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(54) Title: MEDICAL AEROSOL FORMULATION COMPRISING RIBAVIRIN

(57) Abstract: Disclosed herein is an aerosol formulation for use in a metered dose inhaler (MDI) for treating an allergic disease such as asthma. The formulation uses a combination of a non-cholrofluorocarbon (non-CFC) propellent, a co-solvant, and a surfactant to suspend, solubilize, and emulsify ribavirin into micronized particles for easy delivery to the respiratory tract and/or lung of a subject by oral or nasal inhalation in order to treat the allergic disease.

MEDICAL AEROSOL FORMULATION COMPRISING RIBAVIRIN

TECHNICAL FIELD

This disclosure in general relates to a medical aerosol formulation. More particularly, this disclosure relates to an aerosol formulation for use in a metered dose inhaler (MDI), the aerosol formulation is characterized in having micronized particles of ribavirin for treating asthma.

BACKGROUND ART

Description of Related Art

Delivery of drugs to the lung by way of inhalation is an important means for treating a variety of conditions, including common conditions as pneumonia, bronchial asthma and chronic obstructive pulmonary disease and some systemic conditions, such as pain management, hormonal therapy and etc.

Recently, it has been identified that a well known anti-infectious agent, ribavirin, when applied intranasally, is effective in treating allergic disease, such as asthma, pollinosis, bronchial asthma, allergic rhinitis, atopic dermatitis, and anaphylactic shock (see Chiang and Huang, WO 2007/104070). Accordingly, there exist in this art a need to develop a formulation of ribavirin, which contains ribavirin in respirable size and the ribavirin particles may be administered through oral inhalation and/or nasal inhalation, to treat allergic disease of a subject.

This invention address such need by providing an aerosol formulation, which contains micronized particles of ribavirin in respirable size, and the micronized particles are incorporated into a dispersion containing a propellent as a pressurized metered dose inhaler (MDI). For MDI application, the prepared

aerosol formulation is subsequently filled into an aerosol canister equipped with a metered dose valve. Patients can then dispense the formulation via an actuator adapted to direct the dose from the valve to the patient.

SUMMARY

As embodied and broadly described herein, disclosure herein features a novel aerosol formulation for use in a metered dosage inhaler (MDI) and is useful for treating an allergic disease of a subject, particularly, the human suffers from asthma, pollinosis, bronchial asthma, allergic rhinitis, atopic dermatitis, and anaphylactic shock. The aerosol formulation comprises respirable or inhalable micronized particles of an active agent that may be delivered to a subject with an aid of a fluid carrier.

Therefore, it is the first objective of this disclosure to provide an aerosol formulation for use in a metered dosage inhaler (MDI). The aerosol formulation comprises about 0.0001 to 1% by weight of ribavirin; about 0.0001 to 15% by weight of a co-solvent; about 0.0001 to 1% by weight of a surfactant; and about 83 to 99% by weight of a non-chlorofluorocarbon (non-CFC) propellent.

According to specific embodiments of this disclosure, the non-CFC propellent is any of 1,1,1,2-tetrafluoroethane (HFA-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227) or a mixture thereof. In some examples, the non-CFC propellent is HFA-134a.

According to specific embodiments of this disclosure, the co-solvent is selected from the group consisting of propane, butane, n-pentane, isopentane, neopentane, ethanol, isopropanol and propylene glycol. In some examples, the co-solvent is ethanol.

According to specific embodiments of this disclosure, the surfactant is selected from the group consisting of sorbitan monolaurate (SPAN 20), sorbitan monooleate (SPAN 80), sorbitan trioleate (SPAN 85), polyoxyethylene sorbitan monolaurate (TWEEN 20), polyoxyethylene sorbitan monoleate (TWEEN 80), lecithins (EPIKURON 200), oleyl polyoxyethylene ether (BRJI 92), stearyl polyoxyethylene ether (BRJI 72), lauryl polyoxyethylene ether (BRJI 30), block copolymers of oxyethylene and oxypropylene, oleic acid, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monolaurate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol, propoxylated polyethylene glycol, diethylene glycol monoethyl ether, polyvinyl pyrrolidone (PVP), olive oil, corn oil, cotton seed oil, sunflower seed oil and a combination thereof. In one example, the surfactant is less than about 1% by weight of polyethylene glycol. In aconther example, the surfactant is a combination of about 0.5% by weight of polyethylene glycol, and about 0.5% by weight of oleic acid.

It is the second objective of this disclosure to provide a metered dose inhaler, characterized in having the as-described aerosol formulation of the present disclosure.

The details of one or more embodiments of the invention are set forth in the accompanying description below. Other features and advantages of the invention will be apparent from the detail descriptions, and from claims.

It is to be understood that both the foregoing general description and the following detailed description are by examples, and are intended to provide further explanation of the invention as claimed.

DISCLOSURE OF INVENTION

The practices of this invention are hereinafter described in detail with respect to an aerosol formulation, particularly, an aerosol formulation for use in a metered dose inhaler (MDI) and contains ribavirin as a sole active agent for treating an allergic disease such as asthma, pollinosis, bronchial asthma, allergic rhinitis, atopic dermatitis, and anaphylactic shock.

In accordance with one embodiment of the disclosure, an aerosol formulation for use in the MDI is provided. The aerosol formulation comprises about 0.0001 to 1% by weight of ribavirin; about 0.0001 to 15% by weight of a co-solvent; about 0.0001 to 1% by weight of a surfactant; and about 83 to 99% by weight of a non-chlorofluorocarbon (non-CFC) propellent.

Ribavirin is conventionally used as an anti-infectious agent for treating viral infection, recently, it has also been identified that ribavirin alone is effective in treating allergic disease, which includes, but is not limited to, asthma, pollinosis, bronchial asthma, allergic rhinitis, atopic dermatitis, and anaphylactic shock (see Chiang and Huang, WO 2007/104070). For purposes of the formulation of this invention, which are intended for inhalation into the lungs, the medicament or drug is preferably micronized, whereby a therapeutically effective amount of the drug is particulate. Typically, each drug particle has a mean diameter of about 1 to 10 μm, preferably about 1 to 6 μm, and most preferably about 3μm, in order that the drug particles can be inhaled into the respiratory tract and/or lungs. The medicament or drug is present in a therapeutically effective amount, that is, an amount such that the drug can be administered as a

dispersion, aerosol, via oral or nasal inhalation, and causes its desired therapeutic effects, typically preferred with one dose, or through several doses. The drug is typically administered as an aerosol from a conventional valve, e.g., a metered dose valve, through an aerosol adapter also known as an actuator.

In the present disclosure, the aerosol formulation is prepared by micronizing the active drug, ribavirin, and thereby forming particles that are about 1 to 10 μm in diameter; and selecting particles such that the formulation comprising at least or greater than about 90%, such as about 91, 92, 93, 94, 95, 96, 97, 98, 99% or 100% of the micronized ribavirin particles of about 1 to 10 μm in diameter; and mixed the selected micronized ribavirin particles with other ingredients such as cosolvents, surfactants and propellents and sealed the mixture in a crimped canister. The particle size is desirably less than 10 μm in diameter; and preferably between 1 to 6 μm in diameter, and more preferably, about 3 μm in diameter.

The particle size of ribavirin is reduced so as to permit absorption of a substantial amount of ribavirin into the lungs upon inhalation of the formulation. The particle size may be reduced by any known means, for example, by milling or micronization. Micronization technique typically involves placing bulk drug into suitable mill. Such mill is commercially available from, for example, Jetpharma (Switzerland), under the trade name, JET MILL® MC-50D. Briefly, the drug, ribavirin, is placed in an enclosed cavity and subjected to mechanical forces from moving internal parts, *e.g.*, plates, blades, balls, pebbles, and the like. Alternatively, or in addition to parts striking the bulk drug, the housing enclosing the cavity may turn or rotate such that the bulk drug is forced against the moving

parts. Some mills, such as fluid energy mill or airjet mill, include a high-pressure air stream that forces the bulk powder into the air within the enclosed cavity to contact against internal parts. Once the size of the drug is achieved, the process may be stopped and drug having the appropriate size is recovered. Typically, the particle size of ribavirin is reduced by milling the dry powders of ribavirin to a suitable average size, preferably, between 1 to 10 μm in diameter, and more preferably between 1 to 6 μm in diameter, and most preferably, about 3 μm in diameter, which is a range suitable for inhalation. Thus, it is expected that the overall particle range may be broader than the preferred range as stated above. It should be understood that although a large percentage of the particles will be in the narrow range desired, however, this will not generally be true for all particles. The portion of particles within the preferred range may be greater than about 90%, such as about 91, 92, 93, 94, 95, 96, 97, 98, 99% or 100%, depending on the needs of a specific formulation.

The particle size may also be reduced by sieving, homogenization, and/or granulation, among others. These techniques are used either separately or in combination with one another. Typically, milling, homogenization and granulation are applied, followed by sieving to obtain the micronized ribavirin particles having desired particle size.

For optimal function of an aerosol formulation, suitable surfactants and co-solvents are commonly used in combination with a propellent to prevent the active drug, *e.g.*, micronized ribavirin particles, in the formulation from setting so quickly after agitation, so as to prevent the need of repetitive dosing. Thus, the aerosol formulation of the present disclosure comprises finely dispersed

micronized ribavirin particles that are relatively free flowing and capable of being readily dispersed in an inhalation device, such as a metered dose inhaler (MDI); and subsequently inhaled by a patient so that the particles can reach the intended region of the lung. Thus, the particles are respirable and suitable for pulmonary delivery.

Generally, the aerosol formulation of the present disclosure can be prepared by combining (1) the micronized ribavirin particles prepared as described above in an amount sufficient to provide a plurality of therapeutically effective doses; (2) the cosolvent in an amount sufficient to help disperse the micronized ribavirin particles therein and forms a suspension; (3) the surfactant in an amount sufficient to stabilize the formulation; and (4) the fluid or propellent in an amount sufficient to propel a plurality of doses, e.g., from an aerosol canister.

Suitable cosolvents for use in the present aerosol formulation include, but are not limited to, propane, butane, n-pentane, isopentane, neopentane, ethanol, isopropanol and propylene glycol. The aerosol formulation of the present disclosure preferably comprises about 0.0001 to 15% by weight of a cosolvent, and most preferably comprises about 10% by weight of a coslovent. In one example, the formulation comprises about 10% by weight of ethanol as the coslovent.

Surfactants are commonly used to stabilize an aerosol formulation. Suitable surfactants include both non-fluorinated surfactants and fluorinated surfactants known in the art. Examples of suitable surfactants include, but are not limited to, oils derived from natural sources, such as corn oil, olive oil, cotton

seed oil and sunflower seed oil; SPAN surfactants such as sorbitan monolaurate (SPAN 20), sorbitan monooleate (SPAN 80), sorbitan trioleate (SPAN 85), polyoxyethylene sorbitan monolaurate (TWEEN 20); polyoxyethylene sorbitan monoleate (TWEEN 80); lecithins (EPIKURON 200); BRJI surfactants such as oleyl polyoxyethylene ether (BRJI 92), stearyl polyoxyethylene ether (BRJI 72) and lauryl polyoxyethylene ether (BRJI 30); block copolymers of oxyethylene and oxypropylene; oleic acid; diethylene glycol dioleate; tetrahydrofurfuryl oleate; ethyl oleate; isopropyl myristate; glyceryl monooleate; glyceryl monostearate; glyceryl monolaurate; glyceryl monoricinoleate; cetyl alcohol; stearyl alcohol; polyethylene glycol; propoxylated polyethylene glycol; diethylene glycol monoethyl ether; polyvinyl pyrrolidone (PVP); and a combination thereof. The formulation may comprise less than about 1% by weight of a surfactant. In one example, the surfactant is polyethylene glycol. In aconther example, the formulation comprises a surfactant, which is a combination of about 0.5% by weight of polyethylene glycol, and about 0.5% by weight of oleic acid.

Fluorinated lower alkanes, particularly, non-chlorofluorocarbon (non-CFC) gases are particularly suitable propellents for use in this invention. They are generally present in an amount of at least 83% by weight in the formulation, for example, between about 83 to 99% by weigh in the formulation. Examples of the non-CFC gas includes, but is not limited to, 1,1,1,2-tetrafluoroethane (HFA-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227) and a mixture thereof. The formulation preferably comprises about 83 to 99% by weight of a non-CFC propellent; and more preferably about 90% by weight of a non-CFC propellent. In some examples, the non-CFC propellent is HFA-134a. In other examples, the non-CFC propellent is HFA-227.

The components of the formulation of this invention, including micronized ribavirin particles, a cosolvent, a surfactant and a propellent, can be dispersed using conventional mixer or homogenizer, by shaking, or by ultrasound energy. Bulk formulation can be transferred to smaller individual aerosol vials by using valve to valve transfer methods or pressure filling. Aerosol canisters equipped with conventional valves, preferably metered dose valves, can be used to deliver formulations of the invention.

The formulation of the invention can be delivered to the respiratory track and/or lung by oral inhalation in order to affect bronchodilation or in order to treat a condition susceptible of treatment by inhalation, e.g., asthma, pollinosis, bronchial asthma, allergic rhinitis, atopic dermatitis, and anaphylactic shock. The formulation of the invention can also be delivered by nasal inhalation in order to treat a condition susceptible of treatment by inhalation, e.g., asthma, pollinosis, bronchial asthma, allergic rhinitis, atopic dermatitis, and anaphylactic shock.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice of the present invention, exemplary methods and materials are described for illustrative purposes.

The following Examples are provided to illustrate certain aspects of the present invention and to aid those of skilled in the art in practicing this invention. These Examples are in no way to be considered to limit the scope of the invention in any manner.

EXAMPLES

Example 1 Airjet Milling of Ribavirin

Ribavirin was purchased from Archimica (Origgo, Italy) and micronized using a jet milling apparatus (Jet Mill® MC-50D). Approximately 60 g sample was passed through the jet mill. The particles from each milling run were tested on an Aerodynamic Particle Sizer 3225 (USA) to determine the particle size distribution of ribavirin after milling. It was found that over 90% of unmilled ribavirin has a particle size less than 29.6 ± 2 μm; over 90% of the micronized ribavirin has a particle size less than 5.3 ± 0.3 μm and the micronized ribavirin has a mean particle size of about 3.4 ± 0.1 μm. The yield of micronized ribavirin that passed through jet mill was about 72%.

Example 2 Preparation of Aerosol Formulation Using Micronized Ribavirin of Example 1

7.5 g of polyethylene glycol 400 (PEG 400) and 170.4 g of ethanol were stirred mixed for 10 minutes. 7.5 g of micronized ribavirin of Example 1 were added to the PEG 400/ethanol mixture, and stirred mixed for another 20 minutes, followed by sonication for 10 minutes. The resulted ribavirin suspension was fed to Iprocomsa mixer under stirring (about 300 rpm), followed by approximately 1532.4 g HFA-34a propellent and the mixture was used to fill 120 crimped canisters to form the desired aerosol formulation. The thus prepared aerosol

formulation comprises ribavirin, PEG 400, ethanol and HFA-134a in a weight ratio of about 0.5: 0.5: 10: 90.

Examples 3 to 16

Aerosol formulations of Examples 3 to 16 were formulated based on the weight ratio of the components listed in Table 1, and each formulation was prepared in accordance with procedures described above in Example 2.

Comparative Examples 1 to 4

Aerosol formulations in Comparative Examples 1 to 4 were formulated based on the weight ratio of the components listed in Table 1, and each formulation was prepared in accordance with procedures described above in Example 2 except the surfactant and/or co-solvent were eliminated in the formulations of comparative examples.

Table 1

Example	Component (in weight ratio)						
	RBV	PEG 400	Oleic acid	PVP	SPAN 85	EtOH	HFA-134a
Example 2	0.5	0.5	-	-	-	10	90
Example 3	0.5	0.05	-	-	-	10	90
Example 4	0.5	1	-	-	-	10	90
Example 5	0.5	0.25	0.25	-	-	10	90
Example 6	0.5	-	0.5	-	-	10	90

Example 7	0.5	-	1.0	-	-	10	90
Example 8	0.5	-	0.05	-	-	10	90
Example 9	0.5	0.125	0.125	-	-	10	90
Example 10	0.5	0.45	0.05	-	-	10	90
Example 11	0.5	-	0.45	0.05	-	10	90
Example 12	0.5	-	0.45	-	0.05	10	90
Example 13	0.5	0.45	-	-	0.05	10	90
Example 14	0.5	-	0.45	-	0.05	10	90
Example 15	0.5	-	-	0.05	-	10	90
Example 16	0.5	-	-	-	0.05	10	90
Comparative Example 1	0.5	-	-	-	-	-	100
Comparative Example 2	0.5	-	-	-	-	10	90
Comparative Example 3	0.5	-	-	-	-	15	85
Comparative Example 4	0.5	-	-	-	-	20	80

Note: RBV is the abbreviation of the micronized ribavirin particles prepared in accordance with the procedures described in Example 1.

The crimped canister comprising any aerosol formulation as described above and equipped with a metered dose valve was tested for the delivered-dose uniformity and the dose content uniformity in accordance with MDI/DPI Draft Guidance published by US Food and Drug Administration (FDA) in year of 1998, and/or the Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products published by European Medicines Agency (EMEA) in year of 2006. It was identified that the mean of total ten doses is not outside 250 μg/puff ± 15%, or 212.5 - 287.5 μg/puff.

OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features. From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the scope of the following claims.

Claims

1. An aerosol formulation for use in a metered dose inhaler (MDI), comprising:

about 0.0001 to 1% by weight of ribavirin;

about 0.0001 to 15% by weight of a co-solvent;

about 0.0001 to 1% by weight of a surfactant; and

about 83 to 99% by weight of a non-chlorofluorocarbon (non-CFC) propellent.

2. The aerosol formulation of claim 1, wherein the non-CFC propellent is any of 1,1,1,2-tetrafluoroethane (HFA-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227) or a mixture thereof.

3. The aerosol formulation of claim 2, wherein the non-CFC propellent is 1,1,1,2-tetrafluoroethane (HFA-134a).

4. The aerosol formulation of claim 1, wherein the co-solvent is selected from the group consisting of propane, butane, n-pentane, isopentane, neopentane, ethanol, isopropanol and propylene glycol.

5. The aerosol formulation of claim 1, wherein the surfactant is selected from the group consisting of sorbitan monolaurate, sorbitan monooleate, sorbitan trioleate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monoleate, lecithins, oleyl polyoxyethylene ether, stearyl polyoxyethylene ether, lauryl polyoxyethylene ether, block copolymers of oxyethylene and oxypropylene, oleic acid, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate,

glyceryl monostearate, glyceryl monolaurate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol, propoxylated polyethylene glycol, diethylene glycol monoethyl ether, polyvinyl pyrrolidone (PVP), olive oil, corn oil, cotton seed oil, sunflower seed oil and a combination thereof.

6. The aerosol formulation of claim 5, wherein the surfactant is polyethylene glycol.

7. The aerosol formulation of claim 5, wherein the surfactant is a combination of polyethylene glycol and oleic acid, each is about 0.5% by weight in the aerosol formulation.

8. A metered dose inhaler comprising the aerosol formulation of claim 1.

9. The metered dose inhaler of claim 8, wherein the non-CFC propellent is any of 1,1,1,2-tetrafluoroethane (HFA-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227) or a mixture thereof.

10. The metered dose inhaler of claim 9, wherein the non-CFC propellent is 1,1,1,2-tetrafluoroethane (HFA-134a).

11. The metered dose inhaler of claim 8, wherein the co-solvent is selected from the group consisting of propane, butane, n-pentane, isopentane, neopentane, ethanol, isopropanol and propylene glycol.

12. The metered dose inhaler of claim 8, wherein the surfactant is selected from the group consisting of sorbitan monolaurate, sorbitan monooleate,

sorbitan trioleate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monoleate, lecithins, oleyl polyoxyethylene ether, stearyl polyoxyethylene ether, lauryl polyoxyethylene ether, block copolymers of oxyethylene and oxypropylene, oleic acid, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monolaurate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol, propoxylated polyethylene glycol, diethylene glycol monoethyl ether, polyvinyl pyrrolidone (PVP), olive oil, corn oil, cotton seed oil, sunflower seed oil and a combination thereof.

13. The metered dose inhaler of claim 12, wherein the surfactant is polyethylene glycol.

14. The metered dose inhaler of claim 13, wherein the surfactant is a combination of polyethylene glycol and oleic acid, and each is about 0.5% by weight in the aerosol formulation.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61P31/00 (2006.01) A61K31/12 (2006.01) A61K9/12 (2006.01)

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)

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)
EPOQUE: WPIDS, MEDLINE, EPODOC. Ribavirin, Virazole (and other realted terms), HFA-134a, HFA??? (and other realted terms), pMDI, co-solvent, surfactant.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/095681 A2 (VECTRA LIMITED [GB/GB]) 6 August 2009. Whole document specifically pages 1, 8-10, 15-16, 23 and 41	1-14
X	WO 2008/049107 A1 (3M INNOVATIVE PROPERTIES COMPANY [US/US]) 24 April 2008. Whole document specifically pages 30, 33-36.	1-14
Y	WO 2001/045642 A2 (ICN PHARMACEUTICALS, INC [US/US]) 28 June 2001 Pages 1, 2	1-14
Y	WO2007/104070 A1 (FLYSUN DEVELOPMENT CO.LTD) 20 September 2007 Whole document, specifically claims 1-3, 14 and pages 5 & 6	1-14

[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
21 June 2010	29 JUN 2010
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **JONATHAN WILKINSON** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No :

INTERNATIONAL SEARCH REPORT

International application No.
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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.
X	US 2003/0178022 A1 (DAVIES *et al*) 25 September 2003. Whole Document, specifically pages 3-4 and claims 12-14, 17 and 18	1-14
Y		1-14
X	WO2000/030607 A1 (CHIESI FARMACEUTICALS [IT/IT]) 2 June 2000. Whole document, specifically pages 3-12, Tables 1 & 2 and claim 1	1-14
Y		1-14
X	EP 0 372 777 B1 (RIKER LABORATORIES INC.) 7 January 1993. Whole document, specifically examples 1,2,4,5,	1-14
Y		1-14
A	CN 1385165A (LI DAPENG [CN]) 18 December 2002 Abstract	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2010/000686

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2009095681	NONE					
WO	2008049107	EP	2073876				
CN	1385165	NONE					
WO	0145642	AU	50766/01				
WO	2007104070	AU	2006339963	CN	101410122	EP	1993564
		SE	0802191	SE	0950633	US	2009054360
US	2003178022	AU	2002361179	AU	2002361453	BR	0207631
		CA	2470857	EP	1321159	EP	1455873
		EP	1455874	HR	20040559	HU	0402487
		NO	20033722	NZ	534040	PL	369072
		US	2005061314	US	2008017191	WO	03053501
		WO	03055549	YU	64804		
WO	0030607	AU	15553/00	BR	9916865	CA	2352483
		CN	1331581	EP	1133277	IT	MI982558
		MA	26763	NO	20012517	NZ	511923
		US	6713047	US	2004184993	ZA	200104220
EP	0372777	AU	45956/89	CA	2004598	CA	2303601
		DK	595789	EP	0499344	EP	0653204
		EP	0995434	HK	7196	HK	80497
		IL	92457	JP	2200627	MX	9203480
		NZ	231579	NZ	243056	US	5225183
		US	5439670	US	5605674	US	5674473
		US	5681545	US	5683677	US	5695743
		US	5720940	US	5766573	US	5776434
		US	6352684	ZA	8909290		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX