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(54) **Title**: NONHYGROSCOPIC LINEZOLID SALTS

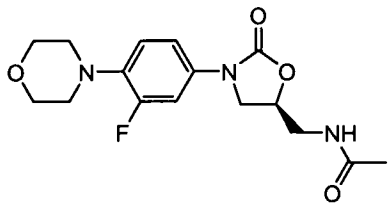
(57) **Abstract**: The present invention relates to an acid addition salt of linezolid with naphthalene- 1,5-disulfonic acid or with p-toluene sulfonic acid such as linezolid mono-naphtalene-1,5- disulfonate (linezolid hydrogennapadisylate), linezolid hemi-naphthalene-l,5-disulfonate (linezolide napadisylate) and linezolid p-toluene sulfonate (linezolid tosylate), to pharmaceutical compositions comprising them, to a process for making them, to a process for making linezolid base, to the use in making a medicine and use in medicine.

NONHYGROSCOPIC LINEZOLID SALTS

BACKGROUND OF THE INVENTION

The present invention relates to novel nonhygroscopic acid addition salts of linezolid, pharmaceutical compositions containing the salts, and methods of making and purifying linezolid base using the salts.

Linezolid is a pharmaceutically active compound useful as an antibacterial agent, e.g. for the treatment of diabetic food infections caused by Gram-positive bacteria. It is represented by the formula (I).



(I)

The marketed pharmaceutical compositions are a sterile isotonic solution for an i.v. infusion, a tablet for oral administration and an aqueous suspension for oral administration. They are marketed, i.a., under brand name ZYVOX by Pfizer. The molecule of linezolid has one asymmetric carbon in the molecule allowing for 2 enantiomers; the marketed compound is the (S)-enantiomer. In the above-marketed compositions, linezolid is present as a free base.

Hereinunder, the name linezolid will be used as the generic name for N-(3-(3-fluoro-4-(morpholin-4-yl)phenyl)-2-oxooxazolidin-5(S)-ylmethyl)acetamide, unless indicated to the contrary.

Linezolid was first disclosed in WO 95/07271 (EP 0717738, US 5,688,792) of the Upjohn Company.

Various solid state forms of linezolid have been disclosed in the prior art: crystalline Form I (J.Med.Chem. 39(3), 673 (1996), Form II (WO 01/057035, US 6,559,305), Form III (WO

2005/035530) and many others (US 2006/0142283), amorphous form (WO 2007/026369) and hydrated forms (US 2006/011350, EP 2033960).

Linezolid may also form acid addition salts. Its molecule comprises two basic nitrogens. The known salts are the dihydrochloride, sulfate or camphosulfonate (see EP 2033960).

Free base of linezolid is only sparingly soluble in water. To the contrary, the known linezolid salts are very well soluble in water.

A good solubility of linezolid salts in water allows making useful concentrated aqueous solutions that may be pharmaceutically acceptable. However, nothing is known about the properties of the linezolid salts, particularly about the stability of them in solid state, which is important for making and storing them in industrial scale. An improvement in this respect is therefore desirable.

SUMMARY OF THE INVENTION

The present invention relates to the discovery of new nonhygroscopic acid addition salts of linezolid that are useful for the making and purification of linezolid base as well as in pharmaceutical compositions.

Accordingly, a first aspect of the invention relates to acid addition salts of linezolid with naphthalene-1,5-disulfonic acid or with p-toluene sulfonic acid. In particular, the invention is related to linezolid mono-naphtalene-1,5-disulfonate (linezolid hydrogennapadisylate), linezolid hemi-naphthalene-1,5-disulfonate (linezolide napadisylate) and linezolid p-toluene sulfonate (linezolid tosylate). The salts exhibit an enhanced stability in the solid state in comparison with the other acid addition salts of linezolid, including the known salts disclosed in EP 2033960, patricularly low hygroscopicity. The solid state forms of the salts of the invention include crystalline and/or amorphous forms, incl. hydrates, solvates and/or clathrates thereof.

Another aspect of the present invention relates to a pharmaceutical composition comprising the linezolid acid addition salt as described above and at least one pharmaceutically acceptable excipient.

Yet another aspect of the present invention relates to a process, comprising combining linezolid base and an acid selected from naphthalene-1,5-disulfonic acid and p-toluenesulfonic

acid in a solvent to form a solution; precipitating the linezolid mono-naphtalene-1,5-disulfonate (linezolid hydrogennapadisylate), linezolid hemi-naphtalene-1,5-disulfonate (linezolid napadisylate) or linezolid p-toluene sulfonate (linezolid tosylate) from said solution,; and optionally isolating the precipitated linezolid acid addition salt.

A further aspect of the present invention relates to a method of making linezolid base , which comprises obtaining a solution of a salt of linezolid with naphthalene-1,5-disulfonic acid or with p-toluenesulfonic acid in an aqueous solvent, precipitation the free base of linezolid from said solution and isolating said linezolid base from the mixture.

Another aspect relates of the invention relates to the use of the salt of linezolid and naphthalene-1,5-disulfonic acid or with p-toluene sulfonic acid for making a medicine, and to the use in medicine.

DETAILED DESCRIPTION OF THE INVENTION

While some linezolid acid addition salts are known in the art, little or nothing is known about their properties. Linezolid dihydrochloride and sulfate were prepared in the EP 2033960. Both salts are very well soluble both in water and in 0.1 N HCl (more than 100 mg/ml). Free base of linezolid may be precipitated from aqueous solutions of both salts by treating these solutions with inorganic or organic base. However, it was found out by the present inventor that both of these salts are physically unstable in solid state. Upon storage at 45 or 50 °C and at 75 or 90% RH, resp., which simulate the conditions of a long-term storage under the access of the aerial humidity, it was found out that these compounds completely liquefy by means of absorption of high amounts of environmental water. Linezolid sulfate liquefies even at room temperature. Thus, both compounds are hygroscopic in essence.

The present inventor conducted a thorough study of the conditions of making various linezolid salts and their properties. First of all, it was found out that combining linezolid with many acids in common solvents did not yield a solid; instead, an oil/gum was formed (e.g., in attempts to make linezolid mesylate, esylate, besylate or maleate with 1 or 2 molar equivalents of the acid).

It was possible to isolate some linezolid salts from their solutions in a solid state. As the linezolid molecule exhibits two basic nitrogens, the isolatable salts comprise both mono-valent salts (base : acid ratio 1 : 1) or di-valent salts (base : acid ratio 1 : 2). The divalent acids may form also hemi-valent salts (base : acid ratio 2 : 1). Apart from the known linezolid salts, the following solid state linezolid salts were prepared: linezolid dihydrobromide (from acetone/water solution or tetrahydrofuran solution), linezolid mono-1,2-ethane disulfonate (from tetrahydrofuran solution), linezolid mono-naphtalene-2-sulfonate (from acetone solution), linezolid mono-p-toluene sulfonate (from acetone/water, tetrahydrofuran or tetrahydrofuran/water solutions), linezolid mono-naphthalene-1,5-disulfonate (from acetone/water solution), linezolid hemi-naphtalene-1,5-disulfonate (from acetone/water solution). Further it was found out that linezolid sulfate can be prepared in a crystalline state (by recrystallization of the known amorphous linezolide sulfate from acetone).

After subjecting all these solid state linezolid salts to a stability study at 40 °C / 75 % relative humidity, it was found out with surprise that most of them are quite hygroscopic. The amount of the absorbed water was sometimes so high that the solids were dissolved in it and the samples liquefied. In particular, the hygroscopicity was observed both for all the prior art salts (dihydrochloride, amorphous sulfate, D-camphor-10-sulfonate) and for most of the newly prepared salts. Some salts are hygroscopic even during storage at ambient conditions (amorphous sulfate, mono-1,2-ethanedisulfonate). The only nonhygroscopic exceptions were linezolid mono-p-toluene sulfonate (linezolid tosylate), linezolid mono-naphtalene-1,5-disulfonate (linezolid hydrogennapadisylate), and linezolid hemi-naphthalene-1,5-sulfonate (linezolid napadisylate). These three salts were thus proven to have extraordinary physical stability in the solid state, superior to that of the other salts of linezolid, which is advantageous in making and using them in industrial scale.

Thus, the present invention provides linezolid tosylate, linezolid hydrogennapadisylate and linezolid napadisylate as three novel and advantageous acid addition salts of linezolid. Preferably they are prepared and used in solid state. The "solid state" includes crystalline and amorphous forms, as well as mixtures thereof, and also includes solvates, hydrates and/or clathrates. Preferably these salts are obtained in a crystalline state, which is advantageous for purification, bulk storage, or use in pharmaceutical compositions and methods of treatment. In an example, the linezolid tosylate can be isolated in at least two crystalline forms, hereinunder denoted as

Form A and Form B, resp.. Both forms differ by their melting ranges (Form A melts in the range 88-93°C, Form B melts in the range 108-120° C, both determined by DSC, 10 °C/min) and by XRPD patterns. The Form B is also obtainable by a solvent-induced solid-solid transformation of the Form A, i.e. by long-term stirring of the suspension of the Form A in a suitable solvent, e.g. in ethyl acetate.

The linezolid hydrogennapadisylate and linezolid tosylate of the present invention are mono-valent salts, i.e., having an acid : base molar ratio of about 1 : 1. Analytical methods, such as titration or ionic chromatography, may show a ratio of acid : base of 0.8 : 1 to 1 : 1.2 in the isolated solid form of the salt as a result of, e.g., traces of unbound acid and/or base and inherent variance associated with the analytical method. Such variation in the acid : base ratio is encompassed by an acid : base ratio of "about 1 : 1." Linezolid napadisylate is a hemi-valent salt, i.e., having an acid : base molar ratio of about 1 : 2. Analytical methods, such as NMR, titration or ionic chromatography, may show a ratio of acid : base of 0.8 : 2 to 1 : 2.4 in the isolated solid form of the salt as a result of, e.g., traces of unbound acid and/or base and inherent variance associated with the analytical method. Such variation in the acid : base ratio is encompassed by an acid : base ratio of "about 1 : 2."

The linezolid napadisylate, linezolid hydrogennapadisylate and linezolid tosylate of the present invention can be made by combining linezolid base and the corresponding acid in a solvent to form a solution, and then precipitating the salt from said solution. Optionally the precipitated linezolid salt can be isolated. The "isolated form" means a product, which is substantially free from solvents and reagents used in the process of making it, except of any solvent and/or reagent that are firmly bound in a definite amount within the crystalline lattice of the solid material to form specific physical forms such as hydrates, solvates and/or clathrates.

A molar equivalent or a slight excess or shortage of the starting acid with reference to the linezolid base is typically used in order to form the invented linezolid salt having an acid : base molar ratio of about 1 : 1. A half molar equivalent or a slight excess or shortage of the starting acid with reference to the linezolid base is typically used in order to form the invented linezolid salt having an acid : base molar ratio of about 1 : 2.

In respect to the solvent for the precipitation reaction, preferred is the solvent, which dissolves the starting linezolid base and the corresponding acid but does not dissolve the formed

salt. From this aspect, a useful solvent comprise , without limitation, acetone, ethyl acetate, 1,4-dioxan, tetrahydrofuran, chloroform, acetonitrile , and combination thereof, in which the linezolid base is well soluble, at least at enhanced temperatures. If the corresponding acids are not sufficiently soluble in these solvents, they may be dissolved in a minimum amount of water or other co-solvent and then combined with the solution of linezolid base.

The linezolid base used in forming the linezolid salts of the present invention (i.e., the starting linezolid base) can be any physical form of linezolid base, including the hydrated forms, in any degree of purity. The starting linezolid base can also be crude linezolid that is present in the reaction mixtures obtained after the chemical synthesis of linezolid (an example is, e.g., WO 95/07271).

There is no specific order in which the linezolid base and the acid is combined in the solvent. Generally the conditions are such that all of the linezolid (and all of the acid) is dissolved in the solvent and the acid is slowly added to the solution. The contacting or combining of the linezolid-containing solvent with the acid is advantageously performed at an ambient or higher than ambient temperature, including the reflux temperature of the solvent.

The precipitation of the linezolid tosylate, hydrogennapadisylate and/or napadisylate can be carried out in various ways. For example, the precipitation can occur spontaneously upon the contacting of the linezolid base with the acid in the organic solvent. Precipitating of the linezolid salt can also be induced by seeding the solution, cooling the solution, evaporating at least part of the solvent, adding an antisolvent, and by combining one or more of these techniques.

The precipitated linezolid tosylate, hydrogennapadisylate and/or napadisylate can be isolated from the solution by conventional techniques, e.g. filtering or centrifugation, and can be washed and dried.

The isolated linezolid tosylate, hydrogennapadisylate and/or napadisylate can be purified if desired. For example, the isolated salt is recrystallized or reprecipitated by dissolving (at least partially, e.g., suspending) it in a solvent, such as any of the above mentioned solvents, at an enhanced temperature (which includes a reflux temperature of the solvent), and then crystallizing or precipitating the salt from the solvent. The recrystallization (reprecipitation) process may be repeated until a desired purity of the isolated linezolid salt is obtained. For clarity, the terms "purify", "purification", "purified", and variations thereof are used herein to indicate an

improvement in the quality or purity of the substance and are not meant in the narrow sense of obtaining near absolute purity. Hence reducing the impurities from 2.0% to 1.5% represents a "purification" of the substance.

The solid state linezolid salts of the present invention can be advantageously used to obtain purified linezolid. In general, crude linezolid can be purified by converting it to a linezolid acid addition salt of the present invention and then converting the linezolid salt back into linezolid base. It was found out with surprise, that the linezolid salts of the present invention (i.e. linezolid hydrogennapadisylate, linezolid napadisylate and linezolid tosylate) are hydrolyzable salts; this means that they may be converted by water into the linezolid free base without any treatment with an external acid or base. Because the linezolid base is only sparingly soluble in water, it spontaneously precipitates from the aqueous solutions of the linezolid salts. The yield of the precipitated linezolid may however be enhanced by adding an inorganic or organic base to the reaction mixture. Thus, in another aspect of the invention, there is provided a process comprising dissolving (at least to a certain extent) any of the linezolid salt of the present invention in a solvent, which comprises water, followed by precipitation of the linezolid base from the solution, optionally with treatment of the solution with an external base. Optionally, the precipitated linezolid base is isolated from the mixture by conventional separation techniques such as filtration or centrifugation, optionally washed and dried. The precipitation is normally spontaneous; however, the effectivity of the conversion may be increased, if desirable, by seeding, cooling the solution, concentrating the volume and/or adding an antisolvent. The "dissolving", which comprises also a partial dissolving, of the salt, comprises either combining the isolated linezolid salt with water, but also formation of the linezolid salt in water, e.g. by contacting the linezolid base and the corresponding acid in a water-comprising solvent.

In general, this precipitation process exhibits a purification effect. In a preferred embodiment, the above purification process results in linezolid base having less than 1% impurities, more preferably less than 0.5%; e.g., at least 99.6% pure.

In general, the process of hydrolysis provides the Form II of the linezolid base. Hydrated forms of linezolid are surprisingly not formed.

The linezolid napadisylate, hydrogennapadisylate and linezolid tosylate of the present invention can also be formulated and used in pharmaceutical compositions. For instance, a

suitable pharmaceutical composition may comprise the above linezolid salt and at least one pharmaceutically acceptable excipient.

Pharmaceutically acceptable excipients are known in the art and include carriers, diluents, fillers, binders, lubricants, disintegrants, glidants, colorants, pigments, taste masking agents, sweeteners, flavorants, plasticizers, and any acceptable auxiliary substances such as absorption enhancers, penetration enhancers, surfactants, co-surfactants, and specialized oils. The proper excipient(s) are selected based in part on the dosage form, the intended mode of administration, the intended release rate, and manufacturing reliability. Examples of common types of excipients include various polymers, waxes, calcium phosphates, sugars, etc. Polymers include cellulose and cellulose derivatives such as HPMC, hydroxypropyl cellulose, hydroxyethyl cellulose, microcrystalline cellulose, carboxymethylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, and ethylcellulose; polyvinylpyrrolidones; polyethylenoxides; polyalkylene glycols such as polyethylene glycol and polypropylene glycol; and polyacrylic acids including their copolymers and crosslinked polymers thereof, e.g., Carbopol® (B.F. Goodrich), Eudragit® (Rohm), polycarbophil, and chitosan polymers. Waxes include white beeswax, microcrystalline wax, carnauba wax, hydrogenated castor oil, glyceryl behenate, glycerylpalmito stearate, and saturated polyglycolyzed glycerate. Calcium phosphates include dibasic calcium phosphate, anhydrous dibasic calcium phosphate, and tribasic calcium phosphate. Sugars include simple sugars, such as lactose, maltose, mannitol, fructose, sorbitol, saccharose, xylitol, isomaltose, and glucose, as well as complex sugars (polysaccharides), such as maltodextrin, amylodextrin, starches, and modified starches. The compositions may be formulated into various types of dosage forms, for instance as solutions or suspensions for parenteral or oral administration, as tablets or capsules for oral administration, ointments or lotions for transdermal administration etc. The above lists of excipients and forms are not exhaustive.

The linezolid acid addition salts of the present invention are useful as antibacterial agents, in treating various diseases caused by some types of bacteria, by administering an effective amount thereof to a patient in need of such treatment. In particular the salts are useful in the treatment of diabetic food infections caused by Gram-positive bacteria. Typically effective amounts range from 1 mg to 500 mg, expressed as the amount of linezolid base, per day.

The invention will be further described with reference to the following non-limiting examples.

Example 1 Linezolid (1:1) naphthalene-1,5-disulfonate

0.5 g of linezolid base was dissolved in 25 ml of acetone at R.T. To the solution, 600 mg of naphthalene-1,5-disulfonic acid dissolved in 5 ml of demi-water was added dropwise, while stirring at R.T. To the solution, an additional 25 ml of acetone was added. The solution was stirred at R.T. in an open flask for about 1 day, during which a white solid was formed. The solid was isolated by filtration over a P3-glass filter (reduced pressure) and air-dried overnight at R.T. The yield was 0.62 g.

Example 2 Linezolid (1:1) p-toluene sulfonate (Form A)

0.5 g of linezolid base was dissolved in 50 ml of acetone at R.T. To the solution, about 300 mg of *p*-toluenesulfonic acid monohydrate dissolved in about 2 ml of demi-water was added dropwise, while stirring at R.T. The solution was stirred at R.T. for about 1 hour, during which no solid was formed. The solution was concentrated in vacuo to about 10 ml. Then, the solution was stirred overnight at R.T. in an open flask. A brownish oil was formed. To the mixture, 50 ml of di-isopropyl ether (IPE) was added. Additional oiling could be observed, converting into a greasy solid after a few hours. Finally, about 2 ml of acetone/methanol (1:1 V/V) was added to speed up recrystallization. The mixture was stirred at R.T. in an open flask for about 5 days, during which evaporation of solvent in combination with crystallization of the drug substance occurred. The solid was vacuum-dried at 40 °C for about 1 day. An off-white fine powder was obtained. The yield was 0.64 g.

Example 3 Linezolid (1:1) p-toluene sulfonate (Form A)

2.0 g of linezolid base was dissolved in 100 ml of tetrahydrofuran (THF) at R.T. To the solution, about 1.13 g of *p*-toluenesulfonic acid monohydrate dissolved in about 5 ml of THF was added dropwise, while stirring at R.T. As a result, a resin was formed. To the mixture, 10 ml of acetone/water (1:1 V/V) was added, resulting in dissolution of the resin. The solution was stirred at R.T. for about 1 day, no crystallization occurred. Then, the solution was vacuum-dried until an oil was left. The oil was resuspended in 20 ml of acetone and a few mg of linezolid

tosylate were added as seeds. The oil recrystallized and a white cake was formed. To the mixture, an additional 20 ml of acetone was added and the suspension was stirred at R.T. for an additional 1 day and stirred at 0 °C for about 15 minutes. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with acetone and air-dried overnight at R.T. The yield was 1.63 g.

Example 4 Linezolid (1:1) naphthalene-1,5-disulfonate

1.0 g of linezolid base was dissolved in 50 ml of acetone at R.T. To the solution, 1.5 g of naphthalene-1,5-disulfonic acid (> 1 eq.) dissolved in 3 ml of demi-water was added dropwise, while stirring at R.T. Initially, some oiling was observed, followed by rapid formation of a solid. To the suspension, an additional 50 ml of acetone was added. The solution was stirred at R.T. in an open flask for about 1.5 hours. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with acetone and air-dried overnight at R.T. An off-white powder with soft lumps was obtained. The yield was 1.93 g.

Example 5 Linezolid (1: 1) p-toluene sulfonate (Form A)

10.0 g of linezolid base was dissolved in 400 ml of tetrahydrofuran (THF) by means of stirring and heating (no reflux). To the solution, about 5.7 g of *p*-toluenesulfonic acid monohydrate dissolved in about 25 ml of THF was added dropwise, while stirring at R.T. During acid addition, 20-40 mg of linezolid tosylate was added as seeds. As a result, oiling took place. To the mixture, 5 ml of demi-water and an additional 20 mg of linezolid tosylate seeds were added. The formed suspension was stirred at R.T. for about 1 hour and stirred at 0 °C for about 45 minutes. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with acetone and air-dried overnight at R.T. The yield was 13.34 g.

Example 6 Linezolid (2:1) naphthalene-1,5-disulfonate

0.5 g of linezolid base was dissolved in 25 ml of acetone at R.T. To the solution, 300 mg of naphthalene-1,5-disulfonic acid dissolved in 3 ml of demi-water was added dropwise, while stirring at R.T. Initially, some opalescence was observed, followed by formation of a white solid. The suspension was stirred at R.T. for 10-15 minutes. The solid was isolated by filtration over a P3-glass filter, washed with acetone and air-dried overnight at R.T. A white, fine powder with lumps was obtained. The yield was 0.48 g.

Example 7 Linezolid (1:1) p-toluene sulfonate (Form B)

0.3 g of linezolid tosylate of Example 6 was suspended in 10 ml of ethyl acetate at R.T. The suspensions were spiked with a few droplets of acetonitrile to ensure that at least a small amount of the sample dissolved. The mixtures were stirred at R.T. for 9 days. The solids were isolated by filtration over a P3-glass filter (reduced pressure) and air-dried at R.T. for about 2 days.

Yield : 0.24 g of off-white powder

TGA : anhydrous form , XRPD : different from that of Example 6

Example 8 Linezolid (1:1) p-toluene sulfonate (Form A)

1.0 g of linezolid base was dissolved in 35 ml of ethyl acetate at reflux. To the hot solution, about 575 mg of *p*-toluenesulfonic acid monohydrate dissolved in about 5 ml of ethyl acetate was added dropwise, while stirring at R.T. As a result, a resin was formed. To the mixture, a few mg of linezolid tosylate, form A was added as seeds, followed by 1 ml of demi-water. As a result, a solid was formed slowly. The suspension was stirred at R.T. for about 1 hour. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with ethyl acetate and air-dried overweekend at R.T.

The yield was 1.07 g.

Example 9 Linezolid (1:1) p-toluenesulfonate (Form A)

1.0 g of linezolid base was dissolved in 10 ml of 1,4-dioxane at reflux. To the hot solution, about 575 mg of *p*-toluenesulfonic acid monohydrate dissolved in about 1 ml of demi-water was added, while stirring at R.T. No solid was formed. To the mixture, a few mg of linezolid tosylate (form A) was added as seeds, followed by 10 ml of 1,4-dioxane. As a result, a solid was formed slowly. The suspension was stirred at R.T. for about 0.5 hour. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with ethyl acetate and air-dried overweekend at R.T.

The yield was 0.45 g.

Example 10 Linezolid (1:1) p-toluenesulfonate (Form B)

1.0 g of linezolid base was suspended in 10 ml of acetonitrile at R.T. To the solution, about 575 mg of *p*-toluenesulfonic acid monohydrate dissolved in about 5 ml of acetonitrile was added dropwise, while stirring at R.T. To the clear solution, stirred at R.T. 20 ml of di-isopropyl ether was added dropwise. The mixture was seeded with a few mg of linezolid tosylate (form A). Then, the mixture was stirred at R.T. for about 3 hours, during which a solid was formed. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with di-isopropyl ether and air-dried overnight at R.T. A white, fluffy powder was obtained.

The yield was 1.33 g.

The invention having been described it will be obvious that the same may be varied in many ways and all such modifications are contemplated as being within the scope of the invention as defined by the following claims.

CLAIMS

1. An acid addition salt of linezolid with naphthalene-1,5-disulfonic acid or with p-toluene sulfonic acid.

2. The acid addition salt of the Claim 1 , which is linezolid mono-naphtalene-1,5-disulfonate (linezolid hydrogennapadisylate), linezolid hemi-naphthalene-1,5-disulfonate (linezolide napadisylate) and linezolid p-toluene sulfonate (linezolid tosylate).

3. The acid addition salt of the Claims 1-2 in a solid, particularly crystalline form, such as linezolid p-toluene sulfonate Form A,and linezolid p-toluene sulfonate Form B.

4. A pharmaceutical composition comprising the acid addition salt of the Claims 1-3 and at least one pharmaceutically acceptable excipient.

5. The composition according to Claim 4 formulated for parenteral, oral or transdermal administration.

6. A process comprising combining linezolid base and an acid selected from naphthalene-1,5-disulfonic acid and p-toluenesulfonic acid in a solvent to form a solution; precipitating the linezolid mono-naphtalene-1,5-disulfonate (linezolid hydrogennapadisylate), linezolid hemi-naphtalene-1,5-disulfonate (linezolid napadisylate) or linezolid p-toluene sulfonate (linezolid tosylate) from said solution,; and optionally isolating the precipitated linezolid acid addition salt.

7. The process according to Claim 6, wherein the solvent comprises acetone, ethyl acetate, 1,4-dioxan, tetrahydrofuran, chloroform, acetonitrile , and combination thereof, optionally in a combination with water or other co-solvent.

8. The process according to Claims 6-7, wherein the linezolid base is present in the reaction mixture obtained after the chemical synthesis of linezolid.

9. A process comprising dissolving any of the linezolid salt of Claims 1-3 in a solvent, which comprises water, followed by precipitation of the linezolid base from the solution, optionally with treatment of the solution with an external base.

10. The process according to the Claim 9, wherein the linezolid salt is obtained by contacting the linezolid base and the corresponding acid in a water-comprising solvent.

11. The process according to Claims 9-10, wherein the linezolid base precipitates as Form II.

12. Use of the linezolid salts of Claims 1-3 and/or compositions according to Claims 4-5 for making a medicament, particularly an antibacterial agent.

13. Use of the linezolid salts of Claims 1-3 for making and/or purification of linezolid base.

14. The acid addition salts of Claims 1-3, and/or the pharmaceutical compositions of Claims 4-5 for use in medicine, as an antibacterial agent, in particular in the treatment of diabetic food infections caused by Gram-positive bacteria.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/006587

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D263/20 A61P31/04 A61K31/5375

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

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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/07271 A1 (UPJOHN CO [US]; BARBACHYN MICHAEL R [US]; BRICKNER STEVEN J [US]; HUTC) 16 March 1995 (1995-03-16) cited in the application example 5 page 4, line 29 - line 34 claims 1, 15	1-14
X	EP 2 033 960 A2 (DIPHARMA FRANCIS SRL [IT]) 11 March 2009 (2009-03-11) cited in the application paragraph [0015] example 4	1-14
E	WO 2009/140466 A2 (REDDYS LAB LTD DR [IN]; REDDYS LAB INC DR [US]; DEVARAKONDA SURYA NARA) 19 November 2009 (2009-11-19) example 9	1-14

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

☒ See patent family annex.

* Special categories of cited documents :

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"L" 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2010	06/04/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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