Time (min)	% Drug dissolved	
	Lamivudine	Tenofovir
5	52	46
10	98	90
15	103	96
20	103	96
30	103	95
45	104	95

The tables of lamivudine and tenofovir prepared according to the present invention were found to be stable. The stability data obtained after 3 months at 40°C/ 75% RH is shown in Table 3.

Table 3

Example 2	Assay			
	Initial	After 1 month	After 2 months	After 3 months
Lamivudine	98.3	100.4	98.2	99.1
Tenofovir	98.6	102.4	100.5	96.9

We claim:

1. A stable single layer tablet dosage form comprising lamivudine and tenofovir disoproxil fumarate prepared by wet granulation process.

2. The dosage form as claimed in claim 1, further comprises one or more pharmaceutical excipients such as diluents, binders, disintegrants, glidants and lubricants.

3. The dosage form as claimed in claim 2, wherein the diluent is selected from mannitol, lactose, microcrystalline cellulose, maltitol, sorbitol, maltodextrin, maltose, starch, calcium carbonate, calcium phosphate dibasic, calcium sulfate or a combination thereof.

4. The dosage form as claimed in claim 2, wherein the binder is selected from hydroxy propyl cellulose, hydroxypropyl methylcellulose, gelatin, hydroxy ethyl cellulose, povidone, starch and methylcellulose or a combination thereof.

5. The dosage form as claimed in claim 2, wherein the disintegrant is selected from sodium starch glycolate, croscarmellose sodium, crospovidone, starch, hydroxypropyl cellulose, magnesium aluminum silicate, pregelatinized starch or a combination thereof.

6. The tablet dosage form as claimed in claim 1, wherein the granulation process comprises the steps of :

a) granulating lamivudine and tenofovir and one or more pharmaceutically acceptable excipients with solvent or with a binder solution,

b) drying the wet granules, and

c) sieving the dried granules to obtain uniform granules of lamivudine and tenofovir

d) blending the granules of step (c) with extragranular excipients,

e) lubricating the granules obtained and compressing into tablets or filling into capsules.

7. The dosage form as claimed in claim 1, wherein the granulation process comprises the steps of :

a) preparing granules comprising lamivudine and one or more pharmaceutically acceptable excipients,

b) preparing granules comprising tenofovir and one or more pharmaceutically acceptable excipients,

c) blending the granules of step (a) and (b), with pharmaceutically acceptable excipients,

d) blending the granules of step (c) with extragranular excipients,

e) lubricating the blended granules and finally compressing the granules into tablets or filled into capsules.

8. A stable tablet dosage form comprising compressed granules of

i) lamivudine granules comprising 10-50% by weight of diluent selected from microcrystalline cellulose, lactose and mannitol, 0.5-10% by weight of binder selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose and povidone, 1-15% by weight of disintegrant selected from croscarmellose sodium, sodium starch glycolate and crospovidone and

ii) tenofovir granules comprising 10-50% by weight of diluent selected from microcrystalline cellulose, lactose and mannitol, 0.5-10% by weight of binder selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose and povidone, 1-15% by weight of disintegrant selected from croscarmellose sodium, sodium starch glycolate and crospovidone prepared by wet granulation.

9. A stable tablet dosage form comprising lamivudine, tenofovir, 10-50% by weight of diluent selected from microcrystalline cellulose, lactose and mannitol, 0.5-10% by weight of binder selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose and povidone, 1-15% by weight of disintegrant selected from croscarmellose sodium, sodium starch glycolate and crospovidone, 0.1-2% by weight of glidant selected from colloidal silicon dioxide and talc, 0.1-5% by weight of glidant selected from magnesium stearate and stearic acid of the total composition, wherein the tablets are prepared by wet granulation.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/7068 A61K31/7076

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)
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, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2009/037449 A (CIPLA LTD [IN]; CURTIS PHILIP ANTHONY [GB]; LULLA AMAR [IN]; MALHOTRA) 26 March 2009 (2009-03-26) page 7, lines 19-26 page 9, lines 16-29 page 10, lines 18-31; claims 9-11; examples 2-5	1-9
P,X	WO 2008/096369 A (MATRIX LAB LTD [IN]; WYAWAHARE NEHA SHESH [IN]; A RAMESH [IN]; BHADGAL) 14 August 2008 (2008-08-14) page 2, lines 1-5 page 5, lines 27,28 page 6, lines 17-24 page 9, lines 5-10 page 16, line 5 - page 17, line 2	1-9

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[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

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Date of the actual completion of the international search	Date of mailing of the international search report
9 June 2009	22/06/2009

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	Toulacis, C

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/068934 A (CIPLA LTD [IN]; CURTIS PHILIP ANTHONY [GB]; LULLA AMAR [IN]; MALHOTRA) 21 June 2007 (2007-06-21) the whole document	1-9
A	MENENDEZ-ARIAS L: "Targeting HIV: antiretroviral therapy and development of drug resistance" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER, HAYWARTH, GB, vol. 23, no. 8, 1 August 2002 (2002-08-01), pages 381-388, XP004386181 ISSN: 0165-6147	1-9
A	FDA: "Guidance for Industry Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV" INTERNET CITATION, [Online] XP002417855 Retrieved from the Internet: URL:http://www.fda.gov/oc/initiatives/hiv/hivguidance.html> [retrieved on 2007-01-31] the whole document	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2009/000339

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