Use of a PPARα agonist and metformin for decreasing the serum triglycerides

The present invention is directed to the use of a PPARα agonist and metformin for the treatment of obesity.

PPARα is a subtype of the PPAR (Peroxisome Proliferator Activated Receptor) family. PPARα is predominantly expressed in tissues catabolizing high amounts of fatty acids, such as liver, heart and brown adipose tissue. Activated PPARs form heterodimers with RXR (Retinoid X Receptor) and the heterodimer binds to a specific response element, termed PPRE (PPAR Response Element), in the regulatory regions of target genes and subsequently alters their transcription. The majority of the genes whose expression is under control of PPARα code for proteins involved in intra- and extracellular lipid metabolism, such as acyl coA oxidase, acyl-coA synthetase and apolipoproteins A-I, A-II and C-III.

Fibrates can be cited as PPARα activators or agonists. In the present invention, the term agonist or activator is used equally to designate a compound that can activate a PPAR receptor.

Fibrates have been documented to lower plasma triglycerides and cholesterol levels and to be beneficial in the prevention of ischemic heart disease in individuals with dyslipidemia. They can also modestly decrease elevated fibrinogen and PAI-1 levels. Fibrate compounds, e.g., gemfibrozil, fenofibrate, bezafibrate, and ciprofibrate, elevate the level of plasma HDL cholesterol.

Metformin is mainly known for its anti-hyperglycaemic activity and is widely used in the treatment of non-insulin-dependent diabetes. In the case of insulin-dependent diabetes, metformin is also administered to the patient in combination with insulin.

EP 1054665 discloses a combination of metformin and of a fibrate chosen from fenofibrate and bezafibrate for the treatment of non-insulin-dependent diabetes. The synergistic effect observed lies in a marked improvement of the hypoglycaemia.

Disclosed herein is the use of a PPARα agonist and metformin for the treatment of obesity.

Further disclosed is the use of a PPARα agonists, metformin and a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical formulation for the treatment of obesity.

By "PPARα agonist" is meant a compound or composition which when combined with PPARα directly or indirectly (preferably binding directly to PPARα) stimulates or increases an *in vivo* or *in vitro* reaction typical for the receptor, e.g. transcriptional regulation activity, as measured by an assay known to one skilled in the art, including, but not limited to, the "co-transfection" or "cistrans" assays described or disclosed in U.S. Patent Nos. 4,981,784, 5,071,773, 5,298,429, 5,506,102, WO89/05355, WO91/06677, WO92/05447, WO93/11235, WO93/23431, WO94/23068, WO95/18380, CA 2,034,220, and Lehmann, et al., J. Bio. Chem. 270:12953-12956 (1995). PPARα agonists may also be identified according to an assay described in US Patent 6,008,239.

PPARα compounds are disclosed in Tontonez et al., Cell 79:1147-1156 (1994), Lehmann et al., J. Biol. Chem. 270(22):1-4, 1995, Amri et al., J. Lipid Res. 32:1449-1456 (1991), Kliewer et al., Proc. Natl. Acad. Sci. USA 94:4318-4323 (1997), Amri et al., J. Lipid Res. 32:1457-1463, (1991) and Grimaldi et al., Proc. Natl. Acad. Sci. USA 89:10930-10934 (1992). PPARα agonist compounds described in US Patent 6,008,239, WO97/27847, WO97/27857, WO97/28115, WO97/28137 and WO97/28149. Certain fibrate compounds as described in WO92/10468 and WO01/80852.

Fibric acid derivatives lower the levels of triglyceride-rich lipoproteins, such as VLDL, raise HDL levels, and have variable effects on LDL levels. The effects on VLDL levels appear to result primarily from an increase in lipoprotein lipase activity,

especially in muscle. This leads to enhanced hydrolysis of VLDL triglyceride content and an enhanced VLDL catabolism. Fibric acid agents also may alter the composition of the VLDL, for example, by decreasing hepatic production of apoC-III, an inhibitor of lipoprotein lipase activity. These compounds are also reported to decrease hepatic VLDL triglyceride synthesis, possibly by inhibiting fatty acid synthesis and by promoting fatty acid oxidation.

Fenofibrate is commercially available as Tricor™ capsules. Each capsule contains 67 mg of micronized fenofibrate.

Clofibrate is commercially available as Atromid-S capsules. Each capsule contains 500 mg of clofibrate. Clofibrate lowers elevated serum lipids by reducing the very low-density lipoprotein fraction rich in triglycerides. Serum cholesterol may be decreased. It may inhibit the hepatic release of lipoproteins (particularly VLDL) and potentiate the action of lipoprotein lipase. The recommended daily dose of clofibrate is 2 g, administered in divided doses.

Gemfibrozil is commercially available as Lopid tablets. Each tablet contains 600 mg of gemfibrozil. Gemfibrozil is a lipid regulating agent that decreases serum triglycerides and very low density lipoprotein cholesterol, and increases high density lipoprotein cholesterol. The recommended daily dose of gemfibrozil is 1200 mg, administered in two divided doses.

In a first aspect, there is provided the use of: metformin; a PPARα agonist, which is either fenofibrate or a compound selected from the group consisting of one of the following or a pharmaceutically acceptable salt thereof: gemfibrozil, fenofibric acid, bezafibrate and ciprofibrate; and a pharmaceutically acceptable carrier, in the manufacture of a pharmaceutical formulation for the treatment of obesity.

In a second aspect, there is provided the use of: metformin; and a PPARα agonist, which is either fenofibrate or a compound selected from the group consisting of one of the following or a pharmaceutically acceptable salt thereof: gemfibrozil, fenofibric acid, bezafibrate and ciprofibrate; in the manufacture of a kit for the treatment of obesity, the kit comprising two separate compositions, the first comprising the PPARα agonist and the second comprising metformin or a pharmaceutically acceptable salt thereof.

The PPARα agonist can be a fibrate selected from the

group consisting of gemfibrozil, fenofibrate, bezafibrate, clofibrate and ciprofibrate, or a fibric acid derivative or a pharmaceutically acceptable salt or ester of said fibric acid derivative.

The preferred fibrate is fenofibrate, fenofibric acid or a pharmaceutically acceptable salt or ester of fenofibric acid.

Metformin can be administered in the form of one of its pharmaceutically acceptable salts, such as the hydrochloride, acetate, benzoate, citrate, fumarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulphonate, maleate, parachlorophenoxyisobutyrate, formate, lactate, succinate, sulphate, tartrate, cyclohexanecarboxylate, hexanoate, octonoate, decanoate, hexadecanoate, octodecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, glutamate, pyrrolidonecarboxylate,

naphthalenesulphonate, 1-glucosephosphate, nitrate, sulphite, dithionate or phosphate.

Among these salts, the hydrochloride, fumarate, embonate and chlorophenoxyacetate are more particularly preferred.

The pharmaceutically acceptable salts of metformin may be obtained in a manner which is known per se by the action of metformin on the corresponding acid.

In another embodiment, there is provided the manufacture of a medicament for treating obesity wherein the treatment comprises co-administering an effective dosage of a PPARα agonist and

comprisesing co-administering an effective dosage of a PPARα agonist and metformin, where the effective dosage of the PPARα agonist is in the range of about 10 to about 3000 mg per day, preferably in the range of about 50 to about 300 mg per day.

In a further embodiment, there is provided the manufacture of a medicament for treating obesity wherein the treatment comprises co-administering an effective dosage of a PPARα agonist and

metformin, where the effective dosage of metformin is in the range of about 10 to about 3000 mg per day, preferably in the range of about 100 to about 1000 mg per day.

According to an embodiment, the amount of metformin or of its salt which is used is from one to twenty times the mass of the PPARα agonist, preferably from one to five times and better from two to five times.

In another embodiment, the PPARα agonist and the merformin are to be administered simultaneously or co-administered.

In another embodiment, the PPARα agonist and the metformin are to be administered sequentially.

As used in this application, "co-administration" means the administration of two or more compounds to the same patient, within a time period of up to about two to about twelve hours. For example, co-administration encompasses (1) simultaneous administration of a first and second compound; (2) administration of a first compound, followed by administration of a second compound about 2 hours after administration of the first compound; and (3) administration of a first compound, followed by administration of a second compound about 12 hours after administration of the first compound. As described herein, the present invention encompasses co-administration of a PPARα agonist and metformin to a patient.

According to the present invention, a pharmaceutical formulation is defined as the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. This includes tablets, powders, capsules, pills, cachets, and lozenges which can be used as solid dosage forms suitable for oral administration.

An effective dosage is defined in the present invention as the amount of a compound that prevents or ameliorates adverse conditions or symptoms of disease(s) or disorder(s) being treated. With respect to the PPARα agonist and metformin, effective dosage means a pharmacological dose in the range defined above. With respect to fibrates, the skilled artisan will understand and appreciate that the effective dosage of a given fibrate will vary with the potency of the fibrate.

Pharmaceutical formulations of the PPARα agonist and/or metformin can be prepared according to known methods. The preferred route of administering the PPARα agonist and metformin is mucosal administration, most preferably oral administration.

For preparing pharmaceutical compositions containing a PPARα agonist and/or metformin, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations may include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which may be in admixture with the finely divided active component. In tablets, the active component may be mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like.

Liquid form preparations may include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution, e.g. in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors,

stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The pharmaceutical preparation can also be a kit comprising two separate compositions, the first comprising the PPARα agonist and the second comprising metformin or a pharmaceutically acceptable salt thereof.

As shown in the examples, the applicant unexpectedly found that a PPARα agonist and metformin significantly reduce the triglycerides level and body weight gain, and thus that such a combination can be used for the treatment of the metabolic syndrome or for the treatment of obesity.

The invention is further illustrated by the following examples, which are not to be construed as limiting, but merely as an illustration of some preferred features of the invention.

EXAMPLE 1: Effect of PPARα agonist and metformin co-administration on body weight in Zucker rats

Studies were designed to evaluate the effects of fenofibrate, a PPARα agonist, and metformin as a combination therapy, on body weight in Zucker rats.

METHOD

Male homozygous Zucker rats of 9 to 11 weeks of age and their lean controls were randomised into groups of 8, based on body weight and fasting plasma insulin levels.

The experimental groups were:

- Lean rats, untreated;
- Obese rats, treated with the vehicle p.o., twice daily
- Obese rats, treated with Fenofibrate, 30 mg/kg, p.o., once daily
- Obese rats, treated with Metformin, 150 mg/kg, p.o., twice daily
- Obese rats, treated with Fenofibrate, 30 mg/kg, p.o., once daily and metformin, 150 mg/kg, p.o., twice daily.

Body weight was recorded every day during 30 days.

The results are summarized in Table 1.

Table 1

	Body weight gain (g)	Body weight gain (% of change vs vehicle treated group)
Lean	33.7 ± 3.0	-52
Vehicle	70.5 ± 4.1	/
Fenofibrate	52.0 ± 5.8	-26
Metformin	67.2 ± 4.0	-5
Fenofibrate + Metformin	44.4 ± 4.1	-37

Values are expressed as mean ± SEM

As shown in this example, the body weight gain is significantly lowered when Zucker rats are treated with Fenofibrate and Metformine. This diminution in the body weight gain is superior when the Zucker rats are treated with both fenofibrate and metformine than when they are treated with fenofibrate or metformin alone. Statistically significant differences between the combination of metformin and fenofibrate and the vehicle treated group are shown in the body weight gain (statistics: global covariance analysis followed by Dunnett's test, $p<0.05$).

Also, when comparing the body weight gain in Zucker rats treated with the combination of fenofibrate and metformine with both monotherapy of fenofibrate and metformine, the result is not a single addition of the effects of fenofibrate and metformine alone, but a synergy.

CLAIMS

1. Use of:

metformin;

a PPARα agonist, which is either fenofibrate or a compound selected from the group consisting of one of the following or a pharmaceutically acceptable salt thereof: gemfibrozil, fenofibric acid, bezafibrate and ciprofibrate; and

a pharmaceutically acceptable carrier,

in the manufacture of a pharmaceutical formulation for the treatment of obesity.

2. The use according to claim 1, wherein the PPARα agonist is fenofibrate, fenofibric acid or a pharmaceutically acceptable salt of fenofibric acid.

3. The use according to claim 1 or claim 2, wherein metformin is used in the form of one of its pharmaceutically acceptable salts, selected from the group consisting of the hydrochloride, acetate, benzoate, citrate, fumarate, embonate, chlorophenoxyacetate, glycolate, palmoate, aspartate, methanesulphonate, maleate, parachlorophenoxyisobutyrate, formate, lactate, succinate, sulphate, tartrate, cyclohexanecarboxylate, hexanoate, octanoate, decanoate, hexadecanoate, octadecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, glutamate, pyrrolidonecarboxylate, naphthalenesulphonate, 1-glucosephosphate, nitrate, sulphite, dithionate and phosphate.

4. The use according to claim 3, wherein metformin is used in the form of its hydrochloride, fumarate, embonate or chlorophenoxyacetate salt.

5. The use according to one of claims 1 to 4, wherein the PPARα agonist and metformin are to be administered simultaneously.

6. The use according to claim 5, wherein the pharmaceutical formulation is a solid form preparation containing metformin and the PPARα agonist in a unit dosage form, wherein the solid form preparation is selected from the group consisting of: powders, tablets, pills, capsules, cachets, lozenges, suppositories and dispersible granules.

7. The use according to claim 6, wherein the unit dosage form is a capsule, tablet, cachet or lozenge.

8. The use according to claim 6 or claim 7, wherein the solid form preparation consists of metformin, the PPARα agonist and a solid carrier consisting of or more substances acting as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or encapsulating materials.

9. The use according to any of claims 6 to 8, wherein the solid form preparation comprises metformin and the PPARα agonist, in addition to magnesium carbonate, magnesium stearate, talc, sugar, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax or cocoa butter.

10. The use according to one of claims 1 to 4, wherein the PPARα agonist and metformin are to be administered sequentially.

11. The use according to any of claims 1 to 10, wherein the effective dosage of the PPARα agonist is in the range of 10 to 3000 mg per day, and the effective dosage of metformin is in the range of 10 to 3000 mg per day.

12. The use according to claim 11, wherein the effective dosage of the PPARα agonist is in the range of 50 to 300 mg per day, and the effective dosage of metformin is in the range of 100 to 1000 mg per day.

13. The use according to any of claims 1 to 12, wherein the amount of metformin or of its salt which is used is from one to twenty times the mass of the PPARα agonist.

14. The use according to claim 13, wherein the amount of metformin or of its salt which is used is from one to five times the mass of the PPARα agonist.

15. The use according to claim 14, wherein the amount of metformin or of its salt which is used is from two to five times the mass of the PPARα agonist.

16. Use of:

metformin; and

a PPARα agonist, which is either fenofibrate or a compound selected from the group consisting of one of the following or a pharmaceutically acceptable salt thereof: gemfibrozil, fenofibric acid, bezafibrate and ciprofibrate;

in the manufacture of a kit for the treatment of obesity, the kit comprising two separate compositions, the first comprising the PPARα agonist and the second comprising metformin or a pharmaceutically acceptable salt thereof.

17. The use according to claim 16, wherein the PPARα agonist is fenofibrate, fenofibric acid or a pharmaceutically acceptable salt of fenofibric acid.

18. The use according to claim 16, wherein the effective dosage of the PPARα agonist is in the range of 50 to 300 mg per day, and the effective dosage of metformin is in the range of 100 to 1000 mg per day.