Title: SOLID FORMS OF ORTATAXEL

Abstract: The present invention relates to solid forms of 13-(N-Boc-β-isobutylserinyl)-14-β-hydroxybacillamin III 1,14-carbonate (Ortataxel). Amorphous Form A, crystalline Form B, mixtures thereof and processes for preparing them are disclosed. Amorphous Form A is prepared by fast precipitation of Ortataxel from a mixture of acetone and water. Form A transforms in Form B when suspended and stirred in a mixture of ethanol and water for 4-8 hours. If the suspension is stirred for less than 4 hours, mixtures of Form B and Form A are obtained. Form B or mixtures of Forms A and B can also be obtained dissolving Ortataxel in a protic organic solvent, followed by addition of water.
SOLID FORMS OF ORTATAXEL

Field of the invention
The present invention relates to solid forms of Ortataxel (13-(N-Boc-β-isobutylserinyl)-14-β-hydroxybaccatin III 1,14-carbonate) (1), mixtures thereof and methods for their preparation.

Background of the invention
Ortataxel (1) is an antitumor compound particularly active against breast, lung, ovary, colon, prostate, kidney and pancreas tumors, even in case of resistance to known antitumor agents such as adriamycin, vinblastine and some platinum derivatives.

Ortataxel can be prepared according to the methods described in U.S. 7,232,916, in U.S. 6,737,534 and in U.S. 6,906,101. These patents disclose in the examples a final purification step consisting of crystallization from a
mixture of acetone and hexane, which gives Ortataxel in the form of a solvate with an acetone content ranging from 4.5 to 6.5%.

The XRPD of the acetone solvate shows distinctive peaks at approximately 7.9, 9.8, 10.6, 10.9, 14.6, 16.9, 19.7, 21.3 deg 2-theta. The DSC curve shows an endothermic peak with onset at about 164°C due to melting and release of the crystallization solvent (confirmed by a weight loss of about 5.0% in TG/DTA) and a weak exothermic peak with maximum at about 212°C followed by an intense endothermic peak with maximum at about 247°C due to melting and incipient decomposition. The IR shows characteristic absorption frequencies at 3521, 3321, 2971, 2953, 1826, 1762, 1706, 1526, 1366, 1238, 1165, 1072, 723 cm⁻¹.

It is well known that volatile impurities in active pharmaceutical ingredients must comply with ICH (International Conference on Harmonisation) guidelines (Q3C); in this specific case an acetone content from 4.5 to 6.5% would not be allowed. Thus, it would be desirable to find a stable crystalline form of Ortataxel which does not contain residual solvents in amounts unacceptable from a regulatory point of view. Such crystalline form should also be chemically and thermodynamically stable, i.e. it should keep the same quality during storage, and should be obtainable through a reproducible method.

**Disclosure of the invention**

It has now been found that Ortataxel exists in two non-solvated physical Forms, herein after referred to as Forms A and B, which can also be obtained as mixtures.

Form A is an amorphous solid, since it shows an X-ray powder diffraction pattern with no discernable peaks. It can be easily prepared from Ortataxel, for example Ortataxel acetone solvate obtained according to the synthetic procedures described in the above-cited patents, by dissolution in a
suitable water-miscible solvent, followed by fast addition of water containing traces (usually 0.001-0.003% w/v) of an organic acid such as acetic or ascorbic acid, preferably citric. "Suitable water-miscible solvent" means a ketone or an aprotic dipolar solvent or a mixture thereof; preferred solvents are acetone, dimethylsulfoxide and mixtures thereof. The process is usually carried out at a temperature ranging from 20 to 30°C; and the preferred organic acid is citric acid. The organic acid avoids undesired formation of the 7-epimer and makes Form A physically and chemically stable for at least 36 months. According to a preferred embodiment, the preparation of Form A is carried out dissolving Ortabaxel in acetone (8 mL/g ortataxel) and precipitating it with a water (40 mL/g ortataxel) containing 0.001-0.003% w/v citric acid, at room temperature.

Form B is a crystalline polymorph melting at 159°C; with respect to the pseudopolymorphic acetone solvate, Form B is characterized by a low solvent content, ease of isolation by filtration or centrifugation and chemical and physical stability for at least 36 months. Form B can be prepared dissolving Ortabaxel, for example the acetone solvate or the above form A, in a protic organic solvent, such as methanol, ethanol or isopropanol, preferably ethanol, containing traces of an organic acid (0.01-0.03% w/v), such as acetic, ascorbic but preferably citric acid, followed by addition of water until precipitation and stirring the resulting mixture at a temperature ranging from 0 to 60°C, preferably at 40°C, for a time ranging from 4 to 8 hours. According to a preferred embodiment, the preparation of Form B is carried out dissolving Ortabaxel in ethanol (8-12 mL/g ortataxel) containing 0.01-0.03% w/v of citric acid, followed by addition of water (13-20 mL/g ortataxel), so that the ethanol/water ratio ranges between 0.5-0.7, and stirring for 6 hours. If stirring is carried out for less than 4 hours, Ortabaxel is obtained as a mixture of Form A and Form.
Ortataxel Forms A and B and mixtures thereof can advantageously be used for the preparation of pharmaceutical compositions for the treatment of cancer. In particular, mixtures of form A and B, which have different bioavailabilities, are useful for the preparation of controlled-release solid Forms. Therefore, a further object of the present invention are pharmaceutical compositions containing Ortataxel crystalline Form A or B or mixtures thereof in admixture with pharmaceutically acceptable carriers and/or ingredients, for example those disclosed in "Remington's Pharmaceutical Sciences", Mack Publishing Co., N.Y., USA.

The invention is now illustrated in greater detail in the following experimental section.

**EXPERIMENTAL SECTION**

**Description of the figures**

X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric/differential thermal analyses (TG/DTA), infrared (IR), and optical microscopy were used to characterize the new solid Forms which are compared with the analytical data of the acetone solvate.

- Figures 1-4: XRPD, DSC, TG/DTA and IR spectra of Form A;
- Figures 5-8: XRPD, DSC, TG/DTA and IR spectra of Form B;
- Figures 9-12: XRPD, DSC, TG/DTA and IR spectra of a mixture of Form A and Form B, containing about 75% of Form B;
- Figure 13: DSC profile of different proportions of Form A and Form B.

**Form A**

The x-ray powder diffraction pattern of Form A (Fig.1) is typical for an amorphous product with complete absence of diffraction peaks.

The DSC curve of Form A (Fig. 2) shows a weak and broad endothermic signal with maximum at about 80°C, a baseline deflection due to \( T_g \) between 133°C and 143°C, an exothermic peak with maximum at about
214°C due to recrystallisation of the melted product and the consequent melting peak with maximum at about 246°C followed by decomposition.

The IR spectrum of Form A (figure 3) shows the characteristic absorption frequencies at 3442, 2961, 1821, 1732, 1714, 1368, 1236, 1162, 1085, 1068, 984, 907, 776, 763, 711 cm⁻¹.

The TG/DT analysis of Form A (fig 4) confirms the DSC analysis showing a DT profile characterized by a baseline deflection due to T_g between 130°C and 143°C, an exothermic peak with maximum at about 211°C due to recrystallisation of the melted product and the consequent melting peak with maximum at about 249°C followed by decomposition. The TG profile shows a weight loss of about 1.0% from 30 to 150°C due to release of residual moisture and a weight loss of about 1.6% which takes place upon recrystallisation followed by a massive weight loss due to a degradative reaction.

The optical microscopy shows that solid Form A is constituted by a glassy irregular particulate with a large variety of dimensions and absence of well-shaped crystal Forms.

Form B

The x-ray powder diffraction pattern of Form B (Fig. 5) shows a crystalline structure with useful distinctive peaks at approximately 3.5, 6.8, 9.9, 10.1, 10.7, 12.1, 13.1, 14.8, 18.2, 19.7, 21.3, 29.3 deg 2-theta.

The DSC curve of Form B (fig 6) shows a weak and broad endothermic signal with maximum below 100°C, a first melting peak with maximum at about 166°C and ΔH_fus of about -20 J/g, an exothermic peak with maximum at about 196°C due to recrystallisation of the melted product and a second melting peak with maximum at about 252°C followed by decomposition.

The IR spectrum of Form B (fig.) 7 shows the characteristic absorption frequencies at 3444, 2961, 1816, 1735, 1720, 1689, 1368, 1237, 1163, 1085,
1068, 1047, 989, 949, 907, 776, 764, 710 cm\(^{-1}\).

The TG/DT analysis of Form B (fig 8) confirms the DSC analysis showing a weak and broad endothermic signal with maximum below 100°C due to release of residual moisture, a first melting peak with maximum at about 164°C, an exothermic peak with maximum at about 200°C due to recrystallisation of the melted product and a second melting peak with maximum at about 253°C followed by decomposition. In the TG profile, a weight loss of about 1.4% from 30 to 150°C due to release of residual moisture is followed by a massive weight loss which takes place above 240°C due to a degradative reaction.

The optical microscopy shows that solid Form B is constituted by acicular (needle-like) crystals.

Mixture of Form A and Form B

The x-ray powder diffraction pattern of the mixture of Form A and Form B (Fig. 9) shows a crystalline structure with distinctive peaks at approximately 3.4, 6.8, 9.9, 10.6, 12.1, 13.1, 14.8, 18.1, 19.7, 21.2 deg 2-theta due to the fraction of Form B in the mixture.

The DSC curve (fig 10) shows a weak and broad endothermic signal with maximum below 100°C, a first melting peak with maximum at about 163°C and \(\Delta H_{\text{fus}}\) of about -15 J/g, an exothermic peak with maximum at about 202°C due to recrystallisation of the melted product and a second melting peak with maximum at about 251°C followed by decomposition.

The IR spectrum (figure 11) shows characteristic absorption frequencies at 3448, 2960, 1816, 1735, 1719, 1688, 1368, 1237, 1164, 1085, 1068, 1048, 989, 949, 906, 776, 764, 710 cm\(^{-1}\).

The TG/DT analysis (fig 12) confirms the DSC analysis showing a weak and broad endothermic signal with maximum below 100°C due to release of residual moisture, a first melting peak with maximum at about
162°C, an exothermic peak with maximum at about 202°C due to recrystallisation of the melted product and a second melting peak with maximum at about 250°C, followed by decomposition. In the TG profile, a weight loss of about 2.7% from 30 to 150°C due to release of residual moisture is followed by a massive weight loss which takes place at 240°C due to a degradative reaction.

Optical microscopy shows that the Mixture of Form A and Form B is constituted by prismatic crystals.

These data clearly indicate that polymorphic Forms A and B of Orataxel are easy distinguishable from the pseudopolymorphic acetone solvate by means of XRPD, DSC, IR and analyses for the solvent content (such as thermogravimetry or gas-chromatography).

**MATERIALS AND METHODS**

**X-Ray Powder Diffraction Pattern (xrpd)**

X-ray powder diffraction patterns were collected on a Philips PW1800 diffractometer. The x-ray generator was operated at 45 kV and 40 mA, using the Cu Kα line as radiation source. The sample was packed on a suitable slit and the irradiated length was 10 mm. The data were collected between 2 and 65 deg 2-theta with a step size of 0.02 deg 2-theta.

**Differential Scanning Calorimetry (DSC)**

Measurements of differential scanning calorimetry were performed using a Mettler TC15 System equipped with a DSC20 measuring cell, using closed aluminum crucibles (40 µl volume) with a pinhole. Heat flow was recorded from 30 to 300°C with a linear heating rate of 10°C/min under a 50 ml/min nitrogen flow. About 5 mg of powder was used for each measurement.

**Thermogravimetry and differential thermal analysis (TG/DTA)**

The analyses were performed using a Seiko TG/DTA6200 simultaneous system using open aluminum pans (40 µl volume). The TG/DT
signals were recorded from 30 to 300°C with linear heating rate (10°C/min) under a 200 ml/min nitrogen flow. About 10 mg of powder was used for each measurement.

Fourier transform infrared spectroscopy (FTIR)

The infrared spectra were recorded with ATR technique using a Fourier-transform spectrometer Perkin Elmer Spectrum One. The spectra were the result of the acquisition and transformation of 16 co-added scans in the 4000-550 cm\(^{-1}\) spectral region at a resolution of 4 cm\(^{-1}\).

Optical microscopy

The analyses were performed using a transmitted-light microscope Zeiss Axioskop. For each analysis a little amount of sample was dispersed in silicone oil, mounted on a specimen slide and covered with a micro cover glass. The observations were carried out under appropriate conditions of illumination, contrast and magnification.

EXAMPLE 1 - Preparation of Form A

Ortaxetaxel (13 g) was dissolved in acetone (112.5 mL). Purified water (555 mL) containing citric acid (12 mg) was rapidly added under stirring, causing the precipitation of an amorphous solid which was filtered and washed with water (65 mL) containing citric acid (18 mg). The sample was dried at 40°C for 48 hours affording 12 g of a white solid having the characteristic XRPD, DSC, IR and TG/DTA reported in figures 1-4 respectively.

EXAMPLE 2 - Preparation of Form B

Ortaxetaxel (14 g) was dissolved in 95% ethanol (168 mL) containing citric acid (28 mg) at 50°C. Cold demineralised water (280 mL) was added to the resulting solution over 15 minutes. The suspension was stirred at 40°C for 6 hours. The mixture was cooled down to 20°C and the white solid was filtered off. The solid was washed with a solution of ethanol (168 mL) and
water (280 mL). The solid was dried under vacuum at 50°C for 40 hours affording 13.4 g of a white solid having the characteristic XRPD, DSC, IR and TG/DTA reported in figures 5-8 respectively.

EXAMPLE 3 - Preparation of a mixture of about 25% Form A and 75% Form B

Oratataxel (14 g) was dissolved in 95% ethanol (168 mL) containing citric acid (28 mg) at 50°C. Cold demineralised water (280 mL) was added to the resulting solution over 15 minutes. The mixture was promptly cooled down to 20°C and the white solid was filtered off. The solid was washed with a solution of ethanol (168 mL) and water (280 mL) containing citric acid (25 mg). The solid was dried under vacuum at 50°C for 40 hours affording 13.4 g of white material having the characteristic XRPD, DSC, IR and TG/DTA reported in figures 9-12 respectively.

EXAMPLE 4 - Preparation of mixtures of Form A and Form B in various proportions

Form A (1 g) was suspended in a mixture of 95% ethanol (12 mL) and water (20 mL) containing citric acid (2 mg) at 40°C. Samples were taken at different times (t=0, t=5 min, t = 30 min, t = 6 h) in order to demonstrate that different proportions of Form A and Form B can be obtained. Figure 13 shows the DSC analysis of the samples compared to the curve of pure Form B.
1. Ortataxel [13-(N-Boc-β-isobutylserinyl)-14-β-hydroxybaccatin III 1,14-carbonate] (1)

amorphous Form A.

2. Process for preparing amorphous Form A of claim 1, which comprises dissolving Ortataxel in a ketone or in an aprotic dipolar organic solvent, followed by addition of water containing 0.001-0.003% w/v of an organic acid.

3. The process according to claim 2 wherein the solvent is acetone or dimethylsulfoxide.

4. The process according to claim 2 or 3 wherein the organic acid is citric or ascorbic acid.

5. The process according to claim 3 wherein the organic acid is citric acid.

6. Ortataxel [13-(N-Boc-β-isobutylserinyl)-14-β-hydroxybaccatin III 1,14-carbonate] (1)
11
crystalline Form B of having the XRPD characterized by the following peaks
3.5, 6.8, 9.9, 10.1, 10.7, 12.1, 13.1, 14.8, 18.2, 19.7, 21.3, 29.3 deg 2-theta.
7. A process for the preparation of Ortataxel Form B of claim 6, which
comprises dissolving Ortataxel in ethanol containing traces of an organic
acidic, followed by addition of water and stirring at a temperature ranging
from 0 to 60°C for a time ranging from 4 to 8 hours.
8. The process of claim 7 wherein the Ortataxel dissolved in ethanol is
Ortataxel acetone solvate or Ortataxel form A as defined in claim 1.
9. The process according to claim 7 or 8 wherein the temperature is
40°C.
10. The process according to claim 9 wherein stirring is carried out for 6
hours.
11. The process according to any one of claims 8 to 10 wherein the
organic acid is citric acid.
12. Mixtures of Ortataxel Form A as defined in claim 1 and Form B as
defined in claim 6.
13. A mixture as defined in claim 12 wherein the amount of Form B is
about 75% by weight.
14. A process for the preparation of the mixtures of Form A and Form B as
defined in claim 12 or 13, which comprises suspending Ortataxel in a mixture
of ethanol and water containing an organic acid and stirring for less than 4
hours and at a temperature ranging from 0 to 60°C.
15. The process according to claim 14 wherein the Ortataxel suspended in
the mixture of ethanol and water is Ortataxel acetone solvate or Ortataxel
Form A.
16. The process according to claim 15 wherein ethanol and water are in a
0.5-0.7 ratio.
17. The process according to claim 16 wherein the temperature is 40°C.
18. The process according to any one of claims 15 - 17 wherein the organic acid is citric acid or ascorbic acid.

19. The process according to claim 18 wherein the organic acid is citric acid.

20. Pharmaceutical compositions containing Ortataxel amorphous form A as defined in claim 1 or Ortataxel crystalline form B as defined in claim 5 or mixtures thereof as defined in claim 12 or 13 in admixture with suitable excipients and/or carriers.

21. Use of Ortataxel amorphous form A as defined in claim 1 or of Ortataxel crystalline form B as defined in claim 6 or of mixtures thereof as defined in claim 12 or 13 for the preparation of pharmaceutical compositions for the treatment of cancer.
Fig. 1 - XRPD diffractogram of Form A
Fig. 2 - DSC profile of Form A

Peak 214.47°C
Onset 113.19 °C
Endset 142.70 °C

Peak 246.37°C

0 2 4 6 8 10 12 14 16 18 20 22 24 min

0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 °C
Fig. 3 - FTIR spectrum of Form A

- 2960.52
- 3422.08
- 1692.83
- 1500.31
- 1462.01
- 1386.34
- 1282.37
- 1732.96
- 1713.47
- 763.28
- 794.97
- 1004.94
- 1023.81
- 1255.97
- 1093.79
- 1089.49
- 1142.06
- 1162.06
- 894.37
- 761.32
- 3000.00
- 4000.00
- 5000.00
- 6000.00
- 7000.00
- 8000.00
- 9000.00
- 10000.00
- 11000.00
- 12000.00
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- 91000.00
- 92000.00
- 93000.00
- 94000.00
- 95000.00
- 96000.00
- 97000.00
- 98000.00
- 99000.00
- 100000.00
Fig. 4 - TG/DT profile of Form A
Fig. 8 - TG/DT profile of Form B

150.0°C
159.9°C
164.1°C
293.3°C

Weight loss: 1.4052%

TG signal
DT signal
Fig. 10 - DSC profile of Mixture of Form A and Form B
Fig. 12 - TG/DSC profile of Mixture of Form A and Form B
Fig 13. - DSC profile of different proportions of Form A and Form B

- Form A
  - t = 0
  - t = 5 min normalized area -1.63 3g⁻¹
  - t = 6 h normalized area -4.70 3g⁻¹

- Form II
  - t = 5 min normalized area -1.82 3g⁻¹
  - t = 6 h normalized area -19.63 3g⁻¹
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

**INV. C07D493/04 A61K31/357 A61P35/00**

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 database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 02/44161 A (INDENA SPA [IT]; PONTIROLI ALESSANDRO [IT]; BOMBARDELLI EZIO [IT]) 6 June 2002 (2002-06-06) cited in the application page 16, line 3</td>
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Date of the actual completion of the international search: 10 March 2009

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Authorized officer: Gutke, Hans-Jürgen
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<td>A</td>
<td>WO 01/02407 A (INDENA SPA [IT]; BOMBARDELLI EZIO [IT]; GABETTA BRUNO [IT]; PONTIROLI) 11 January 2001 (2001-01-11) cited in the application page 27, line 22</td>
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