PHARMACEUTICAL COMPOSITION COMPRISING AN ALPHA-GLUCOSIDASE INHIBITOR AND A 4-OXOBUTANOIC ACID, AND THE USE THEREOF FOR TREATING DIABETES

The present invention relates to a pharmaceutical composition comprising, as active principles, a 4-oxobutanoic acid described in WO 98/07681 and an α-glucosidase inhibitor.

The invention also relates to the use of a 4-oxobutanoic acid and an α-glucosidase inhibitor for the preparation of a medicinal preparation for reducing hyperglycaemia, more particularly the hyperglycaemia of non-insulin-dependent diabetes.

Diabetes is a chronic disease that has a number of pathological manifestations. It is accompanied by disorders of lipid and sugar metabolism and circulatory disorders. In many cases, diabetes tends to progress to various pathological complications. Thus, it is necessary to find a treatment that is suited to each individual suffering from diabetes.

Insulin resistance syndrome (syndrome X) is characterised by a reduction in the action of insulin (Presse Médicale, 26, No. 14, (1997), 671-677) and is involved in a great many pathological conditions such as diabetes and more particularly non-insulin-dependent diabetes, dyslipidaemia, obesity, arterial hypertension and also certain microvascular and macrovascular complications, for instance atherosclerosis, retinopathies, nephropathies and neuropathies.

4-Oxobutanoic acids have already been described for treating diabetes, in patent application WO 98/07681. Some of these compounds act on the early short-lived secretion of insulin.

α-Glucosidase inhibitors are described as anti-hyperglycaemiants and are commonly used in the treatment of type II diabetes (NIDDM). They act on the intestinal wall by retarding the passage of glucose from the intestine into the bloodstream, thus reducing the postprandial level of glucose.

α-Glucosidase inhibitors that may especially be mentioned include acarbose, emiglitate, miglitol and voglibose.

Combinations between an α-glucosidase inhibitor with other compounds that act on diabetes have already been described. Examples of these are the combination of acarbose with metformin and of acarbose with glimepiride (WO 00/40233). Studies have also shown a synergistic effect of the combination of voglibose with sulfonylureas [J. Int. Med. Res.; 1998; 26(5); 219-232].

The specific combination of an α-glucosidase inhibitor with a 4-oxobutanoic acid has not been described.

Thus, an aim of the present invention is to propose a composition for significantly improving a diabetic patient's condition, and more particularly to optimise the utilisation of glucose.

A further aim of the invention is to propose a composition that is suited to the treatment of diabetes by displaying considerable action on the metabolic syndrome of insulin resistance and on the early short-lived secretion of insulin.

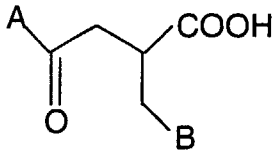
A final aim of the invention is to propose a composition that is particularly suitable for diabetics at the various stages of the disease.

These aims and others are achieved by the present invention, which relates to a pharmaceutical composition comprising, as active principles, at least one α-glucosidase inhibitor and at least one compound of the formula (I), in combination with one or more pharmaceutically acceptable excipients.

This composition is particularly suitable for treating diabetes, more particularly non-insulin-dependent diabetes. It is particularly suitable for reducing the hyperglycaemia of non-insulin-dependent diabetes.

It is also suitable for treating pathologies associated with insulin resistance syndrome, such as, especially, dyslipidaemia, obesity, arterial hypertension, and microvascular and macrovascular complications, for instance atherosclerosis, retinopathies, nephropathies and neuropathies.

The compound of the formula (I) is defined as follows:



(I)

in which the groups A and B are chosen, independently of each other, from:

- a mono-, bi- or tricyclic aryl group containing from 6 to 14 carbon atoms;
- a heteroaromatic group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienyl groups;
- an alkyl group containing from 1 to 14 carbon atoms;
- a cycloalkyl group containing from 5 to 8 carbon atoms;
- a saturated heterocyclic group chosen from tetrahydrofuryl, tetrahydropyranyl, piperidyl and pyrrolidinyl groups;

the groups A and B possibly bearing 1 to 3 substituents chosen from a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_6-C_{14} aryl group, a heteroaryl group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienyl, a (C_6-C_{14})aryl(C_1-C_6)alkyl group, a (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl group, a halogen or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, nitro, amino, carboxyl, (C_1-C_6)alkoxycarbonyl, carbamoyl, (C_1-C_6)alkylsulfonyl, sulfoamino, (C_1-C_6)alkylsulfonylamino, sulfamoyl or (C_1-C_6)alkylcarbonylamino group;

or two of the substituents forming a methylenedioxy group, a solvate thereof or a salt of this acid.

In a preferred embodiment of the invention, the 4-oxobutanoic acids are those of the formula (II) in which A and B are chosen from aryl groups.

Examples of aryl groups that may be mentioned include phenyl, α-naphthyl, β-naphthyl and fluorenyl groups.

The C_1-C_6 alkyl groups may be linear or branched. Examples that may be mentioned include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl and pentyl groups.

The C_1-C_6 alkoxy groups may also be linear or branched.

Examples that may be mentioned include methoxy, ethoxy, propoxy, isopropoxy, butoxy and isobutoxy groups.

The halogens may be chosen from fluorine, chlorine, bromine and iodine.

The present invention also includes the tautomeric forms of the compounds of the general formula (I), the enantiomers, diastereoisomers and epimers of these compounds, and also the solvates thereof.

Examples of salts of the compounds of the general formula (I) include pharmacologically acceptable salts, such as the sodium salts, potassium salts, magnesium salts, calcium salts, amine salts and other salts of the same type (aluminium, iron, bismuth, etc.).

In a preferred embodiment, the 4-oxobutanoic acids are chosen from:

- 2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- 2-cyclohexylmethyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-phenyl-4-oxobutanoic acid
- 2-(β-naphthylmethyl)-4-phenyl-4-oxobutanoic acid
- 2-benzyl-4-(β-naphthyl)-4-oxobutanoic acid
- 2-[(4-chlorophenyl)methyl]-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-methylphenyl)-4-oxobutanoic acid
- 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-4-oxobutanoic acid
- 2-benzyl-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-cyclohexyl-4-oxobutanoic acid
- 4-phenyl-2-[(tetrahydrofur-2-yl)methyl]-4-oxobutanoic acid,

the solvates, enantiomers and salts of these acids.

The 4-oxobutanoic acid is advantageously chosen from:

- (-)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid

- (+)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- (-)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

The α-glucosidase inhibitors that are thus anti-hyperglycaemiants are more particularly chosen from acarbose, miglitol, voglibose and emiglitate.

The compositions of the invention contain therapeutically effective amounts of the various active principles. The ratios of the respective amounts of α-glucosidase inhibitor and of compound of the formula (I) thus vary in consequence.

The weight ratio of α-glucosidase inhibitor to the compound of the formula (I) preferably ranges from 10^{-3} to 40, preferably from 10^{-3} to 10 and better still from 10^{-3} to 5.

The compositions of the invention are preferably administered parenterally, or better still orally, although the other routes of administration, for instance such as rectal administration, are not excluded.

If oral administration is envisaged, the compositions of the invention are in the form of gel capsules, effervescent tablets, coated or uncoated tablets, sachets, sugar-coated tablets, drinkable vials or solutions, microgranules or sustained-release forms.

If parenteral administration is envisaged, the compositions of the invention are in the form of injectable solutions and suspensions packaged in vials or bottles for slow venous infusion.

The forms for oral administration are prepared by mixing the active substance with various types of excipients or of vehicles, such as fillers, disintegration (or crumbling) agents, binders, colorants, flavour enhancers and the like, followed by shaping the mixture.

The colorant can be any colorant permitted for pharmaceutical use.

Examples of flavour enhancers include cocoa powder, mint, borneol and cinnamon powder.

Examples of binders that may be mentioned are polyvinylpyrrolidone, hydroxypropylmethylcellulose, alginic acid, carbomer, carboxymethylcellulose, dextrin, ethylcellulose, starch, sodium alginate, polymethacrylate, maltodextrin, liquid glucose, magnesium aluminium silicate, hydroxyethylcellulose, hydroxypropylcellulose, ethylcellulose, methylcellulose and guar gum.

It is possible to use alginic acid, sodium carboxymethylcellulose, colloidal silicon dioxide, sodium croscarmellose, crospovidone, guar gum, magnesium aluminium silicate, methylcellulose, microcrystalline cellulose, cellulose powder, pregelatinised starch, sodium alginate or sodium starch glycolate as disintegration agent.

The fillers are, for example, cellulose, lactose, calcium hydrogen phosphate or microcrystalline cellulose.

The tablets can be obtained in a conventional manner by compressing granules in the presence of one or more lubricants. Suitable lubricants are calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated plant oil, light mineral oil, magnesium stearate, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, stearyl sodium fumarate, stearic acid, talc and zinc stearate. These tablets can then be coated using polymers in solution or suspension, such as hydroxypropylmethylcellulose or ethylcellulose.

The granules used to do this are prepared, for example, by using the wet granulation process starting with a mixture of the active principles with one or more excipients such as a binder, a crumbling agent (or disintegration agent) and a filler.

To obtain hard capsules, the mixture of active principles with a suitable filler (for example lactose) is incorporated into empty gelatine capsules optionally in the presence of a lubricant such as magnesium stearate, stearic acid, talc or zinc stearate.

Gel capsules or soft capsules are prepared by dissolving the active principles in a suitable solvent (for example polyethylene glycol), followed by incorporation into soft capsules.

The forms for parenteral administration are obtained in a conventional manner by mixing the active principles with buffers, stabilisers, preserving agents, solubilising agents, tonicity agents and suspension agents. In accordance with the known techniques, these mixtures are subsequently sterilised and then packaged in the form of intravenous injections.

As buffer, a person skilled in the art can use buffers based on organophosphate salts.

Examples of suspension agents include methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, acacia and sodium carboxymethylcellulose.

Examples of solubilising agents include castor oil solidified with polyoxyethylene, polysorbate 80, nicotinamide and macrogol.

In addition, stabilisers that are useful according to the invention are sodium sulfite and sodium metasulfite, while mention may be made of sodium p-hydroxybenzoate, sorbic acid, cresol and chlorocresol as preserving agents. For the preparation of an oral solution or suspension, the active principles are dissolved or suspended in a suitable vehicle with a dispersant, a wetting agent, a suspension agent (for example polyvinylpyrrolidone), a preserving agent (such as methylparaben or propylparaben), a flavour enhancer or a colorant.

For the preparation of suppositories, the active principles are mixed in a manner that is known per se with a suitable base constituent, such as polyethylene glycol or semisynthetic glycerides.

For the preparation of microcapsules, the active principles are combined with suitable diluents, suitable stabilisers, agents that promote the sustained release of the active substances or any other type of additive for the formation of a central core that is then coated with a suitable polymer (for

example a water-soluble resin or a water-insoluble resin). The techniques known to those skilled in the art will be used for this purpose.

The microcapsules thus obtained are then optionally formulated in suitable dosage units.

The present invention also relates to the use of an α-glucosidase inhibitor in combination with a compound of the formula (I) as defined above, for the preparation of a medicinal combination for treating diabetes, more particularly non-insulin-dependent diabetes.

According to another of its aspects, the invention relates to the use of an α-glucosidase inhibitor in combination with the said compound of the formula (I), for the preparation of a medicinal combination for reducing the hyperglycaemia of non-insulin-dependent diabetes.

The present invention also relates to a process for treating diabetes, more particularly non-insulin-dependent diabetes, in a mammal, comprising the administration to the said mammal of the composition according to the present invention.

If the α-glucosidase inhibitor and the compound of the formula (I) are incorporated into the same unit dose, the unit dose preferably comprises from 0.1 mg to 400 mg of α-glucosidase inhibitor (the dose depends especially on the active agents under consideration).

If the α-glucosidase inhibitor is chosen from miglitol and acarbose, the unit dose preferably comprises from 10 mg to 400 mg of α-glucosidase inhibitor. If the α-glucosidase inhibitor is voglibose, the unit dose preferably comprises from 0.1 mg to 1 mg of voglibose.

In this case, the unit dose advantageously comprises from 12.5 to 400 mg of compound of the formula (I) (the dose depending especially on the active agents under consideration).

Naturally, the dosage depends on the active agent under consideration, the mode of administration, the therapeutic indication and the age and condition of the patient.

In particular, the daily dosage ranges between 0.1 mg and 1 g of α-glucosidase inhibitor and between 25 and 400 mg of compound of the formula (I).

Specific, but non-limiting examples of the invention will now be presented. The percentages given are expressed on a weight basis, except where otherwise mentioned.

EXAMPLE 1 :

A tablet having the composition below is prepared:

	mass in mg	weight %
Compound P*	50	27.8
Acarbose	75	41.7
Microcrystalline cellulose	15	8.3
Fine lactose powder	20	11.1
Hydroxypropylcellulose	7	3.9
Sodium croscarmellose	10	5.6
Colloidal silica (Aerosil®)	1.5	0.8
Magnesium stearate	1.5	0.8

* Compound P: (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

EXAMPLE 2 :

A tablet having the composition below is prepared:

	mass in mg	weight %
Compound P*	50	17.9
Acarbose	150	53.6
Microcrystalline cellulose	22	7.9
Fine lactose powder	28	10.0
Hydroxypropylcellulose	11	3.9
Sodium croscarmellose	15	5.4
Colloidal silica (Aerosil®)	2	0.7
Magnesium stearate	2	0.7

* Compound P: (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

EXAMPLE 3 :

A tablet having the composition below is prepared:

	mass in mg	weight %
Compound P*	100	40.0
Acarbose	75	30.0
Microcrystalline cellulose	22	8.8
Fine lactose powder	24	9.6
Hydroxypropylcellulose	12	4.8
Sodium croscarmellose	13	5.2
Colloidal silica (Aerosil®)	2	0.8
Magnesium stearate	2	0.8

* Compound P: (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

EXAMPLE 4 :

A tablet having the composition below is prepared:

	mass in mg	weight %
Compound P*	100	28.6
Acarbose	150	42.9
Microcrystalline cellulose	25	7.1
Fine lactose powder	35	10.0
Hydroxypropylcellulose	15	4.3
Sodium croscarmellose	19	5.4
Colloidal silica (Aerosil®)	3	0.9
Magnesium stearate	3	0.9

* Compound P: (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

5

EXAMPLE 5 :

A tablet having the composition below is prepared:

	mass in mg	weight %
Compound P*	200	51.3
Acarbose	75	19.2
Microcrystalline cellulose	30	7.7
Fine lactose powder	40	10.3
Hydroxypropylcellulose	15	3.8
Sodium croscarmellose	22	5.6
Colloidal silica (Aerosil®)	4	1.0
Magnesium stearate	4	1.0

* Compound P: (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

EXAMPLE 6 :

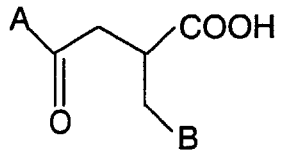
A tablet having the composition below is prepared:

	mass in mg	weight %
Compound P*	200	40.8
Acarbose	150	30.6
Microcrystalline cellulose	35	7.1
Fine lactose powder	50	10.2
Hydroxypropylcellulose	20	4.1
Sodium croscarmellose	27	5.5
Colloidal silica (Aerosil®)	4	0.8
Magnesium stearate	4	0.8

* Compound P: (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

CLAIMS

1. Pharmaceutical composition comprising, as active principles, (i) at least one α-glucosidase inhibitor and (ii) at least one compound of the formula (I), in combination with one or more pharmaceutically acceptable excipients, the compound of the formula (I) being defined as follows:



(I)

in which the groups A and B are chosen, independently of each other, from:

- a mono-, bi- or tricyclic aryl group containing from 6 to 14 carbon atoms;
- a heteroaromatic group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienyl groups;
- an alkyl group containing from 1 to 14 carbon atoms;
- a cycloalkyl group containing from 5 to 8 carbon atoms;
- a saturated heterocyclic group chosen from tetrahydrofuryl, tetrahydropyranyl, piperidyl and pyrrolidinyl groups;

the groups A and B possibly bearing 1 to 3 substituents chosen from a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_6-C_{14} aryl group, a heteroaryl group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienyl, a (C_6-C_{14})aryl(C_1-C_6)alkyl group, a (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl group, a halogen or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, nitro, amino, carboxyl, (C_1-C_6)alkoxycarbonyl, carbamoyl, (C_1-C_6)alkylsulfonyl, sulfoamino, (C_1-C_6)alkylsulfonylamino, sulfamoyl or (C_1-C_6)alkylcarbonylamino group;

or two of the substituents forming a methylenedioxy group, a solvate thereof or a salt of this acid.

2. Composition according to Claim 1 for treating diabetes.

3. Composition according to either of Claims 1 and 2 for treating non-insulin-dependent diabetes.

4. Composition according to Claim 1 for treating at least one of the pathologies associated with insulin resistance syndrome, more particularly chosen from dyslipidaemia, obesity, arterial hypertension, and microvascular and macrovascular complications, for instance atherosclerosis, retinopathies, nephropathies and neuropathies.

5. Pharmaceutical composition according to any one of Claims 1 to 4, characterised in that the weight ratio of α-glycosidase inhibitor to the compound of the formula (I) ranges from 10^{-3} to 40, preferably from 10^{-3} to 10 and better still from 10^{-3} to 5.

6. Pharmaceutical composition according to any one of the preceding claims, characterised in that the α-glucosidase inhibitor is chosen from acarbose, miglitol, voglibose and emiglitate.

7. Composition according to any one of the preceding claims, characterised in that the compound of the formula (I) is chosen from:

- 2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- 2-cyclohexylmethyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-phenyl-4-oxobutanoic acid
- 2-(β-naphthylmethyl)-4-phenyl-4-oxobutanoic acid
- 2-benzyl-4-(β-naphthyl)-4-oxobutanoic acid
- 2-[(4-chlorophenyl)methyl]-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-methylphenyl)-4-oxobutanoic acid
- 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-4-oxobutanoic acid
- 2-benzyl-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-cyclohexyl-4-oxobutanoic acid
- 4-phenyl-2-[(tetrahydrofur-2-yl)methyl]-4-oxobutanoic acid,

the solvates, enantiomers and salts of these acids.

8. Composition according to Claim 7, characterised in that the compound of the formula (I) is chosen from:

- (-)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- (+)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- (-)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

9. Composition according to any one of the preceding claims, which is suitable for oral administration.

10. Use of an α-glucosidase inhibitor in combination with a compound of the formula (I) as defined in Claim 1 for the preparation of a medicinal combination for treating diabetes.

11. Use according to Claim 10 for the preparation of a medicinal combination for treating non-insulin-dependent diabetes.

12. Use of an α-glucosidase inhibitor in combination with a compound of the formula (I) as defined in Claim 1 for the preparation of a medicinal combination for treating at least one of the pathologies associated with insulin resistance syndrome, more particularly chosen from dyslipidaemia, obesity, arterial hypertension, and microvascular and macrovascular complications, for instance atherosclerosis, retinopathies, nephropathies and neuropathies.

13. Use according to any one of Claims 10 to 12, characterised in that the α-glucosidase inhibitor is chosen from acarbose, miglitol, voglibose and emiglitate.

14. Use according to one of Claims 10 to 13, characterised in that the compound of the formula (I) is chosen from:

- 2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- 2-cyclohexylmethyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-phenyl-4-oxobutanoic acid
- 2-(β-naphthylmethyl)-4-phenyl-4-oxobutanoic acid

- 2-benzyl-4-(β-naphthyl)-4-oxobutanoic acid
- 2-[(4-chlorophenyl)methyl]-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-methylphenyl)-4-oxobutanoic acid
- 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-4-oxobutanoic acid
- 2-benzyl-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-cyclohexyl-4-oxobutanoic acid
- 4-phenyl-2-[(tetrahydrofur-2-yl)methyl]-4-oxobutanoic acid,

the solvates, enantiomers and salts of these acids.

15. Use according to any one of Claims 10 to 14, characterised in that the medicinal combination is in the form of a unit dose comprising an α-glucosidase inhibitor and a compound of the formula (I).

16. Use according to the preceding claim, characterised in that the unit dose comprises from 0.1 mg to 400 mg of an α-glucosidase inhibitor and from 12.5 to 400 mg of compound of the formula (I).