(12) STANDARD PATENT (11) Application No. **AU 2011332031 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Pharmaceutical compositions

(51) International Patent Classification(s)
A61K 31/4192 (2006.01) ***A61K 47/38*** (2006.01)
A61K 31/421 (2006.01) ***A61P 31/04*** (2006.01)
A61K 31/422 (2006.01)

(21) Application No: **2011332031** (22) Date of Filing: **2011.11.21**

(87) WIPO No: **WO12/071324**

(30) Priority Data

(31) Number	(32) Date	(33) Country
61/416,807	**2010.11.24**	**US**

(43) Publication Date: **2012.05.31**
(44) Accepted Journal Date: **2017.01.12**

(71) Applicant(s)
Melinta Therapeutics, Inc.

(72) Inventor(s)
Li, Danping

(74) Agent / Attorney
Cullens Pty Ltd, Level 32 239 George Street, Brisbane, QLD, 4000

(56) Related Art
WO 2001/097851 A2
US 2008/0213366 A1
US 2001/0046992 A1
WO 2012/061360 A2
US 2010/0173921 A1

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 May 2012 (31.05.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/071324 A3

(51) **International Patent Classification**:
A61K 31/4192 (2006.01) *A61K 47/38* (2006.01)
A61K 31/421 (2006.01) *A61P 31/04* (2006.01)
A61K 31/422 (2006.01)

(21) **International Application Number**:
PCT/US2011/061643

(22) **International Filing Date**:
21 November 2011 (21.11.2011)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/416,807 24 November 2010 (24.11.2010) US

(63) **Related by continuation (CON) or continuation-in-part (CIP) to earlier application**:
US 61/416,807 (CIP)
Filed on 24 November 2010 (24.11.2010)

(71) **Applicant** *(for all designated States except US)*: **RIB-X PHARMACEUTICALS, INC.** [US/US]; 300 George Street, Suite 301, New Haven, CT 06511 (US).

(72) **Inventor; and**
(75) **Inventor/Applicant** *(for US only)*: **LI, Danping** [US/US]; 4 Colonial Court, Middlebury, CT 06762 (US).

(74) **Agents**: **ELRIFI, Ivor, R.** et al.; Mintz Levin Cohn Ferris Glovsky and Popeo, P.C., One Financial Center, Boston, Massachusetts 02111 (US).

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

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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).

Published:

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

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

(88) **Date of publication of the international search report**:
16 August 2012

(54) **Title**: PHARMACEUTICAL COMPOSITIONS

(57) **Abstract**: The present invention relates to pharmaceutical compositions useful for administration for treating, preventing, or reducing the risk of microbial infections.

WO 2012/071324 A3

PHARMACEUTICAL COMPOSITIONS

REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S.S.N. 61/416,807, filed November 24, 2010, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions useful for administration for treating, preventing, or reducing the risk of microbial infections.

BACKGROUND

An appropriate pharmaceutical carrier system is generally a requirement for the safe and effective delivery of a pharmaceutical active. The entire pharmaceutical composition, i.e. the pharmaceutical drug active formulated in a pharmaceutical carrier, can affect the bioavailability and also the pharmacokinetics and pharmacodynamics of the active. It is therefore important that a pharmaceutical composition be carefully developed and manufactured to deliver the desired pharmaceutical active in a safe and effective manner.

The delivery of antimicrobial agents for treating microbial infections can present special challenges. To provide therapeutic efficacy, it is generally desired that the antimicrobial agent be administered to the patient to achieve systemic concentrations in the bloodstream or target organs above a minimum inhibitory concentration (i.e. the MIC) and for a sufficient time against the particular microbial organism or organisms being targeted. Consequently, an antimicrobial agent that otherwise exhibits an effective antimicrobial profile *in vitro* can be ineffective, or even harmful, unless properly formulated for *in vivo* administration.

Therefore, the development and manufacture of suitable pharmaceutical compositions for the safe and effective delivery of pharmaceutical drug actives, in particular of antimicrobial agents, are important and ongoing needs. The present invention will be seen to meet these and other needs.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions useful for administration for treating, preventing, or reducing the risk of microbial infections in a patient. The present invention also relates to methods for making these pharmaceutical compositions and to the use of a pharmaceutical composition in the preparation of a medicament for treating, preventing, or reducing the risk of microbial infections in a patient.

The present invention relates to a pharmaceutical composition comprising prior to mixing;

(a) an oxazolidinone antimicrobial agent or a pharmaceutically acceptable salt, ester, or prodrug thereof,

(b) a hydroxypropylmethyl cellulose polymer,

(c) a disintegrant,

(d) a lubricant,

(e) a binder and

(f) a filler.

In other embodiments the present invention relates to a pharmaceutical composition comprising;

(a) an oxazolidinone antimicrobial agent or a pharmaceutically acceptable salt, ester, or prodrug thereof,

(b) a hydroxypropylmethyl cellulose polymer,

(c) a disintegrant,

(d) a lubricant, and

(e) a filler.

In other embodiments the present invention relates to a pharmaceutical composition wherein said oxazolidinone antimicrobial agent comprises a pharmaceutically acceptable amount.

In other embodiments the present invention relates to a pharmaceutical composition wherein said oxazolidinone antimicrobial agent comprises a prophylactically effective amount.

In other embodiments the present invention relates to a pharmaceutical composition wherein said oxazolidinone antimicrobial agent is radezolid, linezolid, torezolid, or a pharmaceutically acceptable salt or prodrug thereof.

In other embodiments the present invention relates to a pharmaceutical composition wherein said oxazolidinone antimicrobial agent is radezolid or a pharmaceutically acceptable salt thereof.

In other embodiments the present invention relates to a pharmaceutical composition wherein said pharmaceutically acceptable salt is a hydrochloride salt.

In other embodiments the present invention relates to a pharmaceutical composition wherein said oxazolidinone antimicrobial agent is radezolid monohydrochloride.

In other embodiments the present invention relates to a pharmaceutical composition wherein said hydroxypropylmethylcellulose polymer is a hydroxypropylmethylcellulose acetate succinate, which is also known by the abbreviation HPMCAS.

In other embodiments the present invention relates to a pharmaceutical composition wherein said HPMCAS is selected from HPMCAS-M, HPMCAS-H, and mixtures thereof.

In other embodiments the present invention relates to a pharmaceutical composition wherein said disintegrant is croscarmellose sodium.

In other embodiments the present invention relates to a pharmaceutical composition wherein said lubricant is selected from colloidal silicon dioxide, magnesium stearate, and mixtures thereof.

In other embodiments the present invention relates to a pharmaceutical composition wherein said binder is microcrystalline cellulose.

In other embodiments the present invention relates to a pharmaceutical composition wherein said filler is selected from lactose monohydrate, dicalciumphosphate, and mixtures thereof.

In other embodiments the present invention relates to a pharmaceutical composition wherein said composition comprises a physical mixture.

In other embodiments the present invention relates to a pharmaceutical composition wherein said composition comprises an amphorous dispersion of said oxazolidinone antimicrobial agent.

In other embodiments the present invention relates to a pharmaceutical composition comprising

Ingredients	**Percent by Weight**
Intra Granular	
Radezolid hydrochloride (amount as hydrochloride salt)	20.31%
HPMCAS-M Spray Dried	13.28%
HPMCAS-H Spray Dried	13.28%
Croscarmellose Sodium	4.00%
Microcrystalline cellulose	11.60%
Lactose monohydrate	11.60%
Colloidal silicon dioxide	0.75%
Magnesium Stearate e.g.	0.19%
Extra Granular	
Croscarmellose Sodium	1.50%
Di-Cal Phosphate (DC Grade)	23.38%
Colloidal silicon dioxide	0.06%
Magnesium Stearate e.g.	0.06%

In other embodiments the present invention relates to a method of treating a microbial infection in a patient comprising administering a pharmaceutically effective amount of a pharmaceutical composition of the present invention.

In other embodiments the present invention relates to a method of preventing a microbial infection in a patient comprising administering a prophylactically effective amount of a pharmaceutical composition of the present invention.

In other embodiments the present invention relates to a method of reducing the risk of a microbial infection in a patient comprising administering a prophylactically effective amount of a pharmaceutical composition of the present invention.

In other embodiments the present invention relates to a pharmaceutical composition for treating a microbial infection in a patient.

In other embodiments the present invention relates to a pharmaceutical composition for preventing a microbial infection in a patient.

In other embodiments the present invention relates to a pharmaceutical composition for reducing the risk of a microbial infection in a patient.

In other embodiments the present invention relates to the use of an antibiotic compound in the manufacture of a pharmaceutical composition according to the present invention for treating a microbial infection in a patient comprising administering a pharmaceutically effective amount of said pharmaceutical composition to said patient.

In other embodiments the present invention relates to the use of an antibiotic compound in the manufacture of a pharmaceutical composition according to the present invention for preventing a microbial infection in a patient comprising administering a prophylactically effective amount of said pharmaceutical composition to said patient.

In other embodiments the present invention relates to the use of an antibiotic compound in the manufacture of a pharmaceutical composition according to the present invention for reducing the risk of a microbial infection in a patient comprising administering a prophylactically effective amount of said pharmaceutical composition to said patient.

In other embodiments the present invention relates to a method, composition, or use of the present invention wherein said patient is a human or an animal.

In other embodiments the present invention relates to a method, composition, or use wherein said patient is a human.

Definitions of specific embodiments of the invention as claimed herein follow.

According to a first embodiment of the invention, there is provided a pharmaceutical composition comprising:

(a) radezolid or a pharmaceutically acceptable salt or prodrug thereof;

(b) a hydroxypropylmethyl cellulose polymer;

(c) croscarmellose sodium;

(d) a lubricant selected from the group consisting of colloidal silicon dioxide, magnesium stearate and any mixture thereof;

(e) microcrystalline cellulose; and

(f) a filler selected from the group consisting of lactose monohydrate, dicalcium phosphate and any mixture thereof,

wherein said pharmaceutical composition comprises a physical mixture.

According to a second embodiment of the invention, there is provided a pharmaceutical composition comprising:

(a) radezolid or a pharmaceutically acceptable salt or prodrug thereof;

(b) a hydroxypropylmethyl cellulose polymer;

(c) croscarmellose sodium;

(d) a lubricant selected from the group consisting of colloidal silicon dioxide, magnesium stearate and any mixture thereof; and

(e) a filler selected from the group consisting of lactose monohydrate, dicalcium phosphate and any mixture thereof;

wherein said pharmaceutical composition comprises a physical mixture.

According to a third embodiment of the invention, there is provided a pharmaceutical composition comprising:

(a) radezolid or a pharmaceutically acceptable salt or prodrug thereof;

(b) hydroxypropylmethylcellulose acetate succinate (HPMCAS);

(c) a disintegrant;

(d) a lubricant;

(e) a binder; and

(f) a filler.

According to a fourth embodiment of the invention, there is provided a pharmaceutical composition comprising:

(a) radezolid or a pharmaceutically acceptable salt or prodrug thereof;

(b) hydroxypropylmethylcellulose acetate succinate (HPMCAS);

(c) a disintegrant;

(d) a lubricant; and

(e) a filler.

According to a fifth embodiment of the invention, there is provided a pharmaceutical composition comprising an intragranular composition and an extragranular composition, wherein:

the intragranular composition comprises by percent by weight: radezolid hydrochloride (amount as hydrochloride salt) 20.31%; HPMCAS-M spray dried 13.28%; HPMCAS-H spray dried 13.28%; croscarmellose sodium 4.00%; microcrystalline cellulose 11.60%; lactose monohydrate 11.60%; colloidal silicon dioxide 0.75%; and magnesium stearate 0.19%; and

the extragranular composition comprises by percent by weight: croscarmellose sodium 1.50%; di-cal phosphate (DC Grade) 23.38%; colloidal silicon dioxide 0.06%; and magnesium stearate 0.06%.

According to a sixth embodiment of the invention, there is provided a method of treating a microbial infection in a patient, said method comprising administering to the patient a pharmaceutically effective amount of the pharmaceutical composition of any one of the first to fifth embodiments.

According to a seventh embodiment of the invention, there is provided a method of preventing a microbial infection in a patient, said method comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of any one of the first to fifth embodiments.

According to an eighth embodiment of the invention, there is provided a method of reducing the risk of a microbial infection in a patient, said method comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of any one of the first to fifth embodiments.

According to a ninth embodiment of the invention, there is provided use of the pharmaceutical composition of any one of the first to fifth embodiments in the manufacture of a

medicament for treating a microbial infection in a patient, wherein said medicament is formulated to provide a pharmaceutically effective amount of radezolid to said patient.

According to a tenth embodiment of the invention, there is provided use of the pharmaceutical composition of any one of the first to fifth embodiments in the manufacture of a medicament for preventing a microbial infection in a patient, wherein said medicament is formulated to provide a prophylactically effective amount of radezolid to said patient.

According to an eleventh embodiment of the invention, there is provided use of the pharmaceutical composition of any one of the first to fifth embodiments in the manufacture of a medicament for reducing the risk of a microbial infection in a patient, wherein said medicament is formulated to provide a prophylactically effective amount of radezolid to said patient.

Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge.

[Text continues on page 6]

The foregoing and other aspects and embodiments of the present invention can be more fully understood by reference to the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions useful for administration to a patient for treating, preventing, or reducing the risk of microbial infections. These compositions comprise an oxazolidinone antimicrobial agent, a buffer, a pH modifier, and a solvent.

1. Definitions

The terms "carrier" or "carrier system" means one or more compatible substances that are suitable for delivering, containing, or "carrying" a pharmaceutical active ingredient for administration to a patient or subject.

The terms "patient" or "subject", as used herein, mean a human or an animal. Examples of animals include domesticated animals, nonlimiting examples of which include household companion animals such as cats and dogs, food animals such as cattle, sheep, goats, pigs, poultry, fish, and shellfish, zoo and other exhibition animals, and work and other animals such horses, llamas, rabbits, etc.

As used herein, the term "effective amount" refers to an amount of a pharmaceutical active compound, or a combination of compounds, for example an antimicrobial agent or agents, when administered alone or in combination, to treat, prevent, or reduce the risk of a disease state or condition, for example a microbial infection. The term also refers to an amount of a pharmaceutical composition containing an active compound or combination of compounds. For example, an effective amount refers to an amount of the compound present in a formulation given to a recipient patient or subject sufficient to elicit biological activity, for example, anti-infective activity, such as e.g., anti-microbial activity or anti-bacterial activity.

As used herein, the phrase "pharmaceutically acceptable" refers to those active compounds, materials, compositions, carriers, and/or dosage forms which are, within the

scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

As used herein, the term "pharmaceutically effective amount" refers to an amount of a pharmaceutical active compound, or a combination of compounds, for example an antimicrobial agent or agents, when administered alone or in combination, to treat, prevent, or reduce the risk of a disease state or condition, for example a microbial infection. The term also refers to an amount of a pharmaceutical composition containing an active compound or combination of compounds. For example, a pharmaceutically effective amount refers to an amount of the pharmaceutical active present in a pharmaceutical composition or formulation of the present invention or on a medical device containing a composition or formulation of the present invention given to a recipient patient or subject sufficient to elicit biological activity, for example, activity against a microbial infection.

The term "prophylactically effective amount" means an effective amount of a pharmaceutical active compound, or a combination of compounds, for example an antimicrobial agent or agents, when administered alone or in combination, to prevent, or reduce the risk of a disease state or condition, for example a microbial infection -- in other words, an amount to give a preventative or prophylactic effect. The term also refers to an amount of a pharmaceutical composition containing an active compound or combination of compounds.

The term "treating", as used herein, means to cure an already present disease state or condition, e.g. a microbial infection in a patient or subject. Treating can also include inhibiting, i.e. arresting the development of a disease state or condition, e.g. a microbial infection, and relieving or ameliorating, i.e. causing regression of the disease state or condition, e.g. a microbial infection.

The term "preventing", as used herein means, to completely or almost completely stop a disease state or condition, e.g. a microbial infection, from occurring in a patient or subject, especially when the patient or subject is predisposed to such or at risk of contracting a disease state or condition, e.g., a microbial infection. Preventing can also include inhibiting, i.e. arresting the development, of a disease state or condition, e.g., a microbial infection.

The term "reducing the risk of", as used herein, means to lower the likelihood or probability of a disease state or condition, e.g., a microbial infection, from occurring in a patient or subject, especially when the patient or subject is predisposed to such or at risk of contracting a disease state or condition, e.g., a microbial infection.

One or ordinary skill in the art will appreciate that there can be some overlap in the definitions of "treating", "preventing", and "reducing the risk of".

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the pharmaceutical active compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, e.g., glycine, alanine, phenylalanine, arginine, etc.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990) and

Remington: The Science and Practice of Pharmacy, 20th Edition, Baltimore, MD: Lippincott Williams & Wilkins, 2000, which are incorporated by reference herein in their entirety. For example, salts can include, but are not limited to, the hydrochloride and acetate salts of the aliphatic amine-containing, hydroxyl amine-containing, and imine-containing compounds of the present invention.

Additionally, the compounds of the present invention, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

The compounds of the present invention can also be prepared as esters, for example pharmaceutically acceptable esters. For example a carboxylic acid function group in a compound can be converted to its corresponding ester, e.g., a methyl, ethyl, or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, e.g., an acetate, propionate, or other ester.

The compounds of the present invention can also be prepared as prodrugs, for example pharmaceutically acceptable prodrugs. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention can be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of

prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

In the specification, the singular forms also include the plural, 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. In the case of conflict, the present specification will control.

All percentages and ratios used herein, unless otherwise indicated, are by weight.

Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

2. Compositions of the present invention

The invention relates to a method of treating a microbial infection in a patient comprising administering a pharmaceutically effective amount of a pharmaceutical composition. The invention relates to a method of preventing a microbial infection in a patient comprising administering a prophylactically effective amount of a pharmaceutical composition. The invention relates to a method of reducing the risk of a microbial infection in a patient comprising administering a prophylactically effective amount of a pharmaceutical composition.

The invention relates to a pharmaceutical composition for treating a microbial infection in a patient. The invention relates to a pharmaceutical composition for preventing a microbial infection in a patient. The invention relates to a pharmaceutical composition for reducing the risk of a microbial infection in a patient.

The invention relates to the use of an antibiotic compound in the manufacture of a pharmaceutical composition for treating a microbial infection in a patient comprising administering a pharmaceutically effective amount of said pharmaceutical composition to said patient. The invention relates to the use of an antibiotic compound in the manufacture of a pharmaceutical composition for preventing a microbial infection in a patient comprising administering a prophylactically effective amount of said pharmaceutical composition to said patient. The invention relates to the use of an antibiotic compound in the manufacture of a pharmaceutical composition for reducing the risk of a microbial infection in a patient comprising administering a prophylactically effective amount of said pharmaceutical composition to said patient.

The invention relates to a method, composition, or use wherein said patient is a human or an. In one embodiment, the invention relates to a method, composition, or use wherein said patient is a human.

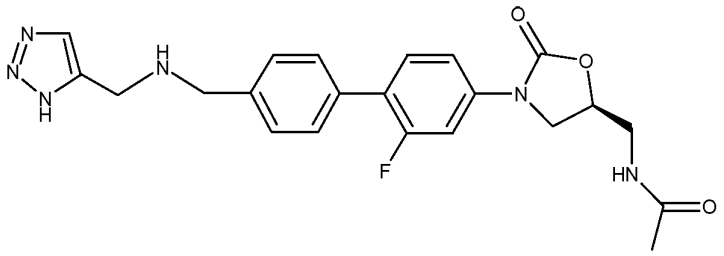
The compositions of the present invention comprise the following essential and optional components.

a. Oxazolidinone Antimicrobial Agent

Oxazolidinone antimicrobial agents and their pharmaceutically acceptable salts, esters, and prodrugs thereof, can be used in the methods, compositions, and uses of the present invention.

Oxazolidinone antimicrobial agents are described in U.S. Patent No. 7,456,206 B2, to Lou et al., issued November 25, 2008; U.S. Patent No. 7,148,219 B2, to Lou et al., issued December 12, 2006, and its certification of correction of March 4, 2008; U.S. Patent No. 7,129,259 B2, to Chen et al., issued October 31, 2006, and its certificate of correction of March 6, 2007; U.S. Patent No. 6,969,726 B2, to Lou et al., issued November 29, 2005, and its certificates of correction of February 27, 2007 and November 27, 2007; U.S. Patent No. 5,688,792, to Barbachyn et al., issued November 18, 1997; PCT Publication WO 2001/94342, to Dong A Pharm. Co. Ltd, published December 13, 2001; and PCT Publication WO 2005/058886 to Dong A Pharm. Co. Ltd, published June 30, 2005.

Nonlimiting examples of oxazolidione antimicrobial agents useful herein include the following compound:



or a pharmaceutically acceptable salt or prodrug thereof. Examples of salts include the hydrochloride salt. A further example of a salt is the monohydrochloride salt. The foregoing compound corresponds to the chemical name, inter alia, N-[3-(2-Fluoro-4'-{[(3H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide. This compound is also known by the USAN, radezolid, and corresponds to the CAS registry number 869884-78-6. The monohydrochloride salt is known by the USAN, radezolid hydrochloride, and to the CAS registry number 869884-77-5.

Other oxazolidione antimicrobial agents useful herein include linezolid and torezolid.

The dose of the oxazolidinone antimicrobial agent and mode of administration of the pharmaceutical composition will depend upon the intended patient or subject and the targeted microorganism, e.g., the target bacterial organism.

The oxazolidinone antimicrobial agent is used in a weight percentage in the composition to provide the desired pharmacological properties, such as e.g. drug bioavailability from the final composition. Weight percentages of the oxazolidinone antimicrobial agent range from about 0.01% to about 5%. In further embodiments, weight percentages range from about 0.1% to about 0.5%. In further embodiments, weight percentages range from about 0.25% to about 0.40%.

b. Hydroxypropylmethylcellulose Polymer

The compositions of the present invention comprise a hydroxypropylmethylcellulose polymer. Examples of hydroxypropylmethylcellulose polymers include hydroxypropylmethylcellulose acetate succinate polymer, abbreviated as HPMCAS. Examples of HPMCAS useful herein include the commercially available HPMCAS-M and HPMCAS-H, both available from Shin-Etsu, Japan.

c. Disintegrant

The compositions of the present invention comprise a disintegrant. An example of a disintegrant is corscarmellose sodium.

d. Lubricant

The compositions of the present invention comprise a lubricant. Examples of lubricants include magnesium stearate, colloidal silicon dioxide, and mixtures thereof.

e. Binder

The compositions of the present invention comprise a binder. An example of a binder is microcrystalline cellulose.

f. Filler

The compositions of the present invention comprise a filler. Examples of fillers include lactose monohydrate, dicalcium phosphate, and mixtures thereof.

g. Other Additional Components

The compositions of the present invention can further comprise one or more additional components selected from a wide variety of excipients known in the pharmaceutical formulation art. According to the desired properties of the tablet or capsule, any number of ingredients can be selected, alone or in combination, based upon their known uses in preparing the compositions of the present invention. Such ingredients include, but are not limited to, water; nonaqueous solvents (e.g. ethanol); coatings; capsule shells; colorants; waxes, gelatin; flavorings; preservatives (e.g., methyl paraben, sodium benzoate, and potassium benzoate); antioxidants [e.g., butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E and vitamin E esters such as tocopherol acetate]; flavor enhancers; sweeteners (e.g., aspartame and saccharin); compression aids; surfactants, etc.

3. Methods of making the pharmaceutical carriers and pharmaceuticals compositions

Useful carriers and compositions for administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in Eds. R. C. Rowe, et al., Handbook of Pharmaceutical Excipients, Fifth Edition, Pharmaceutical Press (2006), *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990), *Remington: The Science and Practice of Pharmacy,* 20th Edition, Baltimore, MD: Lippincott Williams & Wilkins, 2000, and L. Lachman, H.A. Lieberman, J.L. Kanig (1986). *The Theory and Practice of Industrial Pharmacy (3rd Ed.)*. Lea & Febiger, Philadelphia, which are incorporated by reference herein in their entirety.

4. Methods of Treating, Preventing or Reducing the Risk of Microbial Infections

The present invention also provides a method of treating, preventing, or reducing the risk of a microbial infection in a patient or subject. These methods comprise administering a pharmaceutically or prophylactically effective amount of the pharmaceutical actives of the present invention as a pharmaceutical composition or formulation from the carriers of the present invention to a patient or subject at an appropriate dosage.

One of ordinary skill in the art can select an appropriate dosage of the pharmaceutical active. In practicing the methods of the present invention, it is desired that the blood and or tissue level in the patient or subject of the compound be of an appropriate level for a sufficient time interval. As mentioned above, to provide therapeutic efficacy, it is generally desired that the antimicrobial agent be administered to the patient to achieve systemic concentrations in the bloodstream or target organs above a minimum inhibitory concentration (i.e. the MIC) and for a sufficient time against the particular microbial organism or organisms being targeted.

The pharmaceutical compositions of the present invention are useful for treating, preventing, or reducing the risk of a disorder such as a microbial infection in a patient or subject, e.g., a human, or a nonhuman mammal or other animal. This comprises the step or steps of administering a pharmaceutically effective or prophylactically effective amount of a composition of the present invention. Microbial infections or treatments include, *inter alia,* those selected from the group consisting of a skin infection, pneumonia (both nosocomial and community acquired pneumonia), post-viral pneumonia, an abdominal infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio-ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin-resistant *Staphylococcus aureus* infection, a vancomycin-resistant *Enterococci* infection, a linezolid-resistant organism infection, and tuberculosis.

In conjunction with the methods of the present invention, pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) can be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician can consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

Generally, an effective amount of dosage of the pharmaceutical active will be in the range of from about 0.1 to about 100 mg/kg of body weight/day, more preferably from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend

on such variables as the disease or condition that one is intending to treat, prevent, or reduce the risk of, the overall health status of the patient, the relative biological efficacy of the parent compound delivered from the hydrogen sulfate salt, the formulation, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered can be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage can be smaller than the optimum.

5. Examples

Example 1. A pharmaceutical composition for oral administration.

Ingredients	Percent by Weight	mg in Tablet
Intra Granular		
Radezolid hydrochloride (amount as hydrochloride salt)	20.31%	162.51
HPMCAS-M Spray Dried	13.28%	106.24
HPMCAS-H Spray Dried	13.28%	106.24
Croscarmellose Sodium	4.00%	31.98
Microcrystalline cellulose	11.60%	92.76
Lactose monohydrate	11.60%	92.76
Colloidal silicon dioxide	0.75%	6.00
Magnesium Stearate	0.19%	1.50
Extra Granular		
Croscarmellose Sodium	1.50%	12.00
Di-Cal Phosphate (DC Grade)	23.38%	187.00
Colloidal silicon dioxide	0.06%	0.50
Magnesium Stearate e.g	0.06%	0.50
Total	100.00%	800.00

Procedure steps.

1. Pass radezolid hydrochloride and colloidal silicon dioxide through a #20 Mesh screen. Co-screen these together, not sequentially.
2. Bag blend 5 minutes. Sample approximately 0.25g to a glass vial.

3. Pass remaining intragranular ingredients, except the magnesium stearate, through a co-mill U5 at 1000 rpm with a 0.032R screen. Collect all in a single container.

4. Add to V-blender and blend for 1 minute at 24 rpm.

5. Remove approximately 100g of blend.

6. Add radezolid hydrochloride and colloidal silicon dioxide from step 2 to V-blender.

7. Add 100g of blend to container containing radezolid hydrochloride, hand shake, and add to blender, on the same side as the API was added.

8. Blend for 15 min. at 24 rpm.

9. Pass Magnesium Stearate through a #20 Mesh Screen with the approximately100g of blend from step 8.

10. Blend in V (Twin Shell) blender for 4 min. at 24 RPM. Collect 50g sample for bsv, tsv, etc.

11. Dry Granulate on TF Mini Roller compactor to a Solid Fraction of 0.6-0.7. Start with polished smooth rolls, switch to grooved if necessary.

12. Mill Dry Granulated ribbons on the Co-Mill U5 with 0.032"Conidur screen at 100rpm. Stop after approximately 100-300g and measure particle size.

13. If needed, change to different screen. Screen used: 0.032C and complete granulation.

14. Add granules from step 13 and extragranular croscarmellose sodium, colloidal silicon dioxide, and dicalciumphosphateto 4qt. V -Blender and blend for 15 min. at 24 RPM.

15. Pass the extragranular magnesium stearate through a #20 Mesh Screen with approximately 100g of blend from step 14 above.

16. Blend in V (Twin Shell) blender for 4 min. at 24 RPM. Save 100g Final Blend for characterization.

17. Compress on Kilian T100 rotary tablet press with 0.3586 X 0.7174 " Modified Oval to a hardness of approximately 16-20 Kp. Sample using BRPPD stratified sampling plan.

The foregoing formulation is useful for treating, preventing, or reducing the risk of a microbial infection in a patient in need thereof, e.g. a human patient.

INCORPORATION BY REFERENCE

The entire disclosure of each of the patent documents, including certificates of correction, patent application documents, scientific articles, governmental reports, websites, and other references referred to herein is incorporated by reference in its entirety for all purposes.

EQUIVALENTS

The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

2011332031 14 Dec 2016

CLAIMS

1. A pharmaceutical composition comprising:

(a) radezolid or a pharmaceutically acceptable salt or prodrug thereof;

(b) a hydroxypropylmethyl cellulose polymer;

(c) croscarmellose sodium;

(d) a lubricant selected from the group consisting of colloidal silicon dioxide, magnesium stearate and any mixture thereof;

(e) microcrystalline cellulose; and

(f) a filler selected from the group consisting of lactose monohydrate, dicalcium phosphate and any mixture thereof,

wherein said pharmaceutical composition comprises a physical mixture.

2. A pharmaceutical composition comprising:

(a) radezolid or a pharmaceutically acceptable salt or prodrug thereof;

(b) a hydroxypropylmethyl cellulose polymer;

(c) croscarmellose sodium;

(d) a lubricant selected from the group consisting of colloidal silicon dioxide, magnesium stearate and any mixture thereof; and

(e) a filler selected from the group consisting of lactose monohydrate, dicalcium phosphate and any mixture thereof;

wherein said pharmaceutical composition comprises a physical mixture.

3. A pharmaceutical composition comprising:

(a) radezolid or a pharmaceutically acceptable salt or prodrug thereof;

(b) hydroxypropylmethylcellulose acetate succinate (HPMCAS);

(c) a disintegrant;

(d) a lubricant;

(e) a binder; and

(f) a filler.

4. A pharmaceutical composition comprising:

(a) radezolid or a pharmaceutically acceptable salt or prodrug thereof;

(b) hydroxypropylmethylcellulose acetate succinate (HPMCAS);

(c) a disintegrant;

(d) a lubricant; and

(e) a filler.

5. The pharmaceutical composition of claim 3 or claim 4, wherein said disintegrant is croscarmellose sodium.

6. The pharmaceutical composition of any one of claims 3 to 5, wherein said lubricant is selected from colloidal silicon dioxide, magnesium stearate and any mixture thereof.

7. The pharmaceutical composition of any one of claims 3, 5 and 6, wherein said binder is microcrystalline cellulose.

8. The pharmaceutical composition of any one of claims 3 to 7, wherein said filler is selected from lactose monohydrate, dicalciumphosphate and any mixture thereof.

9. The pharmaceutical composition of any one of claims 3 to 8, wherein said composition comprises a physical mixture.

10. The pharmaceutical composition of any one of claims 3 to 9, wherein said composition comprises an amorphous dispersion of said radezolid or said pharmaceutically acceptable salt or prodrug thereof.

11. The pharmaceutical composition of any one of claims 1 to 10, wherein said radezolid or said pharmaceutically acceptable salt or prodrug thereof is provided in a pharmaceutically effective amount.

12. The pharmaceutical composition of any one of claims 1 to 10, wherein said radezolid or said pharmaceutically acceptable salt or prodrug thereof is provided in a prophylactically effective amount.

13. The pharmaceutical composition of any one of claims 1 to 12, wherein said pharmaceutically acceptable salt is a hydrochloride salt.

14. The pharmaceutical composition of any one of claims 1 to 13, wherein said radezolid is radezolid monohydrochloride.

15. The pharmaceutical composition of any one of claims 1, 2 and 11 to 14 when dependent on claim 1 or claim 2, wherein said hydroxypropylmethylcellulose polymer is hydroxypropylmethylcellulose acetate succinate (HPMCAS).

16. The pharmaceutical composition of any one of claims 3 to 10 and 15, wherein said HPMCAS is selected from HPMCAS-M, HPMCAS-H and any mixture thereof.

17. A pharmaceutical composition comprising an intragranular composition and an extragranular composition, wherein:

the intragranular composition comprises by percent by weight: radezolid hydrochloride (amount as hydrochloride salt) 20.31%; HPMCAS-M spray dried 13.28%; HPMCAS-H spray dried 13.28%; croscarmellose sodium 4.00%; microcrystalline cellulose 11.60%; lactose monohydrate 11.60%; colloidal silicon dioxide 0.75%; and magnesium stearate 0.19%; and

the extragranular composition comprises by percent by weight: croscarmellose sodium 1.50%; di-cal phosphate (DC Grade) 23.38%; colloidal silicon dioxide 0.06%; and magnesium stearate 0.06%.

18. A method of treating a microbial infection in a patient, said method comprising administering to the patient a pharmaceutically effective amount of the pharmaceutical composition of any one of claims 1 to 17.

19. A method of preventing a microbial infection in a patient, said method comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of any one of claims 1 to 17.

20. A method of reducing the risk of a microbial infection in a patient, said method comprising administering to the patient a prophylactically effective amount of the pharmaceutical composition of any one of claims 1 to 17.

21. Use of the pharmaceutical composition of any one of claims 1 to 17 in the manufacture of a medicament for treating a microbial infection in a patient, wherein said medicament is formulated to provide a pharmaceutically effective amount of radezolid to said patient.

22. Use of the pharmaceutical composition of any one of claims 1 to 17 in the manufacture of a medicament for preventing a microbial infection in a patient, wherein said medicament is formulated to provide a prophylactically effective amount of radezolid to said patient.

23. Use of the pharmaceutical composition of any one of claims 1 to 17 in the manufacture of a medicament for reducing the risk of a microbial infection in a patient, wherein said medicament is formulated to provide a prophylactically effective amount of radezolid to said patient.

24. The method of any one of claims 18 to 20 or the use of any one of claims 21 to 23, wherein said patient is a human or an animal.

25. The method of any one of claims 18 to 20 or the use of any one of claims 21 to 23, wherein said patient is a human.

Date: 14 December 2016