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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **EXPEDIENTE 04-044-562**

TÍTULO SOLICITADO: **"Formulaciones de azitromicina directamente compresibles"**

PUBLICACIÓN: **Gaceta 543 de 01-09-2004, número de publicación 229**

PRIORIDAD: **US60/343,480 de Diciembre 21 de 2001**

SOLICITANTE: **PFIZER PRODUCTS INC**

APODERADO: **CARLOS R. OLARTE**

TRÁMITE: **SUSTENTACIÓN DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, identificado como aparece al pie de mi firma, reconocido apoderado de la opositora en el trámite de la referencia, estando dentro de los términos de la prórroga solicitada, por medio del presente escrito me permito ratificar y sustentar los argumentos del escrito principal de oposición, también radicado dentro del plazo de ley ante esa entidad.

I. RATIFICACIÓN

Reitero a su Despacho la solicitud de negar el beneficio patentario para la totalidad de las reivindicaciones contenidas en el expediente en referencia, por los argumentos que fueron expuestos en el escrito de oposición de 29/11/2004, en donde se ha explicado la carencia de novedad y de nivel inventivo teniendo en cuenta:

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- Las 13 formas cristalinas de la sustancia **Azitromicina** reveladas en la solicitud en trámite carecen por completo de nivel inventivo si se tiene en cuenta que la US 4.474.768 y la EP 0 298 650 A2, ya revelaban la misma sustancia **"AZITROMICINA"** en las formas cristalinas monohidratada y dihidratada de la misma; que si bien es cierto, no se refieren exactamente a las formas cristalinas aquí descritas, es evidente que las mismas 13 formas cristalinas no son más que simples formas de presentación de materia conocida, excluidas de la posibilidad de obtener patente.

- La aplicación europea **EP 1 103 558 A2** (que a pesar de haber sido publicada en mayo 30 de 2001, tiene prioridad ES9902620 de noviembre 26 de 1999) en la tabla citada en la página 4, resume los diferentes procesos para la preparación de las **formas cristalinas de azitromicina.**

- La aplicación internacional WO 95/30422 publicada en noviembre 16 de 1995 revela el empleo de Azitromicina en forma de sales farmacéuticamente aceptables, en forma **ANHIDRA** o forma hidratada y dosis del mismo, que aunque no son las mismas dosis de la solicitud en trámite, no lo es menos, que la eventual concesión de patente con base en los rangos de dosificación del principio activo "Azitromicina", supondría restringir a los médicos y desarrolladores de medicamentos la posibilidad de proponer y utilizar formulaciones de dicho agente entre 250 y 600mg.

- Los tamaños de partícula revelados y en consecuencia su biodisponibilidad, corresponde simplemente a un fenómeno que es conocido, que no traduce ningún avance sobre el estado de la técnica, y que es el resultado de un proceso rutinario de pre-formulación, consistente en realizar la determinación de la distribución del tamaño de partícula más adecuado para la compresión y ensayos sobre disolución de la forma farmacéutica obtenida.

II. COMPLEMENTO DE INFORMACIÓN

El Informe Internacional de Búsqueda practicado por la Oficina Europea de Patentes a la aplicación internacional PCT/WO03/053416A1, publicada el 3 de julio de 2003, y equivalente a la solicitud en trámite, en tanto invocan la misma

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prioridad, señala la existencia de cuatro (4) anterioridades que afectan la novedad y el nivel inventivo de dicha solicitud y por ende, los de la solicitud colombiana:

- La publicación internacional WO 95/30422 A tantas veces mencionada, se refiere al empleo de Azitromicina en forma de sales farmacéuticamente aceptables, en forma **ANHIDRA** o forma hidratada y dosis del mismo.

  Además, en los ejemplos 14 y 16 a 19 se revela algunos procesos para la elaboración de tabletas de Azitromicina de liberación sostenida, mediante compresión directa en seco.

- La aplicación europea EP 0758 549 publicada el 19 de febrero de 1997 y equivalente a la patente US 5,795,871 publicada en agosto 18 de 1998, desvirtúa lo revelado en las reivindicaciones 1, 9 a 11 y 13 de la solicitud colombiana en trámite, puesto que se refiere a composiciones farmacéuticas que contiene compuestos macrólidos de 14 o 15 miembros como Azitromicina para el tratamiento de cáncer de pulmón, en formas de dosificación como tabletas, tabletas recubiertas, gránulos, etc, las cuales pueden ser preparadas por métodos convencionales.

  También señala que las tabletas pueden ser preparadas por granulación de una mezcla homogénea del compuesto de interés con uno o más excipientes adecuados como ligantes, desintegrantes, lubricantes, y posterior compresión de la mezcla. Alternativamente, las tabletas pueden ser producidas directamente por compresión del compuesto como está, o mediante una mezcla apropiada con excipientes.

- La publicación internacional WO 99/12552 publicada el 18 de marzo de 1998 desvirtúa lo revelado en las reivindicaciones 1, 9 a 11 y 13 de la solicitud colombiana en trámite, puesto que las composiciones farmacéuticas reveladas contienen como principio activo Azitromicina, las cuales son convenientemente administradas por vía oral en forma de tabletas, cápsulas, polvo o gránulos o como soluciones o suspensiones, y en donde las tabletas pueden ser preparadas por compresión en una máquina adecuada del ingrediente activo en una forma que fluya libremente (polvo o gránulos), opcionalmente mezclado con ligantes, lubricantes, diluentes inertes, agentes dispersantes o por moldeo.

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- En el mismo sentido, la publicación internacional WO 00/57886 publicada el 5 de octubre de 2000 desvirtúa lo revelado en las reivindicaciones 1, 10 y 11 de la solicitud colombiana en trámite, puesto que este documento se refiere particularmente a comprimidos dispersables de macrólidos (entre los que se encuentra como principio activo Azitromicina); que son obtenidos mediante: a) la mezcla del principio activo con los desintegrantes que forman parte de la composición, b) posteriormente la granulación vía húmeda, c) el secado de los gránulos obtenidos, d) la adición del resto de excipientes como por ejemplo desintegrantes, agentes diluentes, lubricantes, aromas; y e) la compresión de la mezcla resultante.

EN CONCLUSIÓN

Es claro que la presente solicitud de patente CO 04-044-562 se encuentra afectada principalmente en nivel inventivo, teniendo en cuenta los argumentos expuestos en el escrito de oposición presentada ante ese Despacho y lo contenido en ésta sustentación de oposición.

III. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, las siguientes:

- Informe Internacional de Búsqueda practicado por la Oficina Europea de Patentes a la aplicación internacional PCT/WO03/053416 A1.
- Primera página y apartes de la materia descriptiva de la patente americana US 5,795,871 de agosto 18 de 1998.
- Primera página y apartes de la materia descriptiva de la aplicación internacional PCT/WO 99/12552 de marzo 18 de 1999.
- Primera página y apartes de la materia descriptiva de la aplicación internacional PCT/WO 00/57886 de octubre 5 de 2000.

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(19) Europäisches Patentamt
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(54) MEDICINAL COMPOSITION AS A REMEDY FOR NONSMALL CELL LUNG CANCER

(57) 14- or 15-membered-ring macrolide compounds such as clarithromycin, erythromycin B, etc. have a potent antitumor effect on non-small cell lung cancers which are considered the most difficult tumors to be be subjected to surgical operation and chemotherapy, and are useful as a practical therapeutic agent of non-small cell lung cancer.

EP 0 758 549 A1

US005795871A

United States Patent [19]

Narita et al.

[11] Patent Number: 5,795,871

[45] Date of Patent: Aug. 18, 1998

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[54] PHARMACEUTICAL COMPOSITION FOR TREATMENT OF NON-SMALL CELL LUNG CANCER

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[22] PCT Filed: Apr. 26, 1995

[86] PCT No.: PCT/JP95/00819

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[87] PCT Pub. No.: WO95/28930

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[30] Foreign Application Priority Data

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[51] Int. Cl.[6] A61K 31/70

[52] U.S. Cl. 514/29; 514/28

[58] Field of Search 514/28, 29

[56] References Cited

U.S. PATENT DOCUMENTS

4,331,803	5/1982	Watanabe et al	514/29
4,349,545	9/1982	d'Ambrosio et al.	514/29
4,517,359	5/1985	Kobrehel et al	514/28

OTHER PUBLICATIONS

The Merck Index, 7th Ed., 1989, Merck & Co. Inc. Rahway, N.J. pp. 146, 365, 577, 578 and 1316.

Chem. Abst., vol. 96 (1982) Columbus, OH, USA #1869.

Inci. J. Natl. Cancer Inst. (1981), 67[4], pp. 877–880.

Primary Examiner—Jerome D. Goldberg

Attorney, Agent, or Firm—Lawson & Lund

[57] ABSTRACT

14- or 15-membered-ring macrolide compounds such as clarithromycin, erythromycin B, etc. have a potent antitumor effect on non small cell lung cancers which are considered the most difficult tumors to be be subjected to surgical operation and chemotherapy, and are useful as a practical therapeutic agent of non-small cell lung cancer.

16 Claims, No Drawings

PHARMACEUTICAL COMPOSITION FOR TREATMENT OF NON-SMALL CELL LUNG CANCER

TECHNICAL FIELD

The present invention relates to a pharmaceutical composition effective as an anticancer agent for non-small cell lung cancer comprising a 14- or 15-membered-ring macrolide compound as an effective ingredient.

BACKGROUND ART

In many countries including Japan, Europe and America, the number of patients with lung cancer is fairly large and further increasing year after year with deterioration of atmospheric environment on the earth, contrary to the number of patients with gastric cancer which is reducing year after year. Lung cancers can be histologically classified into non-small cell lung cancers (e.g. squamous cell carcinoma, adeno carcinoma, large cell carcinoma, etc.) and small cell lung cancer. Non-small cell lung cancer has very largely different biological properties and responses to chemotherapeutics from those of small cell lung cancer. Thus, chemotherapeutic formulas are different between these two types of lung cancer.

It is reported that non-small cell lung cancers are the tumors of which chemotherapy is the most difficult, and any useful therapies for advanced inoperable cancers have not been established (*Journal of Clinical Oncology*, vol. 10, pp. 829–838 (1992)). The combination therapy of cisplatin and interferon is reported (European Journal of Cancer, vol. 30A, No. 1, pp. 11–15 (1994)). However, this remedy can not be widely acceptable because of insufficient therapeutic effect and harmful side effects.

Japanese Patent Kokai 5-163293 refers to some specified antibiotics of 16-membered-ring macrolides as a drug delivery carrier capable of transporting anthracycline-type anticancer drugs into the lungs for the treatment of lung cancers. However, the macrolide antibiotics specified herein are disclosed to be only a drug carrier, and there is no reference to the therapeutic use of macrolides against non-small cell lung cancers.

WO 93/18052 refers to the effectiveness of the specified 16-membered-ring macrolides such as bafilomycin, etc. in treating non-small cell lung cancers, but they have not yet been clinically practicable.

Pharmacology, vol. 41, pp. 177–183 (1990) describes that a long-term use of erythromycin increases productions of interleukins 1, 2 and 4, all of which contribute to host immune responses, but there is no reference to the effect of this drug on non-small cell lung cancers.

Teratogenesis, Carcinogenesis, and Mutagenesis, vol. 10, pp. 477–501 (1990) describes that some of antimicrobial drugs can be used as an anticancer agent, but does not refer to their application to non-small cell lung cancers.

In addition, interleukins are known to have an antitumor effect, but have not been reported to be effective against non-small cell lung cancers.

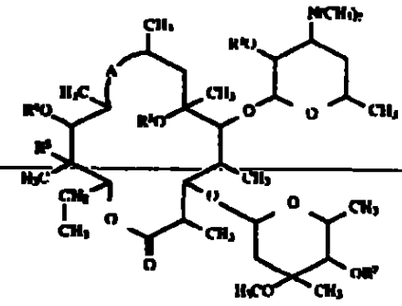
Any 14- or 15-membered-ring macrolides have not been reported to be effective against non-small cell lung cancers.

As stated above, at present, there is no disclosure about practical chemotherapeutic drugs of non-small cell lung cancer, and any chemotherapeutic drugs clinically available are not practicable for the treatment of non-small cell lung cancer. Accordingly, apart from the conventional concept of anticancer chemotherapy, there is a strong need for the development of therapeutic drugs practicably effective for the treatment of non-small cell lung cancers.

DISCLOSURE OF THE INVENTION

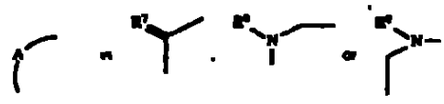
As a result of extensive research of antitumor activity of various compounds in order to solve the above problem, unexpectedly, the present inventors have found that certain 14- or 15-membered-ring macrolide compounds have the ability to inhibit the growth and metastasis of non-small cell lung cancers, a useful effect on the malignant tumor which distantly metastasized to other organs and an excellent treatment effect in patients with advanced inoperable non-small cell lung cancers, and improve the quality of life of the patients. Based on these findings, the present invention has been accomplished.

The present invention is a pharmaceutical composition for the treatment of non-small cell lung cancers comprising as an effective ingredient a compound represented by Formula (I):



(I)

[wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom, an optionally substituted alkyl group or an acyl group, R^5 is a hydrogen atom or —OR^6 (wherein R^6 is a hydrogen atom, an optionally substituted alkyl group or an acyl group, or R^4 and R^6 together form >C—O), and



(wherein R^7 is an oxygen atom or =N—O—$(CH_2)_n$—X—R^8 (wherein n is an integer of 1 to 6, X is an oxygen atom, a sulfur atom or —NY— (wherein Y is a hydrogen atom or an optionally substituted hydrocarbon group), and R^8 is an optionally substituted hydrocarbon group) and R^9 is a hydrogen atom or an optionally substituted hydrocarbon group)] or a pharmaceutically acceptable salt thereof.

Further, the present invention is a method for the treatment of non-small cell lung cancer comprising administering an effective amount of the compound of Formula (I) or a pharmaceutically acceptable salt thereof to humans.

Furthermore, the present invention is use of the compound of Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of the pharmaceutical composition for the treatment of non-small cell lung cancer.

In Formula (I), the alkyl group of the optionally substituted alkyl group as defined for R^1, R^2, R^3, R^4 and R^6 is, for example, a C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, etc.), preferably a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.), and particularly preferably a methyl group because of a stronger antitumor activity.

Examples of the substituent of the optionally substituted alkyl group are hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, ethylcarbonyloxy, etc.), halogen (fluorine, bromine, chlorine, iodine), etc. The alkyl group may optionally have 1 to 3 of these substituents at any available positions, and when there are two or more substituents, they may be the same or different.

The acyl group as defined for R^1, R^2, R^3, R^4 and R^6 in Formula (I) is, for example, a carboxylic acid acyl group or a sulfonic acid acyl group, and preferably a carboxylic acid acyl group because of a stronger antitumor activity.

The carboxylic acid acyl group is, for example, an acyl group derived from a carboxylic acid, and specifically —C(=O)—R^a (wherein R^a is a hydrogen atom or an optionally substituted hydrocarbon group).

The sulfonic acid acyl group is, for example, an acyl group derived from a sulfonic acid, and specifically —SO_2—R^b (wherein R^b is an optionally substituted hydrocarbon group).

The optionally substituted hydrocarbon group for R^a and R^b is the same as the optionally substituted hydrocarbon group defined below.

Preferred examples of the acyl group are a carboxylic acid acyl group such as a formyl group, a C_{1-6} alkyl-carbonyl group (e.g. acetyl, propionyl, etc.), a C_{2-6} alkenyl-carbonyl group (e.g. acryloyl, methacryloyl, etc.) and a C_{6-14} aryl-carbonyl group (e.g. benzoyl, etc.); and a sulfonic acid acyl group such as a C_{1-6} alkylsulfonyl group (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, etc.) and the like. The acyl group may optionally have 1 to 3 substituents in any available positions, and examples of the substituent are halogen (fluorine, chlorine, bromine, iodine), hydroxyl, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), amino, cyano, etc. When there are two or more substituents, they may be the same or different.

Examples of the optionally substituted hydrocarbon group as defined for Y, R^5 and R^6 in Formula (I) are those shown in the following (1) to (5).

(1) a C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine).

(2) a C_{2-6} alkenyl group (e.g. vinyl, allyl, isopropenyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethyl-amino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine).

(3) a C_{2-6} alkinyl group (e.g. ethinyl, 2-propinyl, 2-butinyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine).

(4) a C_{6-14} aryl group (e.g. phenyl, etc.) optionally having 1 to 5 substituents selected from (a) a C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, iso-propyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine), (b) mono- or di-C_{1-6} alkylamino (e.g. methylamino, ethylamino, dimethylamino, diethylamino, etc.), (c) C_{1-6} alkyl-carbonylamino (e.g. acetylamino, etc.), (d) hydroxyl, (e) carboxyl, (f) nitro, (g) cyano, (h) C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), (i) C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and (j) halogen (fluorine, chlorine, bromine, iodine), and

(5) a C_{7-16} aralkyl group (e.g. benzyl, etc.) optionally having 1 to 5 substituents selected from (a) a C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethyl-amino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine), (b) mono- or di-C_{1-6} alkylamino (e.g. methylamino, ethylamino, dimethylamino, diethylamino, etc.), (c) C_{1-6} alkyl-carbonylamino (e.g. acetylamino, etc.), (d) hydroxyl, (e) carboxyl, (f) nitro, (g) cyano, (h) C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), (i) C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and (j) halogen (fluorine, chlorine, bromine, iodine).

The optionally substituted hydrocarbon group is preferably a C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.) optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propionyloxy, etc.) and halogen (fluorine, chlorine, bromine, iodine).

The C_{1-6} alkyl group, the C_{2-6} alkenyl group, the C_{2-6} alkinyl group, the C_{6-14} aryl group and the C_{7-16} aralkyl group as exemplified above for the optionally substituted hydrocarbon group are those optionally having substituents at any available positions, and when there are two or more substituents, they may be the same or different.

R^1, R^2, R^3 and R^4 are preferably each a hydrogen atom or a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.), and more preferably each a hydrogen atom or a methyl group because of a stronger antitumor activity.

R^5 is preferably a hydrogen atom or —OR^6 (wherein R^6 is a hydrogen atom or a C_{1-4} alkyl group such as methyl, ethyl, propyl, isopropyl, etc.), and more preferably a hydrogen atom, a hydroxyl group or a methoxy group because of a stronger antitumor activity.

Preferably, R^7 is an oxygen atom or —N—(—$(CH_2)^n$—X—R^8 (wherein X is an oxygen atom or —$N^{Y'}$— (wherein Y' is a C_{1-4} alkyl group such as methyl, ethyl, propyl, isopropyl, etc.), and R^8 is a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.), a C_{1-4} alkoxy-C_{1-4} alkyl group (e.g. methoxymethyl, methoxy-ethyl, ethoxymethyl, ethoxyethyl, etc.), and n is an integer of 1 to 4) because of a stronger antitumor activity.

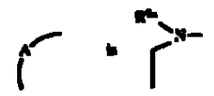
R^9 is preferably a hydrogen atom, a C_{1-4} alkyl group (e.g. methyl, ethyl, propyl, isopropyl, etc.), or the C_{2-4} alkenyl group (e.g. vinyl, allyl, isopropenyl, etc.), and more preferably a C_{1-4} alkyl group (e.g. methyl, etc.) because of a stronger antitumor activity.

Examples of the compound of Formula (I) or salt thereof having a good therapeutic effect on non-small cell lung cancer are the following two Compounds A) and B).

(Compound A): A compound of Formula (I) wherein R^1, R^2, R^4 and R^5 are each a hydrogen atom or a C_{1-4} alkyl group, R^3 is a hydrogen atom or $-OR^{3a}$ (wherein R^{3a} is a hydrogen atom or a C_{1-4} alkyl group), and

[wherein R^{7a} is an oxygen atom or $=N-O-(CH_2)_m-O-R^{8a}$ (wherein m is an integer of 1 to 4, and R^{8a} is a C_{1-4} alkoxy-C_{1-4} alkyl group)] or a salt thereof.

Compound B) : A compound of Formula (I) wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom or a C_{1-4} alkyl group, R^5 is a hydrogen atom or $-OR^{5a}$ (wherein R^{5a} is a hydrogen atom or a C_{1-4} alkyl group), and



(wherein R^{6a} is a hydrogen atom, a C_{1-4} alkyl or a C_{2-4} alkenyl group) or a salt thereof.

In Compounds A) and B), the C_{1-4} alkyl group as defined for R^1, R^2, R^3, R^4 and R^5 is preferably a methyl, the C_{1-4} alkoxy-C_{1-4} alkyl group as defined for R^{8a} is preferably a methoxymethyl group, and the C_{2-4} alkenyl group as defined for R^{6a} is preferably a vinyl group.

The compounds of Formula (I) or salts thereof contain isomers thereof, but preferably natural-type because of a stronger antitumor activity.

Preferable compounds of the present invention are, for example, erythromycin A (R^1, R^2, R^3 and R^4 are each a hydrogen atom, R^5 is a hydroxyl group and -A- is >C=O in Formula (I)), erythromycin B (R^1, R^2, R^3, R^4 and R^5 are each a hydrogen atom, and —A— is >C=O in Formula (I)), clarithromycin (R^1, R^2 and R^4 are each a hydrogen atom, R^3 is a methyl group, R^5 is a hydroxyl group, and —A— is >C=O in Formula (I)), roxithromycin (R^1, R^2, R^3 are R^4 are each a hydrogen atom, R^5 is a hydroxyl group, and —A— is >—N—$CH_2OCH_2CH_2OCH_3$ in Formula (I)) and azithromycin (R^1, R^2, R^3 and R^4 are each a hydrogen atom, R^5 is a hydroxyl group, and —A— is

in Formula (I)), and erythromycin A and clarithromycin are more preferable because of establishing clinically therapeutic effect on non-small cell lung cancer in the present invention.

Examples of the pharmaceutically acceptable salt of the compound of the present invention are salts with inorganic acids (e.g. hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, nitrate, etc.) and salts with organic acids (e.g. acetate, malate, maleate, fumarate, tartrate, succinate, citrate, butyrate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, lactobionate, stearate, etc.) without, however, being limited thereby.

The compounds of the present invention or pharmaceutically acceptable salts thereof can be prepared, for example, by the methods described in U.S. Pat. Nos. 2,823,203, 4,331,803, 4,349,545 and 4,517,359, Tetrahedron Lett., vol. 34, No. 31, pp. 4913–4916 (1993), Journal of Synthetic Organic Chemistry, vol. 38, No. 4, pp. 395–414 (1980) or modifications thereof.

The compounds of the present invention and pharmaceutically acceptable salts thereof have the therapeutic effect on intractable solid cancers such as non-small cell lung cancer in humans and other mammals (e.g. rats, mice, rabbits, dogs, cats, cows, pigs, etc.), and can be used as their bulks because of low toxicity, but usually as dosage forms for the treatment of non-small cell cancer prepared by using pharmaceutically acceptable carriers in the same manner as other antibiotics are prepared. The pharmaceutically acceptable carriers to be used are appropriately chosen from excipients (e.g. calcium carbonate, kaolin, sodium bicarbonate, lactose, starches, crystalline cellulose, talc, granulated sugar, porous materials, etc.), binders (e.g. dextrin, gums, α-starch, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose, pullulan, etc.), disintegrators (e.g. carboxymethylcellulose calcium, croscarmellose sodium, crospovidone, low substituted hydroxypropylcellulose, starch partially in the α-form, etc.), lubricants (e.g. magnesium stearate, calcium stearate, talc, starch, sodium benzoate, etc.), coloring agents (e.g. tar color, caramel, iron sesquioxide, titanium oxide, riboflavins, etc.), correigents (e.g. sweetening agents, flavoring agents, etc.), stabilizers (e.g. sodium sulfite, etc.) and preservatives (e.g. parabens, sorbic acid, etc.).

The pharmaceutical composition of the present invention contains the compound of Formula (I) or a salt thereof in the same amount as it is used as an anti-bacterial agent. Usually, the amount of the compound of Formula (I) or a salt thereof is 0.1 to 100% by weight based on the total weight of the composition, specifically 20 to 100% by weight in case of the solid form such as capsules, tablets, granules, etc., and 5 to 30% by weight in case of the liquid form such as injections, etc. because of stability of the preparations. Examples of the dosage form are tablets (including sugar-coated tablets, film-coated tablets, etc.), pills, capsules, granules, fine granules, powders, syrups, emulsions, suspensions, injections, etc. These preparations can be prepared by conventional methods such as the methods described in Japanese Pharmacopoeia, etc. Specifically, tablets can be prepared by granulating a homogeneous mixture of the compound of the present invention with an excipient, a binder, a disintegrator or other appropriate additives, adding a lubricant and the like, and compressing the mixture for shaping. Alternatively, tablets can directly be prepared by compressing the compound of the present invention as it is or a homogeneous mixture of it with an excipient, a binder, a disintegrator, suitable additives and the like. If desired, the tablets can contain a coloring agent, a corrigent and the like. The tablets can be also coated with an appropriate coating agent. Injection can be prepared by charging a container with a suitable amount of a solution, a suspension or an emulsion of a suitable amount of the compound of the present invention in an aqueous solvent (e.g. water for injection, physiological saline, Ringer's solution, etc.) or in non-aqueous solvent(e.g. vegetable oils, etc.), or a suitable amount of the compound of the present invention, and then sealing the container.

Examples of the carrier for oral compositions are conventional materials in pharmaceutical preparations such as starch, mannitol, crystalline cellulose and sodium carboxymethylcellulose, etc. Examples of the carrier for injections are distilled water, physiological saline, glucose solution and transfusion solutions such as sugar-solution,

electrolyte solution, amino acid solution, albumin, etc. Furthermore, other additives usually used in pharmaceutical preparations can appropriately be also added.

The above-mentioned preparations can appropriately contain suitable amounts of other anticancers (e.g. ifosfamide, mitomycin C, vindesine, cisplatin, vinblastine, procarbazine, vincristine, adriamycin, etc.) or antibiotics (e.g. penicillin G, takesulin, panspurin, amphotericin B, miconazol, sulfamethaxasole, trimethoprim, josamycin, etc.).

The dose of the pharmaceutical composition of the present invention depends on the patient's age, body weight, severity of the disease, administration route, administration frequency and the like, but for example, it is 0.1 to 100 mg/kg, preferably 0.5 to 10 mg/kg per day of the compound (I) or a salt thereof for an adult patient with non-small cell lung cancer, and more preferably each 200 mg twice per day for an adult person weighing 60 kg. The administration route may be oral or parenteral.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated in more detail by the following experiments and examples without, however, being limited thereby.

Experiment 1 Antitumor Effect on Mouse Ehrlich Ascites Carcinoma EAC

Mouse Ehrlich ascites carcinoma EAC cells (5×10^6) were subcutaneously transplanted to ddy mice (7 weeks old). After 7 days, a control group received 0.9% ethanol orally every day during the survival time. An administration group received erythromycin A dissolved in the same vehicle similarly. For comparison, an untreated group was also inquired. Each group consists of 10 mice. 30 Days after the transplantation, the survival rate (%) of mice as well as the mean survival time (MST) were determined, and the results are together shown in Table 1.

Experiment 2 Antitumor Effect on Mouse Leukemia P388

Mouse leukemia P388 cells (10^6) were abdominally transplanted to CDF1 mice (7 weeks old). The administration of erythromycin A was started on the next day. The test was carried out in the same manner as that of Experiment 1, and the results are shown in Table 1.

TABLE 1

Antitumor effect on mouse Ehrlich ascites carcinoma EAC and mouse leukemia P388

Dose of erythromycin (mg/kg)	Antitumor Activity: EAC (ddy mice) Survival rate (%) 30 days	EAC (ddy mice) MST (day)	P388 (CDF1 mice) Survival rate (%) 30 days	P388 (CDF1 mice) MST (day)
1	43*	38.2	37*	36.2
5	63**	44.7	77**	43.6
10	70*	50.8	86*	46.8
Vehicle-control	0	23.6	0	11.9
Untreated	0	24.2	0	12.3

*<0.5, **<0.05

As shown in Table 1, in case of the vehicle-control group, the survival rate after 30 days is 0%, and the mean survival time is short (23.6 days). On the contrary, in case of the erythromycin A (5 mg/kg) administration group, the survival rate after 30 days is 63%, and the mean survival time is long (42.7 days). Furthermore, in case of the untreated group, the survival rate after 30 days is 0%, and the mean survival time is also short (24.2 days).

It is found from these results that erythromycin A has a prolonged survival effect against EAC- and P388-transplanting mice, and an inhibitory effect on the growth of the cancer cells.

Experiment 3 Clinical Effect in Patients With Primary Multiple Non-Small Cell Lung Cancer

A man, 70 years old, 163 cm in high, weighing 55 kg, with primary multiple non-small cell lung cancer was administered orally with erythromycin A every day, and there was no recurrence for 5 years after the therapy.

Experiment 4 Clinical Effect in Patients With Primary Multiple Non-Small Cell Lung Cancer

Fifty patients, 41 to 82 years old, with III to IV stages of primary non-small cell lung cancers regarded as inoperable (43 patients with non-small cell lung cancer and 7 patients with small cell lung cancer) were randomly divided into an clarithromycin (CAM) administration group, which was orally administered with 200 mg of CAM twice every day, and a non-administration group. The survival time after the therapy of the patients of both groups was observed, and a survival curve was drawn according to the method of Kaplan-Maier, and thereby giving the 50% survival time. Results are shown in Table 2.

TABLE 2

Group	case	50% survival time
Comparison of therapeutic effect in patients with non-small cell lung cancer		
CAM administration group	22	930 days
CAM non-administration group	21	299 days
Comparison of therapeutic effect in patients with small cell lung cancer		
CAM administration group	3	246 days
CAM non-administration group	4	251 days

As shown in Table 2, in case of the patients with non-small cell lung cancer, the 50% survival time is 930 days in the CAM administration group, contrary to 299 days in the CAM non-administration group. It is established from the results that the survival time of the CAM administration patients is prolonged much longer than that of the CAM non-administration patients. On the other hand, there is confirmed no difference between both groups in case of the patients with small cell lung cancer. It is found from the fact that CAM has an excellent therapeutic effect in patients with non-small lung cell cancer only.

It is also observed that the CAM administration patients are good in terms of appetite, general conditions and the activity of daily living (ADL), show sluggish progress of disease, and improve the quality of life (QOL) by administration of CAM. In addition, the safety of a long-term administration of CAM to humans is already demonstrated (Chemotherapy, vol. 42, pp. 430–435 (1994)), and the side effects were not found in the above clinical experiments.

Example 1 Preparation of Coated Tablets

Composition (Per Coated Tablet)

(1) Erythromycin A	20.0 mg
(2) Lactose	80.0 mg
(3) Corn Starch	45.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 20.0 mg of erythromycin A, 80.0 mg of lactose and 45.0 mg of corn starch was granulated using 0.03 ml of 10% aqueous gelatin solution (containing 3.0 mg of gelatin), sifted through a 1 mm-mesh sieve, dried at 40° C., and sifted again. The thus-obtained granules were mixed with 2.0 mg of magnesium stearate and compressed. The resulting core tablet was sugar-coated with an aqueous solution of sucrose, titanium oxide, talc and gum arabic, and polished with yellow bees wax to give a coated tablet.

Example 2 Preparation of Tablet

Composition (per tablet)	
(1) Clarithromycin	20.0 mg
(2) Lactose	70.0 mg
(3) Corn Starch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

20.0 mg of clarithromycin and an 3.0 mg of magnesium stearate were granulated using 0.07 ml of 10% aqueous solution of soluble starch (containing 7.0 mg of gelatin), dried and mixed with 70.0 mg of lactose and 50.0 mg of corn starch. The mixture was compressed to give a tablet.

Example 3 Preparation of Injection Solution

Composition (per ampule)	
(1) Erythromycin A	5.0 mg
(2) Lactobionic acid	2.5 mg
(3) Sodium chloride	20.0 mg
(4) Distilled water	ad 2 ml.

5.0 mg of erythromycin A, 2.5 mg of lactobionic acid, 20.0 mg of sodium chloride were mixed to distilled water to a total volume of 2.0 ml. The solution was filtered and charged into a 2 ml-ampule under aseptic conditions. The ampule was sterilized and sealed to obtain an injection solution.

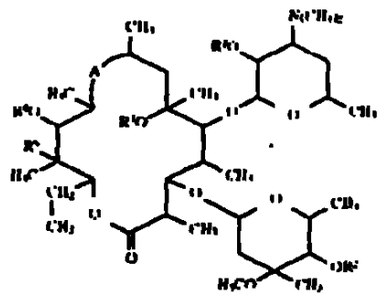
INDUSTRIAL UTILIZABILITY

The pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof of the present invention has a great effect against non-small cell lung cancers which have been considered the most difficult tumors to be subjected to surgical operation and chemotherapy, and is useful as a practical therapeutic agent of non-small cell lung cancers. In addition, it can be used safely without side effects which induce serious conditions unlike the previously used anticancer agents.

We claim:

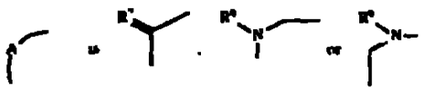
1. A method for the treatment of non-small cell lung cancer in a human comprising:

administering to said human an effective amount of a compound represented by the formula:



(I)

wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom, an optionally substituted alkyl group or an acyl group, R^5 is a hydrogen atom or —OR^9 (wherein R^9 is a hydrogen atom, an optionally substituted alkyl group or an acyl group, or R^4 and R^6 together form >C—O), and



wherein R^7 is an oxygen atom or =N—O—$(CH_2)_n$—X—R^8, wherein:

n is an integer of 1 to 6,

X is an oxygen atom, a sulfur atom or —NY—, (wherein Y is a hydrogen atom or an optionally substituted hydrocarbon group), and

R^8 is an optionally substituted hydrocarbon group; and

wherein R^9 is a hydrogen atom or an optionally substituted hydrocarbon group; or

a pharmaceutically acceptable salt thereof.

2. The method according to claim 1, wherein the optionally substituted alkyl group for R^1, R^2, R^3, R^4 and R^8 is a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen.

3. The method according to claim 1, wherein the acyl group for R^1, R^2, R^3, R^4 and R^6 is a formyl group; or a C_{1-6} alkyl-carbonyl group, a C_{2-6} alkenyl-carbonyl group, a C_{6-14} aryl-carbonyl group or a C_{1-6} alkyl-sulfonyl group, each of which may optionally have 1 to 3 substituents selected from halogen, hydroxyl, C_{1-6} alkoxy, amino and cyano.

4. The method according to claim 1, wherein the optionally substituted hydrocarbon group for Y, R^8 and R^9 is

(1) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen,

(2) a C_{2-6} alkenyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen,

(3) a C_{2-6} alkinyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen,

(4) a C_{6-14} aryl group optionally having 1 to 5 substituents selected from (a) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino,

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carboxyl, nitro, mono C_{1-6} alkylamino, di C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen, (b) mono- or di-C_{1-6} alkylamino, (c) C_{1-6} alkyl carbonylamino, (d) hydroxyl, (e) carboxyl, (f) nitro, (g) C_{1-6} alkoxy, (h) C_{1-6} alkyl-carbonyloxy and (i) halogen, or

(5) A C_{7-16} aralkyl group optionally having 1 to 5 substituents selected from (a) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen, (b) mono- or di-C_{1-6} alkylamino, (c) C_{1-6} alkyl-carbonylamino, (d) hydroxyl, (e) carboxyl, (f) nitro, (g) C_{1-6} alkoxy, (h) C_{1-6} alkyl-carbonyloxy and (i) halogen.

5. The method according to claim 1, wherein the optionally substituted hydrocarbon group for Y, R^9 and R^{10} is a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from hydroxyl, amino, carboxyl, nitro, cyano, C_{1-6} alkoxy, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{1-6} alkyl-carbonyloxy and halogen.

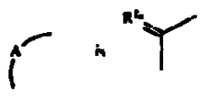
6. The method according to claim 1, wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom or a C_{1-6} alkyl group.

7. The method according to claim 1, wherein R^5 is a hydrogen atom, a hydroxyl group or a methoxy group.

8. The method according to claim 1, wherein R^7 is an oxygen atom or =N—O—$(CH_2)_n$—X—R^8 (wherein X is an oxygen atom or —$N(y^a)$— (wherein y^a is a C_{1-6} alkyl group), and R^8 is a C_{1-6} alkyl group or a C_{1-6} alkoxy-C_{1-6} alkyl group, and n is an integer of 1 to 4.

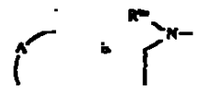
9. The method according to claim 1, wherein R^{10} is a hydrogen atom, a C_{1-6} alkyl group or a C_{2-6} alkenyl group.

10. The method according to claim 1, wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom or a C_{1-6} alkyl group, R^5 is a hydrogen atom or —OR^{5a} (wherein R^{5a} is a hydrogen atom or a C_{1-6} alkyl group), and



[wherein R^{7a} is an oxygen atom or =N—O—$(CH_2)_m$—O—R^{7b} (wherein m is an integer of 1 to 4, R^{7b} is a C_{1-6} alkoxy-C_{1-6} alkyl group)].

11. The method according to claim 1, wherein R^1, R^2, R^3 and R^4 are each a hydrogen atom or a C_{1-6} alkyl group, R^5 is a hydrogen atom or —OR^{5a} (wherein R^{5a} is a hydrogen atom or a C_{1-6} alkyl group), and



[wherein R^{10a} is a hydrogen atom, a C_{1-6} alkyl group or a C_{1-6} alkenyl group].

12. The method of claim 1 wherein said compound is erythromycin A.

13. The method of claim 1 wherein said compound is erythromycin B.

14. The method of claim 1 wherein said compound is clarithromycin.

15. The method of claim 1 wherein said compound is roxithromycin.

16. The method of claim 1 wherein said compound is azithromycin.

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(54) Title: 9a-AZALIDES AS VETERINARY ANTIMICROBIAL AGENTS

(57) Abstract

9a-Azalides are useful in the treatment and prevention of bacterial respiratory and enteric infections in livestock animals, particularly in cattle and swine.

TITLE OF THE INVENTION
9a-AZALIDES AS VETERINARY ANTIMICROBIAL AGENTS

SUMMARY OF THE INVENTION

The present invention provides methods for the treatment or prevention of bacterial respiratory or enteric infections in livestock animals.

BACKGROUND OF THE INVENTION

The morbidity and mortality associated with bacterial respiratory and enteric infections in livestock represent a major economic loss for the animal husbandry industry. In cattle, especially in younger animals, stress as a result of weaning, transportation, dehydration, alteration or deprivation of diet can cause the animals to become highly susceptible to bacterial respiratory infection, especially if the animals are housed in crowded or poorly ventilated quarters. The principal causative bacterial pathogens of bovine respiratory infections are *Pasteurella haemolytica*, *P. multocida*, *Haemophilus somnus* and *Mycoplasma* spp. In pigs respiratory infections caused by *Pasteurella multocida* or *Actinobacillus pleuropneumoniae*, and *Mycoplasma* spp. are associated with considerable losses in some herds. The most common causative organisms for enteric diseases in cattle and swine are *Escherichia coli*, *Treponema hyodysenteriae* and *Salmonella* spp.

The current therapeutic antimicrobial products against respiratory and enteric infections in livestock include a diverse group of older products effective against a broad spectrum of infectious agents, mostly notably among this group are the tetracyclines; and a group of recently introduced products indicated primarily for treatment of bovine respiratory disease, such as quinolones (danofloxacin, enrofloxacin), cephalosporins (cefquinome, ceftiofur), macrolide (tilmicosin), and florfenicol. Resistance to the older antimicrobial agents has developed in the field. Although resistance to the newer products is not yet a problem, it is known that excessive usage favors the emergence of resistance over time, but increasing the numbers of drug families, and thereby mechanisms of action, in use may decrease the probability of

resistance development to any individual compound. Thus, there exists a continuing need to discover antimicrobial compounds that are suitable for use in veterinary medicine; preferably, such compounds will belong to a different chemotype from the antimicrobial agents currently in use in animal or human medicine. Other desirable characteristics of a novel antimicrobial product for veterinary use include high potency against target organisms, high target tissue concentration, and long tissue half-life.

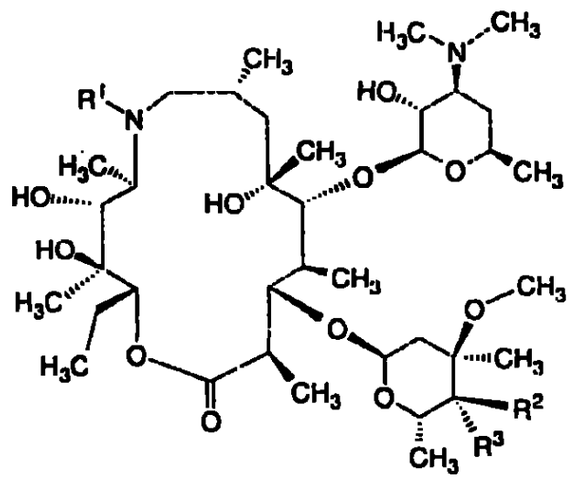
9a-Azalides are antibiotics characterized by a 15-membered lactone ring containing a ring nitrogen atom. 9a-Azalides are disclosed in, for example, US Patent 4,328,334, US Patent 4,517,359, US Patent 4,474,768, US Patent 4,464,527, US Patent 4,526,889, US Patent 4,465,674, US Patent 4,492,688, US Patent 4,512,982, US Patent 4,518,590, European Patent Application No. 136,831, European Patent Application No. 259,789, European Patent Application No. 316,128, European Patent Application No. 467,331, European Patent Application 606,062, and European Patent Application 657,464.

US 4,474,768, 4,464,527, and 4,526,889 disclose azithromycin, N-ethyl and N-propyl homologs of azithromycin, and 4"-epi-azithromycin, respectively, which are said to be active against *Pasteurella multocida* in vitro; however, the patents also state that regarding the compounds disclosed therein their in vivo activity is more limited as regards susceptible organisms. To Applicants' best knowledge, the known 9a-azalides have not been reported as being clinically useful in the treatment and prevention of bovine or swine respiratory or enteric infections.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for the treatment or prevention of bacterial respiratory or enteric infection in a livestock animal which comprises administering to a livestock animal in need of such treatment or prevention a therapeutically or prophylactically effective amount of an 9a-azalide.

In a preferred embodiment the 9a-azalide has the formula I:



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or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable metal complexes thereof, and said metal complex is taken from the group consisting of copper, zinc, cobalt, nickel and cadmium; where

R^1 is hydrogen;

C_{1-3} alkyl optionally substituted by hydroxy, C_{1-3} alkoxy, cyano, C_{1-3} alkoxycarbonyl, halogen, amino, C_{1-3} alkylamino, or di(C_{1-3} alkyl)amino;

allyl; or

propargyl; or

one of R^2 and R^3 is hydrogen and the other is

hydroxy, or

$-NH_2$.

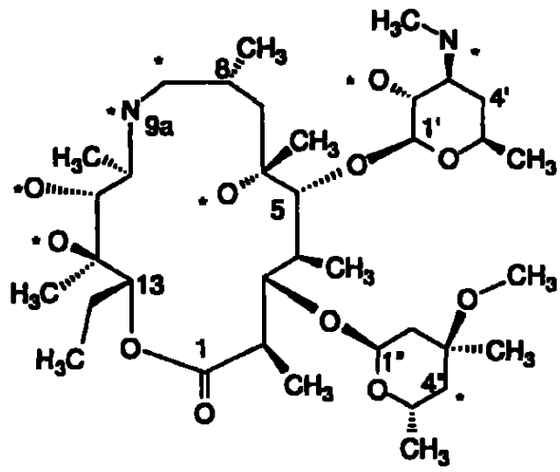
The more preferred 9a-azalides are selected from azithromycin (which is 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A), 4"-epi-azithromycin, 4"-deoxy-4"-aminoazithromycin, and 4"-epi-4"-deoxy-4"-aminoazithromycin.

In another preferred embodiment, the present invention provides a method for the treatment or prevention of bovine or swine bacterial respiratory infections wherein the causative organism is selected from a group consisting of *Pasteurella* spp., an *Actinobacillus*

spp., *Haemophilus somnus* and *Mycoplasma* spp., which comprises administering to a cattle or swine in need of such treatment or prevention a therapeutically or prophylactically effective amount of an 9a-azalide. More preferably, the 9a-azalide is of formula I; and particularly preferred are 9a-azalides selected from azithromycin, 4"-epi-azithromycin, 4"-deoxy-4"-aminoazithromycin, and 4"-epi-4"-deoxy-4"-aminoazithromycin.

In another preferred embodiment, the present invention provides a method for the treatment or prevention of bovine or swine bacterial enteric infections wherein the causative organism is selected from *Escherichia coli, Treponema hyodysenteriae,* and *Salmonella* spp., which comprises administering to a cattle or swine in need of such treatment or prevention a therapeutically or prophylactically effective amount of an 9a-azalide. More preferably the 9a-azalide is of formula I; and particularly preferred are 9a-azalides selected from azithromycin, 4"-epi-azithromycin; 4"-deoxy-4"-aminoazithromycin, and 4"-epi-4"-deoxy-4"-aminoazithromycin.

As used herein "9a-azalide" means a compound having the following core structure in which the asterisks indicate sites for substitution:



The 9a-azalides are named herein as derivatives of azithromycin, which is 9-deoxo-9a-aza-9a-methyl-9a-homocrythromycin A.

The term "therapeutically or prophylactically effective amount" means that amount of an 9a-azalide that will provide a level of antibacterial activity at the target site of infection that is sufficient to inhibit the bacteria in a manner that allows the host animal to overcome or be protected from the infection.

"Treatment or prevention" means use of 9a-azalide following or prior to manifestation of signs and symptoms suggestive of bacterial infection to allow the host animal to overcome or be protected from the infection.

"Bacterial respiratory or enteric infections" means infections of the respiratory or digestive tract for which the causative organism or the likely causative organism is susceptible to 9a-azalide. Such organisms include, but are not limited to, *Pasteurella* species (e. g. *P. haemolytica*, *P. multocida*), *Haemophilus somnus*, *Actinobacillus pleuropneumoniae*, *Mycoplasma* spp., *E. coli*, *Treponema hyodysenteriae*, and *Salmonella* spp. (e.g. *S. typhimurium*, *S. dublin*).

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

9a-Azalides are either known compounds, such as those disclosed in the patents and published patent applications cited hereinabove, or they may be prepared from readily available starting material using conventional chemical synthesis methods.

9a-Azalides may be administered to a host in need of treatment for, or prevention of bacterial respiratory or enteric diseasease

In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed. For example, in the case of oral liquid preparations such as suspensions, elixirs and solutions, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used; or in the case of oral solid preparations such as powders, capsules and tablets, carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be included. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. In addition to the common dosage forms set out above, 9a-azalides may also be administered by controlled release means and/or delivery devices.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains

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Publiée

Avec rapport de recherche internationale.

(54) Title: DISPERSIBLE MACROLIDE COMPOUNDS AND METHOD FOR THE PRODUCTION THEREOF

(54) Titre: COMPOSES DISPERSIBLES DE MACROLIDES ET LEUR PROCEDE DE PREPARATION

(57) Abstract

The invention relates to dispersible tablets containing macrolides as active ingredients either on their own or associated with other active ingredients, in addition to a method for the production thereof. The dispersible tablets are characterized in that the macrolide is chosen from a group that is made up of pristinamycin, azithromycin, roxithromycin, clarithromycin and spiramycin, and is present in a basic form in proportions ranging from 20–60 % of the total weight of said tablets. The dispersible tablets are also characterized in that they contain at least one disintegrator in proportions ranging from 1–25 % of the total weight of said tablets in addition to at least one sweetening agent. Application: antibiotherapy.

(57) Abrégé

La présente invention concerne des comprimés dispersibles renfermant des macrolides en tant que principes actifs, seuls ou associés à d'autres principes actifs, ainsi qu'à leur procédé de préparation. Ces comprimés dispersibles sont caractérisés en ce que le macrolide est choisi dans le groupe constitué par la pristinamycine, l'azithromycine, la roxithromycine, la clarithromycine et la spiramycine, et est présent sous forme de base, dans des proportions comprises entre 20% et 60% du poids total desdits comprimés, et en ce qu'ils comprennent au moins un désintégrant, dans des proportions comprises entre 1% et 25% du poids total desdits comprimés, et au moins un édulcorant. Application: antibiothérapie.

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INSTITUTO NACIONAL DE VIGILANCIA

DE MEDICAMENTOS Y ALIMENTOS

FORMULARIO UNICO DE SOLICITUD REGISTRO SANITARIO AUTOMATICO DE ALIMENTOS EXPEDICIÓN Y RENOVACIÓN DECRETO 3075/97

1. DATOS GENERALES DEL TITULAR

Nombre o Razón Social:	
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2. DATOS ESPECIFICOS DEL PRODUCTO

☐ Alimento producido o envasado en el país	☐ Alimento Importado
☐ Solicitud de Registro Sanitario	
☐ Solicitud Renovación Registro Sanitario Nro.	Vigente hasta:

Fabricante(s) o envasador(es)	Ubicación (Dirección y Ciudad)
1.	
2.	
3.	
4.	

Importador (es)	Ubicación (Dirección y Ciudad)
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2.	
3.	

Nombre del producto:

Marca(s) comercial(es):

CONDICIONES DE CONSERVACIÓN DEL PRODUCTO

☐ Temperatura ambiente	☐ Refrigeración	☐ Congelación
EXPEDIENTE Nro.	REGISTRO SANITARIO Nro.	VIGENTE HASTA

Verificado por: Subdirector de Licencias y Registros:

Declaro que la información presentada en esta solicitud respaldada con mi firma, es veraz y comprobable en cualquier momento, que conozco y acato los reglamentos vigentes que regulan las condiciones sanitarias de las fábricas de alimentos y que el producto cumple estrictamente con las normas técnico-sanitarias expedidas por el Ministerio de Salud, las oficiales colombianas o en su defecto con las normas del Codex Alimentarius. Este producto no será comercializado con indicaciones terapéuticas.

Nombre y firma del propietario, representante legal o apoderado

COMPOSES DISPERSIBLES DE MACROLIDES ET LEUR PROCEDE DE PREPARATION

La présente invention concerne des comprimés dispersibles renfermant des macrolides en tant que principes actifs, seuls ou associés à d'autres principes actifs, ainsi qu'à leur procédé de préparation.

La présente invention concerne plus particulièrement des comprimés dispersibles renfermant de l'azithromycine, de la roxithromycine ou de la clarithromycine en tant que principes actifs, seuls ou en association avec d'autres principes actifs.

En thérapeutique, la simplicité d'utilisation des comprimés, a toujours été considérée comme un avantage majeur, notamment dans le cadre de traitements ambulatoires, comme en témoigne le très grand nombre de spécialités pharmaceutiques qui se présentent sous cette forme.

Toutefois, certains patients et, notamment, les enfants et les personnes âgées, connaissent des difficultés de déglutition telles qu'il leur est difficile et, par conséquent, désagréable d'ingérer des comprimés, même avec une prise associée de liquide.

C'est la raison pour laquelle il est souhaitable de disposer de comprimés aptes à se désintégrer dans un faible volume de liquide, de manière à pouvoir être ingérés sous la forme de solutions ou de suspensions buvables.

Or, de nombreux principes actifs sont connus pour présenter une amertume très difficile à masquer, lorsqu'ils se présentent sous la forme de solutions ou de suspensions buvables.

C'est le cas en particulier des macrolides, qu'ils soient utilisés seuls ou en association avec d'autres principes actifs. Les macrolides ont en commun de comprendre un noyau lactonique central constitué par 14 à 16 chaînons avec peu ou pas de doubles liaisons et pas d'azote. Un ou plusieurs sucres aminés et/ou neutres (désosamine, cladinose, mycarose, mycaminose) sont fixés par des liaisons α ou β-glycosidiques sur ce noyau, encore appelé aglycone. On peut citer comme macrolides dérivés naturels, l'érythromycine A à F, l'oléandomycine, la spiramycine, la midécamycine et la troléandomicyne et comme macrolides semi-synthétiques, la roxithromycine, la dirithromycine, la clarithromycine, la flurithromycine et la

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EXPEDICIÓN Y RENOVACIÓN
DECRETO 3075/97

DOCUMENTOS ANEXOS
☐ Poder debidamente otorgado (según el caso)
Formulario
☐ Certificado de constitución existencia y representación legal del solicitante
☐ Certificado de constitución existencia y representación legal del fabricante
☐ Certificado de libre venta y autorización para consumo (importados)
☐ Certificado de procedencia de fabricante o distribuidor autorizado (importados)
☐ Recibo de pago por derechos de registro
Hoja con la ficha técnica del producto indicando su composición y presentaciones comerciales (empaque y pesos)
Otro Proceso de elaboración del producto
Observaciones:

Nacional:

- formulario,
- cámara de comercio (no mayor a 90 días),
- hoja indicando proceso de elaboración del producto, ingredientes y presentaciones comerciales (pesos y empaque del producto)
- y recibo de consignación si es el caso.

Importado:

- los documentos mencionados anteriormente más
- el certificado de venta libre del país de origen
- el certificado de procedencia (el fabricante autoriza el importador para comercializar el producto en Colombia).
  *Estos documentos deben venir consularizados y avalados ante el Ministerio de Relaciones Exteriores.

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En conséquence, les Inventeurs se sont donné pour but de pallier ce manque et de développer des comprimés dispersibles renfermant des principes actifs et, notamment des macrolides, très amers, et qui, bien qu'étant exempts de sucres, conduisent, lorsqu'ils se désintègrent dans de l'eau, à des suspensions buvables ayant un goût tout à fait acceptable de manière à ce que ces suspensions ne soient pas désagréables à avaler.

La présente invention a, donc, pour objet des comprimés dispersibles qui contiennent un macrolide en tant que principe actif, seul ou en association avec un autre principe actif, lesquels comprimés sont caractérisés en ce que le macrolide est choisi dans le groupe constitué par la pristinamycine, l'azithromycine, la roxithromycine, la clarithromycine et la spiramycine, et est présent sous forme de base, dans des proportions comprises entre 20% et 60% de leur poids total, et en ce qu'ils comprennent au moins un désintégrant, dans des proportions comprises entre 1% et 25% de leur poids total, et au moins un édulcorant.

Au sens de la présente invention, on entend par comprimés "dispersibles", des comprimés capables de se désintégrer complètement en moins de 3 minutes lorsqu'ils sont mis dans un liquide comme de l'eau, et de conduire, ainsi, à une suspension buvable dont l'homogénéité peut être aisément obtenue en agitant celle-ci, par exemple, au moyen d'une petite cuillère. De tels comprimés peuvent, toutefois, être également avalés directement avec une quantité de liquide propre à faciliter leur déglutition.

Malgré l'absence de sucres et, notamment, de saccharose, les comprimés conformes à l'invention présentent de manière surprenante un goût nettement plus agréable que celui présenté par les poudres et granulés dispersibles proposés jusqu'à présent pour les macrolides amers, et ce, même lorsqu'ils renferment des quantités de macrolide élevées.

Selon une première disposition avantageuse de l'invention, le macrolide utilisé est choisi dans le groupe constitué par constitué par l'azithromycine, la roxithromycine et la clarithromycine.

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4.	

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2.	
3.	

Nombre del producto:

Marca(s) comercial(es):

CONDICIONES DE CONSERVACIÓN DEL PRODUCTO

☐ Temperatura ambiente ☐ Refrigeración ☐ Congelación

EXPEDIENTE Nro.	REGISTRO SANITARIO Nro.	VIGENTE HASTA

Verificado por: Subdirector de Licencias y Registros:

Declaro que la información presentada en esta solicitud respaldada con mi firma, es veraz y comprobable en cualquier momento, que conozco y acato los reglamentos vigentes que regulan las condiciones sanitarias de las fábricas de alimentos y que el producto cumple estrictamente con las normas técnico-sanitarias expedidas por el Ministerio de Salud, las oficiales colombianas o en su defecto con las normas del Codex Alimentarius. Este producto no será comercializado con indicaciones terapéuticas.

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Les arômes menthe et vanille/caramel sont particulièrement préférés. L'arôme menthe est généralement présent dans des proportions comprises entre 1% et 7% du poids total des comprimés, tandis que l'arôme vanille/caramel est, lui, présent dans des proportions comprises entre 1% et 10% poids total desdits comprimés.

Les comprimés dispersibles selon l'invention offrent les avantages suivants :

- facilité d'emploi en traitement ambulatoire.
- précision du dosage unitaire.
- facilité de dispersion dans un liquide.
- goût agréable.
- facilité de déglutition en cas d'ingestion directe, c'est-à-dire sans dispersion préalable dans un liquide.
- absence de sucres et, notamment, de saccharose, les rendant particulièrement adaptés au traitement de patients diabétiques.

L'invention a, aussi, pour objet un procédé de préparation de comprimés dispersibles tels que précédemment définis, lequel procédé est caractérisé en ce qu'il comprend :

- le mélange du ou des principes actifs avec 30% à 60% de la quantité de désintégrant(s) destinée à être présente dans les comprimés.
- la granulation humide du mélange résultant en présence d'un liquide de mouillage contenant de l'eau et au moins un agent tensioactif.
- le séchage des granulés ainsi obtenus.
- l'ajout à sec des 40 à 70% restants du ou des désintégrants, de l'édulcorant ou des édulcorants, du ou des agents diluants, agents lubrifiants, agents d'écoulement et du ou des arômes, et
- la compression du mélange résultant.

L'invention sera mieux comprise au moyen du complement de description qui suit et qui se réfère à des exemples de réalisation de comprimés dispersibles conformes à l'invention. Il va de soi, toutefois, que ces exemples sont

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Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Carlos R. Olarte
Apoderado

Oficio Nº: 12427

ASUNTO:	Radicación PCT Nº	04-44562
	Trámite	011
	Evento	379
	Actuación	440
	Folios	036

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorio Franco Colombiano Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 8 MAR. 2005.

202021

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Tr. 40A No. 38-50 Conmutador: 3820840
Fax: 382 28 95. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

Retiro traslado.
Marzo 18-2005.
Frederick H. Torres.