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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING ROSUVASTATIN

(57) Abstract: The present invention relates to pharmaceutical formulations comprising rosuvastatin and/or a pharmaceutically acceptable salt thereof as active agent and use of these formulations in the treatment and/or prophylaxis of atherosclerosis, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, myocardial infarction.
PHARMACEUTICAL COMPOSITIONS COMPRISING ROSUVASTATIN

The present invention relates to pharmaceutical formulations comprising rosuvastatin and/or a pharmaceutically acceptable salt thereof as active agent and use of these formulations in the treatment and/or prophylaxis of atherosclerosis, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, myocardial infarction.

The Prior Art

Rosuvastatin is an HMG-CoA enzyme inhibitor having the chemical name \((3\text{R},5\text{S},6\text{E})-7\text{-}[4-(4\text{-fluorophenyl})-6\text{-}(1\text{-methylethyl})-2 \text{[methyl(methyl sulphonyl)amino]} -5\text{-pyrimidinyl]} -3,5\text{-dihydroxy-6-heptenoic } \text{acid}\) and is illustrated in formula (I):

![Formula (I)]

Rosuvastatin is an oral antilipidemic drug which strongly inhibits HMG CoA reductase enzyme. Rosuvastatin lowers total and LDL cholesterol; reduces plasma triglycerides and apolipoprotein B levels. Due to the chemical structure of its connection points and its relatively high hydrophobicity, it binds to HMG CoA reductase enzyme with higher affinity compared with other statins.

Rosuvastatin lowers LDL cholesterol at 45%, 52%, 55%, 63% respectively when given at doses of 5 mg, 10 mg, 20 mg and 40 mg per day to patients suffering from primary hypercholesterolemia. The clinical studies conducted displayed that rosuvastatin is more effective than other statins.

Rosuvastatin is generally used by the oral route and has bioavailability around 20%. Rosuvastatin formulations in the prior art are in tablet form.
However, rosuvastatin formulations in the prior art pose various problems both at production stage and at use and storage stages after the production due to the stability problem of the active agent.

Rosuvastatin is converted into lactone as a result of "intramolecular esterification" reaction taking place between carboxylic acid in its molecular structure and hydroxyl groups on β and δ carbons of this carboxylic acid. The reaction takes place in acidic environment and basic agents cause reverse reaction. This feature decreases the stability of the substance and therefore shortens its shelf life.

The patents numbered WO 01/54668, WO 01/54669 and EP 0547000 assert that this problem of the active agent can be solved by use of alkaline agents in the formulations.

When the prior art is taken into consideration, most of the studies relate to solution of stability problem of rosuvastatin.

However, as a result of the studies they conducted, the inventors have found that the active agent also has solubility problem and this problem poses an obstacle for production of formulations with high bioavailability.

As it is known, crystal or particle size of the active agent is a parameter which changes absorption speed and rate in gastrointestinal tract as it affects dissolution rate.

Reducing crystal or particle diameter (microcrystallisation or micronization) noticeably increases dissolution rate and absorption of the drugs which are not dissolved much in water. However, reducing the particle size of the drug much is not always desirable in oral administration of the drugs. Major examples of this are as follows: drugs with fine particle size cause more irritation as they are dissolved in gastrointestinal tract fast; drugs such as penicillin G and erythromycin which are degraded in the acidic environment of the stomach fast are degraded while passing through the stomach when administered in fine particle sizes; hydrophobic drugs (such as ezetimibe) turn into big aggregates (micelles), which are harder to be absorbed, due to thermodynamic impulsion when their fine particles are dispersed in aqueous environment.

When the prior art is taken into consideration, there is need for a production method which shall enable determining the particle size that would provide appropriate solubility and
bioavailability in rosuvastatin formulations; and producing formulations comprising rosvastatin with said particle size effectively.

The application numbered WO/2009/156173 discloses pharmaceutical formulations produced with active agents having average particle sizes preferably finer than 100 μm.

The application numbered WO/2009/024889, on the other hand, discloses formulations prepared with the active agent having a \( D_{90} \) particle size of 60 μm or finer.

The application numbered WO/2008/015563, on the other hand, discloses rosvastatin salts and production methods thereof while the particle sizes of rosvastatin salts in the application are preferably finer than 10 μm.

However, these applications do not refer to solubility problem of rosvastatin calcium.

When the prior art is taken into consideration, particle size of the active agent rosvastatin in rosvastatin formulations is generally finer than 100 μm.

However, the inventors have surprisingly found that pharmaceutical formulations produced with the active agent having a \( D_{90} \) particle size coarser than 100 μm are more stable and have higher bioavailability than formulations in the prior art.

The term "rosuvastatin" used throughout the text refers to rosvastatin and its pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or combinations thereof.

The term "\( D_{90} \) particle size" used throughout the text refers to the particle size comprising 90% of rosvastatin particles by volume and is measured by the device Malvern Mastersizer 2000 S (Scirocco 2000) by dry method.

**Detailed Description of the Invention**

The present invention relates to pharmaceutical formulations which are dissolved better; have higher bioavailability and stability than rosvastatin formulations in the prior art; production methods and area of use thereof.
The formulations of the present invention comprise rosuvastatin and/or a pharmaceutically acceptable salt thereof in an effective amount.

The formulations of the present invention comprise rosuvastatin calcium and at least one other pharmaceutically acceptable excipient in an effective amount.

\[ D_{90} \text{ particle size of rosuvastatin calcium used in the formulations of the present invention is coarser than 100 } \mu m. \]

\[ D_{90} \text{ particle size of rosuvastatin calcium used in the formulations of the present invention is preferably coarser than 150 } \mu m. \]

\[ D_{90} \text{ particle size of rosuvastatin calcium used in the formulations of the present invention is finer than 300 } \mu m. \]

The formulations of the present invention are characterised by \( D_{90} \) particle size of rosuvastatin and/or a pharmaceutically acceptable salt thereof in the range of 100 to 300 \( \mu m \), more preferably in the range of 150 to 300 \( \mu m \).

As a result of the studies they conducted, the inventors have found that formulations prepared with rosuvastatin calcium having \( D_{90} \) particle size finer than 100 \( \mu m \) or coarser than 300 \( \mu m \) do not have sufficient solubility profile.

The active agent which is not dissolved sufficiently cannot be absorbed enough in vivo environment to enable effective treatment and this influences the efficiency of the treatment negatively.

To this respect, particle size of rosuvastatin calcium used in these new rosuvastatin formulations developed in scope of the invention is in the range of 100 to 300 \( \mu m \), preferably in the range of 150 to 300 \( \mu m \).

Oral dosage forms produced with rosuvastatin calcium having a particle size adjusted this way have better solubility and bioavailability profile than forms in the prior art.

As for the solubility study given below, film tablet formulation of rosuvastatin calcium in Example 1 was produced with an active agent having a \( D_{90} \) particle size in the range of 50 \( \mu m \) to 500 \( \mu m \) and 6 different tablet dosage forms obtained this way were mixed in a dissolution environment in the range of 37 ± 0.5 °C comprising water (USP Type I) with 75 rpm of rotation speed for 30 minutes in order to determine and compare solubility data.
Test results are given below:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>D$_{90}$=50 μm</th>
<th>D$_{90}$=100 μm</th>
<th>D$_{90}$=150 μm</th>
<th>D$_{90}$=200 μm</th>
<th>D$_{90}$=300 μm</th>
<th>D$_{90}$=500 μm</th>
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<tbody>
<tr>
<td>5</td>
<td>18.3</td>
<td>18.7</td>
<td>19.2</td>
<td>19.5</td>
<td>19.6</td>
<td>18.6</td>
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<td>42.3</td>
<td>42.6</td>
<td>43.1</td>
<td>43.4</td>
<td>41.5</td>
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<tr>
<td>15</td>
<td>58.1</td>
<td>58.2</td>
<td>64.8</td>
<td>65.0</td>
<td>65.2</td>
<td>60.0</td>
</tr>
<tr>
<td>30</td>
<td>72.6</td>
<td>72.3</td>
<td>86.5</td>
<td>86.4</td>
<td>74.1</td>
<td>74.0</td>
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<td>45</td>
<td>84.0</td>
<td>84.6</td>
<td>92.8</td>
<td>93.2</td>
<td>93.6</td>
<td>85.3</td>
</tr>
<tr>
<td>60</td>
<td>84.3</td>
<td>84.8</td>
<td>94.9</td>
<td>94.5</td>
<td>94.7</td>
<td>86.0</td>
</tr>
</tbody>
</table>

At the end of the solubility study conducted, the rosuvastatin calcium tablet formulation which has the best solubility profile is the tablet comprising rosuvastatin calcium having a D$_{90}$ particle size in the range of 150-300 μm.

According to the results, formulations produced with active agents having D$_{90}$ particle size particularly finer than 100 μm and coarser than 300 μm do not ensure sufficient solubility.

An insufficient dissolution profile impedes administration of sufficient amount of active agent, in other words, reduces bioavailability.

Providing high solubility and high bioavailability is quite significant for an active agent like rosuvastatin calcium which is particularly preferred in the treatment of cardiac diseases.

In the present invention, this aim has been attained by adjusting D$_{90}$ particle size of the active agent such that it is coarser than 100 μm, more preferably coarser than 150 μm.

Rosuvastatin calcium comprised in the dosage forms produced according to the present invention is in the range of 1% to 10% by weight.

Rosuvastatin calcium particles according to the present invention can be used in production of an oral dosage form in the prior art.

These oral dosage forms can be tablet, film coated tablet, coated tablet, effervescent tablet, bilayer tablet; modified, fast, slow, controlled, prolonged release tablet; orodispersible tablet, mini tablet, micro tablet, pellet or multiple dosage forms comprising one or more of these forms or in suspension dosage forms.
The formulations of the present invention are preferably in effervescent tablet, bilayer tablet and/or film coated tablet form.

The formulations of the present invention comprise at least one sterol absorption inhibitor in an effective amount as a second active agent. Sterol absorption inhibitor used in the rosuvastatin formulations of the present invention is preferably ezetimibe and/or its pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or combinations thereof.

Pharmaceutical formulations of the present invention can comprise other pharmaceutically acceptable components such as additives and excipients selected from disintegrants, viscosity enhancing agents, filling agents, drying agents, stabilizing agents, lubricants, diluents, binders, glidants, anti-foam agents, wetting agents, effervescent mixtures, sweeteners and flavoring agents.

The disintegrants that can be used in the present invention can be selected from highly dispersive polymers, for instance cross-linked hydroxypropyl cellulose, carboxy methyl cellulose sodium, polyvinylpyrrolidone, high-molecular-weight polymers, microcrystalline cellulose, sodium starch glycolate, povidone, alginic acid, sodium alginate.

The disintegrant used in the formulations of the present invention is preferably a polymeric disintegrand. It is significant that the disintegrant used is polymeric in order to ensure the final product dosage form to be dispersed well and therefore dissolved better.

The diluents that can be used in the present invention comprises one or more components selected from the group comprising alkaline metal carbonates, cellulose derivatives (microcrystalline cellulose, cellulose acetate etc.), dextrin, fructose, dextrose, glyceryl palmito stearate, lactitol, lactose, directly compressible lactose, maltose, mannitol, simethicone, sorbitol, starch, talc, xylitol and/or hydrates thereof and/or derivatives thereof.

The binders that can be used in the present invention comprise one or more components selected from the group comprising potato, wheat or corn starch; microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, hypromellose and polyvinylpyrrolidone.

In the formulations of the present invention; antioxidants, chelating agents, alkalinizing agents and photoprotective agents can be used as stabilizing agent.
The stabilizing agents that can be used in the formulations of the present invention can be selected from alkaline metal salts such as sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; alkaline-earth metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate; organic components such as primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzyl ethylenediamine, diethanolamine, ethylenediamine, meglumine, monosodium glutamate, polacrilin sodium, sodium alginate and/or pharmaceutically acceptable hydrates and/or derivatives thereof.

The formulations of the present invention can optionally comprise at least one stabilizing agent selected from the group given. The amount of the stabilizing agent used in the formulations is less than 1% by weight. Adjusting the particle size of the active agent in the formulations has enabled to obtain stable formulations without requiring use of high amounts of stabilizing agents.

The lubricants that can be used in the present invention comprise one or more components selected from the group comprising highly metallic stearates (magnesium stearate, calcium stearate, aluminium stearate etc.), fatty acid esters (sodium stearyl fumarate etc.), fatty acids (stearic acid etc.), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, lecine, colloidal silicone dioxide, polyethylene glycols (PEG), metallic lauryl sulphates (sodium lauryl sulphate, magnesium lauryl sulphate), sodium chloride, sodium benzoate, sodium acetate and talc and/or hydrates thereof.

The filling agents that can be used in the present invention comprises one or more components selected from the group comprising lactose, sugar, starch, modified starch, mannitol, sorbitol, inorganic salts, microcrystalline cellulose, cellulose, calcium sulphate, xylitol and lactitol.

The sweeteners that can be used in the present invention comprise one or more components selected from the group comprising aspartame, dextrose, fructose, sucralose, sodium cyclamate, mannitol, maltose, saccharine and/or pharmaceutically acceptable salts thereof.

The flavouring agents that can be used in the present invention can be banana, strawberry, lemon, orange, peach, vanilla or similar natural fruit or aromatic plant flavours.
The formulations of the present invention can be produced using any of the production methods in the prior art.

One of the production methods proposed according to the present invention is dry blending which is preferably implemented as follows:

1. An effective amount of rosuvastatin calcium and at least one pharmaceutically acceptable excipient are mixed and sieved;
2. A pharmaceutically acceptable lubricant is added into the mixture obtained and mixed;
3. The final mixture obtained is preferably sent to tablet compression machine to compress tablets;
4. Tablets are preferably coated with film coating solution.

Another production method proposed according to the present invention is as follows:

1. An effective amount of rosuvastatin calcium and at least one pharmaceutically acceptable excipient are mixed and sieved;
2. The mixture obtained is granulated with a granulation solution comprising at least one pharmaceutically acceptable solvent and optionally at least one other active agent;
3. Wet granules are dried and treated with the lubricant;
4. The granules obtained are treated with the lubricant and the final mixture is preferably sent to tablet compression machine.

The method to be used for production method of combined formulations of the present invention comprising at least two active agents is as follows:

1. The first mixture is obtained by mixing and then sieving an effective amount of rosuvastatin calcium and at least one pharmaceutically acceptable excipient;
2. The second active agent is dissolved in a pharmaceutically acceptable solvent and/or a solvent mixture and the granulation solution is obtained;
3. The granulation is enabled by spraying the granulation solution obtained on a pharmaceutically acceptable diluent; the granules obtained are dried and sieved; and the second mixture is obtained by mixing the dry granules with at least one pharmaceutically acceptable excipient;
4. The two mixtures comprising rosuvastatin calcium and a second active agent are preferably sent to tablet compression machine separately and tablets are compressed;
5. The tablets obtained are optionally coated with film coating.
Another production method of combined formulations of the present invention comprising at least two active agents is as follows:

1. The second active agent to be used in the formulations and the diluent are mixed; the mixture obtained is granulated with a granulation solution which is composed of at least one pharmaceutically acceptable binder and one solvent or solvent mixture,

2. The granules obtained are dried; rosuvastatin calcium, at least one pharmaceutically acceptable disintegrant and optionally other excipients are added into the dry granules and mixed again,

3. The end mixture is treated with the lubricant and tablets are compressed,

4. The tablets obtained are optionally coated with film.

Another feature of the formulations of the present invention is that said formulations are used in the treatment and/or prophylaxis of atherosclerosis, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, myocardial infarction.

The examples below are given so as to clarify the invention. These examples do not restrict the scope of the present invention and are evaluated with the description part given in detail above.
Examples.

Example 1. Rosuvastatin Film Tablet Formulation

<table>
<thead>
<tr>
<th>Content</th>
<th>Percent (%) by Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin Calcium</td>
<td>3.50</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>10.00</td>
</tr>
<tr>
<td>Diluent</td>
<td>85.00</td>
</tr>
<tr>
<td>Lubricant</td>
<td>1.50</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

The method to follow for production of the film coated tablet formulation comprising rosvastatin calcium according to the formulations given above is as follows:

1. Rosuvastatin calcium with a D_{90} particle size of 185 \( \mu \text{m} \), at least one pharmaceutically acceptable disintegrant and diluent are mixed and sieved;
2. A pharmaceutically acceptable lubricant is added into this mixture sieved and they are mixed;
3. The final mixture obtained is sent to tablet compression machine to compress tablets;
4. The tablets are coated with film coating solution.
Example 2. Bilayer Tablet Formulation

<table>
<thead>
<tr>
<th>Content</th>
<th>Percent (%) by Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>2.50</td>
</tr>
<tr>
<td>Rosuvastatin Calcium</td>
<td>1.25</td>
</tr>
<tr>
<td>Binder</td>
<td>1.75</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>10.00</td>
</tr>
<tr>
<td>Diluent</td>
<td>80.00</td>
</tr>
<tr>
<td>Other pharmaceutical excipient(s)</td>
<td>4.50</td>
</tr>
<tr>
<td>Solvent/Solvent mixture</td>
<td>Q.S.</td>
</tr>
<tr>
<td><strong>Tablet core weight</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

The method to be followed for production of the bilayer tablet dosage form to be produced according to the formulation given above is as follows:

- Rosuvastatin calcium with a D$_{90}$ particle size of 185 µm, the diluent, the disintegrant and at least one other pharmaceutically acceptable excipient are mixed and sieved (MIXTURE A);
- Granulation solution is obtained by dissolving ezetimibe in a pharmaceutically acceptable solvent;
- Granulation is enabled by spraying the granulation solution obtained on a pharmaceutically acceptable diluent;
- Active agent granules are dried, sieved and mixed with at least one pharmaceutically acceptable excipient and sieved again (MIXTURE B);
- Mixture A and Mixture B are sent to tablet compression machine separately and bilayer tablets are compressed,
- The tablets obtained are optionally coated with film.
Example 3. Rosuvastatin Effervescent Tablet Formulation

<table>
<thead>
<tr>
<th>Content</th>
<th>Percent by Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin Calcium</td>
<td>1.00</td>
</tr>
<tr>
<td>Diluent</td>
<td>5.00</td>
</tr>
<tr>
<td>Effervescent couple</td>
<td>80.00</td>
</tr>
<tr>
<td>Binder</td>
<td>5.00</td>
</tr>
<tr>
<td>Lubricant</td>
<td>0.50</td>
</tr>
<tr>
<td>Sweetener</td>
<td>4.00</td>
</tr>
<tr>
<td>At least 1 other excipient</td>
<td>4.50</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

The production method to be followed for rosuvastatin effervescent tablet that shall be produced according to the formulation given above is as follows:

1. Rosuvastatin calcium having a D$_{90}$ particle size of 190 µm is mixed with the effervescent couple and the diluent,
2. The active agent mixture obtained is granulated wet preferably with deionized water,
3. Rosuvastatin granules obtained are dried and sieved,
4. The other pharmaceutical excipients are added into the dry mixture and the final mixture is sent to tablet compression machine.
CLAIMS

1. A formulation comprising rosuvastatin and/or a pharmaceutically acceptable salt thereof characterized in that $D_{90}$ particle size of the active agent comprised in said formulation is coarser than 100 µm.

2. The formulation according to claim 1 characterized in that the particle size of the active agent comprised in said formulation is coarser than 150 µm.

3. The formulation according to claims 1-2 characterized in that the particle size of the active agent comprised in said formulation is finer than 300 µm.

4. The formulation according to claims 1-3 characterized in that said formulation comprises rosuvastatin calcium in the range of 1% to 10% by weight.

5. The formulation according to any preceding claims characterized in that characterized in that said formulation comprises other pharmaceutically acceptable components such as additives and excipients selected from disintegrates, viscosity enhancing agents, filling agents, drying agents, stabilizing agents, lubricants, diluents, binders, glidants, anti-foam agents, wetting agents, effervescent mixtures, sweeteners and flavoring agents.

6. The formulation according to claim 5 characterized in that said formulation is in the form of tablet, film coated tablet, coated tablet, effervescent tablet, bilayer tablet; modified, fast, slow, controlled, prolonged release tablet; orodispersible tablet, mini tablet, micro tablet, pellet or multiple dosage forms comprising one or more of these forms or in suspension dosage forms.

7. The formulation according to claim 6 characterized in that said formulation is in the form of effervescent tablet, bilayer tablet and/or film coated tablet.

8. A production method for a formulation according to claim 7 characterized in that said method is one of the techniques of wet granulation, dry granulation, dry blending.

9. The production method according to claim 8 characterized in that said method comprises the steps that:
   - An effective amount of rosuvastatin calcium and at least one pharmaceutically acceptable excipient are mixed and sieved,
   - A pharmaceutically acceptable lubricant is added into the mixture sieved and mixed,
   - The final mixture obtained is optionally sent to tablet compression machine in order to compress tablets,
• Tablets are optionally coated with film coating solution.

10. The formulation according to claim 1 characterized in that said formulation comprises at least one other active agent.

11. The formulation according to claim 10 characterized in that said formulation comprises at least one sterol absorption inhibitor as a second active agent.

12. The formulation according to claim 11 characterized in that sterol absorption inhibitor is ezetimibe and/or its pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or combinations thereof.

13. The formulation according to claim 1 characterized in that said formulation is used for production of a drug so as to be used in the treatment and/or prophylaxis of atherosclerosis, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, myocardial infarction.
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

<table>
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<th>INV.</th>
<th>A61K9/20</th>
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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)

A61K

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<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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</table>

**Further documents are listed in the continuation of Box C.**

**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新颖 variant 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**

19 April 2012

**Date of mailing of the international search report**

26/04/2012

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Wei ss, Mari e-France
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<td>wo 2008/015563 A2 (GLENMARK PHARMACEUTICALS LTD [IN] ; JOSHI NARENDRA SHRI RAM [IN] ; KHI LE) 7 February 2008 (2008-02-07) page 1, paragraph 0002 page 11, paragraph 0071 page 12, paragraphs 0074, 0075 page 13, paragraph 0078 page 17, paragraph 0096 example 8-13</td>
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<td>ep 2 216 020 AI (KRKA TOVARNA ZDRAVLJA NOVO [SI]) 11 August 2010 (2010-08-11) page 3, line 46, paragraph 0017 page 4, paragraph 0022-0028 page 5, paragraphs 0034-0036, 0040-0042</td>
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