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Act. 411 PRESENTACIÓN Folios: 83

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

3110/2007

1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☐ Capítulo I.		☒ Capítulo II.	
2) SOLICITANTE (71)		IDENTIFICACIÓN	
Nombre: ALFA WASSERMAN S.P.A Dirección: Contrada Sant' Emidio s.n.c., I-65020 Alanno Scalo, IT		C.C. ☐ NIT: ☒	
Nacionalidad o domicilio: Italia		C.E. ☐ OTRO ☐	
Lugar de constitución: : Italia		Cual _____ NÚMERO _____	
Teléfono: _____ Fax: _____ E. Mail: _____			
3) REPRESENTANTE O APODERADO		IDENTIFICACIÓN	
Nombre: DILIA MARÍA RODRÍGUEZ D'ALEMAN		C.C. ☒ NIT: ☐	
Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C.		C.E. ☐ OTRO ☐	
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Nacionalidad o domicilio: Todos los anteriores, Italianos			
5) PCT (86) Solicitud Internacional No. PCT/ EP2006/001755 Fecha:Febrero 27, 2006 Publicación Internacional No. WO2006/094662 Fecha: Septiembre 14, 2006			
6)Título (54) NUEVAS FORMAS POLIMORFICAS DE RIFAXIMINA, PROCESOS PARA SU PRODUCCION Y SU USO EN LAS PREPARACIONES MEDICINALES			
7) Clasificación Internacional: C07D 498/22, A61K 31/395, A61P 31/04 A61P 1/00			
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SI ☒ NO ☐		Europa	Marzo 3, 2005
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Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina			

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 64,585
FECHA : AGOSTO 13 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-086429-00000-0000
Fecha: 2007-08-23 15:42:36 Dep. 2020 NUECRES
Tra. 11 PATENTE/II Eje: 379 FABRICACION
Act. 411 PRESENTACION Folios: 83

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARKE HODGET Y CO. COLOMBIA	CONSIGNACION	BANCO POPULAR	050-00110-6	67351487	10/08/2007	11,248,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS



RESPONSABLE : _____

10

ES 98 U

P8770 4

TRADUCCIÓN OFICIAL DEL ITALIANO AL ESPAÑOL DE APOSTILLE
CORRESPONDIENTE AL TEXTO REDACTADO EN LENGUA INGLESA Y
ESPAÑOLA DE PODER DE ALFA WASSERMANN S.p.A. A DILIA MARIA
RODRÍGUEZ D'ALEMAN Y CLAUDIA LUCÍA CARO RAMÍREZ. 31 de marzo
de 2004.

PRIMERA DE TRES PÁGINAS DEL DOCUMENTO:

- Encabezado de la firma Clarke, Modet & Co. Colombia. Propiedad industrial y derechos de autor. Poder.
- Dos columnas de texto, a la izquierda en español, a la derecha en inglés, sobre el poder en mención, firmado por Giampaolo Girotti, Representante Legal de ALFA WASSERMANN S.p.A.
- Firma ilegible del notario y sello circular: Vico Carlo di Aldo. Notario en Bologna. Parte superior derecha: sello del notario y estampilla de 10,33 Euros.

SEGUNDA DE TRES PÁGINAS DEL DOCUMENTO, TEXTO EN ITALIANO:

Certificado Notarial de firma y representación legal.

Firma ilegible del notario y sello circular: Vico Carlo di Aldo. Notario en Bologna

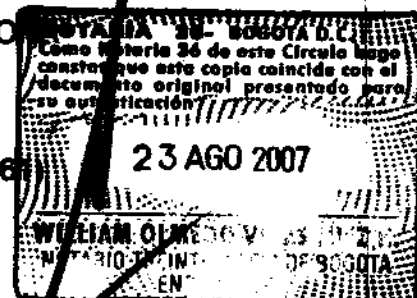
TERCERA DE TRES PÁGINAS DEL DOCUMENTO, TEXTO EN ITALIANO:

PROCURADURÍA DE LA REPÚBLICA DE BOLO

"APOSTILLE"

(Convención de la Haya del 5 de octubre de 1961)

Sandra Cardona Mejia
SANDRA PATRICIA CARDONA MEJIA
TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION No. 1241 INDUSTRIA 1997



5

1. PAIS: ITALIA

El presente acto público

2. Ha sido suscrito por: VICO CARLO

3. Agente en calidad de: NOTARIO EN BOLOÑA

4. Tiene el sello /timbre de: Sello de Estado

CERTIFICADO

5. En: Bolofia 6. El 5 de abril de 2004

7. Por : El Dr. Antonio Gustapane. Procurador Sustituto de la República

8. Con el número : 1179/2004 del Registro de Apostille

9. Sello /timbre: timbre de la Procuraduría de la República – Tribunal de Bolofia

10. Firma: EL PROCURADOR SUSTITUTO DE LA REPUBLICA

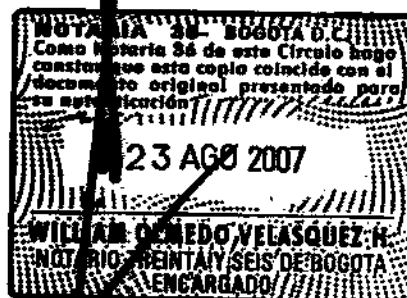
Doctor Antonio Gustapane. Firma ilegible.

Sello del Procurador Sustituto de la República.

FIN DEL DOCUMENTO.

Laudra Cordova

SANDRA PATRICIA CARDONA MEJIA
TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION 11-13-01 DE JUSTICIA 1997



PROPIEDAD INDUSTRIAL Y
DERECHOS DE AUTOR

PODER

Yo (nosotros), abajo firmante(s)

en mi (nuestro) carácter de representante(s) legales de

una sociedad organizada y existente de acuerdo con las leyes de

y en actual cumplimiento de su objeto social, con domicilio en

por el presente instrumento confiero (conferimos) poder especial a favor de DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía No. 41.654.882 de Bogotá, y tp. 20824 y CLAUDIA LUCIA CARO RAMIREZ, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp. 36448, con domicilio en Santa Fé de Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos:

- 1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como: patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres y enseñas comerciales y denominaciones de origen; así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
- 2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how.
- 3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
- 4) Ejercer acciones de oposición, observación, reclamos, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; en acciones o juicios promovidos por el (la) mandante o en contra el (ella).
- 5) Registrar nombres de dominio ante la entidad competente.
- 6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso.
- 7) Ratificar o no la agencia oficiosa.
- 8) Así mismo faculto (facultamos) a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en

a los

días de

de

Giampaolo Girotti
Firma / signature

Dr. Giampaolo Girotti, Chicó
on behalf of ALFA WASSERMANN

POWER OF ATTORNEY

I (we), the undersigned

Giampaolo Girotti

legal representative(s) of

ALFA WASSERMANN S.p.A.

an organization existing under the laws of Italy

and in present execution of its business activity, domiciled at Contrada S. Emilio - ALANNO, Italy

do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No. 40.017.374 of Tunja, residing in Santa Fé de Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

- 1) To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models; Designs, vegetal varieties; Marks, Slogans, Trade Names and emblems and appellations of Origin; as well as their renewals, extensions, assignments, changes of name and/or domicile, agreements and licenses.
- 2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.
- 3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses; as well as their renewals or extensions, assignments, changes of name and/or domicile, agreements and licenses.
- 4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection to the consumer, granting of licenses, protection of trade secrets and other actions related with rights derived from the above-mentioned matters and against the unfair competition, actions resulting from the obtention or exploitation of licenses, recovering damages actions. They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him.
- 5) To register domain names before the competent entity.
- 6) To the effect of this mandate the above-named proxy are empowered to: conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation related object and waive or renounce the rights granted or in process of granting, admit the facts of the case.
- 7) To ratify or not the officious agency.
- 8) I (we) hereby appoint the afore mentioned attorneys with powers to receive notifications and to designate judicial and extrajudicial attorneys, substitute this Power of Attorney and to revoke such substitutions.

Granted and signed by MARIA 38- BOGOTÁ D.C.
on this 30th day of August 2004
at Santa Fé de Bogotá, Colombia
in the presence of the original presented for authentication

23 AGO 2007

ENCARGADO

7

CERTIFICADO NOTARIAL (Cuando el solicitante es SOCIEDAD)
(Poderes otorgados en: El Salvador, Estados Unidos, México y Venezuela)

A los _____ días del mes de _____ de _____
el Notario que suscribe DA FE de que:

1. _____
(nombre de la persona que firma el poder) mayor de edad y domiciliado en _____ firmó de su puño y letra el documento que antecede.
2. Conoce al (a la) otorgante y que este (a) está legalmente capacitado para el otorgamiento.
3. El otorgante ha firmado el referido documento en su carácter de _____ de la persona jurídica _____
4. La citada persona jurídica con sede en _____ está legalmente constituida, que tiene actualmente existencia legal y que el acto para el cual se ha otorgado este poder está comprendido entre los que constituyen su objeto social.
5. El otorgante tiene efectivamente la representación que ostenta, que esta es legítima y que está facultado para otorgar este poder.
6. Las anteriores certificaciones de los puntos 3, 4 y 5, me constan porque he tenido a la vista los documentos auténticos.

Notario Público

NOTA: A continuación de lo anterior, el Consol de Colombia debe autenticar la firma del Notario Público.

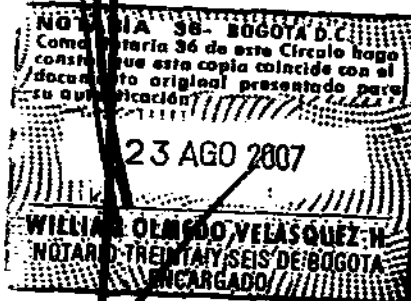
NOTARIAL CERTIFICATE (When the applicant is a CORPORATION)
(Powers of attorney granted in: El Salvador, México, U.S.A. and Venezuela)

This day of 2004
the undersigned Notary CERTIFIES that:

1. Dr. Giampaolo Girotti
(name of the person who signs the power of attorney) of legal age and domiciled in Via Ragazzi del '99 n.5, Bologna, Italy set his hand on the foregoing document.
2. The grantor is to him personally known and that he/she has legal capacity to execute the document.
3. The grantor has executed the foregoing document in his capacity of Chief Operating Officer of the juridical person ALFA WASSERMANN S.p.A.
4. The mentioned juridical person with place of business in ALANNO (PE) Italy is duly organized, has actual legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.
5. The grantor has in fact the referred quality and that his/her representation is legal and that he/she is empowered to grant this power of attorney.
6. I have based the above certifications 3, 4 and 5, on the authentic documents which for such purpose were exhibited to me.

Notary Public

NOTA: Then the Colombian Consol must legalize the signature of the Notary Public.





PROCURA DELLA REPUBBLICA DI BOLOGNA

APOSTILLE

Convention de l'Aja du 5 October 1961

1) Paese ITALIA

Il presente atto pubblico

2) è stato sottoscritto da VICO CARLO

3) agente in qualità di NOTAIO IN BOLOGNA

4) è segnato dal contrassegno / timbro
il sigillo di Stato

ATTESTATO

5) a Bologna

6) il 05 APR 2004

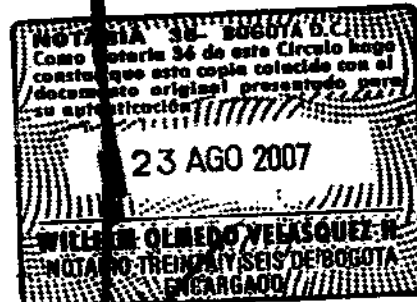
6) da Dr. Antonio Gustapane Sostituto Procuratore della Repubblica

7) sotto il numero 1179 / 2004 Reg. Apostille

8) contrassegno /



Il Sostituto Procuratore della Repubblica
Dr. Antonio Gustapane



(19) World Intellectual Property Organization
International Bureau



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(74) Agents: BIANCHETTI, Giuseppe et al.; Bianchetti
Bracco Minoja S.r.l., Via Plinio, 63, I-20129 Milano (IT).

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GB, GD, GH, GM, GR, GU, ID, IL, IN, IS, JP, KE,
KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
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FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): ALFA
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(72) Inventors; and

(73) Inventors/Applicants (for US only): VISCOMI,
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Valdossola, 26, I-40134 Bologna (IT). CONFORTINI,
Donatella [IT/IT]; Via A. Gramsci, 43, I-40012 Calderara
di Reno (IT). BARBANTI, Maria, Miriam [IT/IT]; Mura
di Porta d'Azeglio, 4, I-40136 Bologna (IT). BRAGA,
Dario [IT/IT]; Via Wiligelmo, 7, I-40133 Bologna (IT).

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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: NEW POLYMORPHOUS FORMS OF RIFAXIMIN, PROCESSES FOR THEIR PRODUCTION AND USE THEREOF
IN THE MEDICINAL

(57) Abstract: Crystalline polymorphous forms of the rifaximin (INN) antibiotic named rifaximin δ and rifaximin ϵ useful in the
production of medicinal preparations containing rifaximin for oral and topical use and obtained by means of a crystallization process
carried out by hot-dissolving the raw rifaximin in ethyl alcohol and by causing the crystallization of the product by addition of water
at a determinate temperature and for a determinate period of time, followed by a drying carried out under controlled conditions until
reaching a settled water content in the end product, are the object of the invention.

WO 2006/094662 A1

**NEW POLYMORPHOUS FORMS OF RIFAXIMIN, PROCESSES FOR
THEIR PRODUCTION AND USE THEREOF IN THE MEDICINAL
PREPARATIONS**

Background of the invention

The rifaximin (INN; see The Merck Index, XIII Ed., 8304) is an antibiotic pertaining to the rifamycin class, exactly it is a pyrido-imidazo rifamycin described and claimed in the Italian Patent IT 1154655, while the
5 European Patent EP 0161534 describes and claims a process for its production starting from the rifamycin O (The Merck Index, XIII Ed., 8301).

Both these patents describe the purification of the rifaximin in a generic way saying that the crystallization can be carried out in suitable solvents or solvent systems and summarily showing in some examples that the product
10 coming from the reaction can be crystallized from the 7:3 mixture of ethyl alcohol/water and can be dried both under atmospheric pressure and under vacuum without saying in any way neither the experimental conditions of crystallization and drying, nor any distinctive crystallographic characteristic of the obtained product.

15 The presence of different polymorphs had not been just noticed and therefore the experimental conditions described in both patents had been developed with the goal to get a homogeneous product having a suitable purity from the chemical point of view, apart from the crystallographic aspects of the product itself.

20 It has now be found, unexpectedly, that some polymorphous forms exist whose formation, in addition to the solvent, depends on the conditions of time and temperature at which both the crystallization and the drying are carried out.

These orderly polymorphous forms will be, later on, conventionally

identified as rifaximin δ (figure 1) and rifaximin ϵ (figure 2) on the basis of their respective specific diffractograms reported in the present application.

The polymorphous forms of the rifaximin have been characterized through the technique of the powder X-ray *diffraction*.

- 5 The identification and characterization of these polymorphous forms and, contemporarily, the definition of the experimental conditions for obtaining them is very important for a compound endowed with pharmacological activity which, like the rifaximin, is marketed as medicinal preparation, both for human and veterinary use. In fact it is known that the
- 10 polymorphism of a compound that can be used as active principle contained in a medicinal preparation can influence the pharmaco-toxicologic properties of the drug. Different polymorphous forms of an active principle administered as drug under oral or topical form can modify many properties thereof like bioavailability, solubility, stability, colour, compressibility, flowability and
- 15 workability with consequent modification of the profiles of toxicological safety, clinical effectiveness and productive efficiency.

- What above mentioned is confirmed with authority by the fact that the authorities that regulate the grant of the authorization for the admission of the drugs on the market require that the manufacturing methods of the active
- 20 principles are standardized and controlled in such a way that they give homogeneous and sound results in terms of polymorphism of the production batches (CPMP/QWP/96, 2003 - Note for Guidance on Chemistry of new Active Substance; CPMP/ICH/367/96 - Note for guidance specifications: test procedures and acceptance criteria for new drug substances and new drug
- 25 products: chemical substances; Date for coming into operation: May 2000).

The need of the above-mentioned standardization has further been strengthened just in the field of the rifamycin antibiotics from Henwood S.Q., de Villiers M.M., Liebenberg W. and Lötter A.P., Drug Development and

67

Industrial Pharmacy, 26 (4), 403-408, (2000), who have ascertained that different production batches of the rifampicin (INN) made from different manufacturers differ among them because they show different polymorphous characteristics, and as a consequence they show different profiles of
5 dissolution together with consequent alteration of the respective pharmacological properties.

By applying the processes of crystallization and drying generically disclosed in the previous patents IT 1154655 and EP 0161534 it has been found that under some experimental conditions the poorly crystalline form of
10 the rifaximin is obtained while under other experimental conditions the other crystalline polymorphous forms of the rifaximin are obtained. Moreover it has been found that some parameters, absolutely not disclosed in the above-mentioned patents, like for instance the conditions of preservation and the relative humidity of the ambient, have the surprising effect to determine the
15 form of the polymorph.

The polymorphous forms of the rifaximin object of the present patent application were never seen or hypothesized, while thinking that a sole homogeneous product would always have been obtained whichever method would have been chosen within the range of the described conditions,
20 irrespective of the conditions used for crystallizing, drying and preserving.

It has now been found that the formation of the δ and ϵ forms depends on the presence of water within the crystallization solvent, on the temperature at which the product is crystallized and on the amount of water present into the product at the end of the drying phase.

25 The form δ and the form ϵ of the rifaximin have then been synthesised and they are the object of the invention.

In particular the form δ is characterised by the residual content of water in the dried solid material in the range from 2.5% and 6% (w/w), more

13

preferably from 3% and 4.5%, while the form ϵ is the result of a polymorphic transition under controlled temperature moving from the form δ .

These results have a remarkable importance as they determine the conditions of industrial manufacturing of some steps of working which could not be considered critical for the determination of the polymorphism of a product, like for instance the maintaining to a crystallized product a quantity of water in a stringent range of values, or the process of drying the final product, in which a form, namely form δ , has to be obtained prior to continuing the drying to obtain the form ϵ , or the conditions of preservation of the end product, or the characteristics of the container in which the product is preserved.

Rifaximin exerts its broad antibacterial activity in the gastrointestinal tract against localized gastrointestinal bacteria that cause infectious diarrhea including anaerobic strains. It has been reported that rifaximin is characterized by a negligible systemic absorption, due to its chemical and physical characteristics (Descombe J.J. et al. Pharmacokinetic study of rifaximin after oral administration in healthy volunteers. *Int J Clin. Pharmacol. Res.*, 14 (2), 51-56, (1994))

Now we have found that it is possible on the basis of the two identified polymorphic forms of rifaximin to modulate its level of systemic adsorption, and this is part of the present invention, by administering distinct polymorphous forms of rifaximin, namely rifaximin δ and rifaximin ϵ . It is possible to have a difference in the adsorption of almost 100 folds in the range from 0.001 to 0.3 $\mu\text{g/ml}$ in blood.

The evidenced difference in the bioavailability is important because it can differentiate the pharmacological and toxicological behaviour of the two polymorphous of rifaximins δ and ϵ .

As a matter of fact, rifaximin ϵ is negligibly absorbed through the oral

B
T

route while rifaximin δ shows a mild absorption.

Rifaximin ϵ is practically not absorbed, might act only through a topical action, including the case of the gastro-intestinal tract, with the advantage of very low toxicity.

5 On the other way, rifaximin δ , which is mildly absorbed, can find an advantageous use against systemic microorganisms, able to hide themselves and to partially elude the action of the topic antibiotics.

In respect of possible adverse events coupled to the therapeutic use of rifaximin of particular relevance is the induction of bacterial resistance to the
10 antibiotics. Generally speaking, it is always possible in the therapeutic practice with antibiotics to induce bacterial resistance to the same or to other antibiotic through selection of resistant strains.

In case of rifaximin, this aspect is particularly relevant, since rifaximin belongs to the rifamycin family, a member of which, the rifampicin, is largely
15 used in tuberculosis therapy. The current short course treatment of tuberculosis is a combination therapy involving four active pharmaceutical ingredients: rifampicin, isoniazid, ethambutol and pyrazinamide and among them rifampicin plays a pivotal role. Therefore, any drug which jeopardized the efficacy of the therapy by selecting for resistance to rifampicin would be
20 harmful. (Kremer L. et al. "Re-emergence of tuberculosis: strategies and treatment", Expert Opin. Investig. Drugs, 11 (2), 153-157, (2002)).

In principle, looking at the structural similarity between rifaximin and rifampicin, it might be possible by using rifaximin to select resistant strains of *M. tuberculosis* and to induce cross-resistance to rifampicin. In order to avoid
25 this negative event it is crucial to have a control of quantity of rifaximin systemically absorbed.

Under this point of view, the difference found in the systemic absorption of the δ and ϵ forms of the rifaximin is significant, since also at sub-inhibitory

15 concentration of rifaximin, such as in the range of from 0.1 to 1 µg/ml, selection of resistant mutants has been demonstrated to be possible (Marchese A. et al. In vitro activity of rifaximin, metronidazole and vancomycin against clostridium difficile and the rate of selection of spontaneously resistant mutants
5 against representative anaerobic and aerobic bacteria, including ammonia-producing species. Chemotherapy, 46(4), 253-266,(2000)).

According to what above said, the importance of the present invention, which has led to the knowledge of the existence of the above mentioned rifaximin polymorphous forms and to various industrial routes for
10 manufacturing pure single forms having different pharmacological properties, is clearly strengthened.

The above-mentioned δ and ε forms can be advantageously used as pure and homogeneous products in the manufacture of medicinal preparations containing rifaximin.

15 As already said, the process for manufacturing rifaximin from rifamycin O disclosed and claimed in EP 0161534 is deficient from the point of view of the purification and identification of the product obtained; it shows some limits also from the synthetic point of view as regards, for instance, the very long reaction times, from 16 to 72 hours, very little suitable for an industrial
20 use and moreover because it does not provide for the in situ reduction of the rifaximin oxidized that may be formed within the reaction mixture.

Therefore, a further object of the present invention is an improved process for the industrial manufacturing of the δ and ε forms of the rifaximin, herein claimed as products and usable as defined and homogeneous active
25 principles in the manufacture of the medicinal preparations containing such active principle.

Description of the invention

As already said, the form δ and the form ε of the antibiotic known as

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rifaximin (INN), processes for their production and the use thereof in the manufacture of medicinal preparations for oral or topical route, are object of the present invention.

A process object of the present invention comprises reacting one molar
5 equivalent of rifamycin O with an excess of 2-amino-4-methylpyridine, preferably from 2.0 to 3.5 molar equivalents, in a solvent mixture made of water and ethyl alcohol in volumetric ratios between 1:1 and 2:1, for a period of time between 2 and 8 hours at a temperature between 40°C and 60°C.

At the end of the reaction the reaction mass is cooled to room
10 temperature and is added with a solution of ascorbic acid in a mixture of water, ethyl alcohol and aqueous concentrated hydrochloric acid, under strong stirring, in order to reduce the small amount of oxidized rifaximin that forms during the reaction and finally the pH is brought to about 2.0 by means of a further addition of concentrated aqueous solution of hydrochloric acid, in
15 order to better remove the excess of 2-amino-4-methylpyridine used in the reaction. The suspension is filtered and the obtained solid is washed with the same solvent mixture water/ethyl alcohol used in the reaction. Such semi finished product is called "raw rifaximin".

The raw rifaximin can be directly submitted to the subsequent step of
20 purification. Alternately, in case long times of preservation of the semi finished product are expected, the raw rifaximin can be dried under vacuum at a temperature lower than 65°C for a period of time between 6 and 24 hours, such semi finished product is called "dried raw rifaximin".

The so obtained raw rifaximin and/or dried raw rifaximin are purified
25 by dissolving them in ethyl alcohol at a temperature between 45°C and 65°C and by crystallizing them by addition of water, preferably in weight amounts between 15% and 70% in respect of the amount by weight of the ethyl alcohol used for the dissolution, and by keeping the obtained suspension at a

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temperature between 50°C and 0°C under stirring during a period of time between 4 and 36 hours.

The suspension is filtered and the obtained solid is washed with water and dried under vacuum or under normal pressure, with or without a drying agent, at a temperature between the room temperature and 105°C for a period
5 of time between 2 and 72 hours.

The achievement of the δ and ϵ forms depends on the conditions chosen for the crystallization. In particular, the composition of the solvent mixture from which the crystallization is carried out, the temperature at which the
10 reaction mixture is kept after the crystallization and the period of time at which that temperature is kept, have proven to be critical.

More precisely, the δ and ϵ rifaximins are obtained when the temperature is first brought to a value between 28°C and 32°C in order to cause the beginning of the crystallization, then the suspension is brought to a
15 temperature between 40°C and 50°C and kept at this value for a period of time between 6 and 24 hours, then the suspension is quickly cooled to 0°C, in a period of time between 15 minutes and one hour, is filtered, the solid is washed with water and then is dried.

The step of drying has an important part in obtaining the δ and ϵ
20 polymorphous forms of the rifaximin and has to be checked by means of a suitable method fit for the water dosage, like for instance the Karl Fisher method, in order to check the amount of remaining water present in the product under drying.

The obtaining of the rifaximin δ during the drying in fact depends on
25 the end remaining amount of water which should be comprised from 2.5% (w/w) and 6% (w/w), more preferably between 3% and 4.5%, and not from the experimental conditions of pressure and temperature at which this critical limit of water percent is achieved.

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In order to obtain the poorly adsorbed ϵ form it has to start from the δ form and it has to be continued the drying under vacuum or at atmospheric pressure, at room temperature or at high temperatures, in the presence or in the absence of drying agents, provided that the drying is prolonged for the time necessary so that the conversion in form ϵ is achieved.

Both the forms δ and ϵ of the rifaximin are hygroscopic, they absorb water in a reversible way during the time in the presence of suitable conditions of pressure and humidity in the ambient and are susceptible of transformation to other forms.

The transitions from one form to another result to be very important in the ambit of the invention, because they can be an alternative manufacturing method for obtaining the form desired for the production of the medicinal preparations. Therefore, the process that allows to turn the rifaximin δ into rifaximin ϵ in a valid industrial manner is important part of the invention.

The process concerning the transformation of the rifaximin δ into rifaximin ϵ comprises drying the rifaximin δ under vacuum or at atmospheric pressure, at room temperature or at high temperatures, in the presence or in the absence of drying agents, and keeping it for a period of time until the conversion is obtained, usually between 6 and 36 hours.

From what above said, it results that during the phase of preservation of the product a particular care has to be taken so that the ambient conditions do not change the water content of the product, by preserving the product in ambient having controlled humidity or in closed containers that do not allow in a significant way the exchange of water with the exterior ambient.

The polymorph called rifaximin δ is characterised from a content of water in the range between 2.5% and 6%, preferably between 3.0% and 4.5% and from a powder X-ray diffractogram (reported in figure 1) which shows peaks at the values of the diffraction angles 2θ of $5.7^\circ \pm 0.2$, $6.7^\circ \pm 0.2$,

7.1°±0.2, 8.0°±0.2, 8.7°±0.2, 10.4°±0.2, 10.8°±0.2, 11.3°±0.2, 12.1°±0.2, 17.0°±0.2, 17.3°±0.2, 17.5°±0.2, 18.5°±0.2, 18.8°±0.2, 19.1°±0.2, 21.0°±0.2, 21.5°±0.2. The polymorph called rifaximin ϵ is characterized from a powder X-ray diffractogram (reported in figure 2) which shows peaks at the values of the diffraction angles 2θ of 7.0°±0.2, 7.3°±0.2, 8.2°±0.2, 8.7°±0.2, 10.3°±0.2, 11.1°±0.2, 11.7°±0.2, 12.4°±0.2, 14.5°±0.2, 16.3°±0.2, 17.2°±0.2, 18.0°±0.2, 19.4°±0.2.

The diffractograms have been carried out by means of the Philips X'Pert instrument endowed with Bragg-Brentano geometry and under the following working conditions:

X-ray tube: Copper

Radiation used: K (α 1), K (α 2)

Tension and current of the generator: KV 40, mA 40

Monocromator: Graphite

Step size: 0.02

Time per step: 1.25 seconds

Starting and final angular 2θ value: 3.0°÷30.0°

The evaluation of the content of water present in the analysed samples has always been carried out by means of the Karl Fisher method.

Rifaximin δ and rifaximin ϵ differ each from other also because they show significant differences as regards bioavailability.

A bioavailability study of the two polymorphs has been carried out on Beagle female dogs, treated them by oral route with a dose of 100 mg/kg in capsule of one of the polymorphs, collecting blood samples from the jugular vein of each animal before each dosing and 1,2,4,6,8 and 24 hours after each dosing, transferring the samples into tubes containing heparin and separating the plasma by centrifugation.

The plasma has been assayed for rifaximin on the validated LC-MS/MS

method and the maximum observed plasma concentration (C_{max}), the time to reach the C_{max} (t_{max}), and the area under the concentration -time curve (AUC) have been calculated.

The experimental data reported in the following table 1 clearly show that rifaximin ϵ is negligibly absorbed, while rifaximin δ is absorbed at a value (C_{max} = 0.308 μ g/ml) comprised in the range of from 0.1 to 1.0 μ g/ml.

Table 1

Pharmacokinetic parameters for rifaximin polymorphs following single oral administration of 100 mg/kg by capsules to female dogs

	C_{max} ng/ml	T_{max} h	AUC₀₋₂₄ ng.h/ml
	Mean	Mean	Mean
Polimorph δ	308.31	2	801
Polimorph ϵ	6.86	4	42

The above experimental results further point out the differences existing among the two rifaximin polymorphs.

The forms δ and ϵ can be advantageously used in the production of medicinal preparations having antibiotic activity, containing rifaximin, for both oral and topical use. The medicinal preparations for oral use contain the rifaximin δ and ϵ together with the usual excipients as diluting agents like mannitol, lactose and sorbitol; binding agents like starchs, gelatines, sugars, cellulose derivatives, natural gums and polyvinylpyrrolidone; lubricating agents like talc, stearates, hydrogenated vegetable oils, polyethylenglycol and colloidal silicon dioxide; disintegrating agents like starchs, celluloses, alginates, gums and reticulated polymers; colouring, flavouring and sweetening agents.

All the solid preparations administrable by oral route can be used in the ambit of the present invention, for instance coated and uncoated tablets,

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capsules made of soft and hard gelatine, sugar-coated pills, lozenges, wafer sheets, pellets and powders in sealed packets.

The medicinal preparations for topical use contain the rifaximin δ and ϵ together with the usual excipients like white petrolatum, white wax, lanoline and derivatives thereof, stearyl alcohol, propylenglycol, sodium lauryl sulfate, ethers of the fatty polyoxyethylene alcohols, esters of the fatty polyoxyethylene acids, sorbitan monostearate, glyceryl monostearate, propylene glycol monostearate, polyethylene glycols, methylcellulose, hydroxymethylpropylcellulose, sodium carboxymethylcellulose, colloidal aluminium and magnesium silicate, sodium alginate.

All the topical preparations can be used in the ambit of the present invention, for instance the ointments, the pomades, the creams, the gels and the lotions.

The invention is herein below illustrated from some examples that do not have to be taken as a limitation of the invention: from what described results in fact evident that the forms δ and ϵ can be obtained by suitably combining between them the above mentioned conditions of crystallization and drying.

Example 1

Preparation of raw rifaximin and of dried raw rifaximin

In a three-necked flask equipped with mechanic stirrer, thermometer and reflux condenser, 120 ml of demineralised water, 96 ml of ethyl alcohol, 63.5 g of rifamycin O and 27.2 g of 2-amino-4-methylpyridine are loaded in succession at room temperature. After the loading, the mass is heated at $47 \pm 3^\circ\text{C}$, is kept under stirring at this temperature for 5 hours, then is cooled to $20 \pm 3^\circ\text{C}$ and, during 30 minutes, is added with a mixture, prepared separately, made of 9 ml of demineralised water, 12.6 ml of ethyl alcohol, 1.68 g of ascorbic acid and 9.28 g of aqueous concentrated hydrochloric acid. At the

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end of the addition, the mass is kept under stirring for 30 minutes at an interior temperature of $20 \pm 3^\circ\text{C}$ and then, at the same temperature, 7.72 g of concentrated hydrochloric acid are dripped until a pH equal to 2.0.

At the end of the addition, the mass is kept under stirring, always at an interior temperature equal to 20°C , for 30 minutes, then the precipitate is filtered and washed by means of a mixture made of 32 ml of demineralised water and of 25 ml of ethyl alcohol. The so obtained "raw rifaximin" (89.2 g) is dried under vacuum at room temperature for 12 hours obtaining 64.4 g of "dried raw rifaximin" which shows a water content equal to 5.6%. The product by further drying under vacuum until the weight of 62.2 g of dried raw rifaximin having a water content equal to 3.3%, whose diffractogram corresponds to the polymorphous form δ characterized from a powder X-ray diffractogram showing peaks at values of angles 2θ of $5.7^\circ \pm 0.2$, $6.7^\circ \pm 0.2$, $7.1^\circ \pm 0.2$, $8.0^\circ \pm 0.2$, $8.7^\circ \pm 0.2$, $10.4^\circ \pm 0.2$, $10.8^\circ \pm 0.2$, $11.3^\circ \pm 0.2$, $12.1^\circ \pm 0.2$, $17.0^\circ \pm 0.2$, $17.3^\circ \pm 0.2$, $17.5^\circ \pm 0.2$, $18.5^\circ \pm 0.2$, $18.8^\circ \pm 0.2$, $19.1^\circ \pm 0.2$, $21.0^\circ \pm 0.2$, $21.5^\circ \pm 0.2$. The product is hygroscopic.

Example 2

Preparation of rifaximin ϵ

Example 1 is repeated and after having obtained the δ form, the solid powder is further dried under vacuum for 24 hours at the temperature of 65°C . The product obtained is rifaximin ϵ characterized from a powder X-ray diffractogram showing peaks at values of angles 2θ of $7.0^\circ \pm 0.2$, $7.3^\circ \pm 0.2$, $8.2^\circ \pm 0.2$, $8.7^\circ \pm 0.2$, $10.3^\circ \pm 0.2$, $11.1^\circ \pm 0.2$, $11.7^\circ \pm 0.2$, $12.4^\circ \pm 0.2$, $14.5^\circ \pm 0.2$, $16.3^\circ \pm 0.2$, $17.2^\circ \pm 0.2$, $18.0^\circ \pm 0.2$, $19.4^\circ \pm 0.2$.

Example 3

Bioavailability in dogs by oral route

Eight pure-bred Beagle females dogs having 20 weeks of age and weighing between 5.0 and 7.5 kg have been divided into two groups of four.

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The first of these group has been treated with rifaximin δ , the second with rifaximin ϵ according to the following procedure.

To each dog have been administered by the oral route 100mg/kg of one of the rifaximin polymorphs into gelatine capsules and blood samples of 2 ml
5 each have been collected from the jugular vein of each animal before each dispensing and 1,2,4,6,8 and 24 hours after the administration.

Each sample has been transferred into a tube containing heparin as anticoagulant and has been centrifuged; the plasma has been divided into two aliquots, each of 500 μ l, and has been frozen at -20°C .

10 The rifaximin contained in the plasma has been assayed by means of the validated LC-MS/MS method and the following parameters have been calculated according to standard non-compartmental analysis:

C_{max} = maximum observed plasma concentration of rifaximin in the plasma;

15 T_{max} = time at which the C_{max} is reached;

AUC = area under the concentration-time curve calculated through the linear trapezoidal rule.

The results reported in the table 1 clearly show how the rifaximin δ is much more absorbed, more than 40 times, in respect of rifaximin ϵ , which is
20 practically not absorbed.

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CLAIMS

1. Polymorph of the antibiotic rifaximin called rifaximin δ characterized from a water content in the range from 2.5% (w/w) to 6% (w/w), preferably
5 comprised between 3.0% and 4.5%, and from a powder X-ray diffractogram showing peaks at values of the diffraction angles 2θ of $5.7^\circ \pm 0.2$, $6.7^\circ \pm 0.2$, $7.1^\circ \pm 0.2$, $8.0^\circ \pm 0.2$, $8.7^\circ \pm 0.2$, $10.4^\circ \pm 0.2$, $10.8^\circ \pm 0.2$, $11.3^\circ \pm 0.2$, $12.1^\circ \pm 0.2$, $17.0^\circ \pm 0.2$, $17.3^\circ \pm 0.2$, $17.5^\circ \pm 0.2$, $18.5^\circ \pm 0.2$, $18.8^\circ \pm 0.2$, $19.1^\circ \pm 0.2$, $21.0^\circ \pm 0.2$, $21.5^\circ \pm 0.2$.
- 10 2. Polymorph of the antibiotic rifaximin called rifaximin ϵ characterized from a powder X-ray diffractogram showing peaks at values of the diffraction angles 2θ of $7.0^\circ \pm 0.2$, $7.3^\circ \pm 0.2$, $8.2^\circ \pm 0.2$, $8.7^\circ \pm 0.2$, $10.3^\circ \pm 0.2$, $11.1^\circ \pm 0.2$, $11.7^\circ \pm 0.2$, $12.4^\circ \pm 0.2$, $14.5^\circ \pm 0.2$, $16.3^\circ \pm 0.2$, $17.2^\circ \pm 0.2$, $18.0^\circ \pm 0.2$, $19.4^\circ \pm 0.2$.
3. Process for the production of the rifaximins δ and ϵ , characterized in that
15 a molar equivalent of rifamycin O is reacted with an excess of 2-amino-4-methylpyridine, preferably from 2.0 to 3.5 molar equivalents, in a solvent mixture made of water and ethyl alcohol in volumetric ratios between 1:1 and 2:1 for a period of time between 2 and 8 hours at a temperature between 40°C and 60°C , the reaction mass is treated at room temperature with a solution of
20 ascorbic acid in a mixture of water, ethyl alcohol and concentrated aqueous hydrochloric acid, the reaction mass is brought to pH 2.0 by means of concentrated aqueous solution of hydrochloric acid, the suspension is filtered, the solid obtained is washed with the same water/ethyl alcohol solvent mixture used in the reaction, the raw rifaximin so obtained is purified by dissolving it in
25 ethyl alcohol at a temperature between 45°C and 65°C , by causing the precipitation by addition of water, preferably in weight amounts between 15% and 70% in respect of the weight amount of ethyl alcohol used for the dissolution, by lowering the temperature of the suspension at values between

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50°C and 0°C under stirring for a period of time between 4 and 36 hours, lastly by filtering the suspension, by washing with water the obtained solid and by drying it under vacuum or under conditions of normal pressure, with or without a drying agent, at a temperature between room temperature and 105°C, for a
5 period of time between 2 and 72 hours.

4. Process according to claim 3 for the production of rifaximin δ characterized in that after the addition of water to the ethanol solution of the raw rifaximin the temperature is lowered to a value between 28°C and 32°C in order to cause the beginning of the crystallization, the so obtained suspension
10 is kept between 40°C and 50°C under stirring for a period of time between 6 and 24 hours, then it is cooled, in a period of time between 15 minutes and one hour, to 0°C before being filtered, and the drying of the solid obtained is carried out until a water content in the range from 2.5% (w/w) to 6% (w/w), preferably comprised between 3.0% and 4.5%.

15 5. Process according to claim 3 for the production of rifaximin ϵ characterized by drying rifaximin δ under vacuum or at atmospheric pressure, at room temperature or at high temperatures, in the presence or in the absence of drying agents, provided that the drying is prolonged for the time necessary so that the conversion in form ϵ is achieved.

20 6. Use of the rifaximin δ in the preparation of medicinal preparations for oral use with antibiotic activity together with the usual excipients like diluting, binding, lubricating, disintegrating, colouring, flavouring and sweetening agents.

7. Use of the rifaximin ϵ in the preparation of medicinal preparations for
25 oral use with antibiotic activity together with the usual excipients like diluting, binding, lubricating, disintegrating, colouring, flavouring and sweetening agents.

8. Use according to each of claims 6 and 7 characterized in that the

26

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/001755

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/22 A61K31/395 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data bases consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, MPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 161 534 A (ALFA FARMACEUTICI S.P.A) 21 November 1985 (1985-11-21) cited in the application examples 1,4,6-14	1-11
X	US 4 341 785 A (MARCHI ET AL) 27 July 1982 (1982-07-27) column 4, line 60 - column 4, line 66 column 6, line 13 - column 6, line 31; example 6	1-11
P,X	WO 2005/044823 A (ALFA WASSERMANN S.P.A; VISCONI, GIUSEPPE, C; CAMPANA, MANUELA; BRAGA,) 19 May 2005 (2005-05-19) the whole document	1-11

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

☒ See patent family annex.

* Special categories of cited documents:

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O document relating to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, each combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/001755

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0161534 A	21-11-1985	AR 241913 A1	29-01-1993
		AU 568934 B2	14-01-1988
		AU 4251585 A	21-11-1985
		CA 1215708 A1	23-12-1986
		DE 3573120 D1	26-10-1989
		DK 214685 A	16-11-1985
		ES 8603489 A1	16-04-1986
		FI 851907 A	16-11-1985
		GR 851144 A1	25-11-1985
		IE 58392 B1	08-09-1993
		IT 1199374 B	30-12-1988
		JP 1778865 C	13-08-1993
		JP 4069634 B	06-11-1992
		JP 60252483 A	13-12-1985
		NO 851921 A	18-11-1985
		PH 22007 A	02-05-1988
		PT 80446 A	01-06-1985
		US 4557866 A	10-12-1985
		ZA 8502971 A	24-12-1985
US 4341785 A	27-07-1982	AR 226212 A1	15-06-1982
		AT 373599 B	10-02-1984
		AT 222781 A	15-06-1983
		AU 537093 B2	07-06-1984
		AU 7065581 A	26-11-1981
		BE 888895 A1	16-09-1981
		CA 1142518 A1	08-03-1983
		CH 648037 A5	28-02-1985
		DE 3120460 A1	11-03-1982
		DK 224781 A	23-11-1981
		EG 14891 A	31-12-1985
		ES 8203388 A1	01-07-1982
		FI 811565 A	23-11-1981
		FR 2482967 A1	27-11-1981
		GB 2079270 A	20-01-1982
		GR 75640 A1	02-08-1984
		IE 51204 B1	29-10-1986
		IT 1154655 B	21-01-1987
		JP 1354051 C	24-12-1986
		JP 57011987 A	21-01-1982
		JP 61023192 B	04-06-1986
		LU 83376 A1	11-09-1981
		NL 8102290 A	16-12-1981
		NO 811731 A	23-11-1981
		PH 17207 A	19-06-1984
		PH 18704 A	05-09-1985
		PT 73064 A	01-06-1981
		SE 453089 B	11-01-1988
		SE 8103216 A	23-11-1981
		ZA 8103430 A	30-06-1982
WO 2005044823 A	19-05-2005	AU 2004200964 A1	26-05-2005
		AU 2004287601 A1	19-05-2005
		BR 0402382 A	28-06-2005
		BR P10407149 A	07-02-2006
		CA 2460384 A1	07-05-2005
		CA 2538546 A1	19-05-2005
		CN 1613858 A	11-05-2005

32

**NUEVAS FORMAS POLIMÓRFICAS DE RIFAXIMINA, PROCESOS PARA SU
PRODUCCIÓN Y SU USO EN LAS PREPARACIONES MEDICINALES**

Antecedentes de la Invención

El rifaximina (INN; ver The Merck Index, XIII Ed., 8304) es un antibiótico que pertenece a la clase de rifamicina, exactamente es una pirido-imidazo rifamicina descrita y reivindicada en la patente italiana EP 1154655, aunque la patente europea EP 0161534 describe y reivindica un proceso para su producción partiendo de la rifamicina O (The Merck Index, XII Ed., 8301).

Ambas patentes describen la purificación de la rifaximina de una manera genérica diciendo que la cristalización puede llevarse a cabo en disolventes adecuados o en sistemas disolventes adecuados y de manera muy resumida muestra en algunos ejemplos que el producto que proviene de la reacción puede ser cristalizado desde la mezcla 7:3 de alcohol etílico/agua y puede ser secado tanto bajo presión atmosférica como bajo vacío sin decir de ninguna manera si las condiciones del experimento de cristalización y secado,

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ni las características cristalográficas distintivas del producto obtenido.

La presencia de polimorfos diferentes ha sido solamente informado y por lo tanto las condiciones experimentales descritas en ambas patentes han sido desarrolladas con el propósito u objetivo de obtener un producto homogéneo que tenga una pureza adecuada desde el punto de vista químico, a parte de los aspectos cristalográficos del producto obtenido. Ahora se ha encontrado, de manera inesperada que algunas formas polimórficas existen cuya formación, en adición del disolvente, dependen de las condiciones de tiempo y temperatura en las cuales tanto la cristalización como el secado se llevan a cabo.

Estas formas polimórficas ordenadamente serán, posteriormente, identificadas convencionalmente como rifaximina δ (figura 1) y rifaximina ϵ (figura 2) sobre la base de sus difractogramas específicos respectivos reportados en la siguiente solicitud.

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Las formas polimórficas de rifaximina han sido caracterizadas mediante la técnica de la difracción de rayos X en el polvo.

La identificación y caracterización de esas formas polimórficas y, contemporáneamente, la definición de las condiciones experimentales para obtenerlas es muy importante para un compuesto al que se le asigna con una actividad farmacológica que, tal como la rifaximina, es comercializado como una preparación medicinal, tanto para uso humano como veterinario. De hecho es conocido que el polimorfismo de un compuesto puede ser usado como un principio activo contenido en una preparación medicinal puede influenciar las propiedades farmacotoxicológicas de la droga. Diferentes formas de polimorfos de un principio activo administradas como droga bajo forma oral o tópica puede modificar muchas propiedades de los mismos como la biodisponibilidad, solubilidad, la estabilidad, el color, la compresibilidad, la fluidez y trabajabilidad con la modificación consiguiente de los perfiles de seguridad toxicológica, efectividad clínica y eficiencia productiva.

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Lo que se mencionó anteriormente es confirmado con autoría por el hecho de que las autoridades son las que regulan el otorgamiento de la autorización para la admisión de las drogas en el mercado requiere que los métodos de fabricación de los agentes activos ~~sean~~ ^{sean} estandarizados y controlados de tal manera que ellos proporcionen ^{"/} resultados homogéneos y armónicos en términos del polimorfismo de las tandas de producción (CPMP/QWP/96, 2003- Nota para la guía sobre química de nuevas sustancias activas; CPMP/ICH/367/96 - Nota para especificaciones de guía: procedimientos de ensayo y criterios de aceptación para nuevas sustancias de drogas y nuevos productos de drogas: sustancias químicas; fecha para entrar en operación: Mayo 2000).

La necesidad de la estandarización anteriormente mencionada ha sido fortalecida adicionalmente justo en el campo de los antibióticos de rifamicina a partir de Henwood S.Q., de Villiers M.M., Liebenberg W. y Lotter A.P., Drug Development and Industrial Pharmacy, 26 (4), 403-408, (2000), quienes han determinado que las tandas de producción diferentes de la rifampicina (INN) hechas por diferentes fabricantes difieren entre ellas porque ellas muestran diferentes características

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de polimorfos, y como una consecuencia ellas muestran diferentes perfiles de disolución junto con alteración consiguiente de las propiedades farmacológicas respectivas.

Al aplicar los procesos de cristalización y secado generalmente descritos en las patentes anteriores IT 1154655 y EP 0161534 se ha encontrado que bajo algunas condiciones experimentales la forma cristalina pobre de la rifaximina es obtenida aunque bajo otras condiciones experimentales las otras formas polimórficas cristalinas de la rifaximina son obtenidas. Más aún se ha encontrado que algunos parámetros, absolutamente no descritos en las patentes anteriormente mencionadas, como por ejemplo las condiciones de preservación y la humedad relativa del ambiente, tienen el efecto sorprendente para determinar la forma del polimorfo.

Las formas polimórficas de la rifaximina objeto de la presente solicitud de patente nunca fueron vistas o hipotetizadas, aunque pensando que un solo producto homogéneo siempre habría de obtenerse no importa el método que se escogiera dentro del rango de las condiciones descritas, y

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respectivamente de las condiciones usadas para la cristalización, el secado, y la preservación.

Se ha encontrado ahora que la formación de las formas δ y ϵ depende de la presencia de agua dentro del disolvente de cristalización, de la temperatura a la cual el producto es cristalizado y de la cantidad de agua presente en el producto al final de la fase de secado.

La forma δ y la forma ϵ de la rifaximina han sido entonces sintetizadas y ellas son el objeto de la invención.

En particular la forma δ está caracterizada por el contenido residual de agua en el material sólido secado en el rango entre 2,5% y 6% (p/p), más preferiblemente entre el 3% y 4.5%, aunque la forma ϵ es el resultado de una transición polimórfica bajo temperatura controlada que se mueve desde la forma δ .

Estos resultados tienen una importancia notable ya que determinan las condiciones de la fabricación industrial de algunas etapas de trabajo que podrían no ser consideradas

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críticas para la determinación del polimorfismo de un producto, como por ejemplo el mantener a un producto cristalizado en una cantidad de agua con un rango muy estricto de valores, o el proceso de secado del producto final, en el cual una forma, particularmente la forma δ debe ser obtenida antes de continuar el secado para obtener la forma ϵ , o las condiciones de preservación del producto final, o las características del contenedor en el cual el producto es reservado.

La rifaximina ejerce su actividad antibacterial amplia en el tracto gastrointestinal contra las bacterias localizadas gastrointestinalmente que causan diarrea infecciosa incluyendo cepas anaeróbicas. Se ha reportado que la rifaximina está caracterizada por una absorción sistémica despreciable debido a sus características químicas y físicas (Descombe J.J. et al. Pharmacokinetic study of rifaximin alter oral administration in healthy volunteers. Int J Clin. Pharmacol. Res., 14 (2), 51-56, (1994))

Ahora hemos encontrado que es posible sobre la base de las dos formas polimórficas identificadas de rifaximina modular

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su nivel de absorción sistémica, y esto es parte de la presente invención mediante administrar formas polimórficas distintas de rifaximin, particularmente rifaximina δ y rifaximina ϵ . Es posible tener una diferencia en el absorción de casi 100 veces en el rango entre 0,001 a 0,3 $\mu\text{g/ml}$ en la sangre.

La evidencia diferenciada en la biodisponibilidad es importante porque puede diferenciar el comportamiento farmacológico y tóxico lógico de los dos polimorfos de rifaximina δ y ϵ .

De hecho, la rifaximina ϵ se absorbe de manera despreciable a través de la vía oral mientras que la rifaximina δ muestra una absorción mejor.

La rifaximina ϵ prácticamente no es absorbida, hecho poderoso solamente mediante una acción tópica, incluyendo el caso del tracto gastrointestinal, con la ventaja de una baja toxicidad.

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De otro lado, la rifaximina δ , que es absorbida suavemente, puede encontrar un uso ventajoso contra organismos sistémicos, capaces de esconderse y de inhibir la acción de antibióticos tópicos.

Con respecto a eventos adversos posibles acoplados al uso terapéutico de la rifaximina de relevancia particular es la inducción de la resistencia bacteriana a los antibióticos. Hablando de manera general, siempre es posible en la práctica terapéutica con antibióticos inducir resistencia bacteriana a los mismos u a otros antibióticos mediante la selección de cepas resistentes.

En el caso de la rifaximina este aspecto es particularmente relevante, ya que la rifaximina pertenece a la familia de la rifamicina, un miembro de la cual, la rifampicina es ampliamente usada en la terapia de la tuberculosis. El tratamiento de curso corto actual de tuberculosis es una terapia de combinación que involucra cuatro ingredientes activos farmacéuticos: rifampicina, isoniazida, etambutol y pirazinamida y entre ellos la rifampicina juega un papel principal. Por lo tanto cualquier droga puede dañar la

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eficacia de la terapia mediante seleccionar en cuanto a resistencia a la rifampicina lo que sería dañoso. (Kremer L. et al. "Re-emergence of tuberculosis: strategies and treatment", Expert Opin. Investig. Drugs, 11 (2), 153-157, (2002)).

En principio, mirando a la similitud estructural entre la rifaximina y la rifampicina, podría ser posible mediante usar rifaximina para seleccionar cepas resistentes de la M. tuberculosis y para inducir una resistencia cruzada con la rifampicina. Para poder evitar este evento negativo es crucial tener un control de la cantidad de rifaximina absorbida sistémicamente.

Bajo este punto de vista, la diferencia encontrada en la absorción sistémica de las forma δ y ϵ de la rifaximina es significativa, ya que también en concentración sub-inhibidora de rifaximina, tal como en el rango entre 0,1 a 1 $\mu\text{g/ml}$, la selección de mutantes resistentes ha sido demostrada que es posible (Marchese A. et al. In vitro activity of rifaximin, metronidazole and vancomycin against clostridium difficile and the rate of selection of spontaneously resistant mutants

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against representative anaerobic and bacteria aerobic, including ammonia-producing species. Chemotherapy, 44(4), 253-266, (2000)).

De acuerdo con lo dicho anteriormente, la importancia de la presente invención, que ha llevado al conocimiento de la existencia de las formas polimórficas de rifaximina mencionadas anteriormente y a diversas rutas industriales para la fabricación de formas simples puras que tienen propiedades farmacológicas diferentes se ven fortalecidas claramente.

Las formas δ y ϵ mencionadas anteriormente pueden ser usadas ventajosamente como productos puros y homogéneos en la fabricación de preparaciones medicinales que contienen rifaximina.

Como ya se dijo, el proceso para fabricar rifaximina de la rifamicina o descrita y reivindicada en la EP 0161534 es deficiente desde el punto de vista de la purificación e identificación del producto obtenido; se muestran algunos límites también desde el punto de vista sintético con

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43

respecto, por ejemplo, a los tiempos muy largos de reacción, desde 16 a 72 horas, muy poco adecuado para un uso industrial y más aún porque no suministra para la reducción in situ de la rifaximina oxidada que puede ser formada dentro de la mezcla de reacción.

Por lo tanto, un objetivo adicional de la presente invención es un proceso mejorado para la fabricación industrial de las formas δ y ϵ de la rifamixina, reivindicadas aquí como productos y utilizables como se definió y principios activos homogéneos en la fabricación de preparaciones medicinales que contienen tales principios activos.

Descripción de la Invención

Como ya se dijo, la forma δ y ϵ del antibiótico conocido como rifaximina (INN), los procesos para su producción y uso del mismo en la fabricación de preparaciones medicinales para rutas orales o tópicas, son objeto de la presente invención.

Un proceso objeto de la presente invención comprende hacer reaccionar un equivalente molar de rifamicina O con un exceso

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de 2-amino-4-metilpiridina, preferiblemente de 2.0 a 3.5 equivalentes molares, en una mezcla de disolvente hecha de agua y de alcohol etílico en proporciones volumétricas entre 1:1 y 2:1, durante un periodo de tiempo entre 2 y 8 horas a temperatura entre 40°C y 60°C.

Al final de la reacción la masa de reacción es enfriada a temperatura ambiente y es agregada con una solución de ácido ascórbico en una mezcla de agua, de alcohol etílico y ácido clorhídrico acuoso concentrado, bajo fuerte agitación para poder reducir la cantidad pequeña de rifaximina oxidado que se forma durante la reacción y finalmente el pH es llevado a cerca de 2,0 mediante una adición adicional de una solución acuosa concentrada de ácido clorhídrico, para poder remover mejor el exceso de 2-amino-4-metilpiridina usado en la reacción. La suspensión es filtrada y el sólido obtenido es lavado con la misma mezcla disolvente agua/alcohol etílico usado en la reacción. Tal producto semideterminado se llama "rifaximina bruta".

En la rifaximina bruta puede ser sometida directamente a una etapa posterior de purificación. Alternativamente, en caso de

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largos tiempos de preservación del producto subterminado son esperados, la rifaximina bruta puede ser secada bajo vacío a temperatura inferior de 65°C por un periodo de tiempo entre 6 y 24 horas, tal producto semiterminado se llama "rifaximina producto seco".

El rifaximina bruto así obtenido y/o el rifaximina bruto secado son purificados mediante disolverlos en alcohol etílico a una temperatura entre 45°C y 65°C y luego cristalizarlos mediante la adición de agua, preferiblemente en cantidades en peso entre 15% y 70% con respecto a la cantidad en peso del alcohol etílico usado para la disolución, y mediante el mantener la suspensión obtenida a una temperatura entre 50°C y 0°C bajo agitación en un periodo de tiempo entre 4 a 36 horas.

La suspensión es filtrada y el sólido obtenido es lavado con agua y secado bajo vacío o bajo presión normal, con o sin un agente de secado, a una temperatura entre la temperatura ambiente y 105°C por un periodo de tiempo entre 2 y 72 horas.

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El logro de las formas δ y ϵ . depende de las condiciones escogidas para la cristalización. En particular, la composición de la mezcla disolvente desde la cual la cristalización se lleva a cabo, la temperatura en la cual la mezcla de reacción es mantenida después de la cristalización y el periodo de tiempo durante el cual esa temperatura es mantenida, han quedado ser críticos.

Más precisamente, las rifaximinas δ y ϵ . son obtenidas cuando la temperatura es primero llevada entre un valor entre 28°C y 32°C para poder causar el inicio de la cristalización, luego la suspensión es llevada a una temperatura entre 40°C y 50°C y se mantiene en este valor durante un periodo de tiempo entre 6 y 24 horas. Luego la suspensión es enfriada rápidamente a 0°C, sin un periodo de tiempo entre 15 minutos y 1 hora, es filtrado, el sólido es lavado con agua y luego es secado. La etapa de secado tiene una parte importante en la obtención de las formas polimórficas δ y ϵ . de la rifaximina y tiene que ser verificado por medio de un método adecuado ajustado a la dosificación de agua, como por ejemplo el método Karl Fisher para poder verificar la cantidad de agua remanente presente en el producto bajo secado.

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La obtención de la rifaximina δ durante el secado de hecho depende en la cantidad remanente final de agua que debería estar comprendida entre 2,5% (p/p) y 6% (p/p), más preferiblemente entre 3% y 4.5%, y no de las condiciones experimentales de presión y temperatura a las cuales este límite crítico de porcentaje de agua es logrado.

Para poder obtener la forma ϵ pobremente absorbida tiene que iniciarse desde la forma δ y tiene que continuarse en secado bajo vacío o a presión atmosférica, a temperatura ambiente o a temperaturas mayores, en la presencia o en la ausencia de agentes de secado, siempre que el secado sea prolongado durante el tiempo necesario de modo que la conversión en la forma ϵ sea lograda.

Ambas formas δ y ϵ de la rifaximina son higroscópicas, ellas absorben agua de una manera reversible durante el tiempo en la presencia de condiciones adecuadas de presión y humedad en el ambiente y son susceptibles de transformación a otras formas.

47

Las transiciones de una forma a otra resultan ser muy importantes en el ámbito de la invención, porque ellas pueden ser un método de fabricación alternativo para obtener la forma deseada para la producción de las preparaciones medicinales. Por lo tanto, el proceso que permite convertir la rifaximina δ a rifaximina ϵ en una manera industrial válida es una parte importante de la invención.

El proceso concerniente a la transformación de la rifaximina δ a rifaximina ϵ comprende secar la rifaximina δ al vacío o a una presión atmosférica, a temperatura ambiente o a temperaturas mayores, en la presencia o ausencia de agentes de secado, y mantenerlas durante un periodo de tiempo hasta que la conversión sea obtenida, usualmente entre 6 y 36 horas.

De lo dicho anteriormente, resulta que durante la fase de preservación del producto de un cuidado particular debe ser tenido en cuenta de modo que las condiciones ambiente no cambian el contenido de agua del producto, mediante preservar el producto en un ambiente que tenga humedad controlada o en contenedores cerrados que no permitan de una manera

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significativa el intercambio de agua con el ambiente exterior.

El polimorfo llamado rifaximina δ está caracterizado de un contenedor de agua en el rango entre 2.5% y 6%, preferiblemente entre 3,0 % y 4,5% y un difractograma de rayos X en polvo (reportado en la figura 1) que muestra picos en los valores de los ángulos de difracción 2θ de $5,7^{\circ} \pm 0,2$, $6,7 \pm 0,2$, $7,1 \pm 0,2$, $8,0 \pm 0,2$, $8,7 \pm 0,2$, $10,4 \pm 0,2$, $10,8 \pm 0,2$, $11,3 \pm 0,2$, $12,1 \pm 0,2$, $17,0 \pm 0,2$, $17,3 \pm 0,2$, $17,5 \pm 0,2$, $18,5 \pm 0,2$, $18,8 \pm 0,2$, $19,1 \pm 0,2$, $21,0 \pm 0,2$, $21,5 \pm 0,2$. El polimorfo llamado rifaximina ϵ está caracterizado por un difractograma de rayos X en polvo (reportado en la figura 2) que muestra picos en los valores de los ángulos de difracción 2θ de $7,0^{\circ} \pm 0,2$, $7,3 \pm 0,2$, $8,2 \pm 0,2$, $8,7 \pm 0,2$, $10,3 \pm 0,2$, $11,1 \pm 0,2$, $11,7 \pm 0,2$, $12,4 \pm 0,2$, $14,5 \pm 0,2$, $16,3 \pm 0,2$, $17,2 \pm 0,2$, $18,0 \pm 0,2$, $19,4 \pm 0,2$.

Los difractogramas han sido llevados a cabo por medio del instrumento X'Pert que está diseñado con una geometría Bragg-Brentano y bajo las siguientes condiciones de trabajo.

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Un estudio de biodisponibilidad de los dos polimorfos han sido llevados a cabo sobre perros hembras Beagle, tratados mediante ruta oral con una dosis de 100 mg/kg en cápsula de uno de los polimorfos, se recolectaron muestras de sangre de la vena yugular de cada animal antes de cada dosis y 1, 2, 4, 6, 8 y 24 horas después de cada dosis, transfiriendo las muestras a tubos que contienen heparina y separando el plasma mediante centrifugación.

El plasma ha sido ensayado para la rifaximina sobre el método LC-MS/MS y la concentración máxima de plasma observada (C_{max}), el tiempo para alcanzar el C_{max} (t_{max}), y el área bajo la curva de concentración-tiempo (AUC) han sido calculados.

Los datos experimentales reportados en la siguiente tabla 1 claramente muestran que la rifaximina ϵ es absorbida de manera despreciable mientras que la rifaximina δ es absorbida en un valor (C_{max} = 0.308 $\mu\text{g/ml}$) comprendido en el rango de 0.1 a 1.0 $\mu\text{g/ml}$.

Tabla 1

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**Parámetros farmacocinéticos para los polimorfos de rifaximina
luego de la administración oral única de 100 mg/kg mediante
cápsulas de perros hembra**

	Cmax ng/ml	Tmax h	AUC 0-24 Ng.h/ml
	Media	Media	Media
Polimorfo δ	308.31	2	801
Polimorfo ϵ	6.86	4	42

Los resultados experimentales anteriores resaltan adicionalmente las diferencias que existen entre los dos polimorfos de rifaximina.

Las formas δ y ϵ pueden ser usadas ventajosamente en la producción de preparaciones medicinales que tienen actividad antibiótica, que contienen rifaximina, tanto para uso oral como tópico. Las preparaciones medicinales para uso oral contienen la rifaximina δ y ϵ junto con los excipientes usuales como agentes de dilución como manitol, lactosa y sorbitol; agentes de aglomeración como almidones, gelatinas, azúcares, derivados de celulosa, gomas naturales y

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polivinilpirrolidona; agentes lubricantes tal como talco, estearatos, aceites vegetales hidrogenados, polietilenglicol y dióxido de silicio coloidal. Agentes de desintegración tales como almidones, celulosas, alginatos, gomas y polímeros reticulados; colorantes, saborizantes y agentes endulzantes.

Todas las preparaciones sólidas administrables mediante ruta oral pueden ser usadas en el ámbito de la presente invención, por ejemplo tabletas recubiertas y no recubiertas, cápsulas hechas de gelatina suave o dura, píldoras recubiertas de azúcar, pastillas, láminas de emparedado, gránulos o polvos en paquetes sellados.

Las preparaciones medicinales para uso tópico que contienen la rifaximina δ y ϵ con los excipientes usuales tal como petrolato blanco, cera blanca, lanolina y derivados de ellos, alcohol estearílico, propilenglicol, lauril sulfato de sodio, éteres de alcoholes grasos de polioxietileno, ésteres de ácidos de polioxietileno graso, monoestearato de sorbitán, monoestearato de glicerilo, monoestearato de propilenglicol, glicoles de polietileno, metilcelulosa,

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54

hidroximetilpropilcelulosa, carboximetilcelulosa de sodio, aluminio coloidal y silicato de magnesio, alginato de sodio.

Todas las preparaciones tópicas pueden ser usadas en el ámbito de la presente invención, por ejemplo en ungüentos, pomadas, cremas, geles y lociones.

La invención se ilustra de aquí en adelante mediante algunos ejemplos que no tienen que ser tomados como una limitación de la invención: de los resultados que se describen el hecho evidente es que las formas δ y ϵ pueden ser obtenidas mediante combinar adecuadamente entre ellas las condiciones anteriormente mencionadas de cristalización y secado.

Ejemplo 1

Preparación de rifaximina bruto y de rifaximina bruto secado

En un frasco de tres cuellos equipado con un agitador mecánico, termómetro y condensador de reflujo, 120 ml de agua desmineralizada, 96 ml de alcohol etílico, 63,5 g de rifamicina O y 27,2 g de 2-amino-4-metilpiridina son cargados en sujeción a temperatura ambiente. Después de la carga, la

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masa es calentada a $47 \pm 3^\circ\text{C}$, es mantenida en agitación a esta temperatura durante 5 horas, y luego es enfriada a $20 \pm 3^\circ\text{C}$ y, durante 30 minutos, se agrega como una mezcla, preparada separadamente, hecha de 9 ml de agua desmineralizada, 12,6 ml de alcohol etílico, 1,68 g de ácido ascórbico y 9,28 de ácido clorhídrico concentrado. Al final de la adición, la masa es mantenida bajo agitación durante 30 minutos a una temperatura interior de $\pm 3^\circ\text{C}$ y luego, a la misma temperatura, se gotea 7,72 g de ácido clorhídrico concentrado hasta que se logre un pH de 2.0-

Al final de la adición, la masa es mantenida bajo agitación, siempre a una temperatura interior igual a 20°C , durante 30 minutos, luego el precipitado es filtrado y lavado por medio de una mezcla hecha de 32 ml de agua desmineralizada y de 25 ml de alcohol etílico. La "rifaximina bruta" así obtenida (89,2 g) es secada bajo vacío a temperatura ambiente durante 12 horas obteniendo 64.4 g de "rifaximina bruta seca" que muestra un contenido de agua igual a 5,6%. El producto es secado adicionalmente bajo vacío hasta que el peso de 62.2 g de rifaximina bruta seca tenía un contenido de agua igual a 3.3%, cuyo difractograma corresponde a la forma polimorfa δ

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caracterizada por el difractograma de rayos X en polvo que muestra picos en los valores de los ángulos 2θ de $5,7^{\circ}\pm 0,2$, $6,7^{\circ}\pm 0,2$, $7,1^{\circ}\pm 0,2$, $8,0^{\circ}\pm 0,2$, $8,7^{\circ}\pm 0,2$, $10,4^{\circ}\pm 0,2$, $10,8^{\circ}\pm 0,2$, $11,3^{\circ}\pm 0,2$, $12,1^{\circ}\pm 0,2$, $17,0^{\circ}\pm 0,2$, $17,3^{\circ}\pm 0,2$, $17,5^{\circ}\pm 0,2$, $18,5^{\circ}\pm 0,2$, $18,8^{\circ}\pm 0,2$, $19,1^{\circ}\pm 0,2$, $21,0^{\circ}\pm 0,2$, $21,5^{\circ}\pm 0,2$. El producto es higroscópico.

Ejemplo 2

Preparación de rifaximina e

El ejemplo 1 se repite y después de haber obtenido la forma δ , el polvo sólido es secado bajo vacío por 24 horas a la temperatura de 65°C . El producto obtenido es rifaximina e caracterizada por el difractograma de rayos X en polvo que muestra los picos en los valores de los ángulos 2θ de $7,0^{\circ}\pm 0,2$, $7,3^{\circ}\pm 0,2$, $8,2^{\circ}\pm 0,2$, $8,7^{\circ}\pm 0,2$, $10,^{\circ}\pm 0,2$, $11,1^{\circ}\pm 0,2$, $11,7^{\circ}\pm 0,2$, $12,4^{\circ}\pm 0,2$, $14,5^{\circ}\pm 0,2$, $16,3^{\circ}\pm 0,2$, $17,2^{\circ}\pm 0,2$, $18,0^{\circ}\pm 0,2$, $19,4^{\circ}\pm 0,2$.

Ejemplo 3

Biodisponibilidad en perros mediante vía oral

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57

Ocho perros hembra Beagle de crianza pura que tienen 20 semanas de nacidos y un peso entre 5,0 y 7,5 kg han sido divididos en dos grupos de cuatro.

El primero de esos grupos ha sido tratado con rifaximina δ , el segundo con rifaximina ϵ de acuerdo con el siguiente procedimiento.

A cada perro se le ha administrado mediante vía oral 100 mg/kg de uno de los polimorfos de rifaximina en cápsulas de gelatina, y se tomaron muestras de sangre de 2 ml de cada uno de la vena yugular de cada animal antes de cada dispensado y 1, 2, 4, 8 y 24 horas después de la administración.

Cada muestra ha sido transferida a un tubo que contiene heparina como anticoagulante y ha sido centrifugada; el plasma ha sido dividido en dos alícuotas, cada una de 500 μ l, y ha sido congelado a -20°C .

La rifaximina contenida en el plasma ha sido ensayada por medios del método LC-MS/MS validado y los siguientes parámetros se han calculado de acuerdo con el análisis estándar no compartimental:

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59

REIVINDICACIONES

1. El polimorfo del antibiótico rifaximina llamado rifaximina δ caracterizado por un contenido de agua en el rango de 2.5% /p/p) a 6% (p/p), preferiblemente comprendido entre 3,0% y 4,5%, y por el difractograma de rayos X en polvo que muestran los picos en polvo de los ángulos de difracción 2θ de $5,7^{\circ} \pm 0,2$, $6,7^{\circ} \pm 0,2$, $7,1^{\circ} \pm 0,2$, $8,0^{\circ} \pm 0,2$, $8,7^{\circ} \pm 0,2$, $10,4^{\circ} \pm 0,2$, $10,8^{\circ} \pm 0,2$, $11,3^{\circ} \pm 0,2$, $12,1^{\circ} \pm 0,2$, $17,0^{\circ} \pm 0,2$, $17,3^{\circ} \pm 0,2$, $17,5^{\circ} \pm 0,2$, $18,5^{\circ} \pm 0,2$, $18,8^{\circ} \pm 0,2$, $19,1^{\circ} \pm 0,2$, $21,0^{\circ} \pm 0,2$, $21,5^{\circ} \pm 0,2$.
2. El polimorfo del antibiótico rifaximina llamado rifaximina ϵ caracterizado por el difractograma de rayos X en polvo que muestran los picos en polvo de los ángulos de difracción 2θ de $7,0^{\circ} \pm 0,2$, $7,3^{\circ} \pm 0,2$, $8,2^{\circ} \pm 0,2$, $8,7^{\circ} \pm 0,2$, $10,^{\circ} \pm 0,2$, $11,1^{\circ} \pm 0,2$, $11,7^{\circ} \pm 0,2$, $12,4^{\circ} \pm 0,2$, $14,5^{\circ} \pm 0,2$, $16,3^{\circ} \pm 0,2$, $17,2^{\circ} \pm 0,2$, $18,0^{\circ} \pm 0,2$, $19,4^{\circ} \pm 0,2$.

59

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Un proceso para la producción de las rifaximina δ y ϵ , caracterizado en que un equivalente molar de rifamicina O reacciona con un exceso de 2 amino-4-metilpiridina, preferiblemente entre 2,0 a 3,5 equivalentes molares, en un solvente de mezcla hecha de agua y alcohol etílico en proporciones volumétricas entre 1;1 y 2;1 por un periodo de tiempo entre 2 y 8 horas a una temperatura entre 40°C y 60°C, la masa de reacción es tratada a temperatura ambiente con una solución de ácido ascórbico en una mezcla de agua, alcohol etílico y ácido clorhídrico acuoso concentrado, la masa de reacción se lleva a un pH de 2,0 mediante la solución de ácido clorhídrico acuosa concentrada, la suspensión es filtrada, el sólido obtenido es lavado con la misma mezcla de disolvente agua/alcohol etílico usada en la reacción, la rifaximina bruta así obtenida es purificada mediante disolverla en alcohol etílico a una temperatura entre 45°C y 65°C, causando la precipitación mediante la adición de agua, preferiblemente en cantidades en peso entre 15% y 70% con respecto de la cantidad en peso del alcohol

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61

etílico usado para la disolución, mediante disminuir la temperatura de la suspensión a valores entre 50°C y 0°C bajo agitación durante un periodo de tiempo entre 4 y 36 horas, por último mediante filtrar la suspensión, mediante lavar con agua el sólido obtenido y mediante secarlo bajo vacío o bajo condiciones de presión normal, con o sin un agente de secado, a una temperatura entre temperatura ambiente y 105°C, durante un periodo de tiempo entre 2 y 72 horas.

4. El proceso de acuerdo a la reivindicación 3 para la producción de la rifaximina δ caracterizada en que después de la adición de agua a la solución de etanol de la rifaximina bruta la temperatura es disminuida a un valor entre 28°C y 32°C para poder causar el inicio de la cristalización, la suspensión así obtenida es mantenida a 40°C y 50°C bajo agitación durante un periodo de tiempo entre 6 y 24 horas, luego es enfriada, durante un periodo de tiempo de 15 minutos y 1 hora a 0°C antes de ser filtrada, y el secado del sodio obtenido se lleva a cabo hasta que

61

62

el contenido de agua está en el rango entre 2,5% (p/p) a 6% (p/p), preferiblemente comprendido entre 3,0% y 4,5%.

5. El proceso de acuerdo a la reivindicación 3 para la producción de la rifaximina ε caracterizada mediante secar la rifaximina δ bajo vacío o a una presión atmosférica a temperatura ambiente o a temperaturas altas, en la presencia o ausencia de agentes de secado, siempre que el secado sea prolongado durante el tiempo necesario de modo que la conversión en la forma ε sea lograda.
6. El uso de la rifaximina δ en la preparación de preparaciones medicinales para uso oral con actividad antibiótica junto con los excipientes usuales como diluyentes, aglomerantes, lubricantes, desintegrantes, colorantes, saborizantes y agentes de endulzamiento.
7. El uso de la rifaximina ε en la preparación de preparaciones medicinales para uso oral con actividad

62

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antibiótica junto con los excipientes usuales como diluyentes, aglomerantes, lubricantes, desintegrantes, colorantes, saborizantes y agentes de endulzamiento.

8. El uso de acuerdo con cada una de las reivindicaciones 6 y 7 caracterizado en que las preparaciones para uso oral son seleccionadas entre tabletas recubiertas y no recubiertas, cápsulas de gelatina dura y suave, píldoras recubiertas de azúcar, láminas de wafer, gránulos y polvos en paquetes sellados.

9. El uso de la rifaximina δ en la preparación de preparaciones medicinales con actividad antibiótica para uso tópico.

10. El uso de la rifaximina ϵ en la preparación de preparaciones medicinales para uso tópico.

11. El uso de acuerdo a cada una de las reivindicaciones 9 y 10 caracterizada en que las preparaciones para

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**NUÉVAS FORMAS POLIMÓRFICAS DE RIFAXIMIN, PROCESOS PARA SU
PRODUCCIÓN Y USOS EN LA MEDICINA**

Resumen:

Las formas polimórficas cristalinas del antibiótico rifaximina (INN) llamado rifaximina δ y rifaximina ϵ útil en la producción de preparaciones medicinales que contienen rifaximina para uso oral y tópico y obtenido por medio de un proceso de cristalización llevado a cabo mediante disolución en caliente del rifaximina rico en alcohol etílico y mediante causar la cristalización del producto mediante agregar agua a una temperatura determinada y durante un periodo de tiempo determinado, seguido mediante el secado llevado a cabo bajo condiciones controladas hasta alcanzar un contenido de agua establecido en el producto final, son el objeto de la invención.

66

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference SCB 1000 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/EP2006/001755	International filing date (day/month/year) 27/02/2006	(Earliest) Priority Date (day/month/year) 03/03/2005
Applicant ALFA WASSERMANN S.P.A		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
 b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001755

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D498/22 A61K31/395 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 161 534 A (ALFA FARMACEUTICI S.P.A) 21 November 1985 (1985-11-21) cited in the application examples 1,4,6-14	1-11
X	US 4 341 785 A (MARCHI ET AL) 27 July 1982 (1982-07-27) column 4, line 60 - column 4, line 66 column 6, line 13 - column 6, line 31; example 6	1-11
P,X	WO 2005/044823 A (ALFA WASSERMANN S.P.A; VISCOMI, GIUSEPPE, C; CAMPANA, MANUELA; BRAGA,) 19 May 2005 (2005-05-19) the whole document	1-11

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

☒ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

I document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

29 June 2006

Date of mailing of the international search report

06/07/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2220 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax (+31-70) 340-3018

Authorized officer

Usue111, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/001755

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0161534	A	21-11-1985	AR 241913 A1	29-01-1993
			AU 568934 B2	14-01-1988
			AU 4251585 A	21-11-1985
			CA 1215708 A1	23-12-1986
			DE 3573120 D1	26-10-1989
			DK 214685 A	16-11-1985
			ES 8603489 A1	16-04-1986
			FI 851907 A	16-11-1985
			GR 851144 A1	25-11-1985
			IE 58392 B1	08-09-1993
			IT 1199374 B	30-12-1988
			JP 1778865 C	13-08-1993
			JP 4069634 B	06-11-1992
			JP 60252483 A	13-12-1985
			NO 851921 A	18-11-1985
			PH 22007 A	02-05-1988
			PT 80446 A	01-06-1985
			US 4557866 A	10-12-1985
			ZA 8502971 A	24-12-1985
US 4341785	A	27-07-1982	AR 226212 A1	15-06-1982
			AT 373599 B	10-02-1984
			AT 222781 A	15-06-1983
			AU 537093 B2	07-06-1984
			AU 7065581 A	26-11-1981
			BE 888895 A1	16-09-1981
			CA 1142518 A1	08-03-1983
			CH 648037 A5	28-02-1985
			DE 3120460 A1	11-03-1982
			DK 224781 A	23-11-1981
			EG 14891 A	31-12-1985
			ES 8203388 A1	01-07-1982
			FI 811565 A	23-11-1981
			FR 2482967 A1	27-11-1981
			GB 2079270 A	20-01-1982
			GR 75640 A1	02-08-1984
			IE 51204 B1	29-10-1986
			IT 1154655 B	21-01-1987
			JP 1354051 C	24-12-1986
			JP 57011987 A	21-01-1982
			JP 61023192 B	04-06-1986
			LU 83376 A1	11-09-1981
			NL 8102290 A	16-12-1981
			NO 811731 A	23-11-1981
			PH 17207 A	19-06-1984
			PH 18704 A	05-09-1985
			PT 73064 A	01-06-1981
			SE 453089 B	11-01-1988
			SE 8103216 A	23-11-1981
			ZA 8103430 A	30-06-1982
WO 2005044823	A	19-05-2005	AU 2004200964 A1	26-05-2005
			AU 2004287601 A1	19-05-2005
			BR 0402382 A	28-06-2005
			BR PI0407149 A	07-02-2006
			CA 2460384 A1	07-05-2005
			CA 2538546 A1	19-05-2005
			CN 1613858 A	11-05-2005

PATENT COOPERATION TREATY

72

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2008/001755

International filing date (day/month/year)
27.02.2006

Priority date (day/month/year)
03.03.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D498/22 A61K31/395 A61P31/04

Applicant
ALFA WASSERMANN S.P.A

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 68.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 23399 - 0 Tx: 523666 epmu d
Fax: +49 89 23399 - 4468

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Usueli, A

Telephone No. +49 89 23399-7368



72

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2006/001755

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1- Reference is made to the following documents:

d1: EP-A-0 161 534

d2: US-A-4 341 785

2- Novelty

In claims 1 and 2 the rifaximin polymorphs have been characterised by some of the peaks of the X-ray diffractogram and, in the case of the form δ , by the indication of the water content. Processes for the preparation of rifaximin are disclosed in examples 1, 4 and 6 to 14 of d1 and in example 6 of d2. The final step of the example 1 of d1 is a crystallization in ethanol. In the other examples of d1 it is stated that the compound obtained has the same chemico-physical characteristic of the compound of 1. The UV, IR, NMR data of the compound obtained in d2 appear identical to the respective data of the example 1 of d1. From these considerations it can be concluded that all the processes mentioned above relate to the preparation of crystalline rifaximin and that the form obtained is very likely always the same.

However, in any of these documents the product has been characterised by the X-ray diffractogram or by the indication of the water content. Conversely, in the present claims the polymorphs have not been characterized by the parameters used in d1 and d2 (i.e. melting point, UV, IR, HNMR, CNMR)

As general rule, the novelty of a compound cannot be acknowledged for the sole reason that said compound has been defined by means of parameters or physical properties which have never been used in the prior art for describing a compound having the same chemical formula (Guidelines C-IV, 7.5).

Additionally, the mere fact that a compound has been obtained by a new process does not imply that said compound is novel.

Hence, in order to demonstrate the novelty of the present compounds, the applicant should provide the evidence that the compound(s) obtained according to the prior art processes present an X-ray diffractogram which is different from the one of present forms. As alternative, novelty should be shown by testing each of the two forms claimed

according to one of the analytical method used in d1 and d2.

In addition to the preparation of rifaximin, d2 discloses also its medical uses and pharmaceutical compositions containing this compound.

In view of d1 and d2, the subject matter of claims 1,2 6 to 11 does not comply with the requirements of Art. 33.2 PCT.

None of the cited documents discloses a process according to present claims 3 to 5.

3- Inventive step

Although the requirements of Art. 33.3 PCT can be assessed only when claims satisfying the requirements of novelty are on file, the following general considerations can be made re inventive activity.

The applicant has set himself the task of providing polymorphic forms of Rifaximin D1 and d2 appear to be equally relevant for the assessment of inventive step. Hence, any of them can be regarded as closest state of the art.

The technical problem can be seen in the provision of alternative forms of Rifaximin.

It is well known in the field of organic chemistry that some compounds, including active ingredients of pharmaceutical compositions, may exist in more than one crystalline or amorphous form.

The processes of crystallization usually comprise the formation of solutions or suspension of the compound, the heating and cooling of the mixture, sometime the addition of seed crystal.

The processes according to the present invention appear to be based upon these well-known techniques.

The mere provision of a new polymorphic form of a compound, cannot be regarded as an activity involving inventive skill since the skilled person knows that a certain compound can exist in different polymorphic forms, the preparation of which usually require the application of standard methods.

Accordingly, in the absence of unexpected property in respect to the known form, a new polymorph cannot be considered inventive for the sole reason that it has been made available.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2006/001755

In this respect it is observed that the description of the application provides various information concerning the pharmacokinetic parameters of the two forms. It has also been noted that the two forms have different pharmacological properties in view of their different systemic absorption. This technical information could possibly contain relevant data that could be used during the prosecution of the examination for the assessment of the inventive step. However, the comparison of the pharmacokinetic behaviour of the two forms claimed, although very important from a scientific and technical perspective, does not appear to be relevant for the assessment of inventive step. On the contrary, it would be very important to underline the different characteristics or the different behaviour of the present forms vis-à-vis the form known from d1 and d2.

Re Item VI

Certain documents cited

d3: WO 2005/044823 A (ALFA WASSERMANN S.P.A; VISCOMI, GIUSEPPE, G;
CAMPANA, MANUELA; BRAGA,) 19 May 2005 (2005-05-19)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 1000 PCT	FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/EP2006/001755	International filing date (day/month/year) 27.02.2006	Priority date (day/month/year) 03.03.2005	
International Patent Classification (IPC) or national classification and IPC INV. C07D498/22			
Applicant ALFA WASSERMANN S.p.A.			
1. This report is the International preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☐ sent to the applicant and to the International Bureau a total of sheets, as follows: ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☒ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 2006-02-27		Date of completion of this report 08.05.2007	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80293 Munich Tel. +49 89 2399 - 0 Fax: 623666 epmu d Fax: +49 89 2399 - 4466		Authorized officer Uselli, Ambrogio Telephone No. +49 89 2399-7388 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2006/001755

Box No. 1 Basis of the report

1. With regard to the language, this report is based on

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements* of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-14 as originally filed

Claims, Numbers

1-11 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify):*
- ☐ any table(s) related to sequence listing *(specify):*

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify):*
- ☐ any table(s) related to sequence listing *(specify):*

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/EP2006/001755

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents:

d1: EP-A-0 161 534

d2: US-A-4 341 785

2- Novelty

In claims 1 and 2 the rifaximin polymorphs have been characterised by some of the peaks of the X-ray diffractogram and, in the case of the form δ , by the indication of the water content. Processes for the preparation of rifaximin are disclosed in examples 1, 4 and 6 to 14 of d1 and in example 6 of d2. The final step of example 1 of d1 is a crystallization in ethanol. In the other examples of d1 it is stated that the compound obtained has the same chemico-physical characteristic of the compound of 1. The UV, IR, NMR data of the compound obtained in d2 appear identical to the respective data of the example 1 of d1. From these considerations it can be concluded that all the processes mentioned above relate to the preparation of crystalline rifaximin and that the form obtained is very likely always the same.

The XRPD of present forms δ and ϵ appear different from the XRPD generated by the applicant for the rifaximin obtained according to the procedures of d1 and d2.

Forms δ and ϵ are therefore novel.

In view of the above it is considered that the subject matter claimed meets the requirements of Art. 33.2 PCT.

3- Inventive step

The applicant has set himself the task of providing polymorphic forms of Rifaximin. D1 and d2 appear to be equally relevant for the assessment of inventive step. Hence, any of them can be regarded as closest state of the art.

The technical problem can be seen in the provision of alternative forms of Rifaximin.

It is well known in the field of organic chemistry that some compounds, including active ingredients of pharmaceutical compositions, may exist in more than one crystalline or amorphous form. It is also well known that hydrate forms of a given compound can exist

82

in various crystalline forms.

The processes of crystallization usually comprise the formation of solutions or suspension of the compound, the heating and cooling of the mixture, sometime the addition of seed crystal.

Though the determination of the exact conditions for obtaining a specific polymorph may require extensive experimental work, this activity is normally based upon well-known techniques such as the procedures mentioned above. The process of present claim 3 does not appear to involve any unconventional procedure. Even the steps of washing and drying the final compound with water belongs to those experimental procedures that a person skilled in the art is used to apply in order to optimise the process or the properties of the final products. For instance, in examples 11, 12 and 13 of d1 the processes for obtaining rifaximin derivatives are concluded by washing and drying steps.

Thus, the skilled person not only knows that an organic compound may exist in different polymorphic and/or solvated forms, but he knows also the general procedures for obtaining these forms.

Accordingly, a skilled person faced with the problem of providing a further form of rifaximin, form which does not need to be characterised by specific properties or advantages, would consider obvious to prepare any new solvate or crystalline form of this compound. In other words, it appears that the skilled person, as far as is not demanded to prepare a form characterised by specific properties, he does not need to exercise any inventive skill because the simple implementation of routine procedures would allow him to solve the problem. Therefore, an inventive activity cannot be acknowledged only because additional forms of rifaximin have been made available.

Accordingly, it is considered that claims 1 to 11 do not meet the requirements of art. 33.3 PCT.

Re Item VI

Certain documents cited

d3: WO 2005/044823 A (ALFA WASSERMANN S.P.A; VISCOMI, GIUSEPPE, C; CAMPANA, MANUELA; BRAGA,) 19 May 2005 (2005-05-19)

83

PATENT COOPERATION TREATY

83

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Bianchetti, Giuseppe
Bianchetti Bracco Minoja S.r.l.
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ITALIE

**RICEVUTO IL
RECEIVED ON**

10 MAG. 2007

BIANCHETTI-BRACCO-MINOJA s.r.l.

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

08.05.2007

Applicant's or agent's file reference
SCB 1000 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2006/001785

International filing date (day/month/year)
27.02.2006

Priority date (day/month/year)
03.03.2005

Applicant
ALFA WASSERMANN S.p.A.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



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83



No. 07-086429- -00000-0000

Fecha: 2007-08-23 15:42:38 Dep. 2020 NUECREACIONE
Tra. 11 PATENTE(YII) Eje: 379 FASENACIONALI
Act. 411 PRESENTACION Folios: 83**Industria y Comercio**
SUPERINTENDENCIA**REQUISITOS MINIMOS PARA ADMISION A TRAMITE**
PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD

☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐INCOMPLETA ☐DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐INCOMPLETA ☐ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐INCOMPLETA ☐Claudia MNEVA
Firma Responsable

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85

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RODRIGUEZ DALEMAN DILIA MARIA
Apoderado(a) y/o Representante de
ALFA WASSERMANN S.P.A.

REFERENCIA	Radicación No.	7 86429
	Solicitud internacional	PCT/EP2006/001755
	Fecha inicio fase nacional	03/10/2007
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	

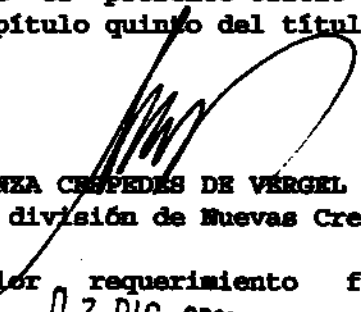
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Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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 CARMONA CEPEDIZ DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 07 DIC. 2007
adpall