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(54) Title: SYNERGIC COMBINATION COMPRISING ANTI-DIABETIC AGENT

(57) Abstract: The present invention relates to pharmaceutical combinations comprising an alpha glucosidase inhibitor and a biguanide that shall be used in the treatment of type-2 diabetes.

SYNERGIC COMBINATION COMPRISING ANTI-DIABETIC AGENT

The present invention relates to alpha-glucosidase inhibitor and biguanide combinations, use of said combinations in the treatment of type-2 diabetes and pharmaceutical compositions comprising them.

- 5 Although alpha-glucosidase inhibitors are not directly effective on insulin secretion, they cause starch derived glucose to enter the circulation more slowly by slowing down the digestion of starchy food. Some examples of the agents in this group are miglitol, acarbose and voglibose.

10 Since they are the kind of agents that act in digestive system, said agents can cause patients to experience side effects such as diarrhoea and bloating.

15 Basically, biguanides provides to lower the amount of glucose in blood circulation by enabling the cells in body to receive more glucose. Agents such as metformin, phenformin, buformin can be given as examples to some of the agents in this group. Lactic acidosis, dyspepsia and diarrhoea are among the side effects frequently encountered in the patients using said drug.

It has been surprisingly observed that an unexpected therapeutic benefit and especially a synergistic therapeutic benefit can be obtained in the treatment of type-2 diabetes when a combination therapy comprising alpha-glucosidase inhibitor and biguanide derivative agents are used together. Said therapeutic benefit can be in form of;

- 20
- reducing the dose amount necessary for obtaining the required therapeutic effect in the case that said combination is used in comparison to the dose amounts when only alpha-glucosidase inhibitors or biguanide is used and/or
 - reducing undesired side effects and/or
 - observing the therapeutic effect in a shorter time and/or

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 - observing the therapeutic effect for a longer time and/or
 - providing a more effective treatment.

Inventors have observed that the most important improvement is that the side effects patients suffer when said agents are taken separately are not experienced in the combined therapy.

30 From another aspect, the pharmaceutical composition in which alpha-glucosidase inhibitor and biguanide are used together or simultaneously induces a better therapeutic benefit than compositions in which said two agents are used separately.

From another aspect, using alpha-glucosidase inhibitor and biguanide combination provides the therapeutic effect to be seen in a short time and to be stronger than the effect seen when said two active agents are used separately. In this way, it is possible to provide a more effective treatment for patients. Surprisingly, all these positive effects observed in combinations in which both active agents are given in a sequential manner are also observed when both active agents are given in the same dosage form at the same time or simultaneously in independent dosage forms. High therapeutic benefit can also be observed as a longer-term therapeutic effect.

According to this, the present invention relates to pharmaceutical compositions comprising an alpha-glucosidase inhibitor and a biguanide together in different dosage forms for sequential use, in different dosage forms for simultaneous use or in the same dosage form for concurrent administration.

In another aspect, the present invention provides a method that treats type-2 diabetes diseases by administering an alpha-glucosidase inhibitor and a biguanide in effective amounts.

The alpha-glucosidase inhibitor that shall be used in combinations of the present invention can be selected from a group comprising miglitol, acarbose, voglibose.

The biguanide that shall be used in the combinations of the present invention can be selected from a group comprising metformin, phenformin, buformin.

The preferred combinations that can be prepared according to the invention comprise a combination of miglitol and metformin or a combination of acarbose and metformin or a combination of voglibose and metformin.

In another aspect, the present invention relates to pharmaceutical compositions comprising pharmaceutically effective amounts of an alpha-glucosidase inhibitor and a biguanide and at least one pharmaceutically acceptable excipient. In said pharmaceutical formulations, the alpha-glucosidase inhibitor and biguanide can be formulated with at least one pharmaceutically acceptable excipient in different formulations as well as formulated together in a single formulation. The different formulations obtained can be combined in a single dosage form or can be prepared in different dosage forms. In the case that formulations are in different dosage forms, said dosage forms can be the same or different from each other.

At the same time, the present invention relates to use of an alpha-glucosidase inhibitor and a biguanide according to the invention for preparation of a drug that shall be used in combination therapy by simultaneous, sequential or separate administration in the treatment of type-2 diabetes.

- 5 The alpha-glucosidase inhibitor comprised in the pharmaceutical compositions of the present invention can be in its pharmaceutically acceptable salt, hydrate, solvate, ester, enantiomer, diastereomer forms structurally and/or in amorphous, crystalline forms or a combination thereof in terms of polymorphic structure or in form of combinations thereof.

- 10 The biguanide comprised in the pharmaceutical compositions of the present invention can be in its pharmaceutically acceptable salt, hydrate, solvate, ester, enantiomer, diastereomer forms and/or in form of its any polymorphic form such as amorphous, crystalline form or a combination thereof. For example, in the case that metformin is used as a biguanide agent, it is preferably in salt form, more preferably in hydrochloride salt form.

- 15 Pharmaceutical compositions of the invention comprising an alpha-glucosidase inhibitor and a biguanide can be prepared in any one of the dosage forms such as tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enterically coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet, orodispersible tablet, chewable tablet. While pharmaceutical compositions comprising an alpha-glucosidase inhibitor and a biguanide in any of these dosage forms together, they can
20 also be in any of these dosage forms in the case that the alpha-glucosidase inhibitor and the biguanide are stored in separate dosage forms. In other words, compositions comprising the combination of the invention can be in any of abovementioned dosage forms or in form of a combination of these dosage forms or in a treatment package form comprising said combination.

- 25 In the case that the alpha-glucosidase inhibitor and the biguanide are in the same dosage form, pharmaceutical formulations of the invention comprising the alpha-glucosidase inhibitor and the biguanide are preferably in form of tablet or effervescent tablet or prolonged release tablet.

- 30 The pharmaceutical compositions of the present invention comprising an alpha-glucosidase inhibitor and a biguanide can comprise various excipients in addition to the alpha-glucosidase inhibitor and the biguanide as active agents.

The pharmaceutical compositions of the present invention comprising an alpha-glucosidase inhibitor and a biguanide comprises at least one excipient selected from a group comprising disintegrant, diluent, lubricant, glidant, effervescent couple comprising at least one acidic and one basic agent, colouring agent, pH regulating agent, surfactant, stabilizing agent, sweetener
5 and/or taste regulating agent, flavoring agent in addition to the active agents.

The disintegrant that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, croscarmellose sodium, crospovidone, hydroxypropyl cellulose, microcrystalline cellulose, methyl cellulose, chitosan, starch, sodium starch
10 glycolate.

The diluent that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol,
15 simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol.

The lubricant that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising calcium stearate, magnesium stearate, polyethylene glycol, sodium benzoate, potassium benzoate, sodium lauryl sulphate, talc, stearic acid, zinc stearate.

The glidant that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising tribasic calcium phosphate, colloidal silicone dioxide, magnesium silicate, magnesium trisilicate, talc.
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The binder that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising carboxymethyl cellulose sodium, ethyl cellulose, gelatine, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose,
25 magnesium aluminium silicate, maltodextrin, methyl cellulose, povidone, starch.

The acidic agent used in the effervescent couple comprising at least one acidic and one basic agent that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising organic acids such as malic acid, citric acid, tartaric acid, fumaric acid; and the basic agent can be selected from a group comprising agents such as sodium
30 carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate.

The pH regulating agent that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising citrate, phosphate, carbonate, tartrate, fumarate, acetate and amino acid salts.

5 The surfactant that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising agents such as sodium lauryl sulphate, polysorbate, polyoxyethylene, polyoxypropylene glycol and the like.

The stabilizing agent that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising tocopherol, tetrasodium edetate, nicotinamide, cyclodextrin.

10 The sweetener and/or taste regulating agent that can be used in the pharmaceutical compositions of the invention can be selected from a group comprising acesulfame, aspartame, dextrose, fructose, maltitol, maltose, mannitol, saccharine, saccharine sodium, sodium cyclamate, sorbitol, sucralose, sucrose, xylitol, sodium chloride.

15 The flavouring agent that can be used in the pharmaceutical compositions of the invention can be selected from flavours comprising menthol, lemon, orange, vanilla, strawberry, raspberry, caramel and the like.

The pharmaceutical compositions of the invention can comprise an alpha-glucosidase inhibitor in the range of 0.1 to 99%, preferably in the range of 1 to 98%, more preferably in the range of 5 to 95 % by weight, for example, in the range of 5, 10, 15, 20, 25, 30% to 35,
20 40, 45, 50, 55, 60, 65, 70, 80, 90%.

The pharmaceutical compositions of the invention can comprise a biguanide in the range of 0.1 to 99%, preferably in the range of 1 to 98%, more preferably in the range of 5 to 95 % by weight, for example, in the range of 5, 10, 15, 20, 25, 30% to 35, 40, 45, 50, 55, 60, 65, 70, 80, 90%.

25 The pharmaceutical compositions of the invention can comprise an alpha-glucosidase inhibitor in the range of 0.01 mg to 500 mg, preferably in the range of 0.1 mg to 300 mg, more preferably in the range of 0.5 mg to 250 mg.

The pharmaceutical compositions of the invention can comprise a biguanide in the range of 100 mg to 1500 mg, preferably in the range of 300 mg to 1200 mg, more preferably in the
30 range of 500 mg to 1000 mg.

The pharmaceutical compositions of the invention comprising an alpha-glucosidase inhibitor and a biguanide can optionally comprise a third active agent in addition to the alpha-glucosidase inhibitor and the biguanide. The third active agent can be selected from a group comprising antacid, anticholinergic, antispasmodic, antiemetic, anti-diabetic, antipropulsive, 5 antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianaemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral, antineoplastic, antiarrhythmic, antiadrenergic, antiepileptic, anti-Parkinson, antiprotozoal, antihelminthic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, tiazolidinedion, biguanide, immunostimulant, 10 immunosuppressant, muscle relaxant, analgesic, psycholeptic, psycho analeptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamin and minerals, vitamin A, vitamin D and its analogues, vitamin B₁, vitamin C, vitamin E, vitamin B₆, vitamin B₂, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

15 The pharmaceutical compositions of the invention comprising an alpha-glucosidase inhibitor and a biguanide comprise a third active agent in addition to said two agents which is preferably selected from a group comprising an anti-diabetic agent meglitinide, tiazolidinedion, sulphonylurea, peptide analogue, organosulfur compound; more preferably an agent selected from a group comprising nateglinide, repaglinide, rosiglitazone, pioglitazone, 20 troglitazone, tolbutamide, acetohexamide, chlorpropamide, glipizide, glyburide, glimepiride, gliclazide, vildagliptin, sitagliptin, saxagliptin, linagliptin.

The pharmaceutical composition of the invention can be obtained by a method comprising the steps of;

- 25 • Mixing the active agents alpha-glucosidase inhibitor and biguanide homogeneously and adding at least one of the abovementioned excipients if necessary or
- Granulating a mixture comprising the active agents alpha-glucosidase inhibitor, biguanide and at least one of the abovementioned excipients with a granulation solution, then mixing them homogeneously with the other excipients or
- 30 • Mixing the active agents alpha-glucosidase inhibitor and biguanide with at least one of the abovementioned excipients, then granulating them with a granulation solution comprising at least one excipient or

- Using any of the abovementioned methods separately for each active agent composition and combining said formulations together or storing them in different dosage forms in the case that the alpha-glucosidase inhibitor and the biguanide are prepared in two separate formulations.

5 The obtained pharmaceutical composition or compositions can be prepared in any of the abovementioned dosage forms. In the case that it is in tablet form, obtained tablets can be treated with film coating agents such as sugar-based coating agents, water-soluble film coating agents, enteric coating agents, delayed release coating agents or a coating compositions comprising any combination thereof.

10 Saccharose can be used alone as sugar-based coating agent or optionally together with any of the agents such as talc, calcium carbonate, calcium phosphate, calcium sulphate, gelatine, gum arabic, polyvinylpyrrolidone and pullulan or a combination thereof.

Water-soluble film coating agent can be selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl
15 hydroxyethyl cellulose and sodium carboxymethyl cellulose; synthetic polymers such as polyvinyl acetal diethyl amino acetate, aminoalkyl methacrylate copolymer and polyvinylpyrrolidone; and polysaccharides such as pullulan or combinations thereof.

Enteric coating agents can be selected from cellulose derivatives such as hydroxypropyl methyl cellulose ftalat, hydroxypropyl methyl cellulose acetate succinate, carboxymethyl
20 ethyl cellulose, cellulose acetate ftalat; acrylic acid derivatives such as methacrylic acid copolymer L, methacrylic acid copolymer LD and methacrylic acid copolymer S; and natural substances such as shellac or combinations thereof.

Delayed release coating agents can be selected from cellulose derivatives such as ethyl cellulose; acrylic acid derivatives such as aminoalkyl methacrylate copolymer RS, ethyl
25 acrylate-methyl methacrylate copolymer emulsion or combinations thereof.

The pharmaceutical composition according to the invention can be used in the prophylaxis and treatment of type-2 diabetes.

d_{10} value of the alpha-glucosidase inhibitor of the pharmaceutical compositions of the invention (such as voglibose, miglitol, acarbose, etc.) is in the range of 0.1 to 50 μg ,

preferably in the range of 1 to 30 μm while d_{50} value of the biguanide (such as metformin hydrochloride) is in the range of 0.1 to 80 μm , preferably in the range of 1 to 50 μm .

The examples below are given to elucidate the combinations of the invention. Yet the invention cannot be limited to these examples.

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EXAMPLE 1: Pharmaceutical compositions comprising miglitol and metformin combination

Content	% of amount (by weight)
Miglitol	10
Metformin Hydrochloride	50
Lubricant	2
Other excipients	30
Release regulating coating agent	8

Metformin and miglitol are granulated. Obtained granules are dried and then mixed with the other excipients. Lubricant is added to the obtained mixture and the final mixture is compressed in tablet compression machine. Tablets are coated with release regulating agent and dried.

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EXAMPLE 2: Pharmaceutical compositions comprising acarbose and metformin combination

Content	% of amount (by weight)
Acarbose	25%
Metformin	25%
Lubricant	2
Other excipients	48

Acarbose and some of the other excipients are mixed and wet-granulated with the granulation solution. Granules are dried and mixed with the rest of the excipients and metformin. The homogeneous composition obtained is mixed with the lubricant and compressed in tablet compression machine in tablet form.

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EXAMPLE 3: Film tablet formulation comprising voglibose and metformin combination

Content	% of amount (by weight)
Voglibose	1,5
Metformin Hydrochloride	50
Lubricant	2
Other excipients	36,5
Coating agent	10

Voglibose and other excipients are mixed and granulated. Metformin hydrochloride and lubricant are added to the obtained granules. Final composition is compressed in form of
5 tablet and dried after coated with the coating agent.

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CLAIMS

1. A pharmaceutical composition comprising an alpha-glucosidase inhibitor and biguanide combination as active agent.
2. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a
5 biguanide according to claim 1, characterized in that said composition comprises an alpha-glucosidase inhibitor in the range of 0.01 mg to 500 mg.
3. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-2, characterized in that said composition comprises an alpha-glucosidase inhibitor in the range of 0.1 mg to 300 mg.
- 10 4. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-3, characterized in that said composition comprises an alpha-glucosidase inhibitor in the range of 0.5 mg to 250 mg.
5. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-4, characterized in that said composition comprises a
15 biguanide in the range of 100 mg to 1500 mg.
6. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-5, characterized in that said composition comprises a biguanide in the range of 300 mg to 1200 mg.
7. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a
20 biguanide according to claims 1-6, characterized in that said composition comprises a biguanide in the range of 500 mg to 1000 mg.
8. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-7, characterized in that the alpha-glucosidase inhibitor is in form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers,
25 diastereomers structurally and/or in any of its amorphous, crystalline forms or a combination thereof in terms of polymorphic structure or combinations thereof.
9. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-8, characterized in that biguanide is in form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers
30 structurally and/or in any of amorphous, crystalline forms or a combination thereof in terms of polymorphic structure or combinations thereof.

10. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-9, characterized in that the alpha-glucosidase inhibitor and biguanide are in the same pharmaceutical formulation.
- 5 11. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-9, characterized in that the alpha-glucosidase inhibitor and biguanide are in different pharmaceutical formulations.
- 10 12. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-9 and 11, characterized in that different formulations comprising the alpha-glucosidase inhibitor and biguanide are combined in the same dosage form.
13. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-9 and 11, characterized in that different formulations comprising the alpha-glucosidase inhibitor and biguanide are in different dosage forms.
- 15 14. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-13, characterized in that said composition is in form of tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enterically coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet, orodispersible tablet, chewable tablet or a combination thereof.
- 20 15. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 10-14, characterized in that said composition is in form of film tablet, effervescent tablet or prolonged release tablet.
- 25 16. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to any preceding claims, characterized in that said composition comprises at least one pharmaceutically acceptable excipient in addition to the alpha-glucosidase inhibitor and biguanide.
- 30 17. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claim 17, characterized in that said composition comprises at least one excipient selected from a group comprising disintegrant, diluent, lubricant, glidant, binder, effervescent couple comprising at least one acidic and one basic agent, colouring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent in addition to the alpha-glucosidase inhibitor and biguanide.

18. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to any preceding claims, characterized in that said composition comprises an alpha-glucosidase inhibitor in the range of 0.1 to 99% by weight.
19. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to any preceding claims, characterized in that said composition comprises a biguanide in the range of 0.1 to 99% by weight.
20. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to any preceding claims, characterized in that said composition comprises a third active agent in addition to the alpha-glucosidase inhibitor and biguanide selected from a group comprising antacid, anticholinergic, antispasmodic, antiemetic, anti-diabetic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianaemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral, antineoplastic, antiarrhythmic, antiadrenergic, antiepileptic, anti-Parkinson, antiprotozoal, antihelminthic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, tiazolidinedion, biguanide, immunostimulant, immunosuppressant, muscle relaxant, analgesic, psycholeptic, psychoanaleptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamin and minerals, vitamin A, vitamin D and its analogues, vitamin B₁, vitamin C, vitamin E, vitamin B₆, vitamin B₂, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.
21. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to any preceding claims, characterized in that the third active agent comprised in said composition in addition to the alpha-glucosidase inhibitor and biguanide is an anti-diabetic agent.
22. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 20 and 21, characterized in that the third active agent that shall be used in said composition in addition to the alpha-glucosidase inhibitor and biguanide is selected from the compounds meglitinide, tiazolidinedion, sulfonylurea, peptide analogue, organosulfur.
23. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 20-22, characterized in that the third active agent that shall be used in said composition in addition to the alpha-glucosidase inhibitor and biguanide is selected from a group comprising nateglinide, repaglinide, rosiglitazone, pioglitazone,

troglitazone, tolbutamide, acetohexamide, chlorpropamide, glipizide, glyburide, glimepiride, gliclazide, vildagliptin, sitagliptin, saxagliptin, linagliptin.

24. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to any preceding claims, characterized in that the alpha-glucosidase inhibitor is selected from a group comprising miglitol, acarbose, voglibose.
25. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to any preceding claims, characterized in that the biguanide is selected from a group comprising metformin, phenformin, buformin.
26. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claim 25, characterized in that biguanide is in metformin hydrochloride salt form in the case that metformin is used as the biguanide.
27. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to any preceding claims, characterized in that the alpha-glucosidase inhibitor is miglitol and the biguanide is metformin.
28. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-26, characterized in that the alpha-glucosidase inhibitor is acarbose and the biguanide is metformin.
29. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to claims 1-26, characterized in that the alpha-glucosidase inhibitor is voglibose and the biguanide is metformin.
30. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and a biguanide according to any preceding claims, characterized in that said composition is used for production of a drug that shall be used in the treatment of type-2 diabetes.
31. A pharmaceutical composition comprising an alpha-glucosidase inhibitor and biguanide combination as active agent, wherein said composition is used sequentially, at the same time or simultaneously.
32. A pharmaceutical composition comprising an a combination of an alpha-glucosidase inhibitor in the range of 0.1 mg to 300 mg and a biguanide in the range of 500 mg to 1000 mg as active agent.
33. A pharmaceutical composition comprising miglitol and metformin hydrochloride combination as active agent, wherein said composition is used sequentially, at the same time or simultaneously.

34. A pharmaceutical composition comprising acarbose and metformin hydrochloride combination as active agent, wherein said composition is used sequentially, at the same time or simultaneously.

5 35. A pharmaceutical composition comprising voglibose and metformin hydrochloride combination as active agent, wherein said composition is used sequentially, at the same time or simultaneously.

10 36. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and biguanide combination according to any preceding claims, characterized in that di_0 value of the alpha-glucosidase inhibitor is in the range of 0.1 to 50 $\mu\eta$ and di_0 value of the biguanide is in the range of 0.1 to 80 $\mu\eta$.

37. The pharmaceutical composition comprising an alpha-glucosidase inhibitor and biguanide combination according to any preceding claims, characterized in that di_0 value of the alpha-glucosidase inhibitor is in the range of 1 to 30 $\mu\eta$ and di_0 value of the biguanide is in the range of 1 to 50 $\mu\eta$.

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INTERNATIONAL SEARCH REPORT

International application No PCT/TR2012/000220
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/155 A61K31/702 A61K31/7032 A61P3/10
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 , WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	wo 2010/138535 AI (SQUIBB BRISTOL MYERS CO [US] ; ASTRAZENECA UK LTD [GB] ; STRUMPH PAUL [U] 2 December 2010 (2010-12-02) *cf. abstract, secti on [0001] at page 1, secti on [0016] at pages 5/6 -----	1-37
X	EP 1 964 562 AI (ESPINOSA ABDALA LEOPOLD DE JE [MX] ; WORLD TRADE IMP EXPORT WTI E A [CH] 3 September 2008 (2008-09-03) *cf. abstract, secti on [0001] at col . 1, secti on [0066] at col . 9, furthermore claims 1 and 10* ----- -/- .	1-37

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 25 April 2013	Date of mailing of the international search report 06/05/2013
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Stol tner, Anton
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INTERNATIONAL SEARCH REPORT

International application No

PCT/TR2012/000220

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X	<p>HAVELES E B: "Trends in diabetes care" , DRUG TOPICS, ADVANSTAR MEDICAL ECONOMICS HEALTHCARE COMMUNICATIONS, US, vol . 145 , no. 19 Suppl , 1 October 2001 (2001-10-01) , pages 29s-36s , XP009168764, ISSN: 0012-6616 *cf. page 32s , col . at the right side, 2nd para, in connecti on with tabl e 3 at page 33s , furthermore page 36s , 2nd para, of left-si ded col . and both 2nd and 3rd paras , of the right col .*</p> <p style="text-align: center;">-----</p>	1-37
Y	<p>WARREN R E: "The stepwi se approach to the management of type 2 diabetes" , DIABETES RESEARCH AND CLINICAL PRACTICE 200409 I E, vol . 65 , no. SUPPL. , September 2004 (2004-09) , pages S3-S8, XP0027173735 , ISSN: 0168-8227 *cf. abstract, tabl e 1 and secti on 4 at page S5*</p> <p style="text-align: center;">-----</p>	1-37

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