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(54) Title: PHARMACEUTICAL COMBINATIONS OF VILDAGLIPTIN AND PPAR AGONISTS

(57) Abstract: A pharmaceutical combination comprising vildagliptin or a pharmaceutically acceptable salt thereof in combination with a PPAR dual agonist or a pharmaceutically acceptable salt thereof.

Description

PHARMACEUTICAL COMBINATIONS OF VILDAGLIPTIN AND PPAR AGONISTS

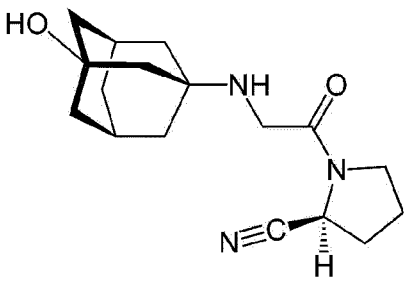
Field of Invention

The present invention relates to a pharmaceutical combination comprising vildagliptin or a pharmaceutically acceptable salt thereof in combination with a PPAR dual agonist or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

Background of Invention

Vildagliptin is a DPP-IV inhibitor used for type 2 or non-insulin dependent diabetes. It increases the amount of insulin produced by the body. It also decreases the amount of glucagon which is produced by the body. Because of these effects, vildagliptin can help to control blood sugar levels in people with diabetes.

DPP-IV inhibitors work by blocking the action of DPP-IV, an enzyme which destroys the hormone incretin. There are two types of incretin hormones found in the body, called glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These hormones are naturally produced by the body in response to food intake. Their function is to help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed. Vildagliptin works by binding to DPP-IV and preventing it from breaking down the GLP-1 and GIP. This increases the levels of these hormones in the body and so increases their effect on controlling blood sugar.



Formula I

Its chemical name is (S)-{[(3-hydroxyadamantan-1 -yl)amino]acetyl}pyrrolidine-2-carbonitril and its chemical structure is shown in the Formula I.

Vildagliptin is marketed under the trademark Galvus® in 50 mg dosage forms by NOVARTIS. It is used against diabetes mellitus, particularly in treating type 2 diabetes. Galvus® includes lactose anhydrose, microcrystalline cellulose, sodium starch glycolate and magnesium stearate.

Tablets comprising combinations of vildagliptin are also available in the market in the strength of 50mg/850mg and 50mg/1 000mg (vildagliptin/metformin). Eucreas® (vildagliptin and metformin combination) is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

However, there is no combination of vildagliptin and PPAR dual agonists in prior art or in the market for the treatment of cardiovascular disease in patients with type-2 diabetes mellitus.

PPAR agonists are drugs which act upon the peroxisome proliferator-activated receptor. Over the last decade, the members of the peroxisome proliferator-activated receptor (PPAR) subclass have emerged as valuable pharmacological targets whose activation can normalize metabolic dysfunctions and reduce some cardiovascular risk factors associated with type-2 diabetes mellitus.

PPAR (peroxisome proliferator-activated receptor) agonists are divided into five classes PPARa (alpha), PPARy (gamma), PPAR5 (delta), dual acting PPARa/γ (alpha/gamma) and PPAR pan (alpha/delta/gamma) agonists.

PPAR alpha agonists (glitazones) are used for dyslipidemia to increase HDL (High Density Lipoprotein), decrease TG (Triglycerides) without effect on LDL (Low Density Lipoprotein). PPAR gamma agonists (fibrates) are insulin sensitizers for type 2 diabetes. PPAR delta agonists are developed to deal with glucose resulting in insulin resistance and diabetes. PPAR pan (alpha/delta/gamma) agonists are for combined treatment of type 2 diabetes and dyslipidemia. PPAR dual (alpha and gamma) agonists (glitazars) are for combined treatment of type 2 diabetes and dyslipidemia.

PPAR alpha agonists are also known as glitazones or thiazolidinediones (TZDs). They comprise pioglitazone, rosiglitazone, ciglitazone, darglitazone, englitazone, lobeglitazone, mitaglitazone, netoglitazone and troglitazone.

PPAR gamma agonists (also known as fibrates) comprise bezafibrate, ciprofibrate, clofibrate, gemfibrozil, fenofibrate, simfibrate, lifibrate, pirifibrate, theofibrate, tiafibrate, timofibrate, tocofibrate.

PPAR delta agonists comprise endurobol.

PPAR dual (alpha and gamma) agonists (also known as glitazars) comprise saroglitazar, aloglitazar, chiglitazar, farglitazar (faraglitazar), imiglitazar, muraglitazar, naveglitazar, ragaglitazar, reglitazar, peliglitazar, pemoglitazar, sodelglitazar, tesaglitazar, oxeglitazar, and sipoglitazar.

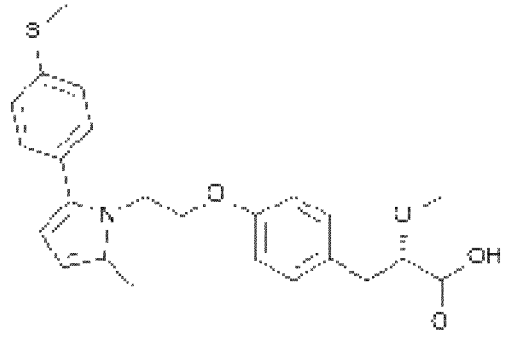
PPAR dual agonists are the glitazars that combine increased insulin sensitization with lipid control. They bind and activate both the alpha and gamma PPAR isoforms and improvement is achieved both in lipid profiles and insulin sensitization while avoiding dyslipidemia and weight gain.

PPAR dual agonists (glitazars) are ideally suitable drugs in treatment of type 2 diabetic patients who have cardiovascular risk secondary to elevated triglyceride concentration. These molecules do not only target the dyslipidemia but also contribute to improved glycemic control.

Vildagliptin increases plasma GLP-1 concentration and elevate cellular cAMP levels in pancreatic beta-cells leading to potentiate insulin secretion, whereas PPAR agonists dual regulate lipid homeostasis, cellular differentiation, proliferation and the immune response. Therefore, it is anticipated that a combination therapy of vildagliptin and PPAR dual agonists may synergistically represents a novel approach to modify metabolic risk factors associated with adverse cardiovascular outcomes in patients with type 2 diabetes.

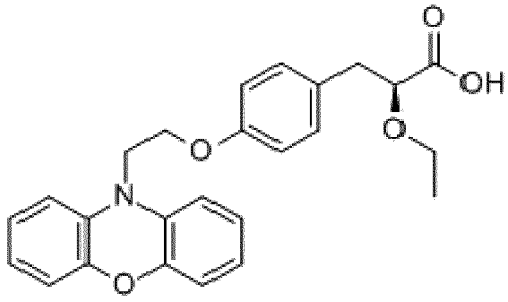
Saroglitazar is marketed under the trade name Lipaglyn recommended in strength of 4 mg, developed by the Zydus Cadila. Lipaglyn has been approved for the treatment of Type II diabetes by the Drug Controller General of India in 2013. Lipaglyn is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus not controlled by statin therapy. In clinical studies, Lipaglyn has demonstrated reduction of

triglycerides (TG), low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, non - high density lipoprotein (non- HDL) cholesterol and an increase in HDL cholesterol. It has also shown favorable glycemic indices by reducing the fasting plasma glucose and glycosylated hemoglobin in diabetic patients. The chemical name of saroglitazar is (2S)-2-ethoxy-3-[4-[2-[2-methyl-5-(4-methylsulfanylphenyl)pyrrol-1-yl]ethoxy]phenyl] propanoic acid and the chemical structure is shown in Formula II.



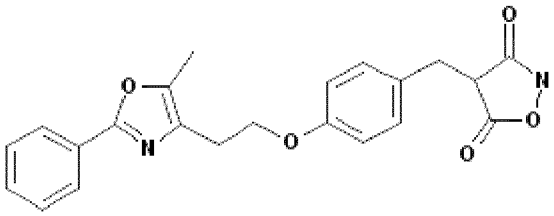
Formula II - Saroglitazar

Ragaglitazar is a dual peroxisome proliferator-activated receptor (PPAR) alpha and gamma agonist intended to restore insulin sensitivity and ameliorate diabetic dyslipidemia. It is first disclosed in the patent numbered W0991 9313 in 1997. The chemical name of Ragaglitazar is (2S)-2-ethoxy-3-[4-(2-phenoxazin-1 0-ylethoxy)phenyl]propanoic acid and the chemical structure is shown in Formula III.



Formula III - Ragaglitazar

Reglitazar is a PPAR dual agonist which is first disclosed in the patent numbered W09518125 in 1993. The chemical name of Reglitazar is 4-[[4-[2-(5-methyl-2-phenyl-1 ,3-oxazol-4-yl)ethoxy]phenyl]methyl]-1 ,2-oxazolidine-3,5-dione and the chemical structure is shown in Formula IV.



Formula IV - Reglitazar

Given these benefits of PPAR agonism, there is a need in the art for a pharmaceutical formulation or a dosage form that is to combine a vildagliptin and a PPAR dual agonist. However, some problems may be occurred while combining these two molecules such as instability and physicochemical and therapeutical incompatibility problems.

In this present invention, a pharmaceutical combination comprising vildagliptin or a pharmaceutically acceptable salt thereof in combination with a PPAR dual agonist or a pharmaceutically acceptable salt thereof has been developed to achieve a stable pharmaceutical combination therapy with a safe and effective release.

Description of the invention

The main embodiment of this present invention is to provide a pharmaceutical combination comprising vildagliptin or a pharmaceutically acceptable salt thereof in combination with a PPAR dual agonist or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

In one embodiment, PPAR (peroxisome proliferator-activated receptor) dual agonist in the pharmaceutical combination of this present invention is selected from the group comprising saroglitazar, ragaglitazar, reglitazar, imiglitazar, aloglitazar, chiglitazar, farglitazar (faraglitazar), muraglitazar, naveglitazar, peliglitazar, pemoglitazar, sodelglitazar, tesaglitazar, oxeglitazar, sipoglitazar or pharmaceutically acceptable salt thereof.

According to one embodiment, vildagliptin is present in an amount of between 1.5 - 90%, preferably 15 - 50% and more preferably 25 - 35% by weight of total formulation.

According to one embodiment, a PPAR dual agonist is present in an amount of between 0.5 - 90.0 %, preferably 1.0 - 50.0 % and more preferably 10.0 - 45.0 % by weight of total formulation.

According to this embodiment, the PPAR dual agonist is preferably saroglitazar or reglitazar or ragaglitazar their acceptable salts thereof.

In this embodiment, saroglitazar or a pharmaceutically acceptable salt used in the formulation is saroglitazar magnesium salt.

According to this embodiment, the pharmaceutical combination of this present invention comprises vildagliptin and saroglitazar or a pharmaceutically acceptable salt thereof.

According to another embodiment, the pharmaceutical combination of this present invention comprises vildagliptin and reglitazar or a pharmaceutically acceptable salt thereof.

According to a further embodiment, the pharmaceutical combination of this present invention comprises vildagliptin and ragaglitazar or a pharmaceutically acceptable salt thereof.

According to this embodiment, vildagliptin present in an amount of between 25 mg and 200 mg and the saroglitazar is present in an amount of 0.1 mg and 5 mg.

According to this embodiment, vildagliptin present in an amount of between 25 mg and 200 mg and the reglitazar is present in an amount of 0.5 mg and 100 mg.

According to this embodiment, vildagliptin present in an amount of between 25mg and 200 mg and the ragaglitazar is present in an amount of 0.5 and 100 mg.

According to one embodiment, the pharmaceutical combination is in the form of tablets (comprising compressed, coated or uncoated), bilayer tablets, multilayer tablets, orally disintegrating tablets, mini tablets, capsules, pellet, sugar pellet, buccal tablets, sublingual tablets, effervescent compositions, effervescent tablets, immediate release tablets, modified release tablets, film-coated tablets, gastric disintegrating tablets, pills, hard or soft gelatin capsules, oral granules, powders, coated bead systems, granules, microspheres, tablet in tablet or inlay tablets, ion exchange resin systems, sterile solutions or suspensions, steril ocular solutions, aerosols, sprays, drops, ampoules, suppositories, ocular systems, parenteral systems, creams, gels, ointments, dragees, sachets; films, orally administrable films, solutions, solids; elixirs, tinctures, suspensions, syrups, colloidal dispersions, dispersions, emulsions and thereof.

In this embodiment, pharmaceutical combination is formulated preferably in the form of tablet or capsule or bilayer tablet comprising vildagliptin or a pharmaceutically acceptable salt and PPAR dual agonist or a pharmaceutically acceptable salt.

One embodiment of the present invention is to obtain a stable pharmaceutical combination comprising vildagliptin or a pharmaceutically acceptable salt and a PPAR dual agonist or a pharmaceutically acceptable salt in one dosage form.

While combining more than one molecule in one dosage form is increasing the patients' quality of life, many challenges also occur such as the physicochemical compatibility and the therapeutical compatibility between the two active agents. It is essential to achieve the compatibility between different active agents and/or between active agents and excipients used. Compounds of different classes cannot always be combined into safe and efficacious dosage forms thereby resulting in incompatible drug combinations. Due to chemical interaction between active agents or between active agents and excipients, stability and release problems may occur.

Stability related problems do occur in many active agents, including vildagliptin, under the influence of ambient and physical conditions. Vildagliptin, however, is an active agent that is highly-susceptible to air and humidity. When vildagliptin is exposed to air and humidity, it degrades structurally and develops chemical behavioral changes that may cause undesired release profile or even additional side effects.

Additionally, it has been known that DPP-4 inhibitors with primary or secondary amine group show incompatibilities, degradation problems or extraction problems with excipients. Vildagliptin has also a secondary amine group on its chemical structure. In solid dosage forms, it may react with many excipients or impurities of excipients, although vildagliptin itself is very stable. Especially decomposition which may be caused by reaction (e.g. by acylation, urea formation or Maillard reaction, or the like) of free base type vildagliptin when combined with an incompatible drug molecule, or its impurity and/or a pharmaceutical excipient to form derivatives with the free base type vildagliptin, such as N-acetyl or N-carbamoyl derivatives. Therefore, in this invention, by the use of suitable excipients within these pharmaceutical combinations, protection against oxidation, decomposition and degradation which cause undesired release profile could be achieved.

According to this embodiment of the present invention is to obtain a pharmaceutical combination comprising vildagliptin or a pharmaceutically acceptable salt and a PPAR dual agonist or a pharmaceutically acceptable salt which provides the desired release profile.

According to one embodiment, pharmaceutical combination of this present invention comprise at least one pharmaceutical excipient selected from the group comprising diluents, disintegrants, binders, glidants, lubricants, super-disintegrants, acidifying agents, alkalizing agents, sweeteners, aromas or mixtures thereof.

Suitable diluents are selected from the group comprising dibasic calcium phosphate, mannitol, lactose, microcrystalline cellulose (MCC), spray-dried lactose, sorbitol, sucrose, trehalose, isomalt, starch, calcium phosphate anhydrate, calcium phosphate dihydrate, calcium phosphate trihydrate, tribasic calcium phosphate, calcium carbonate, calcium sulfate, carboxymethyl cellulose calcium, powdered cellulose, cellulose acetate, pregelatinized starch, sodium carbonate, sodium bicarbonate, isomalt, maltodextrine, dextrose, calcium carbonate, sugars, magnesium carbonate, corn starch or mixtures thereof.

In this invention, to achieve the stability of both vildagliptin or a pharmaceutically acceptable salt and PPAR dual agonist or a pharmaceutically acceptable salt, selection of excipients and the ratio of them are very essential. It is surprisingly found that when dibasic calcium phosphate was used as a diluent, stability and desired release profile could be achieved at the same time due to its non-hygroscopic and hydrophobic properties.

According to this embodiment, in this formulation of the present invention dibasic calcium phosphate is used as a diluent.

According to this embodiment, to achieve desired release of both molecules, in this formulation of the present invention dibasic calcium phosphate is used in an amount of % 5.0 - 90.0 by the weight of total formulation.

Suitable disintegrants are selected from the group comprising crospovidon (cross-linked polyvinylpyrrolidone), copovidon, polyvinylpyrrolidone (povidone), croscarmellose sodium, polycarbophil, low-substitue HPC (hydroxylpropyl cellulose), poloxamer, sodium starch glycolate, microcristalline cellulose, starch, alginic acid and alginates, ion-exchange resins, magnesium aluminum silica, sodium dodecyl sulphate, sodium carboxy methyl cellulose,

carboxy methyl cellulose calcium, docusate sodium, guar gum, polyacrylin potasium, sodium alginate, sodium glysin carbonate, sodium lauryl sulphate or mixtures thereof.

Suitable binders are selected from the group comprising crospovidon (cross-linked polyvinylpyrrolidone), polyvinylpyrrolidone (povidone), pullulan, polymethacrylate, glyceryl behenate, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), methyl cellulose (MC), hydroxyethyl cellulose, sodium carboxymethyl cellulose (Na CMC), carboxymethyl cellulose calcium, ethyl cellulose and other cellulose derivatives, polymetacrylates, polyethylene oxide, polyvinyl alcohol, polycarbophil, polyvinyl acetate and their copolymers, gelatin, starch, xanthan gum, guar gum, alginate, carrageen, kollagen, agar, pectin, hyaluronic acid, carbomer, cellulose acetate phthalate, hydroxypropyl starch, hydroxyethyl methyl cellulose, polaxomer, polyethylene glycol (PEG), sugars, glycose syrups, natural gums, tragacanth gum, polyacrylamide, aluminum hydroxide, benthonite, laponite, setostearyl alcohol, polyoxyethylene-alkyl ethers, acacia mucilage, polydextrose or mixtures thereof.

Suitable glidants are selected from the group comprising colloidal silicon dioxide, talc, aluminum silicate, powdered cellulose, calcium phosphate tribasic, hydrophobic colloidal silica, magnesium oxide, magnesium trisilicate, magnesium silicate or mixtures thereof.

Suitable lubricants are selected from the group comprising magnesium stearate, calcium stearate, mineral oil, sodium stearyl fumarate, talc, polyethylene glycol, glyceryl monostearate, glyceryl palmitostearate, sodium lauryl sulphate, magnesium lauryl sulphate, fumaric acid, zinc stearate, stearic acid, hydrogenated natural oils, silica, paraffin or mixtures thereof.

Super-disintegrant is selected from the group comprising calcium silicate, sodium starch glycolate, croscarmellose sodium, carboxymethyl cellulose calcium, sodium carboxymethyl starch, sodium glycine carbonate, sodium lauryl sulphate, soy polysaccharide, alginic acids and algynates, cross-linked alginic acid, polyacrylin potasium, poloxamer. crospovidone, gellan gum, guar gum, xanthan gum, docusate sodium, magnesium alumina, sodium dodecyl sulfate, ion exchange resins or mixtures thereof.

Acidifying agent is selected from the group comprising fumaric acid, tartaric acid, citric acid monohydrate, citric acid anhydrate, adipic acid, ascorbic acid, acetic acid, hydrochloric acid nitric acid, phosphoric acid, nicotinic acid, acetyl salicylic acid, sulfuric acid, acid salts (such

as amino acid hydrochlorides, sodium citrates, sodium citrate dihydrate, disodium citrate, disodium dihydrogen citrate, sodium acid phosphate) or mixtures thereof.

Alkalizing agent is selected from the group comprising sodium glycine carbonate, ammonia solution, ammonium carbonate, diethanolamine, diisopropanolamine, potassium hydroxide, potassium bicarbonate, potassium carbonate, calcium carbonate, sodium bicarbonate, sodium borate, sodium carbonate, sodium hydroxide, trolamine or mixtures thereof.

Suitable sweeteners may include but not limited to thaumatin, mogroside, inuline, erythritol, mogroside, acesulfame-K, aspartame, saccharin or its sodium and calcium salts, sodium cyclamate, sucrose, fructose, glucose, sorbitol or mixtures thereof.

Suitable aromas may include but not limited to fruit aromas such as orange, banana, strawberry, cherry, wild cherry, lemon, etc., and other aromas such as cardamom, anis, mint, menthol, vanillin or the mixtures thereof.

Coating may also preferably be used for the protection from the moisture. It can be selected from the group comprising polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat IR), polyvinyl alcohol or copolymers or mixtures thereof (Opadry AMB), polymethylmetacrylate derivatives, Ethylcellulose Dispersions (Surelease), Kerry-HPC, polyethylene glycol, polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA) and all kinds of OpadryTM, as well as pigments, dyes, titanium dioxide, iron oxide, talc or polymethylmetacrylate copolymers (Eudragit).

In this present invention, to achieve desired pharmaceutical combination with a desired release profile, compatibility and stability, these formulations have been designed, comprising the following:

tablet:

a. 1.5 - 90.0 % by weight of vildagliptin
b. 0.5 - 90.0 % by weight of PPAR dual agonist
c. 0.1 - 60.0 % by weight of disintegrant
d. 0.1 - 30.0 % by weight of binder
e. 2.0 - 90.0 % by weight of diluent
f. 0.1 - 5.0 % by weight of glidant
g. 0.1 - 5.0 % by weight of lubricant
h. preferably, coating

bilayer tablet:

a. 1.5 - 90.0 % by weight of vildagliptin
b. 0.1 - 60.0 % by weight of disintegrant
c. 0.0 - 30.0 % by weight of binder
d. 0.1 - 90.0 % by weight of diluent
e. 0.1 - 5.0 % by weight of glidant
f. 0.1 - 5.0 % by weight of lubricant

g. 0.5 - 90.0 % by weight of PPAR dual agonist
h. 0.1 - 60.0 % by weight of disintegrant
i. 0.0 - 30.0 % by weight of binder
j. 0.0 - 90.0 % by weight of diluent
k. 0.1 - 5.0 % by weight of glidant
l. 0.1 - 5.0 % by weight of lubricant

m. preferably, coating

capsule:

a. 1.5 - 90.0 % by weight of vildagliptin
b. 0.1 - 60.0 % by weight of disintegrant
c. 0.5 - 40.0 % by weight of pellet
d. 0.1 - 40.0 % by weight of coating

e. 0.5 - 90.0 % by weight of PPAR dual agonist
f. 0.1 - 60.0 % by weight of disintegrant
g. 0.5 - 40.0 % by weight of pellet
h. 0.1 - 40.0 % by weight of coating

Example 1: tablet

ingredients	Amount (%)
vildagliptin	1.5 - 90.0
saroglitazar	0.5 - 90.0

polycarbophil	0.5 - 30.0
dibasic calcium phosphate	5.0 - 90.0
croscarmellose sodium	0.25 - 20.0
colloidal silicon dioxide	0.1 - 0.2
magnesium stearate	0.25 - 2.0
coating	0.2 - 10.0

The production of the formulation is carried out as follows: vildagliptin, saroglitazar, polycarbophil, croscarmellose sodium and dibasic calcium phosphate are mixed. Colloidal silicon dioxide is added and mixed. Then, magnesium stearate is added therein and mixed for a short time. Tablet compression is performed and tablets are preferably coated.

Example 2: bilaver tablet

ingredients	**Amount (%)**
First layer	
vildagliptin	1.5 - 90.0
dibasic calcium phosphate	5.0 - 90.0
crospovidon	1.0 - 30.0
colloidal silicon dioxide	0.1 - 0.2
magnesium stearate	0.25 - 2.0
Second layer	
saroglitazar	0.5 - 90.0
dibasic calcium phosphate	5.0 - 90.0
crospovidon	1.0 - 30.0
microcrystalline cellulose	5.0 - 90.0
colloidal silicon dioxide	0.1 - 0.2
magnesium stearate	0.25 - 2.0
coating	0.2 - 10.0

The production of the formulation is carried out as follows:

First layer: vildagliptin, dibasic calcium phosphate, crospovidon and colloidal silicon dioxide are mixed. Then, magnesium stearate is added and mixed again. The mixture is passed through the roller compactor.

Second layer: saroglitazar, dibasic calcium phosphate, crospovidon, microcrystalline cellulose and colloidal silicon dioxide are mixed. Then, magnesium stearate is added and mixed for a short time. The mixture is passed through the roller compactor.

Granules are sieved and mixed with magnesium stearate. Then, they compressed into bilayer tablets. Tablets are preferably coated.

Example 3: bilayer tablet - hot melt process

ingredients	Amount (%)
First layer	
vildagliptin	1.5 – 90.0
dibasic calcium phosphate	5.0 – 90.0
crospovidon	1.0 – 30.0
microcrystalline cellulose	5.0 – 90.0
Second layer	
reglitazar	0.5 – 90.0
poloxamer	0.5 – 15.0
colloidal silicon dioxide	0.1 - 0.2
magnesium stearate	0.25 – 2.0
coating	0.2 – 10.0

The production of the formulation is carried out as follows: vildagliptin, dibasic calcium phosphate, crospovidon and microcrystalline cellulose are mixed. Reglitazar and poloxamer are mixed and passed through the extruder, cooled and sieved. Both phases are mixed with

first colloidal silicon dioxide and then magnesium stearate for a short time. Tablet compression is performed. Tablets are preferably coated.

Example 4: capsule

ingredients	Amount (%)
Vildagliptin pellet	
vildagliptin	1.5 – 90.0
crospovidon	1.0 – 30.0
polyvinylpyrrolidone	0.1 – 25.0
sugar pellet	5.0 – 90.0
Polymethyl methacrylate	0.5 – 40.0
Ragaglitazar pellet	
ragaglitazar	0.5 – 90.0
polyvinylpyrrolidone	0.1 – 25.0
sugar pellet	5.0 – 90.0
polymethyl methacrylate	0.5 – 40.0
colloidal silicon dioxide	0.1 - 0.2
magnesium stearate	0.25 – 2.0

The production of the formulation is carried out as follows: vildagliptin and ragaglitazar solution is prepared with polyvinylpyrrolidone (solved in a proper solvent) separately. Separately, sugar pellets are coated. Solution of polymethyl methacrylate is prepared and sugar pellets comprising active agents are coated. Pellets are first mixed with crospovidon, colloidal silicon dioxide and then magnesium stearate for a short time. Then, they are filled into capsules.

CLAIMS

1. A pharmaceutical combination comprising vildagliptin or a pharmaceutically acceptable salt thereof in combination with a PPAR dual agonist or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

2. The pharmaceutical combination according to claim 1, wherein the PPAR dual agonist is selected from the group comprising saroglitazar, ragaglitazar, reglitazar, imiglitazar, aloglitazar, chiglitazar, farglitazar, muraglitazar, naveglitazar, peliglitazar, pemoglitazar, sodelglitazar, tesaglitazar, oxeglitazar, sipoglitazar or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical combination according to claim 1, wherein vildagliptin is present in an amount of between 1.5 - 90%, preferably 15 - 50% and more preferably 25 - 35% by weight of total formulation.

4. The pharmaceutical combination according to claim 1, wherein the PPAR dual agonist is present in an amount of between 0.5 - 90.0 %, preferably 1.0 - 50.0 % and more preferably 10.0 - 45.0 % by weight of total formulation.

5. The pharmaceutical combination according to claim 1, wherein the PPAR dual agonist is preferably saroglitazar or reglitazar or ragaglitazar or an acceptable salt thereof.

6. The pharmaceutical combination according to claim 1 or 5, comprising vildagliptin and saroglitazar or a pharmaceutically acceptable salt thereof.

7. The pharmaceutical combination according to claim 1 or 5, comprising vildagliptin and reglitazar or a pharmaceutically acceptable salt thereof.

8. The pharmaceutical combination according to claim 1 or 5, comprising vildagliptin and ragaglitazar or a pharmaceutically acceptable salt thereof.

9. The pharmaceutical combination according to claim 1 or 6, wherein vildagliptin present in an amount of between 25 mg and 200 mg and the saroglitazar is present in an amount of 0.1 mg and 5 mg.

10. The pharmaceutical combination according to claim 1 or 7, wherein vildagliptin present in an amount of between 25 mg and 200 mg and the reglitazar is present in an amount of between 0.5 mg and 100 mg.

11. The pharmaceutical combination according to claim 1 or 8, wherein vildagliptin present in an amount of between 25mg and 200 mg and the ragaglitazar is present in an amount of 0.5 and 100 mg.

12. The pharmaceutical combination according to any preceding claims, wherein said pharmaceutical combination is in the form of tablets comprising compressed, coated or uncoated tablets, bilayer tablets, multilayer tablets, orally disintegrating tablets, mini tablets, capsules, pellets, sugar pellets, buccal tablets, sublingual tablets, effervescent compositions, effervescent tablets, immediate release tablets, modified release tablets, film-coated tablets, gastric disintegrating tablets, pills, hard or soft gelatin capsules, oral granules, powders, coated bead systems, granules, microspheres, sachets, tablet in tablet or inlay tablets, ion exchange resin systems, sterile solutions or suspensions, steril ocular solutions, aerosols, sprays, drops, ampoules, suppositories, ocular systems, parenteral systems, creams, gels, ointments, dragees, films, orally administrable films, solutions, solids; elixirs, tinctures, suspensions, syrups, colloidal dispersions, dispersions, emulsions and thereof.

13. The pharmaceutical combination according to claim 12, wherein said pharmaceutical combination is formulated preferably in the form of tablet or capsule or bilayer tablet.

14. The pharmaceutical combination according to claim 1, wherein at least one pharmaceutically acceptable excipient is selected from the group comprising diluents, disintegrants, binders, glidants, lubricants, super-disintegrants, acidifying agents, alkalizing agents, sweeteners, aromas or mixtures thereof.

15. The pharmaceutical combination according to claim 14, wherein the diluents are selected from the group comprising dibasic calcium phosphate, mannitol, lactose, microcrystalline cellulose (MCC), spray-dried lactose, sorbitol, sucrose, trehalose, isomalt, starch, calcium phosphate anhydrate, calcium phosphate dihydrate, calcium phosphate trihydrate, tribasic calcium phosphate, calcium carbonate, calcium sulfate, carboxymethyl cellulose calcium, powdered cellulose, cellulose acetate, pregelatinized starch, lactose monohydrate, sodium carbonate, sodium bicarbonate,

isomalt, maltodextrine, dextrose, calcium carbonate, sugars, magnesium carbonate, corn starch or mixtures thereof, preferably dibasic calcium phosphate.

16. The pharmaceutical combination according to claim 15, wherein the dibasic calcium phosphate is present in an amount of between 5.0 - 90.0% by weight of total formulation.

17. The pharmaceutical combination according to any preceding claims comprising;

a. 1.5 - 90.0 % by weight of vildagliptin
b. 0.5 - 90.0 % by weight of PPAR dual agonist
c. 0.1 - 60.0 % by weight of disintegrant
d. 0.1 - 30.0 % by weight of binder
e. 2.0 - 90.0 % by weight of diluent
f. 0.1 - 5.0 % by weight of glidant
g. 0.1 - 5.0 % by weight of lubricant
h. preferably, coating

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/074939

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/40 A61K31/422 A61K31/538 A61K45/06 A61K9/14
A61P3/10 A61P5/50 A61P9/00 A61P43/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 2006/270722 Al (THORNBERRY NANCY A [US] ET AL) 30 November 2006 (2006-11-30) abstract paragraph [0001] paragraph [0017] - paragraph [0030] paragraph [0037] paragraph [0097] paragraph [0100] - paragraph [0101] exampl es 1-3 cl aims 1-12	1-17
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 December 2015	21/12/2015

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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