EUROPEAN PATENT SPECIFICATION

Date of publication and mention of the grant of the patent:
03.09.2014 Bulletin 2014/36

Application number: 05004695.2

Date of filing: 03.03.2005

New polymorphous forms of rifaximin, processes for their production and use thereof in the medicinal preparations

Neue polymorphe Formen von Rifaximin, Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel

Nouvelles formes polymorphes du rifaximin, procédés pour leur préparation et leur utilisation en tant que médicaments

Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR
Designated Extension States:
AL BA HR LV MK YU

Date of publication of application:
06.09.2006 Bulletin 2006/36

Proprietor: ALFA WASSERMANN S.p.A.
65020 Alanno Scalo (Pescara) (IT)

Inventors:
• Viscomi, Giuseppe Claudio
  40037 Sasso Marconi, Bologna (IT)
• Campana, Manuela
  40134 Bologna, (IT)
• Confortini, Donatella
  40012 Calderara di Reno, Bologna (IT)
• Barbanti, Maria Miriam
  40136 Bologna (IT)
• Braga, Dario
  40133 Bologna (IT)

Representative: Hiebl, Inge Elisabeth et al
Kraus & Weisert
Patentanwälte PartGmbB
Thomas-Wimmer-Ring 15
80539 München (DE)

References cited:
EP-A- 0 161 534
WO-A-2005/044823
US-A- 4 341 785

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
Description

Background of the invention

[0001] 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 European Patent EP 0161534 describes and claims a process for its production starting from the rifamycin O (The Merck Index, XIII Ed., 8301).

[0002] 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 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.

[0003] 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. It has now been 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.

[0004] 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.

[0005] The polymorphous forms of the rifaximin have been characterized through the technique of the powder X-ray diffraction.

[0006] 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 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 workability with consequent modification of the profiles of toxicological safety, clinical effectiveness and productive efficiency.

[0007] 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 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 products: chemical substances; Date for coming into operation: May 2000).

[0008] 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 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 dissolution together with consequent alteration of the respective pharmacological properties.

[0009] 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 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 form of the polymorph.

[0010] 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, irrespective of the conditions used for crystallizing, drying and preserving.

[0011] 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.

[0012] The form δ and the form ε of the rifaximin have then been synthesised and they are the object of the invention.

[0013] 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 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.
As a matter of fact, rifaximin and toxicological behaviour of the two polymorphous of rifaximins [0018] The evidenced difference in the bioavailability is important because it can differentiate the pharmacological and chemical characteristics of the two polymorphous of rifaximins δ and ε. [0017] 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 μg/ml in blood. [0019] Rifaximin ε is practically not absorbed, might act only through a topical action, including the case of the gastrointestinal tract, with the advantage of very low toxicity. [0020] 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 top antibiotics. [0021] In respect of possible adverse events coupled to the therapeutic use of rifaximin of particular relevance is the induction of bacterial resistance to the 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. [0024] 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 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 against representative anaerobic and aerobic bacteria, including ammonia-producing species. Chemotherapy, 46(4), 253-266,(2000)). [0025] 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 manufacturing pure single forms having different pharmacological properties, is clearly strengthened. [0026] The above-mentioned δ and ε forms can be advantageously used as pure and homogeneous products in the manufacture of medicinal preparations containing rifaximin. [0027] 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 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.

Description of the invention

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

[0031] At the end of the reaction the reaction mass is cooled to room 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 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".

[0032] The raw rifaximin can be directly submitted to the subsequent step of 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".

[0033] The so obtained raw rifaximin and/or dried raw rifaximin are purified 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 temperature between 50°C and 0°C under stirring during a period of time between 4 and 36 hours.

[0034] 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 of time between 2 and 72 hours.

[0035] 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 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 rifaximin 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 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.

[0036] The step of drying has an important part in obtaining the δ and ε 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.

[0037] The obtaining of the rifaximin δ during the drying in fact depends on 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.

[0038] 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.

[0039] 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.

[0040] 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 an important part of the invention.

[0041] 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.

[0042] 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.

[0043] The polymorph called rifaximin δ is characterized 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°±0.2, 6.7°±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 2\(\theta\) 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.

[0045] 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 (\(\alpha_1\)), K (\(\alpha_2\))
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 2\(\theta\) value: 3.0° – 30.0°

[0046] The evaluation of the content of water present in the analysed samples has always been carried out by means of the Karl Fischer method.

[0047] Rifaximin \(\delta\) and rifaximin \(\varepsilon\) 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.

[0048] The plasma has been assayed for rifaximin on the validated LC-MS/MS method and the maximum observed plasma concentration (Cmax), the time to reach the Cmax (tmax), and the area under the concentration - time curve (AUC) have been calculated.

[0049] The experimental data reported in the following table 1 clearly show that rifaximin \(\varepsilon\) is negligibly absorbed, while rifaximin \(\delta\) is absorbed at a value (Cmax = 0.308 \(\mu\)g/ml) comprised in the range of from 0.1 to 1.0 \(\mu\)g/ml.

![Table 1](image)

| Pharmacokinetic parameters for rifaximin polymorphs following single oral administration of 100 mg/kg by capsules to female dogs. |
|---|---|---|
| | Cmax ng/ml | Tmax h | AUC0-24 ng.h/ml |
| | Mean | Mean | Mean |
| Polimorph \(\delta\) | 308.31 | 2 | 801 |
| Polimorph \(\varepsilon\) | 6.86 | 4 | 42 |

[0050] The above experimental results further point out the differences existing among the two rifaximin polymorphs.

[0051] The forms \(\delta\) and \(\varepsilon\) can be advantageously used in the production of medicinal preparations having antibiotic activity, containing rifaximin, for both oral and topical application. The medicinal preparations for oral use contain the rifaximin \(\delta\) and \(\varepsilon\) together with the usual excipients as diluting agents like mannitol, lactose and sorbitol; binding agents like starches, gelatines, sugars, cellulose derivatives, natural gums and polyvinylpyrrolidone; lubricating agents like talc, stearates, hydrogenated vegetable oils, polyethylene glycol and colloidal silicon dioxide; disintegrating agents like starches, celluloses, alginites, gums and reticulated polymers; colouring, flavouring and sweetening agents.

[0052] All the solid preparations administrable by oral route can be used in the ambit of the present invention, for instance coated and uncoated tablets, capsules made of soft and hard gelatine, sugar-coated pills, lozenges, wafer sheets, pellets and powders in sealed packets.

[0053] The medicinal preparations for topical use contain the rifaximin \(\delta\) and \(\varepsilon\) together with the usual excipients like white petrolatum, white wax, lanoline and derivatives thereof, stearylic alcohol, propylene glycol, 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, hydroxypropylcellulose, sodium carboxymethylcellulose, colloidal aluminium and magnesium silicate, sodium alginate.

[0054] 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.

[0055] 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 \(\delta\) and \(\varepsilon\) 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

[0056] 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±3°C, is kept under stirring at this temperature for 5 hours, then is cooled to 20±3°C and, during 30 minutes, is added with a mixture, prepared separately, made of 9 ml of demineralised water, 1.68 g of ascorbic acid and 9.28 g of aqueous concentrated hydrochloric acid. At the end of the addition, the mass is kept under stirring for 30 minutes at an interior temperature of 20±3°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°±0.2, 6.7°±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 product is hygroscopic.

Example 2

Preparation of rifaximin ε

[0057] 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°±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.

Example 3

Bioavailability in dogs by oral route

[0058] 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.

[0059] The first of these group has been treated with rifaximin δ, the second with rifaximin ε according to the following procedure.

[0060] 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 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.

[0061] 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 µl, and has been frozen at -20°C.

[0062] 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:

\[
\text{Cmax} = \text{maximum observed plasma concentration of rifaximin in the plasma;}
\]
\[
\text{Tmax} = \text{time at which the Cmax is reached;}
\]
\[
\text{AUC} = \text{area under the concentration-time curve calculated through the linear trapezoidal rule.}
\]

[0063] The results reported in the following table 1 clearly show how the rifaximin δ is much more absorbed, more than 40 times, in respect of rifaximin ε, which is practically not absorbed.
Claims

1. Polymorph of the antibiotic called rifaximinic $\delta$ characterized from a water content in the range from 2.5% (w/w) to 6% (w/w), preferably comprised between 3.0% and 4.5%, and from a powder X-ray diffractogram showing peaks at values of the diffraction angles $2\theta$ of 5.7° ±0.2, 6.7° ±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, 19.1° ±0.2, 21.0° ±0.2, 21.5° ±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, 19.1° ±0.2, 21.0° ±0.2, 21.5° ±0.2.

2. Polymorph of the antibiotic rifaximin called rifaximin $\varepsilon$ characterized from a powder X-ray diffractogram showing peaks at values of the diffraction angles $2\theta$ 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.

3. Process for the production of the rifaximin $\delta$, characterized in that a molar equivalent of rifamycin $\sigma$ 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 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 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, the suspension 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 is in the range from 2.5%(w/w) to 6%, preferably comprised between 3.0% and 4.5%, whereby 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 period of time between 2 and 72 hours.

4. Process for the production of rifaximin $\varepsilon$, characterized by drying rifaximin $\delta$ obtained according to claim 3 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 $\varepsilon$ is achieved.

5. Use of the rifaximin $\delta$ 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.

6. Use of the rifaximin $\varepsilon$ 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 according to each of claims 5 and 6 characterized in that the preparations are selected from the coated and uncoated tablets, the hard and soft gelatine capsules, the sugar-coated pills, the lozenges, the wafer sheets, the pellets and the powders in sealed packet.

8. Use of the rifaximin $\delta$ in the preparation of medicinal preparations with antibiotic activity for topical use.

9. Use of the rifaximin $\varepsilon$ in the preparation of medicinal preparations with antibiotic activity for topical use.

Table 1

<table>
<thead>
<tr>
<th>Polymorph</th>
<th>$C_{max}$ ng/ml</th>
<th>$T_{max}$ h</th>
<th>AUC0-24 ng.h/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta$</td>
<td>308.31</td>
<td>2</td>
<td>801</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>6.86</td>
<td>4</td>
<td>42</td>
</tr>
</tbody>
</table>
10. Use according to each of claims 8 and 9 characterized in that the preparations for topical use are selected from the ointments, the pomades, the creams, the gels and the lotions.

**Patentansprüche**

1. Polymorph des Antibiotikums Rifaximin, Rifaximin δ genannt, gekennzeichnet durch einen Wassergehalt im Bereich von 2,5% (G/G) bis 6% (G/G), der vorzugsweise zwischen 3,0% und 4,5% liegt, und durch ein Pulver-Röntgendiffraktogramm, das Peaks bei Werten der Beugungswinkel 2θ 5,7°±0,2, 6,7°±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 zeigt.

2. Polymorph des Antibiotikums Rifaximin, Rifaximin ε genannt, gekennzeichnet durch ein Pulver-Röntgendiffraktogramm, das Peaks bei Werten der Beugungswinkel 2θ 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 zeigt.

3. Verfahren zur Herstellung von Rifaximin δ, dadurch gekennzeichnet, dass ein Moläquivalent Rifamycin σ mit einem Überschuss an 2-Amino-4-methylpyridin, vorzugsweise 2,0 bis 3,5 Moläquivalenten, in einem Lösungsmittelgemisch, das aus Wasser und Ethylalkohol in Volumenverhältnissen zwischen 1:1 und 2:1 hergestellt wurde, für einen Zeitraum von zwischen 2 und 8 Stunden bei einer Temperatur zwischen 40°C und 60°C umgesetzt wird, die Reaktionsmasse bei Raumtemperatur mit einer Lösung von Ascorbinsäure in einem Gemisch aus Wasser, Ethylalkohol und konzentrierter wässriger Salzsäure behandelt wird, die Reaktionsmasse mit Hilfe einer konzentrierten wässrigen Salzsäurelösung auf pH 2,0 gebracht wird, die Suspension filtriert wird, der erhaltene Feststoff mit dem selben Wasser/Ethylalkohol-Lösungsmittelgemisch, das in der Reaktion verwendet wurde, gewaschen wird, das so erhaltene rohe Rifaximin gereinigt wird, indem es in Ethylalkohol bei einer Temperatur zwischen 45°C und 65°C gelöst wird, indem die Präzipitation durch Zusatz von Wasser, vorzugsweise in Gewichtsmengen von zwischen 15% und 70%, bezogen auf die Gewichtsmenge an Ethylalkohol, die zur Auflösung verwendet wurde, bewirkt wird, die Temperatur auf einen Wert von zwischen 28 °C und 32°C gesenkt wird, um den Beginn der Kristallisation zu bewirken, die so erhaltene Suspension zwischen 40°C und 50°C für einen Zeitraum von zwischen 6 und 24 Stunden unter Rühren gehalten wird, sie danach in einem Zeitraum von zwischen 15 Minuten und einer Stunde auf 0°C gekühlt wird, bevor sie filtriert wird, und die Trocknung des erhaltenen Feststoffs durchgeführt wird, bis der Wassergehalt im Bereich von 2,5% (G/G) bis 6% liegt, vorzugsweise zwischen 3,0% und 4,5% liegt, wobei es unter Vakuum oder unter Bedingungen von Normaldruck mit oder ohne einem/einem Trocknungsmittel bei einer Temperatur zwischen Raumtemperatur und 105°C für einen Zeitraum von zwischen 2 und 72 Stunden getrocknet wird.

4. Verfahren zur Herstellung von Rifaximin ε, gekennzeichnet durch Trocknen von Rifaximin δ, das gemäß Anspruch 3 erhalten wurde, unter Vakuum oder bei Atmosphärendruck, bei Raumtemperatur oder bei hohen Temperaturen in Gegenwart oder in Abwesenheit von Trocknungsmitteln, mit der Maßgabe, dass die Trocknung für die Zeit verlängert wird, die notwendig ist, damit die Umwandlung in Form ε erreicht wird.


10. Verwendung gemäß jedem der Ansprüche 8 und 9, dadurch gekennzeichnet, dass die Präparate zur topischen Verwendung aus Salben, Pomaden, Cremes, Gelen und Lotionen ausgewählt sind.

Revlendcations

1. Polymorphe de l’antibiotique rifaximine appelé rifaximine δ caractérisé par une teneur en eau dans la plage de 2,5 % (p/p) à 6 % (p/p), de préférence comprise entre 3,0 % et 4,5 %, et par un diffractogramme des rayons X sur poudres montrant des pics aux valeurs d’angles de diffraction 2θ de 5,7°±0,2, 6,7°±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.

2. Polymorphe de l’antibiotique rifaximine appelé rifaximine ε caractérisé par un diffractogramme des rayons X sur poudres montrant des pics aux valeurs d’angles de diffraction 2θ de 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.

3. Procédé de production de rifaximine δ, caractérisé en ce qu’un équivalent molaire de rifamycine γ est mis à réagir avec un excédent de 2-amino-4-méthylpyridine, de préférence de 2,0 à 3,5 équivalents molaires, dans un mélange de solvants constitué d’eau et d’alcool éthylique à des rapports volumétriques entre 1:1 et 2:1 pendant une période de temps entre 2 et 8 heures à une température entre 40 °C et 60 °C, la masse réactionnelle est traitée à température ambiante avec une solution d’acide ascorbique dans un mélange d’eau, alcool éthylique et acide chlorhydrique aqueux concentré, la masse réactionnelle étant aménée à pH 2,0 au moyen d’une solution aqueuse concentrée d’acide chlorhydrique, la suspension est filtrée, le solide obtenu est lavé avec le même mélange de solvants à base d’eau/alcool éthylique que celui utilisé dans la réaction, la rifaximine brute ainsi obtenue est purifiée par dissolution dans l’alcool éthylique à une température entre 45 °C et 65 °C, et induction de sa précipitation par ajout d’eau, de préférence en des quantités en poids entre 15 % et 70 % par rapport à la quantité en poids d’alcool éthylique utilisée pour la dissolution, la température est abaissée à une valeur entre 28 °C et 32 °C afin d’amorcer la cristallisation, la suspension ainsi obtenue est maintenue entre 40 °C et 50 °C sous agitation pendant une période de temps entre 6 et 24 heures, puis elle est refroidie à 0 °C, en une période de temps entre 15 minutes et une heure, avant d’être filtrée, et le séchage du solide obtenu est mis en œuvre jusqu’à ce que la teneur en eau soit dans la plage de 2,5 % à 6 % (p/p), de préférence comprise entre 3,0 % et 4,5 %, ledit séchage s’opérant sous vide ou dans des conditions de pression atmosphérique, avec ou sans agent de séchage, à une température entre 105 °C, pendant une période de temps entre 2 et 72 heures.

4. Procédé de production de rifaximine ε caractérisé par le séchage de la rifaximine δ obtenue selon la revendication 3 sous vide ou à pression atmosphérique, à température ambiante ou à températures élevées, en présence ou en l’absence d’agents de séchage, à condition que le séchage soit prolongé le temps nécessaire pour que la conversion sous la forme ε soit obtenue.

5. Utilisation de la rifaximine δ dans la production de préparations médicales à usage oral ayant une activité antibiotique avec les excipients usuels tels que des agents diluants, liants, lubrifiants, délitants, colorants, aromatisants et édulcorants.

6. Utilisation de la rifaximine ε dans la production de préparations médicales à usage oral ayant une activité antibiotique avec les excipients usuels tels que des agents diluants, liants, lubrifiants, délitants, colorants, aromatisants et édulcorants.

7. Utilisation selon chacune des revendications 5 et 6 caractérisée en ce que les préparations sont choisies parmi les comprimés enrobés et non enrobés, les capsules de gélatine dure et molle, les pilules dragéifiées, les pastilles à sucer, les feuilles gaufrées, les pastilles, et les poudres sous emballage scellé.

8. Utilisation de la rifaximine δ dans la production de préparations médicales ayant une activité antibiotique à usage topique.

9. Utilisation de la rifaximine ε dans la production de préparations médicales ayant une activité antibiotique à usage topique.

10. Utilisation selon chacune des revendications 8 et 9 caractérisée en ce que les préparations à usage topique sont
choisis parmi les onguents, les pommades, les crèmes, les gels et les lotions.
Figure 1
Figure 2
REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader’s convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

• IT 1154655 [0001] [0009]
• EP 0161534 A [0001] [0009] [0027]

Non-patent literature cited in the description

• The Merck Index [0001]
• MARCHESE A. et al. In vitro activity of rifaximin, metronidazole and vancomycin against clostridium difficile and the rate of selection of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia-producing species. Chemotherapy, 2000, vol. 46 (4), 253-266 [0024]