Abstract: The present invention is concerned with new polymorphic forms of pregabalin, processes of preparing the new polymorphic form, pharmaceutical compositions containing the same, therapeutic uses thereof and methods of treatment employing the same.

(54) Title: NEW POLYMORPHIC FORMS OF PREGABALIN

(57) Abstract: The present invention is concerned with new polymorphic forms of pregabalin, processes of preparing the new polymorphic form, pharmaceutical compositions containing the same, therapeutic uses thereof and methods of treatment employing the same.
NEW POLYMORPHIC FORMS OF PREGABALIN

Field of invention
The present invention is concerned with new polymorphic forms of pregabalin, processes of preparing the new polymorphic forms, pharmaceutical compositions containing the same, therapeutic uses thereof and methods of treatment employing the same.

Background of the invention
Polymorphic forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties can have a direct effect on the ability to process and/or manufacture a drug substance and a drug product, as well as on drug product stability, dissolution, and bioavailability. Thus, polymorphism can affect the quality, safety, and efficacy of a drug product.

Polymorphic forms as referred to herein can include crystalline and amorphous forms as well as solvate and hydrate forms, which can be further characterised as follows.

(i) Crystalline forms have different arrangements and/or conformations of the molecules in the crystal lattice.

(ii) Amorphous forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal lattice.

(iii) Solvates are crystal forms containing either stoichiometric or non-stoichiometric amounts of a solvent. If the incorporated solvent is water, the solvate is commonly known as a hydrate.

When a drug substance exists in polymorphic forms, it is said to exhibit polymorphism.
There are a number of methods that can be used to characterise polymorphs of a drug substance. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction hereinafter referred to as XRPD can also be used to support the existence of polymorphs. Other methods, including microscopy, thermal analysis (e.g., differential scanning calorimetry [DSC], thermal gravimetric analysis [TGA], and hot-stage microscopy), and spectroscopy (e.g., infrared [IR], Raman, solid-state nuclear magnetic resonance [ssNMR]) are also helpful to further characterise polymorphic forms.

Drug substance polymorphic forms can exhibit different chemical, physical and mechanical properties as referred to above, including aqueous solubility and dissolution rate, hygroscopicity, particle shape, density, flowability, and compactibility, which in turn may affect processing of the drug substance and/or manufacturing of the drug product. Polymorphs can also exhibit different stabilities. The most stable polymorphic form of a drug substance is often chosen during drug development based on the minimal potential for conversion to another polymorphic form and on its greater chemical stability. However, a meta-stable form can alternatively be chosen for various reasons, including bioavailability enhancement.

Pregabalin, (3S)-3-(aminomethyl)-5-methyl-hexanoic acid, can be represented by the following structural formula:
Pregabalin is an anticonvulsant and is, therefore, employed in an anti-seizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity, and, possibly as an anti-depressant, anxiolytic, and antipsychotic activity.

There are only a few patents and applications concerning pregabalin. EP641330 relates to novel compounds that are analogs of gamma aminobutyric acid (GABA), and methods for the synthesis of these compounds. WO2005/100580A1 provides methods for the conversion of 2-isobutylsuccinonitrile into (S)-3-cyano-5-methylhexanoic acid, which is a useful intermediate in the synthesis of (S)-3-(aminomethyl)-5-methylhexanoic acid (pregabalin).

Therefore this invention is the first to provide, describe and define polymorphic forms of pregabalin. Polymorphic forms of pregabalin now provided by the present invention are hereinafter referred to as Form I, Form II, Form III and Form IV.

**Description of the invention**

Form I according to the present invention is characterised as having one or more characteristic XRPD peaks selected from following (2θ): 11.6 ± 0.2, 13.3 ± 0.2, 16.5 ± 0.2, 20.0 ± 0.2 and 23.4 ± 0.2.

Form I can be further characterised by a typical DSC thermogram as shown in Figure 1.

Form I can be still further characterised by a typical TGA thermogram as shown in Figure 2.

There is also provided by the present invention, therefore, Form II characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 3.
Form II according to the present invention is further characterised as having one or more characteristic XRPD peaks selected from following \((2\Theta): 5.7 \pm 0.2, 11.3 \pm 0.2, 17.0 \pm 0.2\) and \(22.7 \pm 0.2\). Form II according to the present invention is further characterised as having one or more other characteristic XRPD peaks selected from following \((2\Theta): 15.5 \pm 0.2, 17.8 \pm 0.2, 18.6 \pm 0.2\) and \(24.2 \pm 0.2\).

There is also provided by the present invention, therefore, Form III characterised as having one or more characteristic XRPD peaks selected from following \((2\Theta): 6.3 \pm 0.2, 12.6 \pm 0.2, 19.0 \pm 0.2, 20.8 \pm 0.2\) and \(27.0 \pm 0.2\).

There is also provided by the present invention, therefore, Form IV characterised as having one or more characteristic XRPD peaks selected from following \((2\Theta): 9.5 \pm 0.2, 12.3 \pm 0.2, 16.7 \pm 0.2, 19.1 \pm 0.2, 19.8 \pm 0.2\). Form IV according to the present invention is further characterised as having one or more other characteristic XRPD peaks selected from following \((2\Theta): 18.3 \pm 0.2, 18.4 \pm 0.2, 20.2 \pm 0.2, 22.2 \pm 0.2\) and \(23.2 \pm 0.2\).

Further characterising data for Form IV according to the present invention, as obtained by X-ray single crystal analysis at temperature of \(22^\circ\text{C} (295K)\), is crystal structure data collected on Kappa CCD Bruker-Nonius FR591 diffractometer with CuKa radiation using rotating anode.

Crystal structure data at temperature of \(22^\circ\text{C} (295K)\):

Crystal system, space group: orthorhombic, \(P 2_1 2_1 2_1\)

Unit cell dimensions:

\[
\begin{align*}
  a &= 6.48 \pm 0.01 \text{ Å} \\
  b &= 7.86 \pm 0.01 \text{ Å} \\
  c &= 18.62 \pm 0.01 \text{ Å}
\end{align*}
\]

\(\alpha = 90.0^\circ\)  
\(\beta = 90.0^\circ\)  
\(\gamma = 90.0^\circ\)

Volume: \(948 \pm 2 \text{ Å}^3\)

\(Z\), Calculated density: \(4, 1.12 \pm 0.02 \text{ g cm}^{-3}\)

Form IV can be still further characterised by a typical DSC thermogram as shown in Figure 4.
Form IV can be still further characterised by a typical TGA thermogram as shown in Figure 5.

Pregabalin is an anticonvulsant and is thus useful in the anti-seizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity, and, possibly as an anti-depressant, anxiolytic, and antipsychotic activity.

The present invention further provides, therefore, a pharmaceutical composition comprising a therapeutically effective amount of Form I or of Form II or of Form III or of Form IV or a mixture of any thereof according to the invention, together with a pharmaceutically acceptable carrier, diluent or excipients thereof. Excipients are chosen according to the pharmaceutical form and the desired mode of administration.

As used herein, the term "therapeutically effective amount" means an amount of one of said polymorphic forms of pregabalin according to the invention, which is capable of preventing, ameliorating or eliminating a disease state for which administration of anticonvulsant is indicated.

By "pharmaceutically acceptable" it is meant that the carrier, diluent or excipient is compatible with pregabalin according to the invention, and not deleterious to a recipient thereof.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, intratracheal, intranasal, transdermal or rectal administration, Form I or Form II or Form III or Form IV or a mixture of any thereof according to the present invention is administered to animals and humans in unit forms of administration, mixed with conventional pharmaceutical carriers, for the prophylaxis or treatment of the above disorders or diseases. The appropriate unit forms of administration include forms for oral administration, such as tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, forms for sublingual, buccal, intratracheal or intranasal administration, forms for subcutaneous, intramuscular
or intravenous administration and forms for rectal administration. For topical application, Form I or Form II or Form III or Form IV or a mixture of any thereof according to the present invention can be used in creams, ointments or lotions.

To achieve the desired prophylactic or therapeutic effect, the dose of Form I or of Form II or of Form III or of Form IV or a mixture of any thereof according to the present invention can vary between 0.01 and 50 mg per kg of body weight per day. Each unit dose can contain from 0.1 to 1000 mg, preferably 1 to 500 mg, of I or of Form II or of Form III or of Form IV or a mixture of any thereof according to the present invention in combination with a pharmaceutical carrier. This unit dose can be administered 1 to 5 times a day so as to administer a daily dosage of 0.5 to 5000 mg, preferably 1 to 2500 mg.

When a solid composition in the form of tablets is prepared, Form I or Form II or Form III or Form IV or a mixture of any thereof according to the present invention is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose, a cellulose derivative or other appropriate substances, or else they can be treated so as to have a prolonged or delayed activity and so as to release a predetermined amount of active principle continuously.

A preparation in the form of gelatin capsules can be obtained by mixing Form I or Form II or Form III or Form IV or a mixture of any thereof according to the present invention with a diluent and pouring the resulting mixture into soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir or for administration in the form of drops can contain Form I or Form II or Form III or Form IV or a mixture of any thereof according to the present invention typically in conjunction with a sweetener, which is preferably calorie-free, optionally antiseptics such as methylparaben and propylparaben, as well as a flavoring and an appropriate colour.
Water-dispersible granules or powders can contain Form I or Form II or Form III or Form IV or a mixture of any thereof according to the present invention mixed with dispersants or wetting agents, or suspending agents such as polyvinylpyrrolidone, as well as with sweeteners or taste correctors.

Rectal administration is effected using suppositories prepared with binders which melt at the rectal temperature, for example polyethylene glycols.

Parenteral administration is effected using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersants and/or wetting agents, for example propylene glycol or butylene glycol.

Form I or Form II or Form III or Form IV or a mixture of any thereof according to the present invention can also be formulated as microcapsules, with one or more carriers or additives if appropriate.

There is also provided by the present invention Form I or Form II or Form III or Form IV or a mixture of any thereof substantially as hereinbefore described for use in therapy.

The present invention further provides Form I or Form II or Form III or Form IV or a mixture of any thereof substantially as hereinbefore described, for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of anticonvulsant.

More specifically, the present invention provides Form I or Form II or Form III or Form IV or a mixture of any thereof substantially as hereinbefore described, for use in the manufacture of a medicament for anti-seizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity, and, possibly as an anti-depressant, anxiolytic, and antipsychotic activity.

The present invention also provides a method of treating a disease state prevented, ameliorated or eliminated by the administration of anticonvulsant in a
patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of Form I or of Form II or of Form III or of Form IV or a mixture of any thereof substantially as hereinbefore described. More specifically, the present invention provides a method of treating central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity in a patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of Form I or of Form II or of Form III or of Form IV or a mixture of any thereof substantially as hereinbefore described.

The present invention can be further illustrated by the following Figures and non-limiting Examples.

**Brief description of drawings**

Figure 1 shows a DSC pattern of Form I obtained by using MDSC TA instruments Q1000 operating at heating rate of 10°C/min and in stream of nitrogen with flow of 50ml/min.

Figure 2 shows a TGA pattern of Form I obtained by using TGA 7 manufacturer Perkin Elmer, operating at heating rate of 10°C/min, and in stream of nitrogen with flow of 35 ml/min.

Figure 3 shows an XRPD pattern of Form II obtained by Philips X'Pert PRO diffractometer using CuKα radiation.

Figure 4 shows a DSC pattern of Form IV obtained by using MDSC TA instruments Q1000 operating at heating rate of 10°C/min and in stream of nitrogen with flow of 50ml/min.

Figure 5 shows a TGA pattern of Form IV obtained by using TGA 7 manufacturer Perkin Elmer, operating at heating rate of 10°C/min, and in stream of nitrogen with flow of 35 ml/min.
Examples

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present invention. It will thus be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be falling within the scope of the invention.

Example 1
About 300 mg of pregabalin was dissolved in about 20 ml of 1-octanol and about 4 ml of water at about 90°C. The solution was left to evaporate at about 90°C. After about 15 minutes crystallization took place. The suspension was cooled to room temperature, and then filtered yielding pregabalin form I.

Example 2
About 10 mg of pregabalin was dissolved in about 4 ml of acetone and about 1 ml of water by heating. Solution was left to cool down to room temperature in an open flask. After solvents evaporated, crystals of pregabalin form II were observed.

Example 3
About 10 mg of pregabalin was dissolved in about 4 ml of 1-octanol and about 1 ml of water by heating. The solution was left to cool down to room temperature. After about 24 hours crystals of pregabalin form III were observed.

Example 4
About 10 mg of pregabalin was dissolved in about 2 ml of methanol by heating. The solution was left to cool down to room temperature. After about 24 hours crystals of pregabalin form IV were observed.
Example 5
About 10 mg of pregabalin was dissolved in about 5 ml of ethanol by heating. Solution was left to cool down to room temperature. After about 24 hours crystals of pregabalin form IV were observed.

Example 6
About 10 mg of pregabalin was dissolved in about 3 ml of N,N-dimethylacetamide and about 1 ml of water by heating. The solution was left to cool down to room temperature. After about 24 hours single crystals of pregabalin form IV were observed.

Example 7
About 300 mg of pregabalin was dissolved in about 15 ml of acetone and about 7 ml of water at reflux conditions. The solution was slowly cooled yielding crystals of pregabalin form IV.
Claims:
1. A pregabalin polymorphic Form I characterised as having one or more characteristic XRPD peaks selected from following (2\(\Theta\)): 11.6 \(\pm\) 0.2, 13.3 \(\pm\) 0.2, 16.5 \(\pm\) 0.2, 20.0 \(\pm\) 0.2, 23.4 \(\pm\) 0.2 and 28.5 \(\pm\) 0.2.

2. A pregabalin polymorphic Form I characterised by a typical DSC thermogram as shown in Figure 1.

3. A pregabalin polymorphic Form I characterised by a typical TGA thermogram as shown in Figure 2.

4. A pregabalin polymorphic Form II characterised as having an XRPD pattern, or substantially the same XRPD pattern, as shown in Figure 3.

5. A pregabalin polymorphic Form II characterised as having one or more characteristic XRPD peaks selected from following (2\(\Theta\)): 5.7 \(\pm\) 0.2, 11.3 \(\pm\) 0.2, 17.0 \(\pm\) 0.2 and 22.7 \(\pm\) 0.2.

6. A pregabalin polymorphic Form II as claimed in claim 5 having one or more other characteristic XRPD peaks selected from following (2\(\Theta\)): 15.5 \(\pm\) 0.2, 17.8 \(\pm\) 0.2, 18.6 \(\pm\) 0.2, 24.2 \(\pm\) 0.2 and 28.5 \(\pm\) 0.2.

7. A pregabalin polymorphic Form III characterised as having one or more characteristic XRPD peaks selected from following (2\(\Theta\)): 6.3 \(\pm\) 0.2, 12.6 \(\pm\) 0.2, 19.0 \(\pm\) 0.2, 20.8 \(\pm\) 0.2, 27.0 \(\pm\) 0.2.

8. A pregabalin polymorphic Form IV characterised as having one or more characteristic XRPD peaks selected from following (2\(\Theta\)): 9.5 \(\pm\) 0.2, 12.3 \(\pm\) 0.2, 16.7 \(\pm\) 0.2, 19.1 \(\pm\) 0.2 and 19.8 \(\pm\) 0.2.

9. A pregabalin polymorphic Form IV as claimed in claim 8 having one or more other characteristic XRPD peaks selected from following (2\(\Theta\)): 18.3 \(\pm\) 0.2, 18.4 \(\pm\) 0.2, 20.2 \(\pm\) 0.2, 22.2 \(\pm\) 0.2, 23.2 \(\pm\) 0.2.
10. A pregabalin polymorphic Form IV characterised by a typical DSC thermogram as shown in Figure 4.

11. A pregabalin polymorphic Form IV characterised by a typical TGA thermogram as shown in Figure 5.

12. A pregabalin polymorphic Form IV having following crystal structure properties:
   a) **Crystal system, space group**: orthorhombic, P 2i 2i 2i
   b) **Unit cell dimensions**:
      - a = 6.48±0.01 Å
      - b = 7.86±0.01 Å
      - c = 18.62±0.01 Å
   c) **Volume**: 948±2 Å³
   d) Z. **Calculated density**: 4.12±0.02 g cm⁻³

13. A pharmaceutical composition comprising a therapeutically effective dose of Form I or of Form II or of Form III or of Form IV or a mixture of any thereof according to claims 1 to 12, together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

14. Form I or Form II or Form III or Form IV or a mixture of any thereof according to claims 1 to 12 for use in therapy.

15. Form I or Form II or Form III or Form IV or a mixture of any thereof according to claims 1 to 12 for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of anticonvulsant.

16. A method of treating a disease state prevented, ameliorated or eliminated by the administration of anticonvulsant in a patient in need of such treatment, which method comprises administering to the patient a
therapeutically effective amount of Form I or of Form II or of Form III or of Form IV or a mixture of any thereof according to any of claims 1 to 12.
INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003516

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C229/08 A61K31/197 A61P25/08

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)
C07C A61K A61P

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, WPI Data, BEILSTEIN Data, CHEM ABS Data

C DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>CN 1 634 869 A (BEIJING FU KANG REN BIO) PHARM [CN]) 6 July 2005 (2005-07-06) abstract</td>
<td>1,8,9, 13-16</td>
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<td>X</td>
<td>CN 1 827 590 A (BEIJING RUNDEKANG MEDICAL) TECH [CN]) 6 September 2006 (2006-09-06) abstract figures 1, (XRDP)</td>
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<td>US 2006/270871 Al (KHANDURI CHANDRA H [IN]) ET AL) 30 November 2006 (2006-11-30) the whole document</td>
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[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* 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 document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"A" document member of the same patent family

Date of the actual completion of the international search 11 January 2008

Date of mailing of the international search report 21/01/2008

Name and mailing address of the ISA/ European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl Fax (+31-70) 340-3016

Tabanei a, Stefani a

Authorized officer

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>WO 2006/108151 A (TEVA PHARMA [IL]; TEVA PHARMA [US]; ARONHIME JUDITH [IL]; LEVI SIGALIT) 12 October 2006 (2006-10-12) cited in the application the whole document</td>
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<td>A</td>
<td>CN 1 962 612 A (CHONGQING PHARMACEUTICAL RES I [CN]) 16 May 2007 (2007-05-16) abstract</td>
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### Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos. because they relate to subject matter not required to be searched by this Authority, namely
   
   Although claim 16 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **☐** Claims Nos. because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically

3. **☐** Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a).

### Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. **☐** As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.

#### Remark on Protest

- **☐** The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee
- **☐** The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- **☐** No protest accompanied the payment of additional search fees.
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