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(54) Title: PROCESS FOR MAKING CRYSTALLINE FORM A OF LINEZOLID

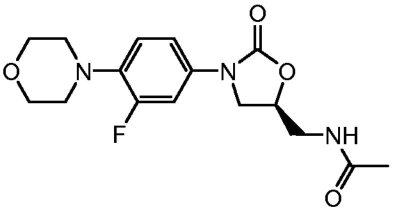
(57) **Abstract**: The invention relates to a process for making a crystalline linezolid, comprising a step of dissolving linezolid in an organic solvent to obtain a solution followed by a step of adding the obtained solution into an antisolvent kept at a pre-selected temperature and optionally seeded with crystals of the desired crystalline form of linezolid.

PROCESS FOR MAKING CRYSTALLINE FORM A OF LINEZOLID

BACKGROUND OF THE INVENTION

The present invention relates to an improved process for making the compound linezolid, especially in its specific crystalline form called Form A.

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.e., 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 (WO 2006/004922, US 2006/0142283), amorphous form (WO 2007/026369) and hydrated forms (US 2006/0111350, EP 20033960)

Among the solid state forms of linezolid, the crystalline Form III of WO 2005/035530 is of certain importance in pharmaceutical industry as it is a sufficiently stable, good crystalline form with a good processability and compatibility with pharmaceutical excipients, particularly for making solid state dosage forms.

The Form III was obtained in the original WO 2005/035530, e.g., by heating linezolid at 130-140°C, refluxing in a solvent such as toluene or xylene or by crystallization from a seeded solution in a solvent.

The WO 2009/063505 obtained the crystalline linezolid (which corresponds to the Form III by evaluating of the disclosed XRPD pattern) by crystallization from various polar aprotic organic solvents, preferably from dioxane/di-isopropyl ether mixture, or by a rapid crystallization from an ester solvent.

As many crystalline forms of linezolid have been disclosed in the literature, there is a risk of misinterpretation of data from different sources. For instance, the Form III of WO 2005/035530 appeared to be identical with the product of WO 95/07271 (Form I) during prosecution. For reasons of clarity the solid state form of linezolid resulting from the processes described in the present application is denoted Form A throughout the specification and is defined by its X-ray powder diffraction (XRPD) data. In respect to the prior art, it can either correspond to previously denoted Form I or to Form III.

While several production processes of making the crystalline linezolid are known in the art, an improvement in this respect is still desirable.

SUMMARY OF THE INVENTION

The present invention relates to the discovery of a new process for making the crystalline linezolid, in particular the Form A of linezolid, as defined hereinafter, which process is useful in a reliable production on an industrial scale. The process is characterized by a rapid and controlled precipitation of the solid linezolid from a solution thereof in an organic solvent by means of an antisolvent kept at a preselected temperature.

According to a first aspect of the present invention, there is provided a process for crystallizing linezolid, especially in the crystalline Form A, comprising a step of dissolving linezolid in an organic solvent to obtain a solution followed by a step of adding the obtained solution into an antisolvent kept at a pre-selected temperature and, optionally, seeded with crystals of the desired crystalline form of linezolid, especially linezolid Form A.

According to particular aspect, the formed linezolid Form A is substantially free from other solid state forms of linezolid, particularly from the Form II and/or from hydrated forms.

According to another particular aspect, the organic solvent is selected from an aliphatic alcohol, a cyclic ether or an aliphatic ester and mixtures thereof. Advantageously, the organic solvents are essentially anhydrous.

According to yet another particular aspect, the antisolvent is a] an aliphatic hydrocarbon, which preferably is a hexane such as n-hexane, a heptane such as n-heptane, a cyclohexane and/or petroleum ether; b] an aliphatic ether, which preferably is methyl-tert.butyl ether; and mixtures thereof.

Advantageously, the temperature of the solution is within the range from 50°C up to the reflux temperature.

According to a first preferred aspect of the process of the invention is the pre-selected temperature of the antisolvent within the range from -20°C to +25°C, preferably at a temperature lower than 0°C.

According to a second preferred aspect of the process of the invention is the pre-selected temperature of the antisolvent less than 15°C, preferably less than 10°C lower than the boiling temperature of the antisolvent and is preferably higher than 80°C.

DETAILED DESCRIPTION OF THE INVENTION

The known processes of making the crystalline linezolid by a “classical” crystallization, i.e. the processes characterized by providing a solution of linezolid at an enhanced temperature and cooling the solution until a crystalline solid starts to precipitate therefrom, have the principal disadvantage in that these processes are hardly controllable, particularly in the large scale production. Dependent on the nature of the solvent, the concentration of the linezolid therein, the chemical purity of the compound, the speed of cooling and intensity of stirring, the crystals can precipitate from the supersaturated solution at different temperatures and with different speed, which can lead to undesirably low batch/to/batch uniformity in the shape and size of crystals. What is even more important, undesired crystalline forms of linezolid may be formed by crystallization instead of the desired form.

The process of the present invention, based on a technique in which a hot solution of linezolid in a solvent is brought into a contact with an anti-solvent (i.e. with a liquid in which the linezolid is practically insoluble) at a defined, pre-determined temperature with a defined, pre-determined speed, and ,optionally, in the presence of seeds of the desired crystalline form of linezolid , allows to form crystals of linezolid under reliable and well controllable conditions, which are particularly important in a large scale production.

The process of the present invention is particularly useful for making the crystalline Form A of linezolid and, therefore, it is discussed hereinunder in details in respect to this form. It is not meant, however, that the invention is limited to processes of making the Form A only.

Throughout the disclosure and claims, the “Form A” of linezolid is a crystalline form of linezolid that is characterized by a XRPD powder diffraction pattern comprising , inter alia, the peaks at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees 2 theta ($\pm$0.2 degrees 2 theta) . Such pattern may be obtained when measured with CuKα1 radiation (λ = 1.54060 Å). The XRPD pattern of the Form A obtained by the process of the present invention substantially corresponds to that as disclosed for the Form III in WO 2005/035530. “Substantially corresponds” is meant to cover variations/differences in the pattern that would not be understood by a worker skilled in the art to represent a difference in crystal structure, but rather differences in technique, sample preparation, impurities, etc.

The Form A of linezolid produced by the process of the present invention has an excellent batch-to-batch uniformity in the size and shape of the formed crystals. Importantly, the process provides for crystals of a relatively small average size, which is advantageous and very suitable property for formulation into pharmaceutical compositions. According to one particular aspect of the invention, the linezolid Form A crystals produced by the process of the present invention are advantageously substantially free from other crystalline forms of linezolid, particularly from the Form II of linezolid, which can be otherwise very easily formed by any process of “classical crystallization”. In this respect, the “substantially free” means that less than

10%, and advantageously less than 5% of other crystalline forms are present in the precipitated and/or isolated product comprising the Form A of linezolid.

In the first step of the process of the present invention, a solution of linezolid in a suitable solvent is provided.

The linezolid starting material useful for making the solution can be in any physical form of linezolid base including the hydrated forms, in any degree of purity. The starting linezolid 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) or after liberation of linezolid base from a linezolid salt. Processes for obtaining linezolid and its isolated forms are well known in the art.

Typically, the solvent is an organic solvent. According to an important aspect, the solvent is essentially anhydrous, i.e. it does not comprise water or may comprise only traces of water. This is because of a risk of forming linezolid hydrates, which should be limited or avoided. The organic solvent is advantageously a polar organic solvent, more advantageously that of having less than 10 carbon atoms; suitable examples comprise, alone or in an admixture: an aliphatic ester, e.g. ethyl acetate, an aliphatic alcohol, e.g. methanol, ethanol, 1-propanol, isopropanol or 1-butanol, a cyclic ether, e.g. 1,4-dioxane.

The solution is provided by dissolving linezolid in the solvent preferably at an enhanced temperature.

Whenever necessary or appropriate, the solution may be filtered hot to remove undesired solid particles, optionally in the presence of a surface active material, e.g. activated carbon, for to improve colour and clarity of the solution.

In the second step, the obtained solution is contacted with the antisolvent, which is kept at a pre-selected temperature.

The useful antisolvent is a liquid, in which the linezolid is essentially insoluble. Advantageously, the antisolvent comprises an aliphatic and/or alicyclic hydrocarbon, preferably the hydrocarbon with 5 to 10 carbon atoms, or an aliphatic ether, preferably that of 4 to 10 carbon atoms. In an example, the antisolvent is a hexane such as n-hexane, a heptane such as n-heptane, a cyclohexane, methyl-*tert.*-butyl ether and/or petroleum ether, and mixtures thereof. Preferably, the antisolvent is free from the traces of water.

The process of the present invention can be essentially performed by two techniques:

a) Contacting with a cold antisolvent with seeding

The enhanced temperature, at which the solution of linezolid in the solvent is provided, comprises any temperature within the range from 50°C up to the reflux temperature. The suitable concentration of linezolid in the solvent is so selected that the solution can be kept at the chosen temperature without any danger of nucleation at said temperature. In an example, the concentration comprises a range of between 2- 100 ml of the solvent per 1 gram of linezolid.

Prior to any addition of the linezolid solution, the antisolvent is temperated and kept cold at a predetermined temperature below +25° C under stirring. Typically, the temperature of the antisolvent is within the range between -20°C to +25°C, preferably between -15 and 0°C.

Typically, the mutual ratio between the antisolvent and the solvent is from 1:1 to 10:1 (v/v), advantageously from 2:1 to 7:1 (v/v).

Immediately before contacting the linezolid solution with the antisolvent, the antisolvent is seeded with seeds of the desired Form A of linezolid. These seeds may be obtained by heating linazolid (produced following US 5,688,792) at 130°C to 140°C under nitrogen atmosphere for 4 hours). This is important as no spontaneous nucleation is allowed. Typically, the relative amount of the seeds in respect to the weight of the linezolid in the solution is 1- 25 %. Seeds of other crystalline forms of linezolid, such as seeds of linezolid Form I and Form III, may be obtained using processes known in the art.

The rate of the addition of the solution into the antisolvent is not specifically limited and is advantageously so selected that the whole volume of the solution is poured into the stirred antisolvent in 30 minutes or less. Care is to be taken that the cooling speed is sufficient to maintain the temperature of the formed mixture at the predetermined value. Advantageously, the actual temperature during the period of contacting the solution with the antisolvent does not exceed ±5°C from the predetermined temperature. Care is also to be taken that the nucleation does not start prior to the contact of the solution with the antisolvent. Thus, the pipelines and valves coming into the contact with the hot solution should be advantageously pre-heated to a suitable temperature.

It should be noted that the order of contacting the solution with the antisolvent cannot be reversed, i.e. the antisolvent may not be added to the hot solution. In such reversed process, the linezolid rather precipitates as the Form II.

By controlled addition of the above linezolid solution into the stirred and seeded antisolvent, the precipitate is formed practically immediately after contacting of both fluids. The precipitate comprises small and uniform particles of the Form A of linezolid. If the above process conditions are met, the precipitate comprises the product, which is essentially free from the Form II of linezolid and/or from any hydrated form thereof.

The precipitated product can be isolated from the mixture by conventional techniques, e.g. filtering or centrifugation, and can be washed, preferably by a fresh antisolvent, and dried.

b) contacting with a hot antisolvent, preferably without seeding

When linezolid is dissolved in an alcoholic solvent, particularly in a propanol or butanol solvent (e.g. in 1-propanol or 1-butanol) at a reflux temperature, whereby a very concentrated solution of linezolid, e.g of more than 100 mg/ml and typically of about 200-400 mg/ml, is obtained, it is advantageous that such concentrated solution is contacted with the antisolvent at a near-to-reflux temperature. Typically such near-to-reflux temperature is less than 15 degrees Celsius, preferably less than 10 degrees Celsius lower than is the boiling temperature of the antisolvent. Advantageously, the temperature both of the solvent and of the antisolvent is higher than 80°C. For instance, when n-heptane is used as the antisolvent, it is typically temperated to about 90°C prior to contacting with the hot linezolid solution.

The antisolvent is advantageously used in a volume ratio from 1:1 to to 10:1 advantageously from 2:1 to 7:1 in respect to the volume of the solvent.

After slow addition of the concentrated linezolid solution into the stirred hot antisolvent, the crystallization of the Form A starts spontaneously even at the enhanced temperature. Although there is no apparent need of seeding the antisolvent in this arrangement, such seeding, particularly with seeds of the Form A, is not excluded.

The rate of the addition of the solution into the antisolvent is not specifically limited and is advantageously so selected that the whole volume of the solution is poured into the stirred antisolvent in 30 minutes or less. Care is to be taken as the reaction mixture may temporarily boil during the mixing.

The suspension is then cooled to a temperature of 25°C or less, whereby the rate of cooling is not specifically prescribed, and is kept at this temperature preferably for a period not exceeding 3 hours. The solid material is isolated from the mixture by conventional techniques, e.g. filtering or centrifugation, and can be washed, preferably by a fresh antisolvent, and dried.

This technique may be also modified in such a way that when linezolid is present as a solution in a solvent, which is other than the alcoholic solvent (e.g. an ethyl acetate reaction mixture after making the linezolid by a synthesis) , it is advantageous to replace the solvent by the alcoholic solvent . For instance, the original reaction solvent may be distilled off and replaced by the corresponding amount of the alcohol.

The linezolid Form A prepared by the process of the present invention can be formulated and used in pharmaceutical compositions. For instance, a suitable pharmaceutical composition may comprise the linezolid Form A 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 Form A prepared by the process of the present invention is useful as antibacterial agent, 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, it is useful in the treatment of diabetic food infections caused by Gram-positive bacteria. Typically the 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.

EXAMPLES

Example 1

Linezolid Form II (0.5 g) is dissolved in 20 ml of ethyl acetate at reflux. The hot solution is dropwise added, through a funnel preheated to 100°C, into 100 ml of n-heptane stirred at -10°C and containing 50 mg of linezolid Form A seeds. After 20 minutes of stirring at a temperature between -10 and 0° C, the suspension is filtered. The solid is washed with n-heptane and dried on air at room temperature. Yield: 0.32 g.

XRPD showed only peaks of form A.

Example 2

Linezolid Form II (0.5 g) is dissolved in 20 ml of ethanol at reflux. The hot solution is dropwise added, through a funnel preheated to 100°C, into 100 ml of n-heptane stirred at -10°C and containing 50 mg of linezolid Form A seeds. After 10 minutes of stirring at a temperature between -10 and 0°C, the suspension is filtered. The solid is washed with n-heptane and dried on air at room temperature. Yield: 0.50 g.

XRPD showed only peaks of form A.

Example 3

Linezolid Form II (0.5 g) is dissolved in 20 ml of 2-propanol at reflux. The hot solution is dropwise added, through a funnel preheated to 100°C, into 50 ml of n-heptane stirred at -10°C and containing 50 mg of linezolid Form A seeds. After 10 minutes of stirring at a temperature between -10 and 0° C, the suspension is filtered. The solid is washed with n-heptane and dried on air at room temperature. Yield: 0.50 g.

XRPD showed only peaks of form A.

Example 4

2.0 g of Linezolid Form III (WO 2005/035530) was dissolved in 10 ml of 1-propanol at reflux. The hot solution was added slowly but at once to 10 ml of hot n-heptane, stirred at 90°C and containing approximately 25 mg of Linezolid Form A as seeds. The suspension was rapidly cooled down to 0°C using ice-water and stirred at 0°C for about 2.5 hour. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with n-heptane and vacuum-dried over weekend at 40°C. The yield was 1.80 g (90%).

XRPD showed only peaks of form A.

Example 5

2.0 g of Linezolid Form III (WO 2005/035530) was dissolved in 5 ml of 1-butanol at reflux. The hot solution was added slowly but at once to 10 ml of hot n-heptane, stirred at 90°C (containing no seeds of Form A. As a result, a solid was formed. The suspension was rapidly cooled down to 0°C using ice-water (took about 5 minutes) and stirred at 0°C for about 1 hour. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with n-heptane and vacuum-dried overnight at 40°C. The yield was 1.83 g (92%).

XRPD showed only peaks of form A.

Example 6

100 g of Linezolid Form III (WO 2005/035530) was dissolved in 250 ml of 1-butanol at reflux. The hot solution was added slowly to 500 ml of hot n-heptane, mechanically stirred at 90°C (200 rpm). The anti-solvent was not seeded prior to mixing. The suspension was cooled down to 20°C using a water bath and stirred at 20°C for 30-60 min (150 rpm). The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with n-heptane and vacuum-dried overnight at 40°C. The yield was 97.32 g (97%).

XRPD showed only peaks of form A.

DSC showed only melting of form A around 178-179°C.

Microscopic observation showed plate-like or rod-like crystals.

Example 7

2.0 g of linezolid Form III (WO 2005/035530) was suspended in 60 ml of ethyl acetate, stirred and heated up to reflux. At reflux, 10 ml of 1-butanol was added, followed by distillation of ethyl acetate. Approximately 55 ml of solvent could be distilled off, leaving a concentrated, but clear solution. GC showed ethyl acetate with a minor amount of 1-butanol. The concentrated hot solution was slowly added to 10 ml of n-heptane, stirred at 90°C. As a result, a solid was formed. The suspension was rapidly cooled to 0°C and stirred at 0°C for about 10 minutes. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with n-heptane and vacuum-dried overnight at 40°C. Off-white, shiny crystals were obtained. The yield was 1.78 g (89%).

XRPD showed only peaks of form A.

Example 8

Step I Preparation of linezolid (according to US 5,688,792)

2 g of (5*R*)-5-(azidomethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-1,3-oxazolidin-2-one was dissolved in 130 ml of ethylacetate. The flask was evacuated and filled with nitrogen, then 150 mg of 10 % Pd/C was added and the mixture hydrogenated at 1 bar of hydrogen pressure, using a Parr apparatus, during 7 hours, then 100 mg of Pd/C was added and hydrogenation was continued over night. The flask was filled with nitrogen and 4.2 ml of pyridine and 2.6 ml of acetic anhydride were added. The mixture was stirred at RT for 3.5 hours. The mixture was filtered over a celite path.

Step II Crystallization of linezolid Form A.

The solution from the Step I, comprising a solution of approximately 2.0 g of crude linezolid in 130 ml of ethyl acetate was heated to reflux. At reflux, 10 ml of 1-butanol was added. Then, ethyl acetate was distilled off, leaving a concentrated yellow solution in 1-butanol with a small residual amount of ethyl acetate. This hot solution was slowly added to 10 ml of n-heptane, stirred at 90°C. To the mixture, a few mg of linezolid Form A and 10 ml of hot n-heptane was added. As a result, slow crystallisation took place. The mixture was rapidly cooled to 0°C and stirred at 0°C for about 10 minutes, during which more solid crystallised. The solid was isolated by filtration over a P3-glass filter (reduced pressure), washed with n-heptane and vacuum-dried overnight at 40°C. The yield was 1.65 g (about 67.5%).

XRPD showed only peaks of form A.

In the above examples, the XRPD spectra were recorded on Bruker-AXS D8 vario (Θ/2Θ geometry, reflection mode, Vantec PSD detector), according to the following settings:

Start angle (2θ): 2.0°

End angle (2θ): 35.0°

Scan step width: 0.02°

Scan step time: between 0.2-5.0 seconds

Radiation type: Cu

Radiation wavelengths: 1.54060 Å ($K\alpha_1$), primary monochromator used

Exit slit: 6.0 mm

Focus slit: 0.2 mm

Divergence slit: Variable (V20)

Antiscatter slit: 11.8 mm

Receiving slit: 20.7 mm

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. A process for making a crystalline linezolid, comprising a step of dissolving linezolid in an organic solvent to obtain a solution followed by a step of adding the obtained solution into an antisolvent kept at a pre-selected temperature and , optionally, seeded with crystals of the desired crystalline form of linezolid.

2. The process according to claim 1, wherein the crystalline linezolid is the Form A of linezolid characterised by a XRPD powder diffraction pattern comprising the peaks at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees 2 theta, when measured with CuKα1 radiation (λ= 1.54060 Å).

3. The process according to claim 1-2, wherein the organic solvent is selected from an aliphatic alcohol, such as methanol, ethanol ,1-propanol, isopropanol, 1-butanol, a cyclic ether, such as 1,4-dioxane, and an aliphatic ester, such as ethyl acetate, and mixtures thereof.

4. The process according to claims 1-3, wherein the temperature of the solution is within the range from 50°C up to the reflux temperature.

5. The process according to claims 1-4 wherein the antisolvent is an aliphatic hydrocarbon, preferably with 5 to 10 carbon atoms, and/or an aliphatic ether, preferably that of 4 to 10 carbon atoms.

6. The process according to claim 5, wherein the hydrocarbon is a hexane such as n-hexane, a heptane such as n-heptane, cyclohexane and/or petroleum ether, the aliphatic ether is methyl-*tert.*-butyl ether; and mixtures thereof.

7. The process according to claims 1-6, wherein the pre-selected temperature of the antisolvent is within the range from -20°C to +25°C, preferably at a temperature lower than 0°C.

8. The process according to claims 1-7, wherein the concentration of the linezolid in the solution is within a range of between 10-100 ml of the solvent per 1 gram of linezolid.

9. The process according to claims 1-6, wherein the pre-selected temperature of the antisolvent is less than 15°C, preferably less than 10°C lower than the boiling temperature of the antisolvent and is preferably higher than 80°C.

10. The process according to claim 9, wherein the solvent is an alcoholic solvent, preferably a propanol or butanol solvent.

11. The process according to claim 9-10, wherein the concentration of the linezolid in the solution is at least 100 mg/ml and preferably of about 200-400 mg/ml.

12. The process according to claims 1-11, wherein the mutual ratio between the antisolvent and the solvent is from 1:1 to 10:1 (v/v), preferably from 2:1 to 7:1 (v/v).

13. The process according to claims 1-12, wherein the antisolvent is seeded with crystals of the crystalline Form A of linezolid and preferably the relative amount of the seeds in respect to the weight of the linezolid in the solution is 1-25 %.

14. The process according to claims 9-12, wherein the antisolvent is not seeded with any seed of linezolid.

15. The process according to claims 1-14, wherein the crystallization provides a precipitate of the crystalline Form A of linezolid, which is essentially free from any other crystalline form of linezolid.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/066348

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D263/20 A61K31/421
ADD.

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/063505 A2 (USV LTD [IN]; SATHE DHANANJAY GOVIND [IN]; BHISE NANDU BABAN [IN]; NAI) 22 May 2009 (2009-05-22) cited in the application example 9 "According to another embodiment...diisopropyl ether"; page 9 - page 10 -----	1-15
X	US 2007/015753 A1 (KUMAR BOBBA VENKATA S [IN] ET AL KUMAR BOBBA VENKATA SIVA [IN] ET AL) 18 January 2007 (2007-01-18) paragraph [0032] - paragraph [0033] claims 1-6, 8-9 ----- -/--	1-15

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

☒ See patent family annex.

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Date of the actual completion of the international search 6 December 2010	Date of mailing of the international search report 21/12/2010
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Sarakinos, Georgios

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2005/035530 A1 (SYMED LABS LTD [IN]; MOHAN RAO DODDA [IN]; KRISHNA REDDY PINGILI [IN]) 21 April 2005 (2005-04-21) cited in the application examples 1-5 -----	1-15
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/066348

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