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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 May 2012 (24.05.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/066401 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 31/47* (2006.01)
A61K 9/08 (2006.01) *A61K 47/06* (2006.01)
A61K 9/10 (2006.01) *A61P 11/06* (2006.01)

(21) International Application Number:
PCT/IB2011/002661

(22) International Filing Date:
10 November 2011 (10.11.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1301/KOL/2010 16 November 2010 (16.11.2010) 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, 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, MD, 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).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

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

WO 2012/066401 A1

(54) Title: STABLE ORAL PHARMACEUTICAL COMPOSITIONS OF MONTELUKAST

(57) Abstract: A stable liquid oral pharmaceutical composition comprising montelukast, a vehicle comprising mineral oil, desiccant and optionally pharmaceutically acceptable additives is provided. The invention also relates to kit for dispensing of oral pharmaceutical compositions of Montelukast. The kit comprises montelukast, a vehicle comprising mineral oil, desiccant and optionally pharmaceutically acceptable additives. The kit comprises a first container comprising pharmaceutical composition of montelukast and optionally desiccant, a second container comprising a vehicle comprising mineral oil, optionally desiccant and pharmaceutically acceptable additives, and instructions for use. montelukast and mineral oil occupy pre-measured volume into the respective unit of the kit.

STABLE ORAL PHARMACEUTICAL COMPOSITIONS OF MONTELUKAST

FIELD OF THE INVENTION

The present invention relates to stable oral pharmaceutical compositions of Montelukast.

The invention also relates to kit for dispensing of oral pharmaceutical compositions of Montelukast.

BACKGROUND OF THE INVENTION

Asthma has close relationship with allergic respiratory disorders such as hay fever, allergic rhinitis etc. The clinical symptoms produced in the course of allergic reaction are the result of an early specific immune response and a late inflammatory reaction. The inhaled allergens mediate the early phase by stimulating high affinity immunoglobulin (I $_g$ E) receptors e.g. mast cells and basophils which in turn release histamine and cytokines. The cytokines released from mast cells and basophils then mediate the late phase by recruiting inflammatory cells into the nasal and upper respiratory tract passages. The influx of eosinophils, macrophages, lymphocytes, neutrophils and platelets starts the vicious inflammatory cycle. This late phase amplifies the initial immune response which in turn triggers the release of more inflammatory cells.

Seasonal allergic rhinitis (hay fever) is caused by deposition of allergens on the nasal mucosa resulting in an immediate hypersensitivity reaction. If the allergens (e.g. dust mite) are carried to the lower airways (i.e. bronchioles), in susceptible subjects, the result is bronchoconstriction of the airways (i.e. asthma). The allergen-induced release of leukotrienes is critical in the pathophysiology of asthma. Leukotrienes are produced by mast cells, eosinophils, neutrophils and alveolar macrophages. Leukotriene combines with receptors on the respiratory tract cells, resulting in some symptoms of asthma such as respiratory tract constriction, edema, and the increase of salivary secretion.

Various drugs like anti-inflammatory pharmaceuticals or bronchodilators are used for the treatment of allergy related diseases and asthma. However, bronchodilators do not treat the inflammatory reaction or lower the sensitivity of the respiratory tract. While anti-inflammatory drugs are usually used as preventive medicine, the major anti-inflammatory

drugs in use nowadays are steroids, but the use of specific leukotriene receptor antagonists or 5-lipoxygenase pathway inhibitors are preferred which results in increased airflow and reduction of symptoms in asthmatic patients.

U. S. Pat. No. 5,565,473 discloses a broad spectrum of compounds, which includes Montelukast.

Montelukast is marketed as Singulair® in USA as oral tablets, granules and chewable tablets. Oral tablet is not a convenient dosage form for some asthmatic patients, especially for children below six years old and the geriatric patients. Geriatric patients may have difficulty in swallowing tablet whereas tablet is usually grounded into powder before administration to children. When the tablet is grounded into powder, impurities are introduced during the grinding process and the drug dosage is difficult to control.

Montelukast as a granular dosage form is to be placed directly in the mouth; which can result into unpleasant taste and grittiness in the mouth.

In another method of administration, Montelukast granules are dissolved in 1 teaspoonful (5 ml) of cold or room temperature baby formula or breast milk; or to be mixed with a spoonful of one of the following soft foods at cold or room temperature: applesauce, mashed carrots, rice, or ice cream, which is inconvenient and can result into inaccurate dosage administration.

Chewable tablets are masticated and swallowed at once, with a drink of water. These tablets are sipped slowly for longer period of time, or otherwise, swallowed like conventional tablets. This wrong usage would either lead to reduced therapeutic efficacy, or may lead to mechanical obstruction of the ileum from impacted chewable tablets. Another major disadvantage with the chewable tablet is unpleasant taste and grittiness mouth feel, leading to poor patient compliance.

US patent application US 2006/0147482 discloses an oral liquid pharmaceutical composition comprising leukotriene antagonist, a buffer agent, water, pharmaceutical alcohol, which may be ethanol or propylene glycol and other additives.

US 2009/0247575 discloses a pharmaceutical composition for oral administration comprising an exceptionally labile active agent, a stabilizing vehicle comprising liquid triglycerides and a desiccant.

Montelukast compositions are susceptible to degradation during manufacture and storage. This degradation is pronounced in the presence of agents such as UV light, heat, oxidizing agents and/or water or moisture. This degradation of Montelukast leads to formation of corresponding sulfoxide. The sulfoxide is an inactive impurity, which reduces the effective dosage of Montelukast when it is administered to a patient. Montelukast undergoes photo-isomerization to form inactive *CIS* isomer when exposed to UV Light. The *CIS* isomer is an inactive impurity, which reduces the effective dosage of Montelukast when it is administered to a patient. It also forms biologically inactive, non-absorbable S-enantiomer on exposure to light and/or water.

Therefore, there exists a continuing need to develop stable oral pharmaceutical compositions of Montelukast.

SUMMARY OF THE INVENTION

The invention provides stable oral pharmaceutical compositions comprising Montelukast, a vehicle comprising mineral oil, desiccant and optionally pharmaceutically acceptable additives.

Yet another embodiment provides stable oral liquid pharmaceutical compositions comprising Montelukast, a vehicle comprising mineral oil, desiccant and optionally pharmaceutically acceptable additives.

Yet another embodiment provides a kit for dispensing pharmaceutical compositions comprising Montelukast, a vehicle comprising mineral oil, desiccant and optionally pharmaceutically acceptable additives.

Yet another embodiment provides a kit for dispensing pharmaceutical compositions comprising a first container comprising pharmaceutical composition of Montelukast and optionally desiccant, a second container comprising a vehicle comprising mineral oil,

optionally desiccant and pharmaceutically acceptable additives, and instructions for use. Montelukast and mineral oil occupy pre-measured volume into the respective unit of the kit.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides stable oral pharmaceutical compositions of Montelukast and a kit containing pharmaceutical compositions of Montelukast.

The term "Montelukast" used herein refers to Montelukast as pharmaceutically acceptable complexes, salts, polymorphs, hydrates, or solvates. Sodium salt of Montelukast is preferred.

As used herein with respect to pharmaceutical compositions, unless otherwise defined, the term "stable" means that the amount of the corresponding sulfoxide within the montelukast in the packaged pharmaceutical composition has not increased by more than 1.0 % by weight from the initial amount of montelukast after storage at 40^0C and 75% relative humidity for 3 months. In a preferred embodiment, the corresponding sulfoxide content has not increased by more than 0.5% by weight of the initial amount of montelukast after storage at 40^0C and 75% relative humidity for 3 months. In the most preferred embodiment, the corresponding sulfoxide content has not increased by more than 0.3% by weight of the initial amount of montelukast after storage at 40^0C and 75% relative humidity for 3 months.

As used herein with respect to pharmaceutical compositions, unless otherwise defined, the term "stable" means that the amount of the corresponding *CIS* isomer within the montelukast in the packaged pharmaceutical composition has not increased by more than 1.0 % by weight from the initial amount of montelukast after storage at 40^0C and 75% relative humidity for 3 months. In a preferred embodiment, the corresponding *CIS* isomer content has not increased by more than 0.5% by weight of the initial amount of montelukast after storage at 40^0C and 75% relative humidity for 3 months. In the most preferred embodiment, the corresponding *CIS* isomer content has not increased by more than 0.3% by weight of the initial amount of montelukast after storage at 40^0C and 75% relative humidity for 3 months.

As used herein with respect to pharmaceutical compositions, unless otherwise defined, the term "stable" means that the amount of the corresponding *S-enantiomer* within the montelukast in the packaged pharmaceutical composition has not increased by more than 0.5 % by weight from the initial amount of montelukast after storage at 40^0C and 75% relative humidity for 3 months. In a preferred embodiment, the corresponding *S-enantiomer* content has not increased by more than 0.3% by weight of the initial amount of montelukast after storage at 40^0C and 75% relative humidity for 3 months. In the most preferred embodiment, the corresponding *S-enantiomer* content has not increased by more than 0.2% by weight of the initial amount of montelukast after storage at 40^0C and 75% relative humidity for 3 months.

The pharmaceutical compositions may be in the form of liquid. Alternatively the pharmaceutical compositions are in form of powder or granules which can be reconstituted (extemporaneous preparations) in the form of liquid. In one embodiment of the invention, pharmaceutical compositions can be suspension or solution. In the preferred embodiment the pharmaceutical composition is a suspension.

As used herein, the terms "suspension" and "solution" are interchangeable with each other. "Suspension" encompasses a system in which a solid is dispersed in a liquid for example in particles of larger than colloidal size. "Solution" encompasses any system in which one substance is dissolved in another.

An extemporaneous preparation of a pharmaceutical composition is one performed at the time of use, which is before the administration of the drug to the patient. The term "extemporaneous preparation" also includes a preparation done by a pharmacist or other healthcare practitioner and administered to a patient in a relatively short period of time after the preparation. More preferably, an extemporaneous preparation is a pharmaceutical composition that is not directly prepared by the pharmaceutical industry and put on the

market to be used as it is, but prepared at a time usually at a time close to the administration to the patient.

The "stable oral pharmaceutical compositions" of the invention comprise Montelukast, a vehicle comprising mineral oil, desiccant and optionally pharmaceutically acceptable additives.

The mineral oil is a mixture of alkanes in the C_{15} to C_{40} range from a non-vegetable (mineral) source. The mineral oil is employed in an amount ranging from about 1.0 % w/v to about 99.0 % w/v, preferably about 25.0 % w/v to about 99.0 % w/v and most preferably from about 92.0 % w/v to about 99.0 % w/v based on the total volume of the composition.

The desiccants are selected from polyhydric alcohols, such as mannitol, sorbitol, xylitol, isomalt and maltitol, as well as tribasic calcium phosphate, dibasic calcium phosphate, calcium phosphate, kaolin, lactose, microcrystalline cellulose, powdered cellulose, precipitate calcium carbonate, starch, dextrose, dextrate, sucrose, anhydrous silicon dioxide, anhydrous ethanol, sodium metabisulfite, sodium sulfate, magnesium sulfate, magnesium oxide and mixtures thereof. The preferred desiccants are colloidal silicon dioxide and magnesium oxide and mixtures thereof.

These agents may be employed in an amount ranging from about 0.1 % w/v to about 30.0 % w/v, preferably about 0.1 % w/v to about 10.0 % w/v and most preferably from about 0.1 % w/v to about 5.0 % w/v based on the total volume of the composition.

The pharmaceutically acceptable additives may include sweeteners, flavours, and preservatives.

Sweeteners are selected from sucrose, fructose, dipotassium glycirhizinate.

Artificial sweeteners like saccharin, saccharin sodium, aspartame; mannitol, xylitol or acesulfame potassium and mixtures thereof are suitable for administration to children. The sweeteners may be employed in an amount ranging from about 0.1% to about 10% w/v, preferably about 0.1% to about 7% w/v and most preferably from about 0.1% w/v to about 2% w/v based on the total volume of the composition.

The preservatives are selected from butylated hydroxy toluene, butylated hydroxy anisole, methyl parahydroxybenzoate, propyl parahydroxybenzoate and sodium benzoate and mixtures thereof.

The amount of preservative to be used is less than about 0.1 % w/v. The preferred amount of the preservative to be used is less than about 0.02 %w/v.

The flavoring agents may be selected from cherry, vanilla, strawberry, lemon, yoghurt, cardamom, fennel, peppermint, or anise etc.

The term "pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for human pharmaceutical use.

The invention is also directed to kits comprising one or more pharmaceutical compositions of the invention. In some embodiments, the kits of the invention comprise a container or other means for holding the compositions of the invention.

In some embodiments, the kit comprises (a) a first container or other means for containing a therapeutically effective amount of the Montelukast in form of powder or granules and (b) a second container or other means for containing a vehicle comprising mineral oil. Optionally, the kit can have additional containers or other means for containing comprising a therapeutically effective amount of additional agents.

Powder or granules of montelukast and salt thereof can be prepared by methods known by one of skill in the art.

Since the kit will contain at least one pharmaceutical active and the at least one vehicle, the minimum number of containers in the given kit will be two. In a preferred embodiments, the maximum number of containers in the kit will be less than or equal to five. In the most preferred embodiment the number of containers in the kit will be two. The containers may be formed in any size or shape useful for the mixing or transferring of components from one container to another. Either or both of the first container and second container can be light-protective containers.

In some embodiments, the kit comprises a container or other means for containing for the separate compositions, such as, a divided bottle or a divided foil packet; however, the separate compositions can also be contained within a single, undivided container.

As herein described the kit may contain mixing element for example a stirrer to physically mix the Montelukast and a vehicle.

Typically, the kit contains printed labeling instructions. The printed labeling may provide instructions for administering any of the compositions, using any of the kits, or performing any other method herein described.

Suitable containers or other means for containing pharmaceutical composition(s) and pharmaceutically acceptable carrier include, but are not limited to, bottles made of high-density polyethylene (HDPE), polypropylene (PP), glass, and metal. Preferably the container is an amber colored glass bottle with a child resistant cap.

In another preferred embodiment, the kit is a unit dose packet (sometimes referred to in the art as a "sachet"), which is typically emptied into the mineral oil in preparing an oral suspension.

The invention in another aspect provides a simple one-step transfer method for preparing a pharmaceutical composition(s). A single dose sachet is designed to be emptied into the mineral oil or alternatively the mineral oil is added to a bottle containing the single dose pharmaceutical composition followed by gentle mixing for about 1-2 minutes result in a homogeneous and uniform dispersion or solution of the drug.

Following are the non limiting example of the inventions:

Example I

Sr No	Ingredients	mg/ml	%w/v
1.	Montelukast Sodium (equivalent to Montelukast 5.0 mg)	5.20	0.52
2.	Silicon Dioxide	5.00	0.50
3.	Magnesium Oxide Light	5.00	0.50
4.	Sucralose	2.0	0.2
5.	Peppermint Oil	0.005 mL	0.5
6.	Butylatedhydroxytoluene	1.00	0.1
7.	Butylatedhydroxyanisole	1.00	0.1
8.	Mineral Oil light q.s. to	1.00	100.00

Brief Manufacturing Procedure:

1. Dissolve Butylatedhydroxytoluene, Butylatedhydroxyanisole and in ½ quantity of Mineral Oil light with stirring to get a clear solution.
2. Dissolve Silicon Dioxide in step-1 solution to get a clear solution.
3. Disperse Sucralose and Magnesium Oxide in step-2 solution with stirring to get uniform suspension.
4. Disperse Montelukast Sodium in step-3 suspension with stirring.

5. Add Peppermint Oil to step 3 suspension with stirring and stir for 10 min.
6. Make up the volume to the required batch size with Mineral Oil light and stir to get uniform suspension.

Example II

Sr No	Ingredients	mg/ml	%w/v
1.	Montelukast Sodium (equivalent to Montelukast 5.0 mg)	5.20	0.52
2.	Silicon Dioxide	5.00	0.50
3.	Magnesium Oxide Light	5.00	0.50
4.	Saccharin	2.0	0.2
5.	Peppermint Oil	0.005 mL	0.5
6.	Butylatedhydroxytoluene	1.00	0.1
7.	Butylatedhydroxyanisole	1.00	0.1
8.	Mineral Oil light q.s. to	1.00	100.00

Brief Manufacturing Procedure:

1. Dissolve Butylatedhydroxytoluene, Butylatedhydroxyanisole and in ½ quantity of Mineral Oil light with stirring to get a clear solution.
2. Dissolve Silicon Dioxide in step-1 solution to get a clear solution.
3. Disperse Saccharin and Magnesium Oxide in step-2 solution with stirring to get uniform suspension.
4. Disperse Montelukast Sodium in step-3 suspension with stirring.
5. Add Peppermint Oil to step 3 suspension with stirring and stir for 10 min.
6. Make up the volume to the required batch size with Mineral Oil light and stir to get uniform suspension.

Example III

Sr No	Ingredients	mg/ml	%w/v
1.	Montelukast Sodium (equivalent to Montelukast 5.0 mg)	5.20	0.52
2.	Silicon Dioxide	5.00	0.50
3.	Magnesium Oxide Light	5.00	0.50
4.	Peppermint Oil USP	0.005 mL	0.5
5.	Mineral Oil light q.s. to	1.00	100.00

Brief Manufacturing Procedure:

1. Dissolve Silicon Dioxide and ½ quantity of Mineral Oil to get a clear solution.
2. Disperse Magnesium Oxide in step-1 solution with stirring to get uniform suspension.
3. Disperse Montelukast Sodium in step-2 suspension with stirring.
4. Add Peppermint Oil to step 2 suspension with stirring and stir for 10 min.
5. Make up the volume to the required batch size with Mineral Oil light and stir to get uniform suspension.

Example IV

Sr No	Ingredients	mg/ml	%w/v
1.	Montelukast Sodium (equivalent to Montelukast 5.0 mg)	5.2	0.52
2.	Silicon Dioxide	5.0	0.5
3.	Magnesium Oxide Light	5.0	0.5
4.	Peppermint Oil USP	0.0015 mL	0.15
5.	Mineral Oil light q.s. to	1.00	100

Brief Manufacturing Procedure:

1. Dissolve Silicon Dioxide and ½ quantity of Mineral Oil to get a clear solution.
2. Disperse Magnesium Oxide in step-1 solution with stirring to get uniform suspension.

3. Disperse Montelukast Sodium in step-2 suspension with stirring.
4. Add Peppermint Oil to step 2 suspension with stirring and stir for 10 min.
5. Make up the volume to the required batch size with Mineral Oil light and stir to get uniform suspension.

Stability Study of Montelukast Suspension prepared in accordance of Example 4:

Composition of Example 4 was subjected to stability studies at 40^0 C and 75% RH for 3 months. After one month, two month and three month sample was removed and checked for various parameters. Data of 1, 2 and 3 month stability studies is shown in Table 1.

Stability Study of Example 4 **Stability Conditions: 40^0 C and 75% RH for 1 Month, 2 Month and 3 Month**				
Parameters	**Initials**	**1 Month**	**2 Month**	**3 Month**
Assay	100.20	100.10	100.90	100.10
Sulfoxide	0.060%	0.288%	0.4165%	0.631%
Cis isomer	0.050%	0.180%	0.180%	0.180%
S-Enantiomer	Nil	Nil	Nil	Nil
Total	0.153%	0.475%	0.741%	0.855%

CLAIMS

1. A stable liquid oral pharmaceutical composition comprising montelukast, a vehicle comprising mineral oil, desiccant and optionally pharmaceutically acceptable additives.
2. The composition of claim 1, wherein the liquid oral pharmaceutical composition is a suspension.
3. The composition of claim 1, wherein the liquid oral pharmaceutical composition is a solution.
4. The composition of claim 1, wherein the desiccant is selected from mannitol, sorbitol, xylitol, isomalt, maltitol, tribasic calcium phosphate, dibasic calcium phosphate, calcium phosphate, kaolin, lactose, microcrystalline cellulose, powdered cellulose, precipitate calcium carbonate, starch, dextrose, dextrate, sucrose, anhydrous silicon dioxide, anhydrous ethanol, sodium metabisulfite, sodium sulfate, magnesium sulfate, magnesium oxide and mixtures thereof.
5. The composition of claim 4, wherein the desiccant is selected from colloidal silicon dioxide, magnesium oxide and mixtures thereof.
6. The composition of claim 1, wherein the pharmaceutically acceptable additives are selected from sweeteners, flavours, preservatives and mixtures thereof.
7. The composition of claim 1, wherein the composition contains not more than about 1.0 % by weight of sulfoxide degradation product after storage at about 40^0 C and about 75% relative humidity for three months.
8. The composition of claim 1, wherein the composition contains not more than about 1.0 % by weight of corresponding *Cis isomer* of montelukast after storage at about 40^0 C and about 75% relative humidity for three months.
9. The composition of claim 1, wherein the composition contains not more than about 0.5 % by weight of *S-enantiomer* of montelukast after storage at about 40^0 C and about 75% relative humidity for three months.

10. A kit for dispensing pharmaceutical composition comprising montelukast, a vehicle comprising mineral oil, desiccant and optionally pharmaceutically acceptable additives.

11. A kit for dispensing pharmaceutical composition comprising a first container comprising pharmaceutical composition of montelukast and optionally desiccant, a second container comprising a vehicle comprising mineral oil, optionally desiccant and pharmaceutically acceptable additives, and instructions for use. montelukast and mineral oil occupy pre-measured volume into the respective unit of the kit.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/002661

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/08 A61K9/10 A61K31/47 A61K47/06
A61P11/06
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)
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, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/247575 A1 (ASOTRA SATISH [CA] ET AL) 1 October 2009 (2009-10-01) cited in the application paragraph [0016] paragraph [0080] - paragraph [0082] examples	1-11
A	WO 2007/126865 A2 (PATRIN PHARMA [US]; TRIVEDI JAY S [US]; QUINN ROBERT P [US]) 8 November 2007 (2007-11-08) example 2	1-11
A	US 2007/184108 A1 (HRAKOVSKY JULIA [IL] ET AL) 9 August 2007 (2007-08-09) the whole document	1-11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2012	07/03/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/002661

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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