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Complete Specification

FORM 2

THE PATENTS ACT, 1970

[39 OF 1970]

COMPLETE SPECIFICATION

[See Section 10; Rule 13]

"A PROCESS TO PREPARE (S)-N-[[3-(3-FLUORO-4-(4-MORPHOLINYL)PHENYL)-2-OXO-5-OXAZOLIDINYL]METHYL]ACETAMIDEXZ

PHARMACIA 8s UPJOHN COMPANY, a Delaware corporation, 301 Henrietta Street, Kalamazoo, Michigan 49001, United States of America,

The following specification particularly describes the nature of the invention and the manner in which it is to be performed:-

This invention relates to a process to prepare (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide, which is novel crystalline form of Linezolid.

This invention generally relates to a novel crystal form "Form II" of a known compound, linezolid, which is pharmaceutically useful as an antibacterial agent.

2. Description of the Related Art

US Patent 5,688,792 discloses the antibacterial agent linezolid as well as a process for its preparation. EXAMPLE 5 reports the linezolid produced had a mp of 181.5-182.5°.

There are many other disclosures of processes to prepare linezolid. J. Med. Chem., 39(3), 673-9 (1996) reports the linezolid was, "recrystallized from ethyl acetate and hexanes ...white crystals, m.p. 181.5-182.5C." It also sets forth the IR spectrum as "3284, 3092, 1753,1728, 1649, 1565, 1519, 1447, 1435".

Tetrahedron Lett., 40(26), 4855 (1999) discloses linezolid and a process to prepare linezolid. However, this document does not set forth the melting point or IR spectrum of the linezolid prepared.

US Patent 5,837,870 (International Publication WO97/37980 of PCT/US97/03458) discloses a process to prepare linezolid. Linezolid is described in EXAMPLE 18, which does not set forth the melting point or IR spectrum of the linezolid prepared.

International Publication W099/24393 of PCT/US98/20934 discloses a process to prepare linezolid. Linezolid is described in EXAMPLES 8, 9 and 12 which do not set forth the melting point or IR spectrum of the linezolid prepared.

The form of linezolid being used in the clinical trials to support the filing of the NDA is Form II.

SUMMARY OF INVENTION Disclosed is a (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide, crystal "Form II" with a powder X-ray diffraction spectrum of:

d-spacing (Å) Two-Theta Angle (°) Relative Intensity (%)

12.44 7.10 2
9.26 9.54 9
6.37 13.88 6
6.22 14.23 24
5.48 16.18 3
5.28 16.79 100
5.01 17.69 2
4.57 19.41 4
4.50 19.69 2
4.45 19.93 6
4.11 21.61 15
3.97 22.39 23
3.89 22.84 4
3.78 23.52 7
3.68 24.16 1
3.52 25.28 13
3.34 26.66 1
3.30 27.01 3
3.21 27.77 1

Also disclosed is (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide, crystal "Form H" with an infrared (IR) spectrum as a mineral oil mull: 3364,1748, 1675,1537, 1517, 1445, 1410, 1401,1358,1329,1287, 1274,1253,1237,1221,1145, cm⁻¹, 1130,1123,1116, 1078, 1066, 1049, 907, 852 and 758

Further disclosed is a process to prepare (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-

further disclosed is a process to prepare (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, crystal "Form II" which comprises:

- (1) producing (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in greater than 98% enantiomeric purity,
- (2) mixing the greater than 98% enantiomerically pure (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in a solvent or mixture of solvents at a temperature below a temperature of about 80° and
- (3) separating the (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide crystal "Form H" from the solvent(s).

DETAILED DESCRIPTION OF THE INVENTION

Linezolid, (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, is a known pharmaceutically useful antibacterial agent, see US Patent 5,688,792 (EXAMPLE 5). Linezolid can be used orally or given by IV as a sterile solution.

When linezolid was originally produced, the crystal form was Form I. Form II differs from Form I in its IR spectrum, X-ray powder diffraction spectrum and melting point.

Once linezolid is synthesized, crystal Form II is prepared by starting with linezolid of high enantiomeric purity. It is preferred that the linezolid be more than 98% enantiomerically pure, it is more preferred that the linezolid be more than 99% pure and it is even more preferred that the linezolid be 99.5% pure. The linezolid of greater than 98% enantiomeric purity to be used to form crystal form II can either be in solution or be a solid. The linezolid starting material, solid or solution, is mixed with a solvent selected from the group consisting of:

water,

acetonitrile,

chloroform, methylene chloride, toluene,

R1-OH where R1 is C1-C6 alkyl,

R1-CO-R2 where R2 is C1-C6 alkyl or phenyl substituted with 1 thru 3 R_i where R_i is as defined above, and where R_i is as defined above,

R1-CO-O-R2 where R1 is C1-C6 alkyl and R_i is as defined above, R1-O-R2 where R1 is C1-C6 alkyl and R_i is as defined above. It is preferred that the solvent be selected from the group consisting of water, ethyl acetate, methanol, ethanol, propanol, *i*-propanol, butanol, acetonitrile, acetone, methyl ethyl ketone, chloroform, methylene chloride, toluene, xylene, diethyl ether, or methyl-*t*-butyl ether. It is more preferred that the solvent be ethyl acetate, acetone, acetonitrile, propanol, or isopropanol. It is most preferred that the solvent be ethyl acetate.

The mixture of linezolid in the solvent is agitated at a temperature below 80° until crystals of Form II are formed and crystals of other solid forms, such as Form I, disappear. It is preferred to dissolve the linezolid in ethyl acetate at a temperature near the boiling point of the solvent. This mixture is cooled to a temperature of about 70°. The mixture may be seeded with crystals of Form H to facilitate crystallization. It is preferred that the solid product is cooled and agitated at a temperature between about 45° and about 60° until the solids consist only of Form n crystals. It is most preferred to maintain the slurry at a temperature of about 55°. It is preferred to mix the linezolid and solvent for at least 10 min, it is even more preferred to mix the linezolid and solvent for at least 20 min and it is most preferred to mix the linezolid and solvent for at least 30 min. The time and temperature will vary depending on the solvent selected. With ethyl acetate it is preferred to mix for not less than 60 minutes.

The crystalline slurry may be further cooled to improve yield, and the solid Form II product may be isolated. The mixture may be further cooled and agitated. Other measures which can be used to facilitate crystallization include, but are not limited to, cooling, concentration of the solution by evaporation or distillation, or through addition of other solvents.

The crystals are isolated by procedures known to those skilled in the art.

Crystal Form II is the most stable form below about 85°. It is preferred to use starting material with less than 0.2% of the R enantiomer of linezolid to minimize or eliminate the formation of a pseudoracemic solid solution of the two enantiomers which tends to crystallize as the Form I solid, even at temperatures below 85°.

It is well known to those skilled in the art that linezolid is useful as an antibacterial agent, see for example US Patent 5,688,792.

DEFINITIONS AND CONVENTIONS The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

DEFINITIONS Linezolid refers to (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide the compound of formula:

All temperatures are in degrees Centigrade.

IR. refers to infrared spectroscopy.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

The term C_j-C_e alkyl means alkyl of 1 thru 6 carbon atoms and isomers thereof where such exist.

EXAMPLES Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

EXAMPLE 1 Preparation of Crystal Form II of Linezolid

Linezolid with better than 99.8 % enantiomeric purity, less than 0.2% of the R enantiomer, (J .99 grams) is mixed with ethyl acetate (J 00 mL). The flask is stoppered and heated to 65° with constant stirring in a temperature controlled oil bath. The linezolid is completely dissolved and the mixture is stirred for an additional 10 minutes. The temperature is maintained at 55° in the flask and one neck of the flask is unstoppered to allow slow evaporation of the solvent. A gentle stream of nitrogen is blown across the open neck to aid in evaporation. Solids spontaneously precipitated from solution and the volume is reduced by about 25% of the initial volume. The flask is sealed and mixed for 90 minutes while maintaining the

mixture at 55°. The mixture was then cooled to about 23° while being stirred. The solids are isolated by vacuum filtration using a sintered glass funnel to give linezolid in crystal form. Analysis by powder X-ray diffraction indicates that the solids are linezolid crystal Form H.

WE CLAIM:

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1. A process to prepare (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide, crystal "Form II" which comprises:

(a) producing (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide in greater than 98% enantiomeric purity;

(b) mixing the greater than 98% enantiomerically pure (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide in a solvent of the kind such as herein described or mixture of solvents of the kind such as herein described at a temperature below a temperature of 80°C and

(c) separating the (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide crystal "Form II" from the solvent(s).

2. A process as claimed in claim 1, wherein the enantiomeric purity is greater than 99%.

3. A process as claimed in claim 2, wherein the enantiomeric purity is greater than 99.5%.

4. A process as claimed in claim 1, wherein the solvent is selected from the group consisting of compounds of the formula:

water,

acetonitrile,

chloroform, methylene chloride, toluene,

Ri-OH, where Ri is C1-C6 alkyl,

R1-CO-R2, where R2 is C1-C6 alkyl or phenyl substituted with 1 through

3 Ri and where Ri is as defined above,

R1-CO-O-R2, where R1 is C1-C6 alkyl and R2 is as defined above, R1-O-R2

where Ri is C1-C6 alkyl and R2 is as defined above.

5. A process as claimed in claim 4, wherein the solvent is selected from the group consisting of water, ethyl acetate, methanol, ethanol, propanol, isopropanol, butanol, acetonitrile, acetone, methyl ethyl ketone, chloroform, methylene chloride, toluene, xylene, diethyl ether, or methyl-t-butyl ether.

6. A process as claimed in claim 4, wherein the solvent is selected from the group consisting of ethyl acetate, acetone, acetonitrile, propanol; or isopropanol.

7. A process as claimed in claim 4, wherein the solvent is ethyl acetate.

8. A process as claimed in claim 1, wherein the (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide is mixed for at least 10 min in the solvent or mixture of solvents.

9. A process as claimed in claim 8, wherein the (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide is mixed for at least 20 min in the solvent of mixture of solvents.

10. A process as claimed in claim 8, wherein the linezolid is mixed for at least 30 min in the solvent or mixture of solvents.

11. A process as claimed in claim 1, wherein the temperature is less than about 75°C.

12. A process as claimed in claim 11, wherein the temperature is from about 45°C to about 60°C.

13. A process as claimed in claim 1, wherein the (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide is isolated as a solid before mixing with a solvent or mixture of solvents.

14. A process as claimed in claim 1, wherein the (S)-N-[[3-(3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide is kept in solution before mixing with a solvent or mixture of solvents.

Dated this 28th day of June, 2002.

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