The present invention provides novel crystalline form of lacosamide, process for its preparation and pharmaceutical compositions comprising it. The present invention also provides a process for the preparation of lacosamide amorphous form.
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
NOVEL POLYMORPH OF LACOSAMIDE

Filed of the Invention

The present invention provides novel crystalline form of lacosamide, process for its preparation and pharmaceutical compositions comprising it. The present invention also provides a process for the preparation of lacosamide amorphous form.

Background of the Invention

Lacosamide is chemically, (2R)-2-(acetylamino)-3-methoxy-N-(phenylmethyl)propanamide and has the structural formula:

![Lacosamide Structural Formula](image)

Lacosamide is a medication developed by Union chimique beige (UCB) for the adjunctive treatment of partial-onset seizures and diabetic neuropathic pain marketed under the trade name Vimpat®.

Polymorphism is defined as "the ability of a substance to exist as two or more crystalline phases that have different arrangement and/or conformations of the molecules in the crystal Lattice. Thus, in the strict sense, polymorphs are different crystalline structures of the same pure substance in which the molecules have different arrangements and/or different configurations of the molecules". Different polymorphs may differ in their physical properties such as melting point, solubility, X-ray diffraction patterns, etc. Although those differences disappear once the compound is dissolved, they can appreciably influence pharmaceutically relevant properties of the solid form, such as handling properties, dissolution rate and stability. Such properties can significantly influence the processing, shelf life, and commercial acceptance of a polymorph. It is therefore important to investigate all solid forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in the
laboratory by analytical methods such as X-ray diffraction (XRD), Differential Scanning Calorimetry (DSC) and Infrared spectrometry (IR).

Solvent medium and mode of crystallization play very important role in obtaining one polymorphic Form over the other.

Lacosamide can exist in different polymorphic forms, which may differ from each other in terms of stability, physical properties, spectral data and methods of preparation.

Lacosamide and its process for preparation were disclosed in U.S. patent no. 5,773,475.

U.S. patent publication no. 2009/029897 (herein after referred to '897 patent) disclosed crystalline form I, form II, form III and amorphous form of lacosamide.

According to the '897 patent, crystalline form I of lacosamide was characterized by an X-ray powder diffraction pattern having peaks expressed as 2Θ at about 8.3, 13.0, 16.6, 17.7 and 21.4 ± 0.2 degrees.

According to the '897 patent, crystalline form II of lacosamide was characterized by an X-ray powder diffraction pattern having peaks expressed as 2Θ at about 5.2, 6.7, 12.6, 16.2, 20.0 and 20.3 ± 0.2 degrees.

According to the '897 patent, amorphous form of lacosamide can be prepared by lyophilization of an aqueous solution of lacosamide.

According to the '897 patent, amorphous form of lacosamide can also be prepared by dissolving lacosamide in t-butyl alcohol and removing the solvent under reduced pressure.


We have discovered a novel crystalline form of lacosamide. The novel form has been found to be stable over the time and reproducible and so, suitable for pharmaceutical preparations.

We have also discovered a novel process for the preparation of lacosamide amorphous form.

Thus, one object of the present invention is to provide novel crystalline form of lacosamide, process for its preparation and pharmaceutical compositions comprising it.
Another object of the present invention is to provide a process for the preparation of lacosamide amorphous form.

Summary of the invention

In one aspect, the present invention provides a crystalline form of lacosamide designated as form HI characterized by peaks in the powder x-ray diffraction spectrum having 2\(\theta\) angle positions at about 8.3, 9.5, 13.1, 14.2, 17.7, 19.9, 20.0, 24.8, 24.9, 25.8 and 26.6 \(\pm\) 0.2 degrees.

In another aspect, the present invention provides a process for the preparation of lacosamide crystalline form HI, which comprises:

a) providing a solution of lacosamide in an chlorinated solvent;
b) removing the solvent from the solution obtained in step (a) to obtain a solid;
c) adding hydrocarbon solvent to the solid obtained in step (b); and
d) isolating lacosamide crystalline form HI.

In another aspect, the present invention provides a pharmaceutical composition comprising crystalline form HI of lacosamide and pharmaceutically acceptable excipients.

In yet another aspect, the present invention provides a process for the preparation of lacosamide amorphous form, which comprises providing a solution of lacosamide in a ketonic solvent and removing the solvent to obtain lacosamide amorphous form.

Brief Description of the Drawing

Figure 1 is an X-ray powder diffraction spectrum of lacosamide crystalline form HI.

Figure 2 is an X-ray powder diffraction spectrum of lacosamide amorphous form. X-ray powder diffraction spectrum was measured on a brucker axs D8 advance X-ray powder diffractometer having a copper-Ka radiation. Approximately 1gm of sample was gently flattered on a sample holder and scanned from 2 to 50 degrees two-theta, at 0.02 degrees two theta per step and a step time of 10.8 seconds. The sample was simply placed on the sample holder. The sample was rotated at 30 rpm at a voltage 40 KV and current 35 mA.
Detailed Description of the Invention

As used herein the term "room temperature" refers to a temperature of about 20°C to about 30°C.

According to one aspect of the present invention, there is provided a crystalline form of lacosamide designated as form H1 characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 8.3, 9.5, 13.1, 14.2, 17.7, 19.9, 20.0, 24.8, 24.9, 25.8 and 26.6 ± 0.2 degrees. The powdered x-ray diffractogram (PXRD) of lacosamide crystalline form H1 is shown in figure 1.

The lacosamide crystalline form H1 may be identified and differentiated from the known polymorphs by its characteristic PXRD pattern. Thus, for example, peaks at 9.5, 14.2 and 26.6 degrees 2θ are present in the PXRD of the lacosamide crystalline form H1 of the present invention, but are absent in the PXRD of the crystalline form 1 of lacosamide disclosed in the US patent publication no. 2009/0298947.

According to another aspect of the present invention, there is provided a process for the preparation of lacosamide crystalline form H1, which comprises:

a) providing a solution of lacosamide in an chlorinated solvent;
b) removing the solvent from the solution obtained in step (a) to obtain a solid;
c) adding hydrocarbon solvent to the solid obtained in step (b); and
d) isolating lacosamide crystalline form H1.

Lacosamide used in step (a) may preferably be lacosamide obtained by the known process.

The chlorinated solvent used in step (a) may preferably be a solvent or mixture of solvents selected from methylene chloride, chloroform, carbontetrachloride and ethylene dichloride. The chlorinated solvent used may alone or in combination with alcoholic solvent or ketonic solvent. More preferably the chlorinated solvent is methylene chloride.

Preferably, the alcoholic solvent may be a solvent or mixture of solvents selected from methanol, ethanol and isopropyl alcohol, and more preferably the alcoholic solvent is methanol.
Preferably, the ketonic solvent may be a solvent or mixture of solvents selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and diethyl ketone, and more preferably the ketonic solvent is acetone.

Removal of the solvent in step (b) may be carried out at atmospheric pressure or at reduced pressure. Removal of the solvent may preferably be carried out until the solvent is almost completely distilled off.

The hydrocarbon solvent used in step (c) may preferably be a solvent or mixture of solvents selected from cyclohexane, hexane, n-heptane, benzene, toluene and xylene, and more preferably the hydrocarbon solvent is cyclohexane.

Lacosamide crystalline form HI may be isolated in step (d) by methods known such as filtration or centrifugation.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising crystalline form HI of lacosamide and pharmaceutically acceptable excipients, and optionally other therapeutic ingredients. The crystalline form HI may preferable be formulated into tablets, capsules, suspensions, dispersions, injectables and other pharmaceutical forms.

According to another aspect of the present invention, there is provided a process for the preparation of lacosamide amorphous form, which comprises providing a solution of lacosamide in a ketonic solvent and removing the solvent to obtain lacosamide amorphous form.

The ketonic solvent used in the process may preferably be a solvent or mixture of solvents selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and diethyl ketone, and more preferably the ketonic solvent is acetone.

Removal of the solvent in the process may be earned out at atmospheric pressure or at reduced pressure. Removal of the solvent may preferably be carried out until the solvent is almost completely distilled off.

Lacosamide used in the present invention can be prepared by the known process, for example, by

a) reacting the D-serine with di-tert-butyl dicarbonate (Boc anhydride) in the presence of sodium hydroxide and dimethylaminopyridine to obtain a residual solid of N-Boc-D-serine;
b) reacting the N-Boc-D-serine obtained in step (a) with methyl iodide in the presence of sodium hydride or butyllithium and ether solvent to obtain a residual solid of (R)-2-((tert-butoxy)carbonylamino)-3-methoxypropanoic acid;

c) condensing the residual solid obtained in step (b) with benzyl amine in the presence of isobutyl chloroformate or ethyl chloroformate and 4-methyl morpholine to obtain (R)-N-benzyl-2-((tert-butoxy)carbonylamino)-3-methoxypropionamide;

d) deprotecting the (R)-N-benzyl-2-((tert-butoxy)carbonylamino)-3-methoxypropionamide obtained in step (c) in an chlorinated solvent in the presence of hydrochloric acid to obtain a residual solid of (R)-2-amino-N-benzyl-3-methoxypropionamide; and

e) reacting the (R)-2-amino-N-benzyl-3-methoxypropionamide obtained in step (d) with acetic anhydride in the presence of dimethylaminopyridine and tetra-butyl ammonium bromide to obtain lacosamide.

The reaction in step (a) may preferably be carried out in an alcoholic solvent. The alcoholic solvent may be selected from methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butanol, isobutyl alcohol or mixture thereof. More preferably the alcoholic solvent is tert-butyl alcohol.

The reaction in step (a) may conveniently be carried out at room temperature.

Preferably, the ether solvent used in step (b) may be a solvent or mixture of solvents selected from tetrahydrofuran, diisopropyl ether, tertrahydroxypropan, 1,4-dioxane, methyl tert-butyl ether, ethyl tert-butyl ether, diethyl ether, di-tert-butyl ether, diglyme, dimethoxyethane, dimethoxymethane and methoxyethane. More preferably the ether solvent is tetrahydrofuran.

The reaction in step (b) may preferably be earned out at below 10°C and more preferably at about 0 to 5°C.

The reaction in step (c) may preferably be earned out in a chlorinated solvent. The chlorinated solvent may be selected from methylene chloride, chloroform, carbon tetrachloride, ethylene dichloride or mixture thereof. More preferable the chlorinated solvent is methylene dichloride.
The reaction in step (c) may preferably be carried out at below 5°C and more preferably at about -10 to -5°C.

Preferably, the chlorinated solvent used in step (d) may be a solvent or mixture of solvents selected from methylene chloride, chloroform, carbon tetrachloride and ethylene dichloride. More preferable the chlorinated solvent is methylene dichloride.

The reaction in step (d) may conveniently be carried out at room temperature.

The reaction in step (e) may preferably be carried out in an organic solvent. The organic solvent may be selected from methylene chloride, chloroform, carbon tetrachloride, ethylene dichloride, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate, ethyl formate, toluene, xylene or mixture thereof. More preferably the organic solvent is methylene chloride, ethyl acetate, toluene or mixture thereof.

The reaction in step (e) may preferably be carried out at below 20°C and more preferably at about 0 to 10°C.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

**Examples**

**Example 1:**

**Preparation of N-Boc-D-serine**

Sodium hydroxide (44 gm) was dissolved in water (300 ml) and stirred for 15 minutes. D-serine (105 gm) was added to the solution and then added dimethylaminopyridine (3 gm). Tert-butyl alcohol (180 gm) was added to the reaction mixture and then added di-tert-butyl dicarbonate (Boc anhydride, 230 gm) for 1 hour. The reaction mass was maintained for 10 hours at room temperature and then concentrated to obtain residual mass. The residual mass was then cooled to 5 to 10°C and pH was adjusted to 2.9 with potassium bisulfate (IN). The reaction mass was extracted with ethyl acetate and the solvent was distilled off under vacuum at below 40°C to obtain a residual solid of N-Boc-D-serine (190 gm).

**Example 2:**

**Preparation of (R)-2-((tert-butoxy)carbonylamino)-3-methoxypropanoic acid**
N-Boc-D-serine (95 gm) as obtained example 1, methylene chloride (380 ml) and tetra-butyl ammonium bromide (1 gm) were added and then cooled to 0 to 5°C. To the reaction mixture was added caustic soda lye (48%, 123 gm) and then maintained for 30 minutes at 0 to 5°C. Dimethyl sulphate (121 gm) was added to the reaction mixture and then maintained for 30 minutes. The temperature of the reaction mass was raised to room temperature and then maintained for 3 hours at room temperature. To the reaction mass was added water (300 ml) and then the layers were separated. The pH of the aqueous layer was adjusted to pH is 2.8 with aqueous citric acid (50%) and extracted with methylene chloride. The solvent was distilled off to obtain a residual solid of (R)-2-((tert-butoxy)carbonylamino)-3-methoxypropanoic acid (92.5 gm).

Example 3:
Preparation of (R)-2-((tert-butoxy)carbonylamino)-3-methoxypropanoic acid

Tetrahydrofuran (350 ml), sodium hydride (40 gm) and imidazole (5 gm) were added and then cooled to 0 to 5°C. To the reaction mixture was added a solution N-Boc-D-serine (100 gm) in tetrahydrofuran (900 ml) for 30 minutes and then maintained for 30 minutes at 0 to 5°C. Methyl iodide (85 gm) was added to the reaction mixture and then maintained for 30 minutes. The temperature of the reaction mass was raised to room temperature and maintained for 2 hours. To the reaction mass was added methanol (50 ml) and then concentrated to obtain a residual mass. To the residual mass was added water (1000 ml) and then the layers were separated. The pH of the aqueous layer was adjusted to 2.8 with aqueous citric acid (50%) and extracted with methylene chloride. Then concentrated to obtain a residual solid of (R)-2-((tert-butoxy)carbonylamino)-3-methoxypropanoic acid (75 gm).

Example 4:
Preparation of (R)-2-((tert-butoxy)carbonylamino)-3-methoxypropanoic acid

Tetrahydrofuran (350 ml) was added to imidazole (5 gm) and then cooled to 0 to 5°C. To the reaction mixture was added butyllithium (40 gm) and then added a solution N-Boc-D-serine (100 gm) in tetrahydrofuran (900 ml) for 30 minutes at 0 to 5°C. Methyl iodide (85 gm) was added to the reaction mixture and then maintained for 30 minutes.
The temperature of the reaction mass was raised to room temperature and maintained for 2 hours. To the reaction mass was added methanol (50 ml) and then concentrated to obtain a residual mass. To the residual mass was added water (1000 ml) and then the layers were separated. The pH of the aqueous layer was adjusted to 2.8 with aqueous citric acid (50%) and extracted. The organic layer was dried with sodium sulfate and then concentrated to obtain a residual solid of (R)-2-((tert-butoxy)carbonylamino)-3-methoxypropanoic acid (78 gm).

Example 5:

Preparation of (R)-N-benzyl-2-((tert-butoxy)carbonylamino)-3-methoxypropionamide

(R)-2-((Tert-butoxy)carbonylamino)-3-methoxyproanoic acid (92.5 gm) as obtained in example 2 was dissolved in methylene chloride (925 ml) and then cooled to -10°C. To the solution was added isobutyl chloroformate (57 ml) and then added 4-methylmorpholine (46.5 ml). The reaction mass was maintained for 30 minutes at -5°C and then added a solution of benzyl amine (46 ml) in methylene chloride (46 ml). The temperature of the reaction mass was raised to room temperature and then added water (140 ml). The separated organic layer was dried with sodium sulfate and the solvent was distilled off to obtain a residual mass. To the residual mass was added n-hexane (1200 ml) and stirred for 2 hours at room temperature. The solid obtained was collected by filtration and dried to obtain 116 gm of (R)-N-benzyl-2-((tert-butoxy)carbonylamino)-3-methoxypropionamide.

Example 6:

Preparation of (R)-N-benzyl-2-((tert-butoxy)carbonylamino)-3-methoxypropionamide

(R)-2-((Tert-butoxy)carbonylamino)-3-methoxyproanoic acid (9 gm) was dissolved in methylene chloride (90 ml) and then cooled to -10°C. To the solution was added ethyl chloroformate (5.5 ml) and then added 4-methylmorpholine (5 ml). To the reaction mass was added a solution of benzyl amine (4.5 ml) in methylene chloride (4.5 ml) and the temperature was raised to room temperature. To the reaction mass was added
water (14 ml) and then the layers were separated. The organic layer was dried with sodium sulfate and then concentrated to obtain a residual mass. To the residual mass was added n-hexane (120 ml) and stirred for 2 hours at room temperature. The solid obtained was collected by filtration and dried to obtain 11 gm of (R)-N-benzyl-2-((tert-butoxy)carbonylamino)-3-methoxypropionamide.

**Example 7:**

**Preparation of (R)-2-amino-N-benzyl-3-methoxypropionamide**

(R)-N-Benzyl-2-((tert-butoxy)carbonylamino)-3-methoxypropionamide (116 gm) as obtained example 5 was dissolved in methylene chloride (1000 ml) and then added hydrochloric acid (36%, 203 ml). The contents were maintained for 1 hour at room temperature and then added water (190 ml). The pH of the separated aqueous layer was adjusted to 10 to 11 with sodium hydroxide solution (30%) and then extracted with methylene chloride. The solvent was distilled off to obtain a residual solid of (R)-2-amino-N-benzyl-3-methoxypropionamide (62 gm).

**Example 8:**

**Preparation of (R)-2-acetamido-N-benzyl-3-methoxypropionamide (Lacosamide)**

(R)-2-Amino-N-benzyl-3-methoxypropionamide (62 gm) as obtained example 7 was dissolved in methylene chloride (620 ml) and stirred for 10 minutes. To the solution was added dimethylaminopyridine (1 gm) and tetra-butyl ammonium bromide (1 gm) at room temperature. The contents were cooled to 0 to 5°C and then added acetic anhydride (34 ml) for 15 minutes. The temperature of the reaction mass was raised to room temperature and then added water (120 ml). The separated organic layer was dried with sodium sulfate and then concentrated to obtain a residual mass. To the residual mass was added ethyl acetate and maintained for 30 minutes. The reaction mass was then cooled to 0 to 5°C and maintained for 2 hours, filtered. The solid obtained was dried to give 48 gm of lacosamide.

**Example 9:**

**Preparation of lacosamide crystalline form HI**
Lacosamide (10 gm) as obtained in example 8 was dissolved in methylene chloride (100 ml) and stirred for 15 minutes to obtain a solution. The solution was then cooled to 10 to 15°C and the solvent was distilled off under vacuum at below 30°C to obtain a solid, and then maintained for 2 hours. To the solid was added cyclohexane (100 ml) and maintained for 30 minutes at 10 to 15°C. The separated solid was filtered and dried to obtain 9.3 gm of lacosamide crystalline form HI.

Example 10:
Preparation of lacosamide crystalline form HI

Lacosamide (10 gm) was dissolved in chloroform (90 ml) and stirred for 15 minutes. The solution was then cooled to 10 to 15°C and the solvent was distilled off under vacuum at below 30°C to obtain a solid, and then maintained for 2 hours. To the solid was added hexane (100 ml) and maintained for 30 minutes at 10 to 15°C, filtered. The solid obtained was dried to obtain 9.1 gm of lacosamide crystalline form HI.

Example 11:
Preparation of lacosamide crystalline form HI

Lacosamide (5 gm) was dissolved in a mixture of methylene chloride (45 ml) and methanol (5 ml), and then cooled to 10 to 15°C. The solvent was distilled off under vacuum at below 30°C to obtain a solid and then maintained for 2 hours. Cyclohexane (40 ml) was added to the solid and maintained for 1 hour at room temperature. The separated solid was filtered and dried to obtain 4.0 gm of lacosamide crystalline form HI.

Example 12:
Preparation of lacosamide crystalline form HI

Lacosamide (5 gm) was dissolved in a mixture of methylene chloride (40 ml) and acetone (10 ml), and then cooled to 10 to 15°C. The solvent was distilled off under vacuum at below 30°C to obtain a solid and then maintained for 2 hours. Cyclohexane (100 ml) was added to the solid and maintained for 1 hour at room temperature, filtered. The solid obtained was dried to get 4.0 gm of lacosamide crystalline form HI.
Example 13:

Preparation of lacosamide amorphous form

Lacosamide (10 gm) was dissolved in acetone (200 ml) and stirred for 15 minutes to obtain a solution. The solvent was distilled off under vacuum at below 20°C and then maintained for 3 hours to obtain 9.5 gm of lacosamide amorphous form.

Example 14:

Preparation of lacosamide amorphous form

Lacosamide (5 gm) was dissolved in methyl ethyl ketone (100 ml) and stirred for 15 minutes to obtain a solution. The solvent was distilled off under vacuum at below 20°C and then maintained for 2 hours to obtain 4.5 gm of lacosamide amorphous form.
We claim:

1. A lacosamide crystalline form H1, characterized by peaks in the powder x-ray diffraction spectrum having 2Θ angle positions at about 8.3, 9.5, 13.1, 14.2, 17.7, 19.9, 20.0, 24.8, 24.9, 25.8 and 26.6 ± 0.2 degrees.

2. A lacosamide crystalline form H1, characterized by an x-ray powder diffractogram as shown in figure 1.

3. A process for the preparation of lacosamide crystalline form H1 as claimed in claim 1, which comprises:
   a. providing a solution of lacosamide in an chlorinated solvent;
   b. removing the solvent from the solution obtained in step (a) to obtain a solid;
   c. adding hydrocarbon solvent to the solid obtained in step (b); and
   d. isolating lacosamide crystalline form H1.

4. The process as claimed in claim 3, wherein the chlorinated solvent used in step (a) is a solvent or mixture of solvents selected from methylene chloride, chloroform, carbon tetrachloride or ethylene dichloride.

5. The process as claimed in claim 4, wherein the chlorinated solvent is methylene chloride.

6. The process as claimed in claim 4, wherein the chlorinated solvent used is alone or in combination with alcoholic solvent or ketonic solvent.

7. The process as claimed in claim 6, wherein the alcoholic solvent is a solvent or mixture of solvents selected from methanol, ethanol and isopropyl alcohol.

8. The process as claimed in claim 6, wherein the ketonic solvent is a solvent or mixture of solvents selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and diethyl ketone.

9. The process as claimed in claim 3, wherein the hydrocarbon solvent used in step (c) is a solvent or mixture of solvents selected from cyclohexane, hexane, n-heptane, benzene, toluene and xylene.

10. The process as claimed in claim 9, wherein the hydrocarbon solvent is cyclohexane.

11. A process for the preparation of lacosamide amorphous form, which comprises providing a solution of lacosamide in a ketonic solvent and removing the solvent to obtain lacosamide amorphous form.
12. The process as claimed in claim 11, wherein the ketonic solvent is a solvent or mixture of solvents selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and diethyl ketone.

13. The process as claimed in claim 12, wherein the ketonic solvent is acetone.

14. A pharmaceutical composition that comprises crystalline form HI of lacosamide and pharmaceutically acceptable excipients, and optionally other therapeutic ingredients.

15. The pharmaceutical composition as claimed in claim 14, wherein the polymorphic form is formulated into tablets, capsules, suspensions, dispersions, injectables and other pharmaceutical forms.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

<table>
<thead>
<tr>
<th>IPC(8)</th>
<th>A01N 37/18 (201 2.01)</th>
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<td>USPC</td>
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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)

USPC: 514/616
IPC (8) A01N 37/18 (2012.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched 514/616, A01N 37/18 (text search-see search terms below)

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

PubWEST (USPT, PGIB, EPAB, JPAB) and Google Patent/Scholar

Search terms: ketonic solvent, lacosamide, polymorph, XRD, PXRD, DSC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
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<td>US 20090289947 A1 (Mundorfer et al) 3 December 2009 (03.12.2009) claims 3-4, paras [0011], [0040], [0056H0057], [0096]-[0097], [0164]</td>
<td>1-9, 14-15</td>
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<td>Y</td>
<td>WO2010052011 A1 (Bouvy et al.) 14 May 2010 (14.05.2010) pg. 24, In. 18-20</td>
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Further documents are listed in the continuation of Box C.

- Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier application or patent but published on or after the international filing date
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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

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Date of the actual completion of the international search

09 March 2012

Date of mailing of the international search report

20 MAR 2012

Name and mailing address of the ISA/US

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