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Inventors/Applicants (for US only): GAITONDE, Abhay [IN/IN]; MERCK DEVELOPMENT CENTRE PRIVATE LIMITED [IN/IN]; Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad 410 208, Maharashtra (IN).

Applicants (for all designated States except US):
GENERICS [UK] LIMITED [GB/GB]; Darakes Lane, Potters Bar, Hertfordshire EN6 1AG (GB).

KOKANE, Dattatrey [IN/IN]; Merck Development Centre Private Limited, Plot 1 A/2, M.I.D.C. Industrial Estate, Taloja, Panvel, District Raigad 410 208, Maharashtra (IN).


The present invention relates to a process for preparing polymorphic form A of 2-[[5-(5-methoxy-1H-indol-3-yl)-pentylyl]hydrazone]carboximidamide maleate (tegaserod maleate). The invention further relates to tegaserod maleate form A substantially free of other polymorphic forms and chemical impurities, to compositions comprising tegaserod maleate form A and to the use of said compositions in the treatment of gastrointestinal disorders such as irritable bowel syndrome and heartburn.

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Title: PROCESS FOR THE PREPARATION OF FORM A OF TEGASEROD

Abstract: The present invention relates to a process for preparing polymorphic form A of 2-[[5-(5-methoxy-1H-indol-3-yl)-pentylyl]hydrazone]carboximidamide maleate (tegaserod maleate). The invention further relates to tegaserod maleate form A substantially free of other polymorphic forms and chemical impurities, to compositions comprising tegaserod maleate form A and to the use of said compositions in the treatment of gastrointestinal disorders such as irritable bowel syndrome and heartburn.
Field of the invention

The present invention relates to a process for preparing polymorphic form A of 2-[(5-methoxy-1H-indol-3-yl)methylene]-IV-pentylhydrazinecarboximidainide maleate (tegaserod maleate) of formula (I).

The invention further relates to tegaserod maleate form A substantially free of other polymorphic forms and chemical impurities, to compositions comprising tegaserod maleate form A and to the use of said compositions in the treatment of gastrointestinal disorders such as irritable bowel syndrome and heartburn.

Background of the invention

Tegaserod is a 5-HT₄ receptor partial agonist that is used to treat gastrointestinal disorders such as irritable bowel syndrome, heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, constipation and gastroesophageal reflux.

Tegaserod and a process for its preparation were first described in US 5510353. However, this patent does not disclose any process for the preparation of tegaserod salts. Tegaserod maleate per se is disclosed and its melting point is reported in this patent as 190°C, but the method by which the melting point is determined is not given. Further, there is no disclosure of or claim to any crystalline form.
The Journal of Medicinal Chemistry, 1995, vol. 38, no. 13, pages 2331-2338, also describes a process for preparing tegaserod. According to this publication, 5-methoxy-indole-3-carboxaldehyde was coupled with N-amino-IV '-pentyl guanidine hydroiodide in methanol in the presence of concentrated hydrochloric acid to obtain tegaserod. Also described is a process for the preparation of the hydrochloride salt of tegaserod and crystallisation of tegaserod hydrochloride from methanol and diethyl ether. However, information on the crystalline form obtained is not disclosed.

From the above it is clear that a process for the preparation of the maleate salt of tegaserod is not reported in US 5510353 or in the Journal of Medicinal Chemistry, 1995, vol. 38, no. 13, pages 2331-2338. The only information available is the melting point of tegaserod maleate, which is reported in US 5510353 as 190°C. Further, there is no disclosure of any crystalline form.

Later patents and patent applications show that tegaserod maleate does indeed exist in different polymorphic forms.

US 2005/0119328 discloses four polymorphic forms, form I to form IV of tegaserod maleate. None of these forms is the same as form A of tegaserod maleate.

WO 2005/014544 describes crystalline form A of tegaserod maleate. There is also disclosed a process for preparing form A, comprising the step of crystallising tegaserod maleate from a solution consisting of an acetate ester and water. Preferred embodiments comprise using ethyl acetate and water, but other solvents that are mentioned include n-butyl acetate or isopropyl acetate and water. The application further discloses crystalline form B crystallised from THF and methanol, then recrystallised from ethanol and ether at 90°C. Also disclosed are three crystalline solvate forms namely acetone, isopropanol and ethanol solvates. Form A is identified as being more stable than the other disclosed forms in the presence of heat and water. Form B readily converts to form A when heated.

WO 2005/058819 discloses forms B, Bl, B2, B3, C, D and E of tegaserod maleate. Also claimed is a process for preparing form A of tegaserod maleate, comprising the steps of
dissolving tegaserod maleate in a solvent and recovering the crystalline solid as a precipitate, where the solvent as shown in examples is acetonitrile, butyl lactate, methyl ethyl ketone, sec-butanol, dioxane, methanol/water (20:80), ethanol/water (20:80), isopropanol/water (1:1), isopropanol/water (20:80), acetonitrile/water (1:1), acetonitrile/water (20:80), chloroform/2-ethoxyethanol (1:1), chloroform/2-ethoxyethanol (25:75), water/2-ethoxyethanol (1:1), n-butanol, water/1-methyl-2-pyrrolidone (75:25), dimethyl sulfoxide, IV,iV-dimethylformamide, l-methyl-2-pyrrolidone, or IV,iV-dimethylacetamide.

There is always a need for alternative methods of preparing compounds for pharmaceutical use in order to provide the skilled person with the optimum tools to prepare pharmaceutical products that are both safe and efficacious.

Object of the invention

It is an object of the present invention to provide a novel process for preparing polymorphic form A of tegaserod maleate that is substantially free of other polymorphic forms and chemical impurities.

Summary of the invention

According to a first aspect of the present invention, there is provided a process for preparing polymorphic form A of tegaserod maleate, comprising the steps of:

(a) dissolving tegaserod maleate or tegaserod and maleic acid in an alcohol;
(b) adding ether to precipitate tegaserod maleate; and
(c) isolating the precipitated tegaserod maleate.

In step (a) either tegaserod maleate or tegaserod and maleic acid can be used. Preferably tegaserod maleate is used.

The alcohol used in step (a) is preferably a C\textsubscript{14} alcohol, which may be selected from the non-exhaustive group comprising methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, and mixtures thereof. Preferably the alcohol used in step (a) is
methanol. Preferably, the alcohol is used in step (a) at reflux temperature. Preferably, the alcohol is heated in step (a) until a clear solution is obtained.

In a preferred embodiment, the ether used in step (b) is tert-butyl methyl ether (TBME).

In alternative embodiments, the ether can be selected from the non-exhaustive group comprising diisopropyl ether (DIPE), diethyl ether (DEE), tetrahydrofuran (THF), dioxane, dimethoxyethane, cyclopentyl methyl ether (CPME), dimethyl ether, diethoxyethane, anisole, and tert-butyl ethyl ether.

In another embodiment, in step (c) the precipitate is isolated by filtration. Preferably, the precipitate is isolated by vacuum filtration, more preferably at a temperature of 25-30°C.

In a preferred embodiment, the tegaserod maleate polymorphic form A obtained is substantially free of other polymorphic forms. In another preferred embodiment, the tegaserod maleate polymorphic form A obtained is substantially free of chemical impurities.

In another embodiment, the tegaserod maleate polymorphic form A is prepared on an industrial scale, preferably in batches of 0.5kg, 1kg, 5kg, 10kg, 50kg, 100kg, 500kg, or more.

According to another aspect of the present invention, there is provided polymorphic form A of tegaserod maleate, prepared by a process according to the first aspect of the present invention. Preferably the polymorphic form A of tegaserod maleate is characterized by an X-ray diffraction pattern having peaks at 5.4, 6.0, 6.6 and 10.8 ± 0.2 degree two theta. Preferably the polymorphic form A of tegaserod maleate is characterized by a DSC curve having one endothermic peak at about 185-188°C.

Preferably the polymorphic form A of tegaserod maleate is substantially free of other polymorphic forms. For the purposes of the present invention, polymorphic form A of tegaserod maleate, which is "substantially free" of other polymorphic forms, comprises less than about 10% by weight of other polymorphic forms of tegaserod maleate, preferably less than about 5%, preferably less than about 4%, preferably less than about 3%, preferably less than about 2%, preferably less than about 1% (as measured by XRPD).
Preferably the polymorphic form A of tegaserod maleate is substantially free of chemical impurities. For the purposes of the present invention, polymorphic form A of tegaserod maleate, which is "substantially free" of chemical impurities, is about 90%, preferably about 95%, preferably about 96%, preferably about 97%, preferably about 98%, preferably about 99% or more chemically pure (as measured by HPLC).

According to another aspect of the present invention, there is provided polymorphic form A of tegaserod maleate, characterized by an X-ray diffraction pattern having peaks at 5.4, 6.0, 6.6 and 10.8 ± 0.2 degree two theta, substantially free of other polymorphic forms, preferably comprising less than about 10% by weight of other polymorphic forms of tegaserod maleate, preferably less than about 5%, preferably less than about 4%, preferably less than about 3%, preferably less than about 2%, preferably less than about 1% (as measured by XRPD). Preferably the polymorphic form A of tegaserod maleate is substantially free of chemical impurities, i.e. preferably the polymorphic form A of tegaserod maleate is about 90%, preferably about 95%, preferably about 96%, preferably about 97%, preferably about 98%, preferably about 99% or more chemically pure (as measured by HPLC).

According to another aspect of the present invention, there is provided polymorphic form A of tegaserod maleate, characterized by an X-ray diffraction pattern having peaks at 5.4, 6.0, 6.6 and 10.8 ± 0.2 degree two theta, substantially free of chemical impurities, preferably wherein the polymorphic form A of tegaserod maleate is about 90%, preferably about 95%, preferably about 96%, preferably about 97%, preferably about 98%, preferably about 99% or more chemically pure (as measured by HPLC). Preferably the polymorphic form A of tegaserod maleate is substantially free of other polymorphic forms, i.e. preferably the polymorphic form A of tegaserod maleate comprises less than about 10% by weight of other polymorphic forms of tegaserod maleate, preferably less than about 5%, preferably less than about 4%, preferably less than about 3%, preferably less than about 2%, preferably less than about 1% (as measured by XRPD).

The polymorphic form A of tegaserod maleate according to the present invention may be suitable for use in medicine, preferably for treating a gastrointestinal tract disorder such as irritable bowel syndrome, heartburn, bloating, postoperative ileus, abdominal pain or
discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, constipation or gastroesophageal reflux.

According to another aspect of the present invention, there is provided a composition comprising polymorphic form A of tegaserod maleate according to the present invention and one or more pharmaceutically acceptable excipients. Preferably the composition is suitable for treating a gastrointestinal tract disorder such as irritable bowel syndrome, heartburn, bloating, postoperative ileus, abdominal pain or discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, constipation or gastroesophageal reflux.

According to another aspect of the present invention, there is provided a method of treating or preventing a gastrointestinal tract disorder, comprising administering a therapeutically or prophylactically effective amount of polymorphic form A of tegaserod maleate according to the present invention to a patient in need thereof. The gastrointestinal tract disorder may be irritable bowel syndrome, heartburn, bloating, postoperative ileus, abdominal pain or discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, constipation or gastroesophageal reflux. The patient may be a mammal such as a human.

**Detailed description of the invention**

In the pharmaceutical industry, polymorphism control of an active pharmaceutical ingredient (API) is critical, since different polymorphs can have different chemical and physical stability, solubility, morphology, and hygroscopicity. During the manufacturing process, it is often necessary to convert a less stable form to a more stable form.

A first aspect of the present invention describes a process for the preparation of polymorphic form A of tegaserod maleate, which is the most stable form. The process of preparing this polymorph is simple and reproducible and results in polymorphic form A of tegaserod maleate substantially free of other polymorphic forms and chemical impurities. Further, the process of the present invention is amenable to scale up and the polymorph has a uniform crystallinity.
For the purposes of this invention, the term "substantially free" means that the polymorphic form A of tegaserod maleate is present at greater than or equal to about 90%. In particular, polymorphic form A of tegaserod maleate, which is "substantially free" of other polymorphic forms, comprises less than about 10% by weight of other polymorphic forms of tegaserod maleate, preferably less than about 5%, preferably less than about 4%, preferably less than about 3%, preferably less than about 2%, preferably less than about 1% (as measured by XRPD). Polymorphic form A of tegaserod maleate, which is "substantially free" of chemical impurities, is about 90%, preferably about 95%, preferably about 96%, preferably about 97%, preferably about 98%, preferably about 99% or more chemically pure (as measured by HPLC).

Preferably the process of the present invention comprises the steps of:
(a) dissolving tegaserod maleate or tegaserod and maleic acid in an alcohol;
(b) adding ether to precipitate tegaserod maleate; and
(c) isolating the precipitated tegaserod maleate.

It has been found that, when tegaserod maleate is used in step (a), any form of tegaserod maleate may be used as the starting material. The alcohol used in step (a) is preferably a C_{14} alcohol, which may be selected from the non-exhaustive group comprising methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, and mixtures thereof. Preferably the alcohol used in step (a) is methanol. It is further preferred that the tegaserod maleate or the tegaserod and maleic acid are dissolved completely in the alcohol resulting in a clear solution. In this respect, preferably the tegaserod maleate or the tegaserod and maleic acid are dissolved in the alcohol at high temperatures, preferably reflux temperatures.

Addition of the ether causes polymorphic form A of tegaserod maleate to precipitate out of solution. The precipitate is pure form A of tegaserod maleate substantially free from other polymorphic forms, typically comprising less than 5% by weight of other polymorphic forms of tegaserod maleate, preferably less than 4%, more preferably less than 3%, more preferably less than 2%, most preferably less than 1%. In a further embodiment, the ether may be selected from the non-exhaustive list comprising tert-butyl methyl ether (TBME),
tert-butyl ethyl ether, diisopropyl ether (DIPE), diethyl ether (DEE), tetrahydrofuran (THF), dioxane, dimethoxyethane, cyclopentyl methyl ether (CPME), dimethyl ether, diethoxyethane, and anisole. A number of less commonly used ethers may also be employed in the working of this invention and it is within the skillset of the skilled person to determine the suitability of other ethers without undue experimentation over and above the teaching of this invention. Preferably the ether used in step (b) is not dioxane, 2-methoxyethanol or 2-ethoxyethanol.

It will be apparent to the skilled person that isolating the precipitate may be achieved by any of a number of means known in the art. The inventors have found that filtering the precipitate is advantageous. Particularly preferred is filtering the precipitate from the solution at about 25-30°C. Preferably, the precipitate is vacuum filtered at about 25-30°C.

Another aspect of the invention is a pharmaceutical composition made by mixing tegaserod maleate prepared according to the first aspect of the invention and one or more pharmaceutically acceptable excipients. It will of course be understood that the number and type of excipients can be varied within the scope of the invention and depend on the type of formulation required. It is well within the skillset of the skilled person to determine the excipients required for a particular composition.

Another aspect of the invention is a process for making a pharmaceutical composition, comprising mixing tegaserod maleate according to the invention and one or more excipient(s). Solid pharmaceutical compositions of the present invention comprise the active ingredient tegaserod maleate as prepared by a process according to the invention and one or more excipient(s). Optionally, a further active ingredient can also be present in the composition, preferably an agent that complements or enhances the therapeutic effect of tegaserod; such agents may include 5-HT3 receptor antagonists, omeprazole, rabeprazole, dipeptidyl peptidase IV (DPP-IV) inhibitors etc. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, soft and hard gelatine capsules, suppositories etc.

The dosage form is preferably suitable for oral application. The compositions are preferably formulated in a unit dosage form, each dosage containing about 1 to about 100 mg, more usually about 1 to about 6 mg of tegaserod maleate. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and
other mammals, each unit containing a predetermined quantity of tegaserod maleate calculated to produce the desired therapeutic effect, in association with one or more suitable pharmaceutical excipient(s).

Pharmaceutical excipients for the solid dosage forms comprise in particular binders, disintegrants, diluents and lubricants. Other and further excipients can also be used, depending on the dosage form required. The skilled person is well equipped to determine the quality and quantity of excipient(s) needed without undue experimentation.

A further aspect of the invention is a method for the treatment of gastrointestinal tract disorders such as irritable bowel syndrome, heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, constipation and gastroesophageal reflux in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of tegaserod maleate or a pharmaceutical composition according to the present invention as described above.

A yet further aspect provides the use of a composition comprising a pharmaceutically effective amount of tegaserod maleate form A according to the present invention and one or more pharmaceutically acceptable excipients to treat gastrointestinal tract disorders such as irritable bowel syndrome, heartburn, bloating, postoperative ileus, abdominal pain and discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, constipation and gastroesophageal reflux.

Examples

Preparation of polymorphic form A of tegaserod maleate

Tegaserod maleate (2 g) was dissolved in methanol (50 vol) and heated to 66°C until a clear solution was obtained. To the clear solution was added tert-butyl methyl ether (50 vol) at 66°C. Solid tegaserod maleate precipitated out at this temperature. Then the solution was cooled to 25°C within 50-60 minutes. The solid obtained was filtered and dried under vacuum at 35°C for 2 hours.
The product was identified as polymorphic form A of tegaserod maleate by XRPD (peaks at 5.4, 6.0, 6.6 and 10.8 ± 0.2 degree two theta) and by DSC (one endothermic peak at about 185-188°C).

Yield = 75%.

Polymorphic purity > 99% (as measured by XRPD).

Chemical purity > 99% (as measured by HPLC).
Claims

1. A process for preparing polymorphic form A of tegaserod maleate, comprising the steps of:
   (a) dissolving tegaserod maleate or tegaserod and maleic acid in an alcohol;
   (b) adding ether to precipitate tegaserod maleate; and
   (c) isolating the precipitated tegaserod maleate.

2. A process according to claim 1, wherein tegaserod maleate is used in step (a).

3. A process according to claim 1 or 2, wherein the alcohol used in step (a) is methanol.

4. A process according to any one of claims 1 to 3, wherein the alcohol is used in step (a) at reflux temperature.

5. A process according to any one of claims 1 to 4, wherein in step (a) the alcohol is heated until a clear solution is obtained.

6. A process according to any one of claims 1 to 5, wherein the ether used in step (b) is tert-butyl methyl ether (TBME), tert-butyl ethyl ether, diisopropyl ether (DIPE), diethyl ether (DEE), tetrahydrofuran (THF), dioxane, dimethoxyethane, cyclopentyl methyl ether (CPME), dimethyl ether, diethoxyethane, or anisole.

7. A process according to claim 6, wherein the ether is tert-butyl methyl ether (TBME).

8. A process according to any one of claims 1 to 7, wherein in step (c) the precipitated tegaserod maleate is recovered by filtration.

9. A process according to any one of claims 1 to 8, wherein the polymorphic form A of tegaserod maleate obtained is substantially free of other polymorphic forms.
10. A process according to any one of claims 1 to 9, wherein the polymorphic form A of tegaserod maleate obtained is substantially free of chemical impurities.

11. A process according to any one of claims 1 to 10, wherein the polymorphic form A of tegaserod maleate is prepared on an industrial scale.

12. Polymorphic form A of tegaserod maleate, prepared by a process according to any one of claims 1 to 11.

13. Polymorphic form A of tegaserod maleate according to claim 12, characterized by an X-ray diffraction pattern having peaks at 5.4, 6.0, 6.6 and 10.8 ± 0.2 degree two theta.

14. Polymorphic form A of tegaserod maleate according to claim 12 or 13, characterized by a DSC curve having one endothermic peak at about 185-188°C.

15. Polymorphic form A of tegaserod maleate according to any one of claims 12 to 14, substantially free of other polymorphic forms.

16. Polymorphic form A of tegaserod maleate according to claim 15, comprising less than about 10% by weight of other polymorphic forms of tegaserod maleate (as measured by XRPD).

17. Polymorphic form A of tegaserod maleate according to any one of claims 12 to 16, substantially free of chemical impurities.

18. Polymorphic form A of tegaserod maleate according to claim 17, wherein the polymorphic form A of tegaserod maleate is 90% or more chemically pure (as measured by HPLC).

19. Polymorphic form A of tegaserod maleate, characterized by an X-ray diffraction pattern having peaks at 5.4, 6.0, 6.6 and 10.8 ± 0.2 degree two theta, substantially free of other polymorphic forms.
20. Polymorphic form A of tegaserod maleate according to claim 19, comprising less than about 10% by weight of other polymorphic forms of tegaserod maleate (as measured by XRPD).

21. Polymorphic form A of tegaserod maleate, characterized by an X-ray diffraction pattern having peaks at 5.4, 6.0, 6.6 and 10.8 ± 0.2 degree two theta, substantially free of chemical impurities.

22. Polymorphic form A of tegaserod maleate according to claim 21, wherein the polymorphic form A of tegaserod maleate is 90% or more chemically pure (as measured by HPLC).

23. Polymorphic form A of tegaserod maleate according to any one of claims 12 to 22, for use in medicine.

24. Polymorphic form A of tegaserod maleate according to any one of claims 12 to 23, for treating a gastrointestinal tract disorder.

25. Polymorphic form A of tegaserod maleate according to claim 24, wherein the gastrointestinal tract disorder is irritable bowel syndrome, heartburn, bloating, postoperative ileus, abdominal pain or discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, constipation or gastroesophageal reflux.

26. A composition comprising polymorphic form A of tegaserod maleate according to any one of claims 12 to 25 and one or more pharmaceutically acceptable excipients.

27. A composition according to claim 26, for treating a gastrointestinal tract disorder.

28. A composition according to claim 27, wherein the gastrointestinal tract disorder is irritable bowel syndrome, heartburn, bloating, postoperative ileus, abdominal pain or discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, constipation or gastroesophageal reflux.
29. A method of treating or preventing a gastrointestinal tract disorder, comprising administering a therapeutically or prophylactically effective amount of polymorphic form A of tegaserod maleate according to any one of claims 12 to 25 to a patient in need thereof.

30. A method according to claim 29, wherein the gastrointestinal tract disorder is irritable bowel syndrome, heartburn, bloating, postoperative ileus, abdominal pain or discomfort, epigastric pain, nausea, vomiting, regurgitation, intestinal pseudo-obstruction, constipation or gastroesophageal reflux.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D209/14 A61K31/404 A61P1/00

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    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

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>WO 2005/014544 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; PFEFFER SABINE [DE]; VITZ) 17 February 2005 (2005-02-17) cited in the application abstract examples in particular example 2 claims</td>
<td>12,19, 21,26,29</td>
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<td>X</td>
<td>WO 2005/058819 A (TEVA PHARMA [IL]; TEVA PHARMA [US]; MENDELOVICI MARIOARA [IL]; ARONHIM) 30 June 2005 (2005-06-30) cited in the application abstract examples 1-5 claims 1,3,6</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

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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

22 September 2008

Date of mailing of the international search report

30/09/2008

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
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