



(51) International Patent Classification:

A61K 9/20 (2006.01) A61K 9/16 (2006.01)  
A61K 31/422 (2006.01) A61K 9/28 (2006.01)  
A61P 3/10 (2006.01)

(21) International Application Number:

PCT/EP2013/065699

(22) International Filing Date:

25 July 2013 (25.07.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

12005508.2 27 July 2012 (27.07.2012) EP  
61/676,442 27 July 2012 (27.07.2012) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: PHARMACEUTICAL FORMULATION COMPRISING ALEGLITAZAR AND COMPLEXING AGENT

(57) Abstract: The present invention relates to complexes comprising aleglitazar and complexing agent. The invention further relates to a process for producing said complexes. Finally, the invention relates to the use of a pharmaceutical formulation comprising a PPAR modulator and cyclodextrin for the treatment of diabetes.

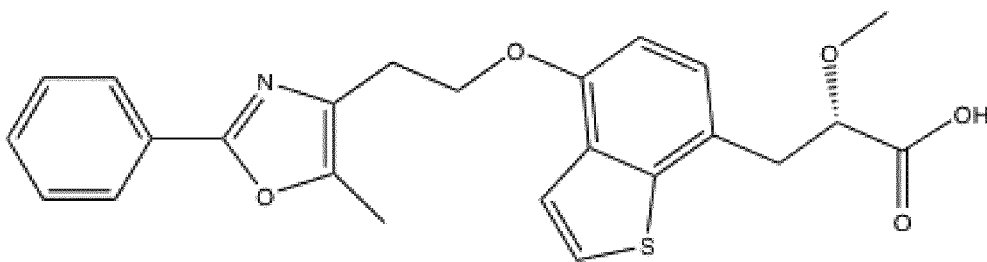


## Pharmaceutical Formulation Comprising Aleglitazar and Complexing Agent

## Background of the invention

The present invention relates to pharmaceutical formulations comprising aleglitazar and complexing agent. The invention further relates to a process for producing said pharmaceutical formulations. Finally, the invention relates to the use of a pharmaceutical formulation comprising a PPAR modulator and cyclodextrin for the treatment of diabetes.

"Aleglitazar" is reported to be the INN name of (S)-2-methoxy-3-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzo[b]thiophen-7-yl]propionic acid and can be characterized by the following chemical formula (I):



formula (I)

In US 2007/0249842 A1 the synthesis of the compound aleglitazar is described in detail.

Aleglitazar is reported to belong to the class of Peroxisome Proliferator-Activated Receptor agonist (hence a PPAR modulator). In the field of molecular biology PPARs are a group of nuclear receptor proteins. The function of this group is to work as transcription factors, regulating the expression of genes. Since there are various types of PPARs, PPAR $\alpha$ , PPAR $\beta$  and PPAR $\gamma$ , they can play different roles in the regulation of cellular differentiation, development and metabolism and tumorigenesis.

Aleglitazar can show affinity to PPAR $\alpha$  as well as to PPAR $\gamma$ . Thus, it may combine the advantageous effects of a PPAR $\alpha$ -activation (for example increasing HDL, lowering LDL and triglycerides, lipoproteins) with the advantageous effects of PPAR $\gamma$ -activation (for example the insulin resistance and glucose levels are decreased). Due to its positive therapeutic effects to multiple symptoms, aleglitazar can be a medical drug.

Aleglitazar, for example aleglitazar-sodium, may form primary pin-like particles of 1 to 5  $\mu\text{m}$ . However, these primary particles tap into agglomerates of over 100  $\mu\text{m}$ . These resulting agglomerates are reported to involve some difficulties in view to their processability. For example, the flowability of aleglitazar agglomerates and/or pharmaceutical formulations containing the respective aleglitazar agglomerates may be improved, especially when prepared in a large scale.

In the art a spray granulation process is proposed in order to overcome the illustrated drawbacks and to provide a suitable pharmaceutical formulation. Reference is made to WO 2010/084066. However, said process is regarded to be still improvable, in particular in view of processability and content uniformity, especially if the ideal process conditions are not exactly met.

Hence, it was an object of the present invention to overcome the drawbacks of the prior art formulations.

In particular, it was an object of the invention to provide an aleglitazar formulation which can be advantageously produced even in larger scale. The formulations should show advantageous processability (e.g. superior flowability).

Further, the resulting dosage form should have advantageous content uniformity.

Moreover, the use of time and cost consuming processes, such as spray granulation, should be avoided and a reliable process without the need of a complex and cost consuming preparation should be provided.

Moreover, it was an object of the invention to provide aleglitazar in a form having superior storage properties.

5 In addition, aleglitazar should be provided in a form, which allows oral application.

#### Summary of the invention

10 According to the present invention, the above objectives can be achieved by complexing aleglitazar. More specific, that a composition comprising aleglitazar and complexing agent possesses desirable properties and overcomes the drawbacks of the prior art. The aleglitazar composition of the present invention preferably is present in form of a complex and can be used to be processed in pharmaceutical formulations. Furthermore the above drawbacks can be overcome by a process for  
15 producing said composition comprising dissolving or suspending aleglitazar and complexing agent in a solvent and isolating the resulting aleglitazar composition, preferably the aleglitazar complex.

20 Preferably, said complex can be regarded as a supramolecular, non-covalent inclusion complex.

The aleglitazar/complexing agent composition can lead to a novel solid form of aleglitazar, preferably to a form of molecular dispersity.

25 A subject of the present invention is a composition comprising aleglitazar (a) and complexing agent (b). Generally, the term “a complexing agent” can refer to one or more complexing agent(s) and mixtures thereof.

30 A further subject of the present invention is a pharmaceutical formulation comprising (a) aleglitazar and (b) a complexing agent and optionally one or more excipient(s) (c).

It was found that the pharmaceutical formulation of the present invention can exhibit a greatly enhanced content uniformity. The superior content uniformity of the pharmaceutical formulation of the present invention can ensure that the appropriate dose can be applied to the patient.

5

Even further, it was found that the composition and the pharmaceutical formulation of the present invention can be very stable over a long time period. This is important since aleglitazar is applied in low doses, even little degradation of the drug can lower its beneficial effects.

10

Additionally, the composition of the invention provides for an easier as well as a less time and labour consuming handling of the corresponding pharmaceutical formulation, e.g. when processed into a dosage form.

15 Another subject of the present invention is a process for producing an aleglitazar/complexing agent composition comprising the steps of dissolving or suspending aleglitazar (a) and complexing agent (b) in a solvent and isolating the resulting aleglitazar complex.

20 Further the subject-matter of the present invention relates to a process of producing a pharmaceutical formulation comprising the steps:

- i) dissolving (a), (b) and optionally further excipient(s) (c),
- ii) homogenizing the solution,
- 25 iii) optionally mixing the solution with further excipient(s) (c) and optionally granulating the mixture,
- iv) removing solvent from the solution of (ii) or the mixture of (iii),
- v) optionally adding further excipient(s) (c) to the mixture of step iv),
- vi) optionally processing the mixture of step v) to a solid oral dosage
- 30 form.

Another subject of the present invention is a pharmaceutical formulation comprising a PPAR modulator, preferably a dual acting PPAR modulator (i.e. a modulator having affinity to PPAR $\alpha$  as well as to PPAR $\gamma$ ), in particular, aleglitazar, and cyclodextrin for the treatment of diabetes, preferably diabetes type

- 5 II. The pharmaceutical formulation or the oral dosage form of the present invention can be used as a PPAR agonist in a method for treating metabolic diseases, such as diabetes and hypercholesterolemia, said method comprises administering an effective amount of the pharmaceutical formulation or the oral dosage form in a subject in need thereof.

10

The above-illustrated subjects of the present invention are alternative solutions to the above-outlined problems.

#### Detailed Description of the Invention

15

The term “aleglitazar“ as used in the present application can refer to aleglitazar in the form of the free acid as well as to its pharmaceutically acceptable salts, solvates, hydrates, polymorphs and mixtures thereof. The pharmaceutically acceptable salts can be maintained by reaction, preferably with an inorganic base.

- 20 Thereby, the carboxylic acid hydrogen atom of aleglitazar can be replaced with a metal atom, for example an alkali metal atom. In a preferred embodiment the aleglitazar is used in the form of its sodium salt.

- 25 In a particularly preferred embodiment the pharmaceutical formulation of the present invention comprises aleglitazar as the sole pharmaceutical active agent. In an alternative embodiment the pharmaceutical formulation of the invention can comprise aleglitazar in combination with further pharmaceutical active agent(s).

- 30 In a preferred embodiment of the present invention aleglitazar and the complexing agent form a complex, preferably an inclusion complex. For this purpose the entire and complete amount of aleglitazar is entrapped or intercalated into the molecular cavities of a complexing agent, i.e. aleglitazar is only present in modified or

complexed form. The formation of the inclusion complex generally can lead to a glassy-amorphous solid form of aleglitazar.

Preferably, the inclusion complexes of the present invention can be non-covalent inclusion complexes. Furthermore, preferably the inclusion complexes of the present invention can be supramolecular inclusion complexes. In particular, all inclusion complexes of the present invention can be non-covalent and supramolecular inclusion complexes. The term "supramolecular" is understood as describing self-organizing molecular interactions that result in the formation of new structures that stay together without establishing a covalent linkage.

In another preferred embodiment of the invention, the complexing agent (b) can be not nitrogenous. Nitrogenous complexing agents may cause ionic linkages between aleglitazar and the complexing agent. These may have undesirable effects for the aleglitazar complex, for example the drug is not or not fully released from the surrounding cavity of the complexing agent and therefore (partially) washed out of the body without showing any beneficial effect.

In a preferred embodiment of the invention, the complexing agent has a water-solubility at 25°C of 15 to 1000 mg/ml, preferably 50 to 800 mg/ml and more preferably 100 to 650 mg/ml. The water-solubility can be determined according to the column elution method of the Dangerous Substances Directive (67/548/EEC), Annex V, chapter A6.

In a further preferred embodiment of the invention the complexing agent (b) can have a molecular weight of less than 3000 g/mol. The complexing agent can exhibit a certain cavity to form complexes with aleglitazar, preferably inclusion complexes with aleglitazar. Thus, the complexing agent can be an extensive molecule with a respective molecular weight. It is still preferred that the complexing agent can have a known and explicit molecular weight in order to be able to define a definite molecular ratio between aleglitazar and the complexing agent.

In a preferred embodiment of the invention the molecular ratio of aleglitazar (a) to complexing agent (b) can be from 5:1 to 1:20 preferably from 3:1 to 1:15, more preferably from 2:1 to 1:5, most preferably from 1:1 to 1:3.

- 5 Generally, the composition and the pharmaceutical formulation of the present invention comprising (a) aleglitazar and (b) complexing agent can be achieved if the molecular ratio of aleglitazar (a) to complexing agent (b) is as mentioned above. For a further preferred embodiment aleglitazar (a) and the complexing agent (b) may form an inclusion complex, in which the molar ratio of aleglitazar to  
10 complexing agent is from 3:1 to 1:5, preferably from 2:1 to 1:4 and more preferably from 1:1 to 1:3.

- In a preferred embodiment of the present invention the complexing agent (b) can be a cyclodextrin. The cyclodextrin can be a naturally occurring cyclodextrin or a  
15 chemically modified cyclodextrin. Preferably the cyclodextrin is selected from  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, 2-hydroxypropyl- $\beta$ -cyclodextrin, randomly methylated  $\beta$ -cyclodextrin, sulfobutylether- $\beta$ -cyclodextrin,  $\gamma$ -cyclodextrin and 2-hydroxypropyl- $\gamma$ -cyclodextrin.

- 20 The term "sulfobutylether- $\beta$ -cyclodextrin" as used in the present application can refer to sulfobutylether- $\beta$ -cyclodextrin as well as to the sodium salt of sulfobutylether- $\beta$ -cyclodextrin.

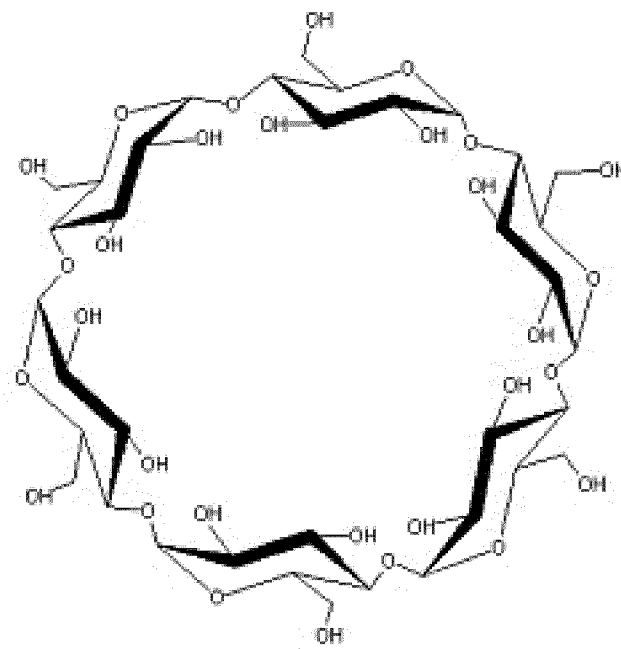
- In a more preferred embodiment the cyclodextrin is a  $\beta$ -cyclodextrin, especially  
25 sulfobutylether- $\beta$ -cyclodextrin (SBECD) and 2-hydroxypropyl- $\beta$ -cyclodextrin (HPBCD).

In an alternative preferred embodiment the cyclodextrin is  $\gamma$ -cyclodextrin.

- 30 The term "cyclodextrin" may refer to non-reducing cyclic saccharides. Preferably, said cyclic saccharides comprise six, seven or eight glucose units, linked by alpha-

1,4 interglycosidic bonds. In the present invention cyclodextrins comprising seven or eight glucopyranose units (cyclooctaamylose) are preferred.

In preferred embodiment of the present invention an aleglitazar composition, preferably an aleglitazar inclusion complex, can be achieved by the use of  $\alpha$ -cyclodextrin, preferably  $\alpha$ -cyclodextrin hydrate.  $\alpha$ -cyclodextrin is a ring-shaped molecule, made up of six glucose units and linked by alpha-1,4 bonds.  $\alpha$ -cyclodextrin can be characterized by the following chemical formula (II):

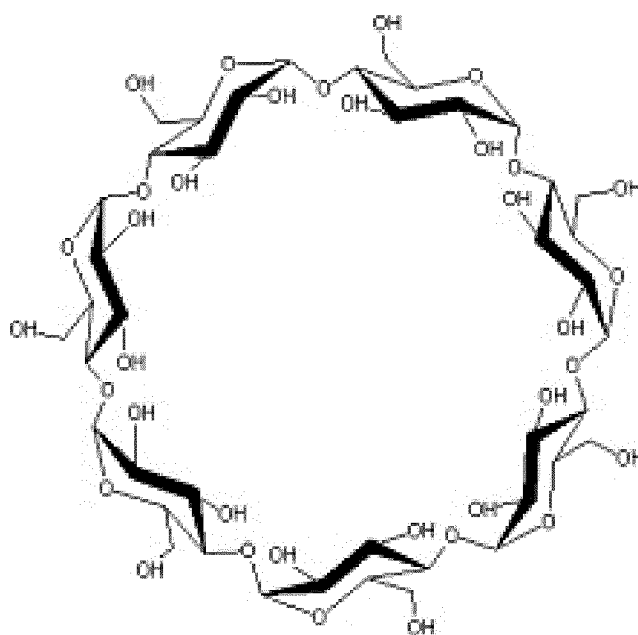


formula (II)

In a more preferred embodiment of the present invention an aleglitazar composition, preferably an aleglitazar inclusion complex, can be achieved by the use of  $\beta$ -cyclodextrin, preferably sulfobutylether- $\beta$ -cyclodextrin (SBECD) and 2-hydroxypropyl- $\beta$ -cyclodextrin (HPBCD). Sulfobutylether- $\beta$ -cyclodextrin (SBECD) is a ring-shaped molecule made up of seven glucose units linked by alpha-1,4 bonds, wherein 6 to 7 of the hydroxy groups are sulfobutylated. 2-hydroxypropyl- $\beta$ -cyclodextrin (HPBCD) is also a ring-shaped molecule made up of seven glucose

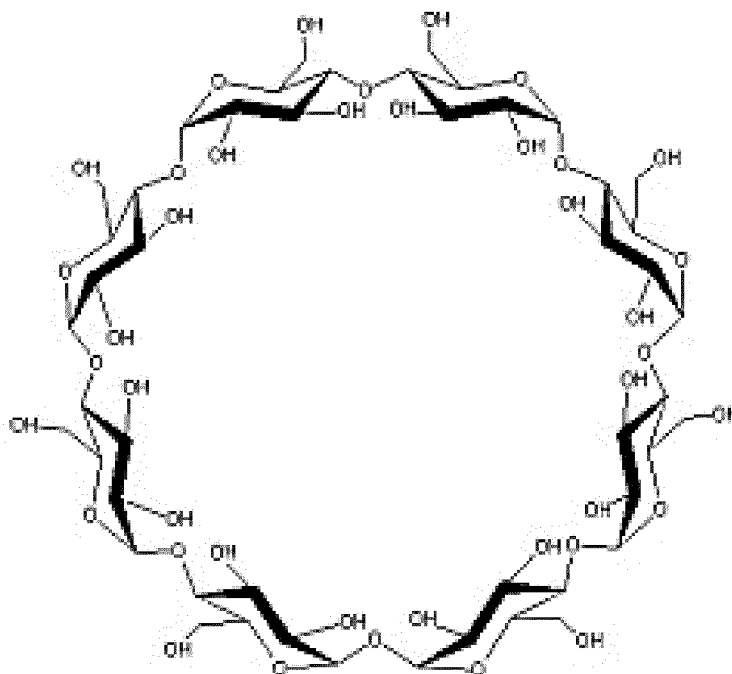
units linked by alpha-1,4 bonds, wherein 4 to 5 of the hydroxy groups are 2-hydroxypropylated.

Unsubstituted  $\beta$ -cyclodextrin can be characterized by the following chemical  
5 formula (III):



formula (III)

In an alternative preferred embodiment of the present invention an aleglitazar  
10 composition, preferably an aleglitazar inclusion complex, can be achieved by the use of  $\gamma$ -cyclodextrin.  $\gamma$ -cyclodextrin is a ring-shaped molecule, made up of eight glucose units, linked by alpha-1,4 bonds.  $\gamma$ -cyclodextrin can be characterized by the following chemical formula (IV):



formula (IV)

The term " $\gamma$ -cyclodextrin" preferably refers to a "non-substituted form" (as shown  
5 in the above formula). This means, the  $\gamma$ -cyclodextrin preferably is not chemically modified, i.e. neither alkylated nor hydroxyl-alkylated.

In a preferred embodiment an aleglitazar/cyclodextrin composition can have a bulk  
density of from 100 to 900 mg/cm<sup>3</sup>, preferably from 120 to 800 mg/cm<sup>3</sup>, more  
10 preferably from 140 to 700 mg/cm<sup>3</sup>, especially from 150 to 600 mg/cm<sup>3</sup>.

Furthermore, it is particularly preferred that cyclodextrins are used in the form of  
cyclodextrin hydrate, particularly  $\gamma$ -cyclodextrin can be used in the form of  $\gamma$ -  
cyclodextrin hydrate.

15

Furthermore, as mentioned above, the  $\gamma$ -cyclodextrin can preferably be used in the  
form of a crystalline hydrate. Generally,  $\gamma$ -cyclodextrins can exist in two main  
classes of crystal structures, namely the cage and tubular (or columnar) structure.  
In the cage structure (often called also a "HERRING BONE arrangement"), the

cyclodextrin cavities are not aligned. Contrary, in the tubular structure,  $\gamma$ -cyclodextrin monomers stick to each other on their top, forming a cylindrical multi-molecular channel, where, for example, slim but long molecules (for example linear polymers) could fit in and form a stable complex. In the present  
5 invention it is preferred that  $\gamma$ -cyclodextrin having a cage structure can be used.

Furthermore, it is preferred that  $\gamma$ -cyclodextrin can be used in the form of a hydrate, wherein each molecule of  $\gamma$ -cyclodextrin comprises between 12 and 14 molecules of water. In addition, crystalline  $\gamma$ -cyclodextrin having a monoclinic  
10 space group can be used.

Moreover, preferably  $\gamma$ -cyclodextrin having a bulk density of from 400 to 700 mg/cm<sup>3</sup> is used. The bulk density and tapped density can be determined according to Ph.Eur. 6.0, in particular chapter 2.9.15  
15

Generally, cyclodextrins can form an inner cavity. Within this application said cavity is referred to as "nanocavity".

Further preferred cyclodextrins for an inclusion complex of aleglitazar are  
20 sulfobutylether- $\beta$ -cyclodextrin (SBECD) and 2-hydroxypropyl- $\beta$ -cyclodextrin (HPBCD). In case the inclusion complex is obtained with one of said substituted  $\beta$ -cyclodextrins the carboxylic group and the other oxygen atoms of the guest molecule, aleglitazar, are considered to form H-bonds on the rim of the cyclodextrin. Thus, the guest molecule, aleglitazar, is fully penetrating into the  
25 cavity substantially filling the space of the cavity.

Since the aleglitazar can preferably be completely included into the cavity, the cyclodextrin „shell“ can prevent the aleglitazar from negative environmental influences, as for example ultraviolet radiation and oxygen. Therefore, the stability  
30 of the aleglitazar in the complex can be increased.

An aleglitazar-cyclodextrin inclusion complex can be preferably characterized by the complete inclusion of the aleglitazar molecule into the nanocavity of the cyclodextrin(s). The completeness of the inclusion process can be monitored via XRD. In a preferred embodiment of the invention the completeness of said inclusion process can be determined by the absence of the characteristic signals of crystalline aleglitazar in the XRD-spectroscopy. Consequently, aleglitazar being present in said inclusion complex can preferably be regarded as a novel solid form of aleglitazar, namely in form of non-crystalline aleglitazar or in form of a solid molecular dispersion.

The average particle size of cyclodextrin aleglitazar inclusion complexes, preferably of the sulfobutylether- $\beta$ -cyclodextrin (SBECD), 2-hydroxypropyl- $\beta$ -cyclodextrin (HPBCD) and  $\gamma$ -cyclodextrin aleglitazar inclusion complexes, can be between 2 and 100  $\mu\text{m}$ , preferably between 5 and 25  $\mu\text{m}$  and particularly between 6 and 15  $\mu\text{m}$ .

The term "average particle size" can refer to the D50 value of the particle size distribution, which is determined by the light scattering method, using a Mastersizer 2000 apparatus made by Malvern Instruments (wet measurement, 2000 rpm, ultrasonic waves for 60 sec., data interpretation via Fraunhofer method).

The volume mean particle size (D50), which is also denoted D50 value of the integral volume distribution, is defined in the context of this invention as the particle diameter, at which 50 percent by volume of the particles have a smaller diameter than the diameter which corresponds to the D50 value. Likewise, 50 percent by volume of the particles have a larger diameter than the D50 value. Analogous, the D90 value of the integral volume distribution is defined as the particle diameter, at which 90 percent by volume of the particles have a smaller diameter than the diameter which corresponds to the D90 value. Correspondingly, the D10 value of the integral volume distribution is defined as the particle diameter, at which 10 percent by volume of the particles have a smaller diameter than the diameter which corresponds to the D10 value.

Furthermore, the cyclodextrin aleglitazar inclusion complexes can preferably be provided in a solid, particulate form, having a bulk density of 450 to 900 mg/cm<sup>3</sup>.

5 The aleglitazar inclusion complexes can preferably be regarded as a glassy-amorphous solid phase of aleglitazar. The glassy-amorphous solid phase of aleglitazar, re-wetted in an aqueous system, preferably can show some liquid crystalline properties that remind of the lyotropic liquid crystalline material.

10 When viewed under a polarized light, different liquid crystal phases can appear, having a distinct Schlieren Texture. The contrasting areas in the texture each correspond to a domain, where the liquid crystalline molecules are oriented in a different direction. Within a domain, however, the molecules can be well-ordered. The polarized light microscopic photos taken from e.g. the aleglitazar/ $\gamma$ -cyclodextrin complex of this invention can clearly indicate the specific, liquid  
15 crystalline-like mesophase texture.

In a preferred embodiment the pharmaceutical formulation can comprise the composition of the invention.

20 In another preferred embodiment of the present invention the pharmaceutical formulation can further comprise one or more excipients(s) (c), selected from surfactants (c1), wicking agents (c2), fillers (c3), binders (c4), disintegrants (c5), lubricants (c6), glidants (c7) and plasticizers (c8).

25 Surfactants (c1) can be regarded as substances lowering the interfacial tension between two phases, thus enabling or supporting the formation of dispersions or working as a solubilizer. Common surfactants are alkylsulfates (for example sodium lauryl sulfate), alkyltrimethylammonium salts, alcohol ethoxylates and the like. Surfactants can be used in an amount of 0.05 to 2 % by weight, preferably of  
30 0.1 to 1.5 % by weight, based on the total weight of the pharmaceutical formulation.

Wicking agents (c2) can be regarded as substances with the ability to draw a biological fluid (preferably water) into a solid, preferably by physisorption. Physisorption is defined as a form of adsorption, in which the solvent molecules can loosely adhere to the surfaces of the wicking agent, preferably via van der Waals interaction between the surface of the wicking agent and the adsorbed fluid molecule (preferably water). Usually, a wicking agent can do this with or without swelling. Preferably, the wicking agent is a swelling wicking agent. Usually, a non-swelling wicking agent that attracts water will ultimately have a volume that is essentially composed of the volume of the wicking agent and the volume of water attracted to it. Usually, a swelling wicking agent will have a volume that is essentially composed of the volume of the wicking agent, the volume of water attracted to it, and an additional volume created by steric and molecular forces. For example, microcrystalline cellulose can be used as wicking agent. Wicking agents (c2) can be used in an amount of 0.1 to 40% by weight, based on the total weight of the pharmaceutical formulation.

Fillers (c3) or diluents can be used to increase the bulk volume and weight of a low-dose drug to a limit, at which a pharmaceutical dosage is formed. Fillers should fulfil several requirements, such as being chemically inert, non-hygroscopic, biocompatible, being easily processable and possessing good biopharmaceutical properties. Examples of fillers are lactose, sucrose, glucose, mannitol, calcium carbonate, cellulose and others. Fillers (c3) can be used in an amount of 0.1 to 60% by weight, based on the total weight of the pharmaceutical formulation.

Binders (c4) may be added to the pharmaceutical formulation in order to ensure that oral dosage forms, preferably tablets, can be formed with the required mechanical strength. The binder can, for example, be starch, polyvinyl pyrrolidone or cellulose derivatives. The binding agent can be present in an amount of 0 to 40 % by weight, based on the total weight of the pharmaceutical formulation.

Disintegrants (c5) are compounds, which enhance the ability of the dosage form, preferably the ability of the tablet when in contact with a liquid, preferably water,

to break into smaller fragments. Preferred disintegrants are sodium carboxymethyl starch, cross-linked polyvinyl pyrrolidone (crospovidone), sodium carboxymethyl glycolate (for example Explotab<sup>®</sup>), swelling polysaccharide, for example soy polysaccharide, carrageenan, agar, pectin, starch and derivatives thereof, protein, for example formaldehyde-casein, sodium bicarbonate or mixtures thereof. Disintegrants can be used in an amount of 0 to 20% by weight, preferably of 1 to 10 % by weight, based on the total weight of the pharmaceutical formulation.

The function of lubricants (c6) is reported to ensure that tablet formation and ejection can occur with low friction between the solid and the die wall. The lubricant is preferably a stearate or fatty acid, more preferably an earth alkali metal stearate, such as magnesium stearate. The lubricant is suitably present in an amount of 0 to 2 % by weight, preferably of about 0.1 to 1.0% by weight, based on the total weight of the pharmaceutical formulation. Lubricants can generally increase the powder flowability.

Glidants (c7) can also be used to improve the flowability. Traditionally, talc was used as glidant, but is nowadays nearly fully replaced by colloidal silica (for example Aerosil<sup>®</sup>). Preferably, the glidant agent is present in an amount of up to 3 % by weight, based on the total weight of the pharmaceutical formulation. Preferably, the silica has a specific surface area of 50 to 400 m<sup>2</sup>/g, measured by gas adsorption according to Ph. Eur. 6.0, chapter 2.9.26, multipoint method, volumetric determination.

Plasticizers (c8) usually are reported to be compounds capable of lowering the glass transition temperature ( $T_g$ ) of a non-erodible material, preferably of lowering  $T_g$  from 1 to 50 °C. Plasticizers (c8) usually are low molecular weight compounds (having a molecular weight of 50 to 500 g/mol) and can comprise at least one hydrophilic group. Examples of suitable plasticizers are dibutyl sebacetate (DBS), Myvacet<sup>®</sup> (acetylated monoglycerides), triacetin (GTA), citric acid esters, like acetyltriethyl citrate (ATEC) or triethyl citrate (TEC), propylene glycol, dibutyl phthalate, diethyl phthalate, or mixtures thereof.

Regarding the above-mentioned pharmaceutically acceptable excipients, the application refers to “Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete”, edited by H. P. Fiedler, 4<sup>th</sup> Edition, Editio Cantor, Aulendorf and earlier editions, and “Handbook of Pharmaceutical Excipients”,  
5 Third Edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

In this regard it is generally noted that due to the nature of pharmaceutical excipients it cannot be excluded that a certain compound meets the requirements  
10 of more than one of the components (b) and (c1) to (c8). For example, in the present pharmaceutical formulation microcrystalline cellulose may act both as wicking agent and as filler. However, in order to enable an unambiguous distinction, it is preferred in the present application that one and the same pharmaceutical compound can only function as one of the compounds (b) or (c1)  
15 to (c8). For example, if cyclodextrin functions as complexing agent (b), it cannot additionally function as filler (c3).

In a still further embodiment of the present invention the pharmaceutical formulation can be a solid oral dosage form, preferably a tablet.

20

The present invention further can relate to a process for producing an aleglitazar composition comprising the steps suspending or dissolving, preferably completely dissolving, aleglitazar (a) and a complexing agent (b) in a solvent and isolating the resulting aleglitazar complex. In a preferred embodiment one or more  
25 pharmaceutical excipient(s) (c) may also be dissolved in the above-mentioned solvent.

In a first step of the above-mentioned process, aleglitazar (a) and complexing agent (b) can be partly or completely, preferably completely, dissolved in a  
30 solvent. The solvent may be water or an organic solvent or a mixture thereof. Generally, suitable organic solvents might be selected from C<sub>3</sub>-C<sub>6</sub> ketone, a C<sub>5</sub>-C<sub>9</sub> aliphatic or aromatic hydrocarbon, optionally substituted for example with

halogen, a C<sub>3</sub>-C<sub>6</sub> ester, a C<sub>2</sub>-C<sub>6</sub> alcohol, C<sub>2</sub>-C<sub>6</sub> ether, DMAc, DMSO, NMP and mixtures thereof.

5 In a preferred embodiment the organic solvent is an alcohol, preferably a C<sub>2</sub>-C<sub>6</sub> alcohol, still more preferably ethanol and isopropyl alcohol. Ethanol is particularly preferred.

Generally, the organic solvent can comprise mixtures of two or more of the above - mentioned solvents.

10

In a preferred embodiment the solvent can be a mixture of alcohol and water, wherein the mixing ratio alcohol to water is for example from 1:5 to 5:1.

Following the first step, the solution/suspension may preferably be homogenized.

15

During homogenization the aleglitazar/complexing agent composition, preferably the complex, may be formed. Afterwards the composition, preferably the complex, can be isolated, preferably by drying the complex to remove the residual solvent.

In a preferred embodiment of the present invention the process for producing a pharmaceutical formulation can comprise the steps of

20

- i) dissolving aleglitazar (a) and complexing agent (b) and further optionally excipient(s) (c), for example (c1), in a solvent,
- ii) homogenizing the solution,
- iii) optionally adding an excipient (c), for example (c2), to the solution,
- 25 iv) drying the resulting mixture,
- v) optionally adding further excipient(s) (c) to the mixture of step iv), and
- vi) optionally processing the mixture of step v) into an oral pharmaceutical dosage form.

30

In step i) aleglitazar (a) and complexing agent (b) and optionally further excipient(s) (c), preferably an optional surfactant (c1), preferably sodium laurylsulfate, can be partly or completely, preferably completely, dissolved in a

suitable solvent. The solvent may be water or an organic solvent as mentioned above. In a preferred embodiment the organic solvent is an alcohol, preferably a C<sub>2</sub>-C<sub>6</sub> alcohol, still more preferably ethanol and isopropyl alcohol. Ethanol is particularly preferred.

5

Generally, the organic solvent can comprise mixtures of two or more of the above - mentioned solvents.

10

In a preferred embodiment the solvent can be a mixture of alcohol and water, wherein the mixing ratio alcohol to water is for example from 1:5 to 5:1.

15

Step ii), i.e. homogenizing the solution of step i), can preferably be carried out by stirring the solution. To this end, suitable stirring units with low energetic forces, e.g. magnetic stirrer or paddle stirrer (R1001 by IKA<sup>®</sup>) or high mixing forces, for example ultra turrax<sup>®</sup> by IKA<sup>®</sup>, can be used.

20

In another preferred embodiment of the invention, step ii), homogenizing the solution of step i), can comprise ultrasonic treatment, optionally combined with stirring.

25

Generally, ultrasonic treatment can be carried out by immersing the mixture resulting from step i) into an ultrasonic device, for example an ultrasonic bath. Examples of ultrasonic-treatment are hydrodynamic cavitation, sono-fragmentation and/or sono-cavitation or co-grinding. For example, ultrasonic treatment can be carried out with Tesla ultrasonic equipment.

30

Ultrasonic treatment can preferably be performed by using ultrasonic waves having a frequency of 5 to 100 kHz, more preferably of 10 to 80 kHz. Furthermore, ultrasonic treatment can preferably be performed by using ultrasonic waves having an intensity of 50 to 5000 W, more preferably 500 to 1000 W. As an example, 1000 W and 20 kHz or 500 W and 58 kHz can be used.

In addition to the ultrasonic treatment (for example hydrodynamic cavitation, sono-fragmentation or sonocavitation), the reaction mixture may be agitated (for example by using traditional propeller stirrer), preferably with a rotation speed of 300 to 450 rpm (rotation per minute).

5

Preferably, the aleglitazar complex, in particular the aleglitazar inclusion complex, can be formed while homogenizing the solution.

10 In optional step iii) the homogenized solution of step ii) can optionally be mixed with further excipient(s) (c), for example with a wicking agent (c2), preferably microcrystalline cellulose.

15 Preferably, a wetted mass is formed, wherein particles are attached to each other, thereby forming larger particles. The attachments may occur through physical forces, preferably van der Waals forces. The attachment of particles preferably does not occur through chemical reactions. The wetted mass can preferably be granulated by kneading it in a mixer, preferably in a fluid or intensive mixer or in a planetary compulsory mixer and then brought into the desired particle form and

20

In step iv) the residual solvent can be removed from the solution of step ii) or the optional mixture of step iii). The removal of the solvent can be conducted under elevated temperature and/or under reduced pressure. In a preferred embodiment the solvent is removed at a temperature of between 30 and 90 °C, preferably between 25 35 and 75°C, more preferably between 40 and 60 °C. The solvent can preferably be removed at a pressure from 0.01 to 900 mbar, preferably from 1 to 200 mbar, more preferably from 5 to 100 mbar, still more preferably from 10 to 50 mbar, in particular from 30 to 40 mbar. At laboratory scale the duration of step iv) may range from 0.5 to 2.0 hours, preferably about 90 minutes. The removal of the 30 solvent can be, for example, carried out in a vacuum rotary evaporator, for example a Büchi® Rotavapor.

The resulting mixture, preferably granulates, can be dried. For drying the mixture, common dryers can be used, preferably a drying chamber, more preferably a drying chamber at 30 °C.

- 5 Step v) can optionally comprise adding further excipient(s) (c) to the mixture of step iv). In a preferred embodiment of the invention a filler (c3), a disintegrant (c5) and/or a lubricant (c6) can be added. The filler (c3), preferably lactose, can be an inert volume-enhancing compound. The disintegrant (c5), preferably cross-linked PVP, can ensure the break-up of the dosage form or the pharmaceutical
- 10 formulation into smaller pieces, when coming into contact with a liquid, preferably water. The lubricant (c6), preferably magnesium stearate, can be employed to reduce dynamic friction. Preferably, while adding the excipient(s) (c), the mixture of step iv) can be blended.
- 15 Step vi) of optionally processing the mixture of step v) to a solid oral dosage form can preferably comprise manufacturing the formulation into tablets or filling the formulation into capsules, preferably hard gelatine capsules.

Optionally, manufacturing the formulation into tablets can preferably be carried

20 out by compressing said formulation on a rotary press, e.g. on a Fette<sup>®</sup> (Fette GmbH, Germany) or a Riva<sup>®</sup> piccola (Riva, Argentina). If a rotary press is applied, the main compression force can range from 1 to 50 kN, preferably 3 to 40 kN. In a further preferred embodiment a coating, such as a film coating, can be applied to the tablet.

25

The resulting tablets can preferably have a hardness of 30 to 400 N, more preferred of 50 to 250 N, wherein the hardness can be measured according to Ph.Eur. 6.0, Chapter 2.9.8.

- 30 In addition, the resulting tablets can preferably have a friability of less than 5 %, particularly preferably less than 2 %, especially less than 1 %. The friability can be

determined in accordance with Ph. Eur. 6.0, chapter 2.9.7. The friability of tablets generally refers to tablets without coating.

For the optional filling of the formulation into capsules, preferably into hard  
5 gelatine capsules, dependent dosing systems (for example an auger) or preferably independent dosing systems (for example MG2, Matic (IMA)) can be used.

In a further preferred embodiment the dosage form, the oral dosage form preferably can have a content uniformity wherein the acceptance value is at most  
10 15, preferably 0.1 - 10, more preferably 1 - 7.5, in particular at most 2 - 6.5. The acceptance value of the content uniformity is determined by assaying 10 individual dosage forms and calculating the corresponding acceptance value in accordance with Ph.Eur., 5.3, Chapter 2.9.40.

15 Generally, it is noted that all comments made above with respect to the pharmaceutical formulation of the present invention also apply to the process of manufacturing such a pharmaceutical formulation.

Another preferred embodiment of the invention can relate to a pharmaceutical  
20 formulation comprising a PPAR modulator, preferably a dual acting PPAR modulator, in particular, aleglitazar and cyclodextrin for the treatment of diabetes mellitus type II. The pharmaceutical formulation or the oral dosage form of the present invention can be used as a PPAR agonist in a method for treating metabolic diseases, such as diabetes and hypercholesterolemia, said method  
25 comprising administering an effective amount of the pharmaceutical composition or the oral dosage form to a subject in need thereof.

In a further embodiment of the present invention the subject pharmaceutical formulation can be used in the treatment of diabetes mellitus type II of patients  
30 with LDL values of more than 100 mg/ml, preferably 150 to 300 mg/ml.

Normally, the LDL-value is not determined directly but is calculated by the following formula:

$$\text{LDL(cholesterol) g} = \text{total(cholesterol)} - \text{HDL(cholesterol)} - \text{triglyceride}/5$$

5

For the determination of total(cholesterol), HDL(cholesterol) and triglyceride the taking of a blood sample from a fasting person, preferably from a person fasting since 12- 16 hours, is unavoidable. Afterwards the sample can be searched for example by chromatography.

10

Generally, the comments given above about preferred embodiments of the aleglitazar/cyclodextrin compositions also apply to the pharmaceutical formulation of the present invention.

15 The present invention is illustrated by the following examples.

## EXAMPLES

### Example 1: Preparation of the aleglitazar-sodium/ HPBCD composition

20

12.6 g HPBCD (calculated on dry basis) was dissolved in 40 ml purified water. After the addition of 0.24 g aleglitazar-sodium the resulting suspension was stirred at 23° until a homogenous solution was obtained. The solution was filtered through a membrane of 0.22 µm nominal pore size. The filtered liquid was chilled and  
25 lyophilized in bulk and the resulting solid material was ground and sieved.

The resulting composition has a bulk density of 0.19 g/cm<sup>-3</sup> and comprises

|    |                     |                                                |
|----|---------------------|------------------------------------------------|
| 30 | Aleglitazar-sodium: | 1.85% (as it is) determined by UV-spectrometry |
|    | Residual water:     | 4.9 % determined by Karl-Fischer titration     |
|    | HPBCD:              | 93.3%                                          |

**Example 1a**

8.10 g Aleglitazar-sodium/ HPBCD composition according to Example 1 and 0.30 g sodium lauryl sulfate were blended together with 30.00 g of lactose monohydrate in a Turbula® T10B shaker mixer for 15 minutes. After addition of 10.00 g of lactose monohydrate the mixture were blended again for 15 minutes. Afterwards further 10.00 g of lactose monohydrate were given to the mixture and blending was continued for 15 minutes. Subsequently the blend was sieved over a sieve with a mesh size of 125 µm. Then 6.50 g microcrystalline cellulose and 4.50 g sodium croscarmellose were added to the mixture. A further blending in a Turbula® T10B shaker mixer was carried out for 10 minutes. After addition of 0.60 g magnesium stearate blending was continued for 3 minutes. The final blend was compressed on a rotary press Riva Piccola into 5 mm biconvex tablets, each containing

15

Aleglitazar-sodium/ HPBCD composition

according to Example 1

8.10 mg (11.57%)

Lactose monohydrate

50.00 mg (71.43%)

Sodium lauryl sulfate

0.30 mg (0.43%)

20 Microcrystalline cellulose

6.50 mg (9.29%)

Sodium croscarmellose

4.50 mg (6.43%)

Magnesium stearate

0.60 mg (0.86%)

**Example 1b**

25

8.69 g Aleglitazar-sodium/ HPBCD composition according to Example 1, 0.30 g sodium lauryl sulfate and 20.00 g Prosolv SMCC 90 were blended in a Turbula® T10B shaker mixer for 15 minutes. After the addition of 48.9 g Prosolv SMCC 90 the mixture was blended again for 15 minutes. Afterwards further 48.9 g of Prosolv SMCC 90 were given to the mixture and blending was continued for 15 minutes. Subsequently, the blend was sieved over a sieve with a mesh size of 125 µm. After adding 90.0 g Avicel PH 102 and 19.21 g Solutab (sodium

croscarmellose) to the sieved mixture, the resulting mixture was blended for 10 minutes. After the addition of 1.8 g magnesium stearate blending was continued for 3 minutes. The final blend was compressed on a rotary press Riva Piccola into 5 mm biconvex tablets, each containing

5

Aleglitazar-sodium/ HPBCD composition

|                        |                 |
|------------------------|-----------------|
| according to Example 1 | 8.69 mg (3.62%) |
|------------------------|-----------------|

|                       |                 |
|-----------------------|-----------------|
| Sodium lauryl sulfate | 2.50 mg (1.04%) |
|-----------------------|-----------------|

|                              |                     |
|------------------------------|---------------------|
| Prosolv <sup>®</sup> SMCC 90 | 117.80 mg (49.08 %) |
|------------------------------|---------------------|

|                               |                   |
|-------------------------------|-------------------|
| 10 Avicel <sup>®</sup> PH 102 | 90.00 mg (37.50%) |
|-------------------------------|-------------------|

|         |                  |
|---------|------------------|
| Solutab | 19.21 mg (8.00%) |
|---------|------------------|

|                    |                  |
|--------------------|------------------|
| Magnesium stearate | 1.80 mg (0.75 %) |
|--------------------|------------------|

### Example 2: Preparation of the Aleglitazar-sodium/ SBECD composition

15

12.4 g HPBCD (calculated on dry basis) was dissolved in 40 ml purified water. After the addition of 0.24 g aleglitazar-sodium the resulting suspension was stirred at 23° until a homogenous solution was obtained. The solution was filtered through a membrane of 0.22 µm nominal pore size. The filtered liquid was chilled and

20

lyophilized in bulk and the resulting solid material was ground and sieved.

The resulting composition has a bulk density of 0.33 g/cm<sup>-3</sup> and comprises

|                        |                                                |
|------------------------|------------------------------------------------|
| 25 Aleglitazar-sodium: | 1.86% (as it is) determined by UV-spectrometry |
|------------------------|------------------------------------------------|

|                 |                                            |
|-----------------|--------------------------------------------|
| Residual water: | 4.6 % determined by Karl-Fischer titration |
|-----------------|--------------------------------------------|

|        |       |
|--------|-------|
| HPBCD: | 93.5% |
|--------|-------|

### Example 2a

30

8.06 g Aleglitazar-sodium/ SBECD composition according to Example 2 and 0.30 g sodium lauryl sulfate were blended together with 30.00 g of lactose

monohydrate in a Turbula<sup>®</sup> T10B shaker mixer for 15 minutes. After addition of 10.00 g of lactose monohydrate the mixture were blended again for 15 minutes. Afterwards further 10.00 g of lactose monohydrate were given to the mixture and blending was continued for 15 minutes. Subsequently the blend was sieved over a  
5 sieve with a mesh size of 125 µm. Then 6.55 g microcrystalline cellulose and 4.50 g sodium croscarmellose were added to the mixture. A further blending in a Turbula<sup>®</sup> T10B shaker mixer was carried out for 10 minutes. After addition of 0.60 g magnesium stearate blending was continued for 3 minutes. The final blend  
10 was compressed on a rotary press Riva Piccola into 5 mm biconvex tablets, each containing

Aleglitazar-sodium/SBECD composition

|    |                            |                   |
|----|----------------------------|-------------------|
|    | according to Example 2     | 8.06 mg (11,51%)  |
|    | Lactose monohydrate        | 50.00 mg (71.42%) |
| 15 | Sodium lauryl sulfate      | 0.30 mg (0.43%)   |
|    | Microcrystalline cellulose | 6.55 mg (9.36%)   |
|    | Sodium croscarmellose      | 4.50 mg (6.43%)   |
|    | Magnesium stearate         | 0.60 mg (0.86%)   |

## Claims

1. Composition comprising:
  - (a) aleglitazar, and
  - 5 (b) a complexing agent.
2. Composition according to claim 1, wherein aleglitazar (a) and the complexing agent (b) are present in form of a complex, preferably in form of an inclusion complex.
- 10 3. Composition according to claim 1 or 2, wherein the complexing agent (b) is not nitrogenous.
4. Composition according to any one of the previous claims, wherein the complexing agent (b) has a water solubility at 25 °C of 15 to 1000 mg/ml, preferably 50 to 800 mg/ml.
- 15 5. Composition according to any one of the previous claims, wherein the complexing agent (b) has a molecular weight of less than 2500 g/mol.
- 20 6. Composition according to any one of the previous claims, wherein the molecular ratio of aleglitazar (a) to complexing agent (b) is from 5 : 1 to 1 : 20.
7. Composition according to any one of the previous claims, wherein the complexing agent (b) is a cyclodextrin, preferably (2-hydroxypropyl)- $\beta$ -cyclodextrin, sulfobutylether- $\beta$ -cyclodextrin or  $\gamma$ -cyclodextrin.
- 25 8. Pharmaceutical formulation comprising a composition according any one of claims 1 to 7 and optionally one or more excipient(s) (c), selected from surfactants (c1), wicking agents (c2), fillers (c3), binders (c4), disintegrants (c5), lubricants (c6), glidants (c7) and plasticizers (c8).
- 30

9. Pharmaceutical formulation according to claim 8, wherein the pharmaceutical formulation is a solid oral dosage form, preferably a tablet.

10. Process for producing a composition according any one of the claims 2 to 7,  
5 comprising the steps of dissolving or suspending aleglitazar (a) and complexing agent (b) in a solvent and isolating the resulting aleglitazar complex.

11. Process for producing a pharmaceutical formulation according to claim 8 or 9 comprising the steps:

10

- i) dissolving (a), (b) and optionally further excipient(s) (c),
- ii) homogenizing the solution,
- iii) optionally mixing the solution with further excipient(s) (c) and optionally granulating the mixture,
- 15 iv) removing solvent from the solution of (ii) or the mixture of (iii),
- v) optionally adding further excipient(s) (c) to the mixture of step iv),
- vi) optionally processing the mixture of step v) to a solid oral dosage form.

20 12. Process for producing a pharmaceutical formulation according to claim 11, wherein the formulation is a tablet or a capsule.

13. Pharmaceutical formulation comprising a dual-acting PPAR modulator and cyclodextrin for the treatment of diabetes mellitus type II.

25

14. Pharmaceutical formulation according to claim 13, with which patients with a LDL value of more than 100 mg/dl, preferably between 150 to 300 mg/ml, are treated.

30 15. Pharmaceutical formulation according to claim 13 or 14, wherein the dual-acting PRAR modulator is aleglitazar.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2013/065699

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>INV. A61K9/20 A61K31/422 A61P3/10 A61K9/16 A61K9/28<br>ADD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                      |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>A61K A61P<br>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched<br>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>EPO-Internal, BIOSIS, EMBASE, SCISEARCH, WPI Data                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                      |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                      |
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| * Special categories of cited documents :<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier application or patent but published on or after the international filing date<br>"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)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"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<br>"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<br>"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<br>"&" document member of the same patent family |                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                      |
| Date of the actual completion of the international search<br><br>18 September 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                       | Date of mailing of the international search report<br><br>26/09/2013 |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                       | Authorized officer<br><br>Venturini, Francesca                       |

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/065699

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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| A         | <p>WO 2010/084066 A1 (HOFFMANN LA ROCHE [CH]; GLOMME ALEXANDER [CH]; WOJTERA PAUL [CH]) 29 July 2010 (2010-07-29) cited in the application claims; examples</p> <p>-----</p>                                                                                                                                                                                         | 1-14                  |
| A         | <p>SCHMID G ET AL: "Preparation and Application of Gamma-Cyclodextrin in New Trends in Cyclodextrins and Derivatives", 1 January 1991 (1991-01-01), 19910101, PAGE(S) 27 - 54, XP008107760, ISBN: 978-2-86411-049-1</p> <p>-----</p>                                                                                                                                 | 1-14                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/065699

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