PHARMACEUTICAL COMPOSITION COMPRISING ALEGLITAZAR

The invention relates to a pharmaceutical composition and in particular to a pharmaceutical composition comprising aleglitazar or a salt thereof. More particularly, the invention relates to a pharmaceutical composition comprising 0.01 mg to 0.9 mg of aleglitazar or a salt thereof obtainable by

(a) spraying a solution comprising aleglitazar or a salt thereof on a diluent and a disintegrant;

(b) mixing the composition obtained in step (a) with a lubricant; and

(c) optionally compressing the composition obtained in step (b).

The invention also relates to a process for the manufacture of a pharmaceutical composition comprising:

(a) spraying a solution comprising aleglitazar or a salt thereof on a diluent and a disintegrant;

(b) mixing the composition obtained in step (a) with a lubricant; and

(c) optionally compressing the composition obtained in step (b).

Aleglitazar is (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid. It belongs to the class of Peroxisome Proliferator Activated Receptors (PPAR) agonists. Aleglitazar is described in WO 02/092084. The sodium salt of aleglitazar is sodium (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propanoate.

Peroxisome Proliferator Activated Receptors are members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. Various subtypes thereof have been identified and cloned. These include PPARα, PPARβ

(also known as PPARδ), and PPARγ. There exist at least two major isoforms of PPARγ. While PPARγ1 is ubiquitously expressed in most tissues, the longer isoform PPARγ2 is almost exclusively found in adipocytes. In contrast, PPARα is predominantly expressed in the liver, kidney and heart. PPAR's modulate a variety of body responses including glucose- and lipid- homeostasis, cell differentiation, inflammatory responses and cardiovascular events.

Studies provide evidence that a coagonism on PPARα and PPARγ results in compounds with enhanced therapeutic potential, i. e. with an improved lipid profile effect on top of the normalization of glucose- and insulin-levels (Keller and Wahli: Trends Endocrin. Metab. 1993; 4:291-296, Macdonald and Lane: Current Biology Vol.5 pp.618-621 (1995)).

Aleglitazar is capable of binding and activating both PPARα and PPARγ simultaneously and very efficiently. Therefore, aleglitazar combines the anti-glycemic effect of PPARγ activation with the anti-dyslipidemic effect of PPARα activation. Consequently, plasma glucose and insulin are reduced (=insulin sensitization), triglycerides lowered and HDL cholesterol increased (=improved lipid profile). In addition, it lowers LDL cholesterol, decrease blood pressure and counteract inflammatory atherosclerosis. Since multiple facets of the type II diabetes disease syndrome are addressed by PPARα and γ coagonists, Aleglitazar has an enhanced therapeutic effect compared to the compounds already known in the art.

It was surprisingly found that a pharmaceutical composition comprising aleglitazar in a dose range of 0.01 to 0.9 mg is particularly efficient in treating or preventing diabetes type II. Due to a particularly low solubility and a high activity, aleglitazar had never been successfully included in a homogenous low dose solid formulation suitable for commercial and industrial processes.

In a first aspect, there is provided a pharmaceutical composition comprising 0.01 mg to 0.9 mg of aleglitazar or a salt thereof obtainable by

(a) spraying a solution comprising aleglitazar or a salt thereof on a diluent and a disintegrant;

(b) mixing the composition obtained in step (a) with a lubricant; and

(c) optionally compressing the composition obtained in step (b).

In a second aspect, there is provided a pharmaceutical composition comprising:

Aleglitazar or sodium salt thereof	0.01 - 0.9 mg
Disodium phosphate	1 - 1.5 mg
Sodium dihydrogen phosphate	0.01 - 0.3 mg
Sodium lauryl sulfate	0.1 - 2 mg
Povidone	0.1 - 20 mg
Lactose	20 - 110 mg
Microcrystalline cellulose	5 - 100 mg
Croscarmellose sodium	0.5 - 20 mg
Magnesium stearate	0.5 - 3 mg.

In a third aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for the treatment or prophylaxis of diabetes type II or cardiovascular diseases.

In a fourth aspect, there is provided a process for the manufacture of a pharmaceutical composition aleglitazar or a salt thereof comprising:

(a) spraying a solution comprising aleglitazar or a salt thereof on a diluent and a disintegrant;

(b) mixing the composition obtained in step (a) with a lubricant; and

(c) optionally compressing the composition obtained in step (b).

In the present description the term "diluent" refers to an excipient which fills out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. Suitable diluents include e.g. pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate sugar, sugar alcohols, corn starch, sucrose, silicic anhydride, polysaccharides, N-methyl pyrrolidone (Pharmasolve (ISP)) and mixtures thereof. The term sugar and sugar alcohols comprises mannitol, lactose, fructose, sorbitol, xylitol, maltodextrin, dextrates, dextrins, lactitol and mixtures thereof.

Binders are added to tablet formulations to add cohesiveness to powders thereby providing the necessary bonding to form granules which under compaction form a compact mass as tablet. Methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethyl

propylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, starch and starch pregelatinized are suitable examples of binders. Mixtures of two, three or more binders can be used in the formulation.

The solution comprising aleglitazar can be an aqueous or an organic solution. The preferred organic solvent is ethanol.

Buffer solutions are used as a mean for keeping pH at a nearly constant value. A buffer solution is usually an aqueous solution consisting of a mixture of a weak acid and its conjugate base or a weak base and its conjugate acid. It has the property that the pH of the solution changes very little when a small amount of acid or base is added to it. Examples of buffers are acetic acid/sodium acetate buffer, potassium or sodium dihydrogenphosphate/ dipotassium or disodium phosphate buffer, boric acid/sodium hydroxide buffer, tris (tris-(hydroxymethyl)-aminomethane)-buffer, carbonate/bicarbonate and EDTA-buffer.

The solution comprising aleglitazar is preferably a buffered aqueous solution, preferably buffered with a phosphate buffer. The phosphate buffer is preferably a buffer comprising disodium phosphate and sodium dihydrogen phosphate.

The term "surfactant" refers to an excipient that lowers the surface tension of a liquid. Examples of surfactant include tween 80, polyoxyethylene-polyoxypropylene copolymer and sodium lauryl sulfate.

The term "disintegrant" refers to an excipient which expands and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption. Suitable disintegrants include e.g. lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, carboxymethylcellulose calcium, carboxymethylcellulose sodium, crossprovidone, sodium starch glycolate and mixtures thereof.

Suitable lubricants, including agents that act on the flowability of the powder by reducing interparticle friction and cohesion to be compressed, are colloidal silicon dioxide, such as aerosil, talc, stearic acid, magnesium stearate, calcium stearate, glyceryl behenate, sodium stearyl fumarate and silica gel.

The term "coating" refers to an excipient which is applied on the surface of a tablet and which protects tablet ingredients from deterioration by moisture in the air and make large or unpleasant-tasting tablets easier to swallow. Examples of coating agent include PVA (polyvinyl alcohol), HPMC (hydroxypropylmethyl cellulose) and PEG (polyethylene glycol).

The term "aleglitazar or a salt thereof" refers to aleglitazar or to the reaction product of aleglitazar with a base wherein the carboxylic acid hydrogen atom of aleglitazar has been replaced by a metal atom. A preferred salt of aleglitazar is the sodium salt of aleglitazar.

Unless otherwise stated all percentages are given in weight percent of the total weight of the composition.

The weight range of aleglitazar or the salt thereof refers to the weight of aleglitazar in the form of the free acid or, in case of the salt, to the weight of the same mole quantity of aleglitazar in the form of the free acid.

The amount of aleglitazar or the salt thereof in the pharmaceutical composition or in the process is preferably between 0.01 and 0.9 mg, preferably between 0.01 and 0.6 mg, more preferably between 0.15 and 0.6 mg. Further preferred amounts of aleglitazar are 0.15 or 0.3 mg.

Preferred is a pharmaceutical composition or a process, wherein the solution comprising aleglitazar or a salt thereof in step (a) is an aqueous solution.

Further preferred is a pharmaceutical composition or a process, wherein the solution comprising aleglitazar or a salt thereof in step (a) is an organic solution, preferably an ethanolic solution.

Preferred is a pharmaceutical composition or a process according to the invention, wherein the solution of step (a) is an aqueous solution, preferably buffered with a phosphate buffer. The buffer is preferably selected from the buffers mentioned above and is more preferably disodium phosphate and sodium dihydrogen phosphate.

When the buffer is Na_2HPO_4 and NaH_2PO_4 the molarity of the buffer system is preferably ranging from 0.05 to 0.4 mM, preferably from 0.1 to 0.2 mM. The pH of the buffered solution is preferably ranging between 6.0 and 12.

Further preferred is a pharmaceutical composition or a process according to the invention, wherein the diluent is selected from sugar, microcrystalline cellulose, lactose, starch and mixtures thereof and is preferably a mixture of lactose and microcrystalline cellulose.

Also preferred is a pharmaceutical composition or a process according to the invention, wherein the aqueous solution of step (a) comprises a binder selected from povidone, HPMC and starch pregelatinized.

The amount of binder is preferably between 1 and 15 %, more preferably between 2 and 10 %, more preferably between 4 and 6 % of the total weight of the composition.

The binder is preferably povidone. Starch pregelatinized is further preferred.

Preferred is a pharmaceutical composition or a process according to the invention, wherein the solution of step (a) comprises a surfactant selected from tween 80, polyoxyethylene-polyoxypropylene copolymer and sodium lauryl sulfate.

The amount of surfactant is preferably between 0.1 and 2 %, more preferably between 0.25 and 1 %, more preferably between 0.4 and 0.6 % of the total weight of the composition.

The surfactant is preferably sodium lauryl sulfate.

The disintegrant is preferably selected from crosslinked polyvinyl pyrrolidone, starch, croscarmellose sodium, carboxymethylcellulose sodium and sodium starch glycolate.

The amount of disintegrant is preferably between 0.5 and 15 %, more preferably between 1 and 10 %, more preferably between 2 and 3 % of the total weight of the composition.

The disintegrant is preferably croscarmellose sodium.

Also preferred is a pharmaceutical composition or a process according to the invention, wherein the lubricant is selected from stearic acid, magnesium stearate, glyceryl behenate and sodium stearyl fumarate.

The amount of lubricant is preferably between 0.2 and 3 %, more preferably between 0.5 and 1.0 % of the total weight of the composition.

The lubricant is preferably magnesium stearate.

The composition preferably comprises a sodium salt of aleglitazar.

The invention also preferably relates to a pharmaceutical composition comprising:

Aleglitazar or sodium salt thereof	0.01 - 2 %
Disodium phosphate	0.5 - 1.5 %
Sodium dihydrogen phosphate	0.005 - 0.25 %
Sodium lauryl sulfate	0.1 - 2 %
Povidone or HPMC	1 - 15 %
Lactose	15 - 85 %
Microcrystalline cellulose	3 - 85 %

Croscarmellose sodium	0.5 - 15 %
Magnesium stearate	0.2 - 3 %.

The invention also preferably relates to a pharmaceutical composition comprising:

Aleglitazar or sodium salt thereof	0.01 - 0.9 mg
Disodium phosphate	1 - 1.5 mg
Sodium dihydrogen phosphate	0.01 - 0.3 mg
Sodium lauryl sulfate	0.1 - 2 mg
Povidone or HPMC	0.1 - 20 mg
Lactose	20 - 110 mg
Microcrystalline cellulose	5 - 100 mg
Croscarmellose sodium	0.5 - 20 mg
Magnesium stearate	0.5 - 3 mg.

If desired, the pharmaceutical compositions of the present invention may also contain one or more antioxidants in order to prevent e.g. any oxidation of the drug compound. Suitable antioxidants for use herein include, but are not limited to, butylated hydroxyanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, ascorbic acid and mixtures thereof. A preferred antioxidant is butylated hydroxyanisole and butylated hydroxytoluene in a mixture of 1:1.

Furthermore, the invention also relates to a pharmaceutical composition comprising:

Aleglitazar	0.01 - 2 %
Butylated Hydroxyanisole	0.01 - 0.5 %
Butylated Hydroxytoluene	0.01 - 0.5 %
Sodium lauryl sulfate	0.1 - 2 %
Povidone	1 - 15 %
Lactose	15 - 85 %

Microcrystalline cellulose	3 - 85 %
Croscarmellose sodium	0.5 - 15 %
Magnesium stearate	0.2 - 3 %.

The invention also relates to a pharmaceutical composition comprising:

Aleglitazar	0.01 - 0.9 mg
Butylated Hydroxyanisole	0.01 - 0.5 mg
Butylated Hydroxytoluene	0.01 - 0.5 mg
Sodium lauryl sulfate	0.1 - 2 mg
Povidone	0.1 - 20 mg
Lactose	20 - 110 mg
Microcrystalline cellulose	5 - 100 mg
Croscarmellose sodium	0.5 - 20 mg
Magnesium stearate	0.5 - 3 mg.

The above composition, comprising an anti-oxidant, is preferred when an ethanolic solution is used in step (a).

The pharmaceutical composition of the invention can be in the form of a tablet or a capsule and is preferably in the form of a tablet.

The preferred weight of the tablet is between 50 and 250 mg, preferably between 60 and 200mg, more preferably between 70 and 150 mg. A particularly preferred weight is 130 mg.

The pharmaceutical composition of the invention can be coated with any suitable coating known in the art, preferably for example with Opadry II white.

The invention also relates to a pharmaceutical composition as described above for use as medicament, and preferably for use as medicament for the treatment or prophylaxis of diabetes type II or cardiovascular diseases.

Furthermore, the invention also relates to the use of a pharmaceutical composition as described above for the treatment or prophylaxis of diabetes type II or cardiovascular diseases.

The invention further relates to a method of treatment or prophylaxis of diabetes type II aor cardiovascular diseases comprising the step of administering a pharmaceutical composition as described above to a patient in need thereof.

Aleglitazar is particularly indicated for the reduction of cardiovascular mortality, non-fatal myocardial infarction or stroke, in particular in patients having stable coronary heart syndrome and diabetes type II.

For the preparation of the composition the following procedure can be followed.

A buffered solution is prepared, comprising of water, aleglitazar, buffer salts, binder and surfactant. Aleglitazar is preferably in the amount of 0.2 to 0.8 % (m/v). The active is preferably completely dissolved in the granulation liquid. The diluents and the disintegrant are added to a fluid bed granulator. The solution is uniformly sprayed on to the excipients to archieve granules with excellent content uniformity for these low dosage strengths and an appropiate particle size distribution (d63.2 is preferably in the range from 0.15 to 0.8 mm (mesh size through which pass 63.2% of the granules)) to avoid high potent dust exposure and obtain good flowability properties. The granulate is preferably dried afterwards in the fluid bed dryer. This is preferably followed by sieving of the resultant granules through a mesh screen to obtain the fluid bed granules (FBG). The dried granules are preferably blended with the lubricant and then pressed into tablets using conventional tablet pressing equipment. The tablets of the invention may take any appropriate shape, such as discoid, round, oval, oblong, cylindrical, triangular, hexagonal, and the like. The drug load in the kernels is ranging from 0.01 to 0.3 %, preferably from 0.05 to 0.15 %. Tablet hardness is preferably above 60 N to assure good coating and packaging properties. The tablets have preferably an oval shape to allow good swallow and handling properties. All of the tablets showed rapid disintegration (less than 300 seconds, aqueous medium, standard basket method and equipment). The pressed tablets can be film coated with a coating inducing a 4% weight increase.

The invention is illustrated hereinafter by Examples which have no limiting character.

Examples

Example 1: tablet

Aleglitazar or sodium salt thereof	0.3 mg
Disodium phosphate	1.106 mg
Sodium dihydrogen phosphate	0.037 mg
Sodium lauryl sulfate	0.625 mg
HPMC	6.25 mg
Lactose	100.43 mg
Microcrystalline cellulose	12.5 mg
Croscarmellose sodium	2.5 mg
Magnesium stearate	1.25 mg
Opadry II White	5.00 mg.

A buffered aqueous solution comprising alglitazar (0.3 % (w/v)), disodium phosphate, sodium dihydrogen phosphate, HPMC and sodium lauryl sulfate was prepared. The active was completely dissolved in the granulation liquid. Agitation was required in order to achieve complete disolution. Lactose, microcrystalline cellulose and croscarmellose sodium were added to a fluid bed granulator. The solution was uniformly sprayed (spraying rate between 180 – 220 g/min; inlet air temperature 60 to 80 °C, air pressure 2 to 4 bar, product temperature 22°C to 35°C) on to the solid excipients to archieve granules. The obtained granules hd excellent content uniformity for this low dosage strength and an appropiate particle size distribution (d63.2 is 250 µm) hereby avoiding high potent dust exposure. Moreover, the granules had good flowability properties. The granulate was dried afterwards in the fluid bed dryer. This was followed by sieving of the resultant granules through a mesh screen (2 mm sieve size, 1000 rpm rotation speed) to obtain the fluid bed granules (FBG). The dried granules were blended with the lubricant and then pressed into tablets using conventional tablet pressing equipment.

Example 2: tablet

Aleglitazar or sodium salt thereof	0.3 mg
Disodium phosphate	1.106 mg

Sodium dihydrogen phosphate	0.037 mg
Sodium lauryl sulfate	0.625 mg
Povidone	6.25 mg
Lactose	100.43 mg
Microcrystalline cellulose	12.5 mg
Croscarmellose sodium	2.5 mg
Magnesium stearate	1.25 mg
Opadry II White	5.00 mg.

The procedure described in Example 1 was repeated here with povidone instead of HPMC. The granules had content uniformity, size distribution and flowability properties similar to those of the granules of Example 1. The dried granules were blended with the lubricant and then pressed into tablets using conventional tablet pressing equipment.

Example 3: tablet

Aleglitazar	0.15 mg
Butylated Hydroxyanisole	0.0125 mg
Butylated Hydroxytoluene	0.0125 mg
Sodium lauryl sulfate	0.625 mg
Povidone	6.25 mg
Lactose	101.7 mg
Microcrystalline cellulose	12.5 mg
Croscarmellose sodium	2.5 mg
Magnesium stearate	1.25 mg
Opadry II White	5.00 mg.

An ethanolic solution comprising aleglitazar, butylated hydroxyanisole, butylated hydroxytoluene, povidone and sodium lauryl sulfate was prepared. The active was

completely dissolved in the granulation liquid. Lactose, microcrystalline cellulose and croscarmellose sodium were added to a fluid bed granulator. The solution was uniformly sprayed (200 to 400 g/min) on to the solid excipients to archieve granules. The granules had content uniformity, size distribution and flowability properties similar to those of the granules of Examples 1 and 2. The dried granules were blended with the lubricant and then pressed into tablets using conventional tablet pressing equipment.

Claims

1. Pharmaceutical composition comprising 0.01 mg to 0.9 mg of aleglitazar or a salt thereof obtainable by

   (a) spraying a solution comprising aleglitazar or a salt thereof on a diluent and a disintegrant;

   (b) mixing the composition obtained in step (a) with a lubricant; and

   (c) optionally compressing the composition obtained in step (b).

2. Pharmaceutical composition according to claim 1, wherein the solution of step (a) is an aqueous solution.

3. Pharmaceutical composition according to claim 1 or 2, wherein the solution of step (a) is buffered with a phosphate buffer.

4. Pharmaceutical composition according to any one of claims 1 to 3, wherein the diluent is selected from sugar, microcrystalline cellulose, lactose, starch and mixtures thereof.

5. Pharmaceutical composition according to any one of claims 1 to 4, wherein the solution of step (a) comprises a binder selected from povidone, HPMC and starch pregelatinized.

6. Pharmaceutical composition according to claim 5, wherein the binder is povidone.

7. Pharmaceutical composition according to any one of claims 1 to 6, wherein the solution of step (a) comprises a surfactant selected from polysorbate 80, polyoxyethylene-polyoxypropylene copolymer and sodium lauryl sulfate.

8. Pharmaceutical composition according to claim 7, wherein the surfactant is sodium lauryl sulfate.

9. Pharmaceutical composition according to any one of claims 1 to 8, wherein the disintegrant is selected from crosslinked polyvinyl pyrrolidone, starch, croscarmellose sodium, carboxymethylcellulose sodium and sodium starch glycolate.

10. Pharmaceutical composition according to claim 9, wherein the disintegrant is croscarmellose sodium.

11. Pharmaceutical composition according to any one of claims 1 to 10, wherein the lubricant is selected from stearic acid, magnesium stearate, glyceryl behenate and sodium stearyl fumarate.

12. Pharmaceutical composition according to claim 11, wherein the lubricant is magnesium stearate.

13. Pharmaceutical composition according to any one of claims 1 to 12, comprising a sodium salt of aleglitazar.

14. Pharmaceutical composition comprising:

Aleglitazar or sodium salt thereof	0.01 - 0.9 mg
Disodium phosphate	1 - 1.5 mg
Sodium dihydrogen phosphate	0.01 - 0.3 mg
Sodium lauryl sulfate	0.1 - 2 mg
Povidone	0.1 - 20 mg
Lactose	20 - 110 mg
Microcrystalline cellulose	5 - 100 mg
Croscarmellose sodium	0.5 - 20 mg
Magnesium stearate	0.5 - 3 mg.

15. Pharmaceutical composition according to any one of claims 1 to 14 in the form of a tablet.

16. Use of the pharmaceutical composition according to any one of claims 1 to 15 in the manufacture of a medicament for the treatment or prophylaxis of diabetes type II or cardiovascular diseases.

17. Process for the manufacture of a pharmaceutical composition aleglitazar or a salt thereof comprising:

(a) spraying a solution comprising aleglitazar or a salt thereof on a diluent and a disintegrant;

(b) mixing the composition obtained in step (a) with a lubricant; and

(c) optionally compressing the composition obtained in step (b).

18. Process according to claim 17, wherein the solution of step (a) is an aqueous solution.

19. Process according to claim 17 or 18, wherein the solution of step (a) is buffered with a phosphate buffer.

20. Process according to any one of claims 17 to 19, wherein the diluent is selected from sugar, microcrystalline cellulose, lactose, starch and mixtures thereof.

21. Process according to any one of claims 17 to 20, wherein the solution of step (a) comprises a binder selected from povidone, HPMC and starch pregelatinized.

22. Process according to claim 21, wherein the binder is povidone.

23. Process according to any one of claims 17 to 22, wherein the solution of step (a) comprises a surfactant selected from polysorbate 80, polyoxyethylene-polyoxypropylene copolymer and sodium lauryl sulfate.

24. Process according to claim 23, wherein the surfactant is sodium lauryl sulfate.

25. Process according to any one of claims 17 to 24, wherein the disintegrant is selected from crosslinked polyvinyl pyrrolidone, starch, croscarmellose sodium, carboxymethylcellulose sodium and sodium starch glycolate.

26. Process according to claim 25, wherein the disintegrant is croscarmellose sodium.

27. Process according to any one of claims 17 to 26, wherein the lubricant is selected from stearic acid, magnesium stearate, glyceryl behenate and sodium stearyl fumarate.

28. Process according to claim 27, wherein the lubricant is magnesium stearate.

29. Process according to any one of claims 17 to 28, comprising a sodium salt of aleglitazar.