Title: CONTROL OF METABOLIC ABNORMALITIES

Abstract: The invention relates to the control of metabolic abnormalities in an individual using embutsartan.
Control of metabolic abnormalities

Technical field

The invention relates to the control of metabolic abnormalities in an individual.

Background

Type II diabetes mellitus is defined by increased levels of blood glucose (e.g. fasting plasma glucose concentration of 7.0 mmol/l or greater). However, individuals with diabetes typically also have other metabolic abnormalities including lipoprotein disturbances characterised by low levels of high density lipoprotein (HDL) cholesterol and high levels of triglycerides. Such metabolic abnormalities are important determinants of the cardiovascular complications of diabetes, including diseases of the heart and kidneys.

In an effort to prevent the complications of diabetes, a variety of classes of agents have been used for the control of blood glucose in patients with diabetes including: (a) insulin sensitisers such as: glitazones (e.g. troglitazone, pioglitazone, enoglitzazone, rosiglitazone, and the like); biguanides such as: phenformin and metformin; protein tyrosine phosphatase 1-B inhibitors; and dipeptidyl peptidase IV inhibitors; (b) insulin or insulin mimetics; and (c) sulfonylureas such as tolbutamide and glipizide. α glucosidase inhibitors, examples of which include miglitol, voglibose and acarbose, have also been used for the control of blood glucose. There are a number of limitations that apply to the use of some agents including side effects at doses often required for effective blood glucose control. This has limited the use of some agents in clinical practice.

Angiotensin II receptor blockers (ARBs) such as losartan and irbesartan are typically used for the treatment of hypertension in a range of patient groups including for example, those with diabetes or a pre-diabetic condition; see for example WO2004/017896A2 to Merck & Co., Inc. According to WO2004/017896A2, an individual having any of these conditions may have one or more of hyperglycemia, dyslipidemia and hypertension. The therapy provided in WO2004/017896A2 is based on the key finding therein that a dual peroxisome proliferator activated receptor α/γ (PPARα/γ)
agonist can be used for treatment of both hyperglycemia and dyslipidemia and accordingly, when combined with an ARB, the three major contributors to diabetic complications, hyperglycemia, dyslipidemia and hypertension, can be treated. Specifically, WO2004/017896A2 discusses a combination of a dual PPARα/γ agonist (such as cinnamates and dihydrocinnamates, L-tyrosine derivatives, phenyl propanoic acid and other propanoic acid derivatives, propionic acid derivatives, iso-oxazolidinedione and oxazolidinedione derivatives, thiazolidinedione, trycyclics, carboxylic acids, malonic acids, oxobenzylglycine derivatives, alkanoate derivatives, benzamide derivatives, glitazones, phenyalkyloxy phenyl derivatives and isoprenols) for the purpose of treating hyperglycemia and dyslipidemia, with an ARB for the purpose of treating hypertension.

Certain ARBs are also partial PPARγ agonists and accordingly, may be useful for treatment of disease where hyperglycemia, dyslipidemia and hypertension are major contributors to morbidity and mortality; see WO2004/014308 to Bethesda Pharmaceuticals, Inc. It is important to note that according to WO2004/014308, not all ARBs of the sartan class are capable of partial agonism of the γ receptors so as to sufficiently normalise carbohydrate and lipid metabolism for treatment of hyperglycemia and dyslipidemia. Indeed, according to WO2004/014308, only certain ARBs have this potential, specifically, telmisartan and irbesartan. According to WO2004/014308, other ARBs such as valsartan, losartan, candesartan, olmesartan and eprosartan do not partially activate PPARγ at achievable therapeutic doses sufficient to promote adipogenesis and hence treat dyslipidemia. However, some of these compounds are discussed in WO2004/014308 as being appropriate in combination therapy with telmisartan or irbesartan as a hypotensive agent. According to WO2004/014308, because ARBs have important structural chemical differences, any unusual or unexpected results obtained with one ARB cannot be used to predict that similar results would be obtained with another ARB.

Summary

In certain embodiments there is provided a use of embusartan for controlling blood glucose level in an individual.
In still further embodiments there is provided a composition for use in controlling blood glucose level in an individual, the composition including embusartan and an \( \alpha \)-glucosidase inhibitor, the composition being further characterised in that it does not contain a dual PPAR\( \alpha/\gamma \) agonist.

In other embodiments there is provided a composition for use in controlling blood glucose level in an individual, the composition consisting essentially of embusartan and an \( \alpha \)-glucosidase inhibitor.

In further embodiments there is provided a composition for use in controlling blood glucose level in an individual, the composition consisting of embusartan and an \( \alpha \)-glucosidase inhibitor.

In other embodiments there is provided a use of embusartan in the manufacture of a medicament for controlling blood glucose level in an individual.

In further embodiments there is provided a combination therapy for controlling blood glucose level in an individual, the therapy consisting of providing embusartan and providing an \( \alpha \)-glucosidase inhibitor to the individual.

In certain embodiments there is provided a use of embusartan for treating an individual for diabetes mellitus.

In still further embodiments there is provided a composition for use in treating an individual for diabetes mellitus, the composition including embusartan and an \( \alpha \)-glucosidase inhibitor, the composition being further characterised in that it does not contain a dual PPAR\( \alpha/\gamma \) agonist.

In other embodiments there is provided a composition for use in treating an individual for diabetes mellitus, the composition consisting essentially of embusartan and an \( \alpha \)-glucosidase inhibitor.
In further embodiments there is provided a composition for use in treating an individual for diabetes mellitus, the composition consisting of embusartan and an $\alpha$-glucosidase inhibitor.

In other embodiments there is provided a use of embusartan in the manufacture of a medicament for treating an individual for diabetes mellitus.

In further embodiments there is provided a combination therapy for treating an individual for diabetes mellitus, the therapy consisting of providing embusartan and providing an $\alpha$-glucosidase inhibitor to the individual.

In certain embodiments there is provided a use of embusartan for the prevention of new onset diabetes mellitus in an individual.

In still further embodiments there is provided a composition for use in the prevention of new onset diabetes mellitus in an individual, the composition including embusartan and an $\alpha$-glucosidase inhibitor, the composition being further characterised in that it does not contain a dual PPAR$\alpha/\gamma$ agonist.

In other embodiments there is provided a composition for use in the prevention of new onset diabetes mellitus in an individual, the composition consisting essentially of embusartan and an $\alpha$-glucosidase inhibitor.

In further embodiments there is provided a composition for use in the prevention of new onset diabetes mellitus in an individual, the composition consisting of embusartan and an $\alpha$-glucosidase inhibitor.

In other embodiments there is provided a use of embusartan in the manufacture of a medicament for the prevention of new onset diabetes mellitus in an individual.

In further embodiments there is provided a combination therapy for the prevention of new onset diabetes mellitus in an individual, the therapy consisting of providing embusartan and providing an $\alpha$-glucosidase inhibitor to the individual.
In certain embodiments there is provided a use of embusartan for treating an individual having a condition characterised by abnormal PPARγ function.

In still further embodiments there is provided a composition for use in treating an individual having a condition characterised by abnormal PPARγ function, the composition including embusartan and an α-glucosidase inhibitor, the composition being further characterised in that it does not contain a dual PPARα/γ agonist.

In other embodiments there is provided a composition for use in treating an individual having a condition characterised by abnormal PPARγ function, the composition consisting essentially of embusartan and an α-glucosidase inhibitor.

In further embodiments there is provided a composition for use in treating an individual having a condition characterised by abnormal PPARγ function, the composition consisting of embusartan and an α-glucosidase inhibitor.

In other embodiments there is provided a use of embusartan in the manufacture of a medicament for treating an individual having a condition characterised by abnormal PPARγ function.

In further embodiments there is provided a combination therapy for treating an individual having a condition characterised by abnormal PPARγ function, the therapy consisting of providing embusartan and providing an α-glucosidase inhibitor to the individual.

In certain embodiments there is provided a use of embusartan for controlling blood pressure in an individual.

In still further embodiments there is provided a composition for use in controlling blood pressure in an individual, the composition including embusartan and an α-glucosidase inhibitor, the composition being further characterised in that it does not contain a dual PPARα/γ agonist.
In other embodiments there is provided a composition for use in controlling blood pressure in an individual, the composition consisting essentially of embusartan and an \( \alpha \)-glucosidase inhibitor.

In further embodiments there is provided a composition for use in controlling blood pressure in an individual, the composition consisting of embusartan and an \( \alpha \)-glucosidase inhibitor.

In other embodiments there is provided a use of embusartan in the manufacture of a medicament for controlling blood pressure in an individual.

In further embodiments there is provided a combination therapy for controlling blood pressure in an individual, the therapy consisting of providing embusartan and providing an \( \alpha \)-glucosidase inhibitor to the individual.

In further embodiments there is provided a use of embusartan for controlling blood triglycerides in an individual.

In still further embodiments there is provided a composition for use in controlling blood triglycerides in an individual, the composition including embusartan and an \( \alpha \)-glucosidase inhibitor, the composition being further characterised in that it does not contain a dual PPAR\( \alpha/\gamma \) agonist.

In other embodiments there is provided a composition for use in controlling blood triglycerides in an individual, the composition consisting essentially of embusartan and an \( \alpha \)-glucosidase inhibitor.

In further embodiments there is provided a composition for use in controlling blood triglycerides in an individual, the composition consisting of embusartan and an \( \alpha \)-glucosidase inhibitor.

In other embodiments there is provided a use of embusartan in the manufacture of a medicament for controlling blood triglycerides in an individual.
In further embodiments there is provided a method of preventing the development of new onset diabetes mellitus in an individual including:

- selecting an individual having a pre-diabetic state; and

- administering embusartan to a selected individual.

Typically the pre-diabetic state consists of one or more of metabolic syndrome, impaired glucose tolerance, impaired fasting glucose and insulin resistance. In certain embodiments, the selected individual does not have hypertension.

**Brief description of the figure**

Figure 1. Activation of PPARγ receptor 24 hr after compound stimulation in stably transfected CHO cells (GAL4 system).

**Detailed description of the embodiments**

Embusartan, (methyl 6-butyl-1-[[3-fluoro-2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-oxo-1,2-dihydropyridine-4-carboxylate) is a trisubstituted biphenyl compound, the key use of which has been in the treatment of hypertension: see US Patent number 5,596,006 to Bayer Aktiengesellschaft.
The inventors have surprisingly found that embusartan is also a full selective activator of PPARγ. Indeed, as discussed herein, the inventors have found that embusartan is a full PPARγ agonist with an EC50 value between 15 and 20 µM in the GAL4 system.

Given this activity, the inventors have recognised that embusartan has additional new uses, not only for the control of blood glucose levels in diabetic and pre-diabetic conditions, but also for improvement in lipid metabolism, and for control of blood pressure (the latter being distinct from treatment of hypertension). A further advantage of embusartan is that this compound has potential for treatment of atherosclerosis, a condition that is common to many individuals having diabetes or a pre-diabetic state and some other conditions characterised by abnormal blood glucose level.

In the specification and claims "embusartan" includes methyl 6-butyl-1-[(3-fluoro-2'-1H-tetrazol-5-yl)bisphenyl-4-yI]-methyl]-2-oxo-1,2-dihydropyridine-4-carboxylate, its
polymorphs, solvates, hydrates, pharmaceutically acceptable salts, and combinations thereof.

Accordingly in certain embodiments there is provided a use of embusartan for controlling blood glucose in an individual. An individual suitable for treatment with this method may have diabetes or a pre-diabetic state such as metabolic syndrome, impaired glucose tolerance, impaired fasting glucose, insulin resistance or syndrome X.

Such individuals may have elevated blood glucose levels, or in other words, an impaired fasting blood glucose of 110mg/dL or greater or a two-hour 75-g oral glucose tolerance test value of 140 mg/dL or greater. Typically, in accordance with the method, blood glucose is lowered so as to achieve a blood glucose level characterised by an impaired fasting blood glucose of less than 110mg/dL or a two-hour 75-g oral glucose tolerance test values of less than 140 mg/dL.

In this embodiment, the individual may have elevated levels of haemoglobin A1c.

The individual may or may not have hypertension. Generally speaking, hypertension is present when the systolic blood pressure is greater than about 140 mmHg or when the diastolic blood pressure is greater than about 90 mmHg.

Useful amounts of embusartan include about 50 mg to 400 mg daily. Embusartan can be provided once daily or twice daily (i.e. once with a morning meal and once with an evening meal), although other dosage schedules may be more appropriate in circumstances with which the skilled worker is familiar.

In certain embodiments, the method consists of the step of providing embusartan alone. However, it will be understood that in other embodiments, the method may consist essentially of providing embusartan with another compound for controlling blood glucose levels (or related indices), such as an α-glucosidase inhibitor. An example of a useful α-glucosidase inhibitor is acarbose. In such embodiments acarbose can be provided in amounts as low as from about 25 to 300 mg per day, preferably 100 to 200 mg per day. One skilled in the art will appreciate that these amounts of acarbose are
between one-third and two-thirds less than required for treatment when acarbose is the only agent used for lowering blood glucose. Accordingly, one advantage of this embodiment is that, in providing synergy between embusartan and acarbose (discussed further herein) it permits use of acarbose for control of blood glucose in a manner that avoids the toxicity often observed when acarbose is used alone at higher doses.

In further embodiments, the method includes providing embusartan, acarbose and a further compound for lowering blood glucose (such as a glitazone or a biguanide), provided that the further compound is not a dual PPAR\(\alpha/\gamma\) agonist. Examples of useful molecules include metformin and rosiglitazone. These are typically applied in daily amounts ranging from 850-2550 mg and 4-8 mg, respectively.

Typically embusartan or embusartan and another compound such as acarbose is provided as a tablet, pill or other formulation suitable for oral administration. These compounds may be combined to provide a composition or they may be provided sequentially as separate compounds. These formulations are discussed in further detail below.

In other embodiments there is provided a use of embusartan for treating diabetes mellitus in an individual. Generally speaking, a hallmark of diabetes mellitus is a blood glucose concentration of 7.0 mmol/l or greater.

The individual may or may not have hypertension.

Useful amounts of embusartan include about 50 mg to 400 mg daily, preferably 100 to 200 mg daily. Embusartan can be provided once daily or twice daily (i.e once with a morning meal and once with an evening meal), although other dosage schedules may be more appropriate in circumstances with which the skilled worker is familiar.

In certain embodiments, the method consists of providing embusartan alone. However, it will be understood that in other embodiments, the method may consist of providing embusartan with another compound for the treatment of diabetes, such as an \(\alpha\) glucosidase inhibitor. An example of a useful \(\alpha\) glucosidase inhibitor is acarbose. In
such embodiments acarbose can be provided in amounts as low as from about 25 to 300 mg per day, preferably 100 to 200 mg per day. Other examples of glucosidase inhibitors include miglitol and voglibose.

In further embodiments, the method includes providing embusartan, acarbose and a further compound for the treatment of diabetes glucose (such as a glitazone or a biguanide), provided that the further compound is not a dual PPARα/γ agonist. Examples of useful molecules include metformin and rosiglitazone. These are typically applied in daily amounts ranging from 850-2550 mg and 4-8 mg, respectively.

Typically embusartan or embusartan and another compound such as acarbose is provided as a tablet, pill or other formulation suitable for oral administration. These compounds may be combined to provide a composition or they may be provided sequentially as separate compounds. These formulations are discussed in further detail below.

In other embodiments there is provided a use of embusartan for preventing the new onset of diabetes (usually defined on the basis of a fasting blood glucose concentration of 7.0 mmol/l or more) in an individual. The pre-diabetic state may be characterised by metabolic syndrome, impaired glucose tolerance, impaired fasting glucose, insulin resistance or syndrome X. Useful amounts of embusartan range from 50 to 400 mg daily, preferably 100 to 200 mg daily.

The individual may or may not have hypertension.

Useful amounts of embusartan range from about 50 mg to 400 mg daily, preferably 100 to 200 mg daily. Embusartan can be provided once daily or twice daily (i.e. once with a morning meal and once with an evening meal), although other dosage schedules may be more appropriate in circumstances with which the skilled worker is familiar.

In certain embodiments, the method consists of providing embusartan alone. However, it will be understood that in other embodiments, the method may consist of providing embusartan with another compound for preventing diabetes, such as an α glucosidase
inhibitor. An example of a useful α glucosidase inhibitor is acarbose. In such embodiments acarbose may be provided in doses as low as from about 25 to 300 mg per day, preferably 10 to 100 mg per day. Other examples of glucosidase inhibitors include miglitol and voglibose.

In further embodiments, the method includes providing embusartan, acarbose and a further compound for preventing diabetes (such as a glitazone or a biguanide), provided that the further compound is not a dual PPARα/γ agonist. Examples of useful molecules include metformin and rosiglitazone. These are typically applied in daily amounts ranging from 850-2550 mg and 4-8 mg, respectively.

Typically embusartan or embusartan and another compound such as acarbose is provided as a tablet, pill or other formulation suitable for oral administration. These compounds may be combined to provide a composition or they may be provided sequentially as separate compounds. These formulations are discussed in further detail below.

In certain embodiments there is provided a use of embusartan for treating an individual having a condition characterised by abnormal PPARγ function. Abnormal PPARγ function is characterised by comprised, defective, or otherwise reduced PPARγ activation. Examples of conditions characterised by abnormal PPARγ function include proliferative, autoimmune, immunomodulatory and inflammatory disease and certain infective disease.

Useful amounts of embusartan range from about 50 mg to 400 mg daily, preferably 100 to 200 mg daily. Embusartan can be provided once daily or twice daily (i.e once with a morning meal and once with an evening meal), although other dosage schedules may be more appropriate in circumstances with which the skilled worker is familiar.

In certain embodiments, the method consists of providing embusartan alone. However, it will be understood that in other embodiments, the method may consist of providing embusartan with another compound for treating an individual having a condition characterised by abnormal PPARγ function, such as an α glucosidase inhibitor. An
example of a useful α-glucosidase inhibitor is acarbose. In such embodiments acarbose may be provided in amounts as low as from about 25 to 300 mg per day, preferably 10 to 100 mg per day. Other examples of glucosidase inhibitors include miglitol and voglibose.

In further embodiments, the method includes the step of providing embusartan, acarbose and a further compound for treating an individual having a condition characterised by abnormal PPARγ function (such as a glitazone or a biguanide), provided that the further compound is not a dual PPARα/γ agonist. Examples of useful molecules include metformin and rosiglitazone. These are typically applied in daily amounts ranging from 850-2550 mg and 4-8 mg, respectively.

Typically embusartan or embusartan and another compound such as acarbose is provided as a tablet, pill or other formulation suitable for oral administration. These compounds may be combined to provide a composition or they may be provided sequentially as separate compounds. These formulations are discussed in further detail below.

In other embodiments there is provided a use of embusartan for controlling blood pressure in an individual. The individual may have a systolic blood pressure of less than about 140 mmHg and/or a diastolic blood pressure of less than about 90 mmHg. An individual suitable for treatment with this method may have diabetes or a pre-diabetic state such as metabolic syndrome, impaired glucose tolerance, impaired fasting glucose, insulin resistance or syndrome X.

Useful amounts of embusartan include about 50 mg to 400 mg daily, preferably 100 to 200 mg daily. Embusartan can be provided once daily or twice daily (i.e. once with a morning meal and once with an evening meal), although other dosage schedules may be more appropriate in circumstances with which the skilled worker is familiar.

In certain embodiments, the method consists of providing embusartan alone. However, it will be understood that in other embodiments, the method may consist of providing embusartan with another compound suitable for the treatment of patients with diabetes
or a pre-diabetic state, such as an $\alpha$ glucosidase inhibitor. In such embodiments acarbose can be provided in amounts as low as 100 or 200 mg per day. Accordingly, one advantage of this embodiment is that it permits the use of a low dose of acarbose. Other examples of glucosidase inhibitors include miglitol and voglibose.

In further embodiments, the method includes providing embusartan, acarbose and a further compound for lowering blood pressure (such as a diuretic, a calcium channel blocker or an angiotensin converting enzyme inhibitor), provided that the further compound is not a dual PPAR$\alpha$/gamma agonist. Examples of useful molecules include hydrochlorothiazide, amlodipine, and ramipril. These are typically applied in daily amounts ranging from 25-100 mg, 2.5-10 mg and 5-10 mg, respectively.

Typically embusartan or embusartan and another compound such as acarbose is provided as a tablet, pill or other formulation suitable for oral administration. These compounds may be combined to provide a composition or they may be provided sequentially as separate compounds. These formulations are discussed in further detail below.

Embusartan, the combination of embusartan and an $\alpha$ glucosidase inhibitor and certain other combinations including these compounds and others (but not including a compound that is dual PPAR$\alpha$/gamma agonist) are useful for the prevention or treatment of diabetes and for reducing the risk of the complications of diabetes, such microvascular and macrovascular diseases, through effects on blood glucose (or related indices such as haemoglobin A1c), dyslipidaemia, PPARgamma or blood pressure. These treatments should be useful for such patients, irrespective of the presence or absence of hypertension.

The group of individuals mentioned herein as being likely to benefit from embusartan, the combination of embusartan and acarbose or other combinations including these compounds includes but is not limited to patients with diabetes, those at risk of developing diabetes, individuals with an increased body mass index (greater than 25 kg/m$^2$), patients with a disease characterised by abnormal PPARgamma function, those at risk of developing a disease characterised by abnormal PPARgamma function, individuals at
risk of developing hypertension, patients with a disturbance of lipid metabolism (such as for example triglycerides > 150 mg/dl or low density lipoprotein > 130 mg/dl cholesterol or total cholesterol > 200 mg/dl or high density lipoprotein cholesterol < 60 mg/dl), patients with renal dysfunction (such as for example, those with a plasma creatinine level greater than 1.5 mg/dl in men and 1.4 mg/dl in women), individuals with a pre-diabetic state (such as for example metabolic syndrome, impaired glucose tolerance, impaired fasting glucose, insulin resistance or syndrome X), and patients with first-degree relatives who are suffering or have suffered from diabetes.

Preference is given to the group of patients with diabetes or patients at increased risk of developing new onset diabetes, such as those with a pre-diabetic state (for example metabolic syndrome, impaired glucose tolerance, impaired fasting glucose, insulin resistance or syndrome X).

Metabolic syndrome or syndrome X is defined here on the basis of NCEP ATP III criteria, which are the presence of three or more of the following factors: 1) increased waist circumference (>102 cm [>40 in] for men, >88 cm [>35 in] for women); 2) elevated triglycerides (≥150 mg/dl); 3) low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); 4) non-optimal blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic); and 5) impaired fasting glucose (≥110 mg/dl).

Impaired glucose tolerance and impaired fasting glucose is defined here on the basis of American Diabetes Association criteria. Impaired glucose tolerance is two-hour 75-g oral glucose tolerance test values of 140 to 199 mg per dL (7.8 to 11.0 mmol/l). Impaired fasting glucose is defined as fasting plasma glucose values of 100 to 125 mg per dL (5.6 to 6.9 mmol/l).

Insulin resistance is defined here as a fasting blood insulin level greater than 20 mcU/mL.

On use of the combination therapy, two unexpected synergistic effects are observed in the action. Surprisingly, a synergistic effect on blood pressure is achieved by administering the combination according to an embodiment of the invention compared
with the administration of embusartan alone, i.e. blood pressure control is improved by the combination beyond that which can be achieved by embusartan alone. Also surprisingly, a synergistic effect on blood glucose level is achieved by administering the combination according to an embodiment of the invention compared with administering acarbose alone, i.e. blood glucose control is improved by the combination beyond that which can be achieved by acarbose alone. As consequence of these synergistic effects, it is possible to reduce the employed amounts of acarbose used in the combination compared with the amounts required for monotherapy. Additionally, as a consequence of these synergistic effects, it is possible to reduce the frequency of the administration of acarbose to two times per day compared the three times daily requirement for acarbose when used alone.

It may be expedient where appropriate to supplement the combination therapy by adding one or more further components. Examples which may be mentioned are HMG CoA reductase inhibitors (i.e. statins) or platelet aggregation inhibitors (for example, aspirin). These other components may be added singly or together.

The combination therapy is further distinguished by a surprisingly good tolerability. The reduction in dose and frequency of acarbose administration improves tolerability and reduces the incidence of side effects associated with higher dose, higher frequency acarbose administration.

The synergistic effect of the combination therapy of embusartan and acarbose is preferably observed when the combination therapy contains 0.01 to 30 mg/kg, in particular 0.1 to 5 mg/kg, of acarbose and 0.01 to 30 mg/kg, in particular 0.1 to 10 mg/kg, of embusartan, in each case based on kg of the individual's bodyweight on oral administration.

The synergistic effect of the combination therapy of embusartan and acarbose is furthermore also observed when the combination comprises acarbose in a dosage of 5 to 500 mg, preferably in a dosage of 30 to 350 mg, particularly preferably in a dosage of 50 to 100 mg and embusartan in a dosage of 1 to 1000 mg, preferably in a dosage of 5 to 500 mg, particularly preferably in a dosage of 25 to 500 mg.
The synergistic effect of the combination therapy of embusarten and acarbose is also observed when the active ingredients of the combination are present in a ratio of 1 : 10 to 10 : 1, preferably 1 : 5 to 5 : 1, particularly preferably 1 : 2 to 2 : 1, in relation to acarbose and embusarten. "Ratio" means the ratio by weight of the individual components.

It may where appropriate be necessary to deviate from the stated amounts, in particular depending on the bodyweight or the nature of the administration route, on the individual behaviour towards the medicament, the nature of the formulation thereof and the time or interval over which administration takes place. Thus, it may be sufficient in some cases to make do with less than the aforementioned minimum amount, whereas in other cases the upper limit mentioned must be exceeded. It may be advisable where relatively large amounts are administered to divide these into a plurality of single doses over the day.

In still further embodiments there is provided a composition for use in preventing the development of new onset diabetes mellitus in an individual, the composition including embusarten and an α-glucosidase inhibitor, the composition being further characterised in that it does not contain a dual PPARα/γ agonist. The composition may however include other components for controlling blood glucose level, so long as such additional components do not comprise a dual PPARα/γ agonist.

In other embodiments there is provided a composition for use in preventing the development of new onset diabetes mellitus in an individual, the composition consisting essentially of embusarten and an α-glucosidase inhibitor. The composition essentially does not have further components for control of blood glucose level in an individual. It may however, have other components including a pharmaceutically acceptable carrier, excipient, diluent, lubricant or like component for assisting in the manufacture, stability and half life of the composition. These are discussed further below.

In further embodiments there is provided a composition for use in preventing the development of new onset diabetes mellitus in an individual, the composition consisting of embusarten and an α-glucosidase inhibitor.
Embусartan is typically provided in the above identified compositions between about 50-400 mg daily. Typically the amount is about 100-200 mg daily. Typically the amount is about 100 mg.

Where embusartan is provided in the composition in the form of a tablet, the tablet may contain embusartan in a range between 50-100 mg. This may be taken twice a day.

Typically, the α-glucosidase inhibitor is acarbose, although other inhibitors are contemplated. Other examples of glucosidase inhibitors include miglitol and voglibose. Acarbose is typically provided in an amount of about from 25-300 mg daily. Typically the amount is about 100-200 mg daily. One skilled in the art will appreciate that these amounts of acarbose are one third to two thirds less than that required when acarbose is the only agent used for lowering blood glucose. Accordingly, one advantage of this embodiment is that it permits use of a low dose of acarbose for control of blood glucose. Typically the amount is about 100-200 mg.

Where acarbose is provided in the composition in the form of a tablet, the tablet may contain acarbose in a range between 50-100 mg. This may be taken twice a day.

A particularly useful composition is one in which embusartan is combined with acarbose. In this composition, embusartan is provided in an amount of about 50 to 400 mg daily, preferably 100 to 200 mg daily and acarbose is provided in an amount of about from 25-300 mg daily, preferably 100 to 200 mg per day.

Although somewhat dependent on dosage schedules with which one skilled in the art will be familiar, it is particularly important that this composition be provided in a form that permits the potential of the composition for control of blood glucose levels, particularly after eating, to be realised. Accordingly, typically the composition is provided in a form for oral administration, such as a pill, tablet, caplet, capsule or the like.

It is also advantageous to provide in the composition an ingredient for facilitating the potential of embusartan and acarbose to stimulate metabolism of blood glucose immediately after eating. These are discussed below.
Other useful ingredients include those for facilitating slow release of embusartan and acarbose, so as to permit normalisation of blood glucose levels during fasting. These are discussed below.

In other embodiments there is provided a use of embusartan in the manufacture of a medicament for controlling blood glucose level in an individual.

In further embodiments there is provided a use of embusartan in the manufacture of a medicament for treating an individual for diabetes mellitus.

In further embodiments there is provided a use of embusartan in the manufacture of a medicament for preventing the new onset of diabetes in a individual.

In further embodiments there is provided a use of embusartan in the manufacture of a medicament for treating an individual having a condition characterised by abnormal PPARγ function.

In further embodiments there is provided a use of embusartan in the manufacture of a medicament for controlling blood pressure in an individual.

In other embodiments, embusartan is provided with one or more of metformin, a blood pressure lowering drug, such as a diuretic, calcium channel blocker or an angiotensin converting enzyme inhibitor (provided that said drug is not a dual PPARα/γ agonist) and an CoA reductase inhibitor such as simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin and lovastatin).

Embusartan may be synthesised for use in the above embodiments according to the processes discussed in US Patent number 5,596,006 to Bayer Aktiengesellschaft, the contents of which are incorporated herein by reference in its entirety.

Typically, embusartan is provided in an amount to manufacture a medicament having a concentration of embusartan of between about 0.5 to 90% by weight. Typically where the medicament is in tablet form, embusartan is provided in the medicament in an amount of about 50 to 200 mg per tablet.
In certain embodiments, the medicament consists of embusartan as the only active ingredient. In these embodiments, the medicament may include other components including a pharmaceutically acceptable carrier, excipient, diluent, lubricant or like component for assisting in the manufacture, stability and half life of the composition. These are discussed further below.

In other embodiments, the medicament consists essentially of embusartan and one or more further active ingredients, provided that the further active ingredient is not a dual PPARα/γ agonist. An example of a further active ingredient is an α glucosidase inhibitor, such as acarbose. Other examples of glucosidase inhibitors include miglitol and voglibose. In these embodiments, the medicament may include other components including a pharmaceutically acceptable carrier, excipient, diluent, lubricant or like component for assisting in the manufacture, stability and half life of the composition. These are discussed further below.

Acarbose may be synthesised for use in the above embodiments according to the processes discussed in US 4,904,769 to Bayer Aktiengesellschaft the contents of which are incorporated herein by reference in its entirety.

Embustaran and acarbose are particularly suitable for formulation in a fixed combination in the form of a solid oral dosage form. It is generally known that the factors on which the patients’ reliability of intake (compliance) crucially depend are the number of dosage forms per time of intake and the size and weight of the (solid oral) pharmaceutical form. Hence both the number of the different medicaments to be taken separately should be as small as possible (advantage of a fixed combination), and the size and weight of a solid oral dosage form should be as small as possible while having full therapeutic potency, in order to make intake as pleasant as possible for the patient. It is thus possible to attain fixed combinations in the form of solid oral pharmaceutical formulations of minimal size and minimal weight. The fixed combinations of embusartan and acarbose accordingly provide maximum patient compliance and thus crucially improve the safety and reliability of therapy.
The release of active ingredient can be controlled by combining them and modifying the composition or the functionality. For example, the abovementioned temporal uncoupling of the onset of action is possible even in fixed combinations through delayed release of active ingredient (slowing of release) of one component.

The solid oral dosage forms mentioned herein are produced by general standard processes. Ingredients are those which are pharmaceutically accepted and physiologically unobjectionable, for example: as fillers cellulose derivatives (e.g. microcrystalline cellulose), sugars (e.g. lactose), sugar alcohols (e.g. mannitol, sorbitol), inorganic fillers (e.g. calcium phosphates), binders (e.g. polyvinylpyrrolidone, gelatin, starch derivatives and cellulose derivatives), and all other excipients required to produce pharmaceutical formulations of the desired properties, e.g. lubricants (magnesium stearate), e.g. disintegrants (e.g. crosslinked polyvinylpyrrolidone, sodium carboxymethylcellulose), e.g. wetting agents (e.g. sodium lauryl sulphate), e.g. release-slowering agents (e.g. cellulose derivatives, polyacrylic acid derivatives), e.g. stabilizers, e.g. flavourings, e.g. coloured pigments.

Liquid formulations are likewise produced by a standard method using pharmaceutically usual excipients and contain the active ingredients either dissolved or suspended. Typical administration volumes of these pharmaceutical preparations are 1 to 10 ml. Examples of excipients in these liquid formulations are: solvents (e.g. water, alcohol, natural and synthetic oils, e.g. medium chain-link triglycerides), solubilizers (e.g. glycerol, glycol derivatives), wetting agents (e.g. polysorbate, sodium lauryl sulphate), and further excipients required to produce pharmaceutical formulations of the desired properties, e.g. viscosity-increasing agents, e.g. pH-correcting agents, e.g. sweeteners and flavourings, e.g. antioxidants, e.g. stabilizers, e.g. preservatives.

The main ingredients of the shells of capsule formulations are, for example, gelatin or hydroxypropylmethylcellulose.

A combination may be not only a dosage form which contains all the components (otherwise known as fixed combinations), and combination packs containing the components separate from one another, but also components which are administered simultaneously or sequentially, as long as they are employed for the prophylaxis or treatment of the same disease.

The active ingredients of a combination can be converted in a known manner into the usual formulations, which may be liquid or solid formulations. Examples are tablets, coated tablets, pills, capsules, granules, aerosols, syrups, emulsions, suspensions, solutions.

Since a combination is well tolerated and in some cases is effective even in low dosages, a wide range of formulation variants is possible. Thus, one possibility is to formulate the individual active ingredients of a combination separately. In this case, it is not absolutely necessary for the individual active ingredients to be taken at the same time; on the contrary, sequential intake may be advantageous to achieve optimal effects. It is appropriate with such separate administration to combine the formulations of the individual active ingredients, for example tablets or capsules, simultaneously together in a suitable primary packaging. The active ingredients are present in the primary packaging in each case in separate containers which may be, for example, tubes, bottles or blister packs. Such separate packaging of the components in the joint primary packaging is also referred to as a kit.

Further formulation variants which are suitable may be fixed combinations; these are pharmaceutical forms in which the components are present together in a fixed ratio of amounts. Such fixed combinations may be, for example, in the form of oral solutions, and they are typically solid oral pharmaceutical preparations, e.g. capsules or tablets.

**Example 1**
Manufacture of a tablet composition:

120 mg of the combination of any one of Examples 9 to 12, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

5 The mixture is granulated with a 5% strength solution (m/m) of PVP in water. The granules are dried and then mixed with the magnesium stearate for 5 min. This mixture is compressed using a conventional tablet press. A guideline force used for the compression is 15 kN.

Tablet weight 232 mg, diameter 8 mm, radius of curvature 12 mm.

10 Example 2

Bioavailability of embusartan in the presence or absence of concurrent treatment with acarbose

Study population

20 healthy non-hypertensive, non-diabetic volunteers not receiving treatment with any glucose lowering agent or blood pressure lowering drug.

Design

Randomized crossover trial in which participants receive embusartan 100 mg bd plus either acarbose 100 mg bd or matching placebos. Treatment will be administered twice daily before breakfast (morning) and before dinner (evening). There are two 5-day active treatment phases separated by a one week washout period.

Outcomes
Plasma embusartan levels and its main metabolite BAY 10-6734 (M1) would be measured at 0, 2, and 8 hours after each dose on each day of the two active treatment phases.

The following indices would then be assessed comparing active acarbose and placebo treatment periods:

- Area Under the Curve (AUC) – the principle index for comparative bioavailability
- $C_{\text{max}}, C_{\text{min}}, C_{\text{max}}/C_{\text{min}}$
- Inter-subject variability in $C_{\text{max}}$ and $C_{\text{min}}$
- Intra-subject variability in $C_{\text{max}}$ and $C_{\text{min}}$
- Test/reference ratio in inter- and intra-subject variability
- Comparison of average plasma embusartan levels once steady state had been reached (day 3)

The following measures would also be taken:

- Office blood pressure measured using standard measurement protocols and electronic sphygmomanometers, recorded at the same time as plasma samples collected
- Clinical side effects including but not limited to flatulence, diarrhoea, dizziness, and headache
- Biochemical parameters including PPAR $\gamma$

Example 3

Efficacy and tolerability of embusartan in the presence or absence of concurrent treatment with acarbose

Study population

900 patients with type 2 diabetes (fasting plasma glucose $\geq 7.0$ mmol/L) and non-optimal blood pressure (JNC-7 pre-hypertension/ESH-ESC high normal blood pressure: systolic 130-139 mmHg or diastolic 80-89 mmHg; JNC-7 stage 1/ESH-ESC grade 1
hypertension: systolic 140-159 mmHg or diastolic 90-99 mmHg), not receiving treatment with any other glucose lowering agent or blood pressure lowering drug.

Design

Following a two-week placebo run-in period, eligible patients will randomized in a 3 x 3 factorial design, with 100 patients assigned to each of 9 treatment combinations. In all patients assigned active acarbose, treatment will be begin with 25 mg once daily and will be increased in a stepwise manner over two weeks until the full dose is reached. Treatment and follow-up is scheduled to continue for 12 weeks after randomization, with a further 2 week assessment following withdrawal of all study treatments.

Treatment will be administered twice daily before breakfast (or the first meal of the day) and before dinner (evening).

Number of patients allocated to study treatments

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Embusartan 100 mg</th>
<th>Embusartan 200 mg</th>
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<tr>
<td>Placebo</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Acarbose 100 mg</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Acarbose 200 mg</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Outcomes

Efficacy: Difference in systolic and diastolic blood pressures (office) from randomization to 12 weeks (embusartan 100 mg vs 200 mg vs placebo; acarbose 100 mg vs 200 mg vs placebo)

Difference in fasting blood glucose concentration from randomization to 12 weeks (embusartan 100 mg vs 200 mg vs placebo; acarbose 100 mg vs 200 mg vs placebo)

Difference in haemoglobin A1c from randomization to 12 weeks (embusartan 100 mg vs 200 mg vs placebo; acarbose 100 mg vs 200 mg vs placebo)

Difference in triglycerides, HDL cholesterol and other lipoproteins from randomization to 12 weeks (embusartan 100 mg vs 200 mg vs placebo; acarbose 100 mg vs 200 mg vs placebo)

Tolerability: Proportion of patients experiencing suspected side-effects including, but not limited to, flatulence, diarrhoea, dizziness, and headache (embusartan 100 mg vs 200 mg vs placebo; acarbose 100 mg vs 200 mg vs placebo)

Interactions: Tests of homogeneity of treatment effects (on efficacy, tolerability and safety) comparing each study treatment (doses combined) vs placebo in the presence or absence of the other study treatment (doses combined). In the presence of evidence of heterogeneity, further dose-specific analyses will be conducted to determine whether such effects are dose-dependent.

The results of this study will be used to determine the doses of embusartan and acarbose to be incorporated in the second phase of this development program.
Example 4

Efficacy and tolerability of embusartan and embusartan plus low-dose acarbose in comparison with placebo among patients managed with oral glucose-lowering agents

Study population

600 patients with type 2 diabetes (fasting plasma glucose ≥7.0 mmol/L) and non-optimal blood pressure (JNC-7 pre-hypertension/ESH-ESC high normal blood pressure: systolic 130-139 mmHg or diastolic 80-89 mmHg; JNC-7 stage 1/ESH-ESC grade 1 hypertension: systolic 140-159 mmHg or diastolic 90-99 mmHg), managed with one or more of the following: metformin, a sulfonylurea, a thiazolidinedione. Patients may be managed without antihypertensive treatment or with one or more of the following: a diuretic, a calcium antagonist or an ACE inhibitor.

Design

All potentially eligible patients will enter a two-week run-in period during which active treatment with acarbose will be increased in a stepwise manner from 25 mg once a day to the full twice daily dose used in the combination treatment. Patients that meet the entry criteria and tolerate run-in treatment will be randomized in a parallel group design with 200 patients assigned to each of three treatment conditions. The daily dose of embusartan will be equal in the two active treatment groups. Treatment assignment will be stratified background use of metformin, sulfonylurea and thiazolidinedione. Randomized treatment and follow-up is scheduled to continue initially for 12 weeks after randomization.

Treatment will be administered twice daily with the first mouthful of breakfast (morning) and the first mouthful of dinner (evening). Patients assigned embusartan alone will receive active treatment in the evening and placebo in the morning.
| Placebo vs Embusartan alone vs Composition comprising embusartan plus acarbose |
|---|---|---|
| N=200 | N=200 | N=200 |

**Outcomes**

**Efficacy:** Difference in systolic and diastolic blood pressures (office) from randomization to 12 weeks (each active treatment vs. placebo; each active treatment vs. the other)

Difference in 24 hour blood pressure profile (each active treatment vs. placebo) – subgroup of 50 patients in each group

Difference in fasting blood glucose concentration from randomization to 12 weeks (each active treatment vs placebo; each active treatment vs. the other)

Difference in haemoglobin A1c from randomization to 12 weeks (each active treatment vs placebo; each active treatment vs. the other)

Difference in triglycerides, HDL cholesterol and other lipoproteins from randomization to 12 weeks (each active treatment vs placebo; each active treatment vs. the other)

**Tolerability:** Proportion of patients experiencing suspected side-effects including, but not limited to, flatulence, diarrhoea, abdominal pain, dizziness and headache (each active treatment vs placebo)
Interactions: Tests of homogeneity of treatment effects (on efficacy and tolerability) comparing each study treatment vs placebo, stratified by oral glucose control treatment at baseline.

5 Example 5

Efficacy and tolerability of embusartan and embusartan plus low-dose acarbose in comparison with placebo among patients managed with insulin

Study population

600 patients with type 2 diabetes (fasting plasma glucose ≥ 7.0 mmol/L) and non-optimal blood pressure (JNC-7 pre-hypertension/ESH-ESC high normal blood pressure: systolic 130-139 mmHg or diastolic 80-89 mmHg; JNC-7 stage 1/ESH-ESC grade 1 hypertension: systolic 140-159 mmHg or diastolic 90-99 mmHg), managed with insulin, with or without additional oral therapy. Patients may be managed without antihypertensive treatment or with one or more of the following: a diuretic, a calcium antagonist or an ACE inhibitor.

Design

All potentially eligible patients will enter a two-week run-in period during which active treatment with acarbose will be increased in a stepwise manner from 25 mg once a day to the full twice daily dose used in the combination treatment. Patients that meet the entry criteria and tolerate run-in treatment will be randomized in a parallel group design with 200 patients assigned to each of three treatment conditions. The daily dose of embusartan will be equal in the two active treatment groups. Randomized treatment and follow-up is scheduled to continue initially for 12 weeks after randomization.
Treatment will be administered twice daily with the first mouthful of breakfast (morning) and the first mouthful of dinner (evening). Patients assigned embusartan alone will receive active treatment in the evening and placebo in the morning.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>vs</th>
<th>Embusartan alone</th>
<th>vs</th>
<th>Composition comprising embusartan plus acarbose</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=200</td>
<td></td>
<td>N=200</td>
<td></td>
<td>N=200</td>
</tr>
</tbody>
</table>

5 Outcomes

Efficacy: Difference in systolic and diastolic blood pressures (office) from randomization to 12 weeks (each active treatment vs. placebo; each active treatment vs. the other)

Difference in 24 hour blood pressure profile (each active treatment vs. placebo) – subgroup of 50 patients in each group

Difference in fasting blood glucose concentration from randomization to 12 weeks (each active treatment vs placebo; each active treatment vs. the other)

Difference in haemoglobin A1c from randomization to 12 weeks (each active treatment vs placebo; each active treatment vs. the other)

Difference in triglycerides, HDL cholesterol and other lipoproteins from randomization to 12 weeks (each active treatment vs placebo; each active treatment vs. the other)
Tolerability: Proportion of patients experiencing suspected side-effects including, but not limited to, flatulence, diarrhoea, abdominal pain, dizziness and headache (each active treatment vs placebo)

Interactions: Tests of homogeneity of treatment effects (on efficacy and tolerability) comparing each study treatment vs placebo.

Example 6

Double-blind extension of Examples 4 and 5 for assessment of safety of embusartan and embusartan plus low-dose acarbose

10 Study population

1200 patients with type 2 diabetes (fasting plasma glucose ≥ 7.0 mmol/L) and non-optimal blood pressure (JNC-7 pre-hypertension/ESH-ESC high normal blood pressure: systolic 130-139 mmHg or diastolic 80-89 mmHg; JNC-7 stage 1/ESH-ESC grade 1 hypertension: systolic 140-159 mmHg or diastolic 90-99 mmHg), managed with oral glucose lowering agents or insulin. Patients may be managed without antihypertensive treatment or with one or two of the following: diuretic, beta-blocker, alpha blocker or calcium antagonist

Design

Patients assigned embusartan alone or embusartan plus acarbose in the first 12-week phase, will continue on allocated treatment (blind to acarbose assignment and embusartan dose frequency) for a further 40 weeks. Patients assigned placebo in the first 12-week phase, will be re-randomized to embusartan alone or embusartan plus acarbose for a further 52 weeks.
Treatment will be administered twice daily with the first mouthful of breakfast (morning) and the first mouthful of dinner (evening). Patients assigned embusartan alone will receive active treatment in the evening and placebo in the morning.

<table>
<thead>
<tr>
<th>Embusartan alone</th>
<th>vs</th>
<th>Composition comprising embusartan and acarbose</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=600</td>
<td></td>
<td>N=600</td>
</tr>
</tbody>
</table>

**Outcomes**

**Safety:** Serious adverse events, including but not limited to cardiovascular mortality, acute coronary syndrome, stroke, heart failure, and total cardiovascular events.

Adverse events including but not limited to flatulence, diarrhoea, dizziness and headache.

**Example 7**

*Meta-analysis of 12-week outcomes in Examples 4 and 5 comparing embusartan alone, embusartan plus low-dose acarbose, and placebo*

**Study population**

1200 patients with type 2 diabetes (fasting plasma glucose ≥ 7.0 mmol/L) and non-optimal blood pressure (JNC-7 pre-hypertension/ESH-ESC high normal blood pressure: systolic 130-139 mmHg or diastolic 80-89 mmHg; JNC-7 stage 1/ESH-ESC grade 1 hypertension: systolic 140-159 mmHg or diastolic 90-99 mmHg), managed with one or
two oral glucose lowering agents or insulin. Patients may be managed without antihypertensive treatment or with one or two of the following: diuretic, beta-blocker, alpha blocker or calcium antagonist.

**Design**

5 All potentially eligible patients will enter a two-week run-in period during which active treatment with acarbose will be increased in a stepwise manner from 25 mg once a day to the full twice daily dose used in the combination treatment. Patients that meet the entry criteria and tolerate run-in treatment will be randomized in a parallel group design with 400 patients assigned to each of three treatment conditions. The daily dose of embusartan will be equal in the two active treatment groups. Randomized treatment and follow-up is scheduled to continue initially for 12 weeks after randomization.

Treatment will be administered twice daily with the first mouthful of breakfast (morning) and the first mouthful of dinner (evening). Patients assigned embusartan alone will receive active treatment in the evening and placebo in the morning.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>vs</th>
<th>Embusartan alone</th>
<th>vs</th>
<th>Composition comprising embusartan plus acarbose</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=400</td>
<td></td>
<td>N=400</td>
<td></td>
<td>N=400</td>
</tr>
</tbody>
</table>

**Analysis**

All statistical analyses will be conducted with stratification by study (and, thereby, the use of insulin as background therapy)
Outcomes

Efficacy: Difference in systolic and diastolic blood pressures (office) from randomization to 12 weeks (each active treatment vs. placebo; each active treatment vs. the other)

5 Difference in 24 hour blood pressure profile (each active treatment vs. placebo) – subgroup of 100 patients in each treatment group

Difference in fasting blood glucose concentration from randomization to 12 weeks (each active treatment vs placebo; each active treatment vs. the other)

10 Difference in haemoglobin A1c from randomization to 12 weeks (each active treatment vs placebo; each active treatment vs. the other)

Difference in triglycerides, HDL cholesterol and other lipoproteins from randomization to 12 weeks (each active treatment vs placebo; each active treatment vs. the other)

15 Tolerability: Proportion of patients experiencing suspected side-effects including, but not limited to, flatulence, diarrhoea, abdominal pain, dizziness and headache (each active treatment vs placebo)

Interactions: Tests of homogeneity of treatment effects (on efficacy and tolerability) between studies

20
Example 8

Efficacy and tolerability of embusartan alone or embusartan plus low-dose acarbose compared with placebo for the prevention of new onset diabetes among patients with metabolic syndrome

5 Study population

2000 patients with metabolic syndrome (as defined by NCEP III) and an estimated annual risk of developing new onset diabetes of 7.5% (for comparison, the rate in STOP-NIDDM was 12.5% annually).

Design

10 Following a two-week run-in period on low-dose acarbose (to identify those patients who cannot tolerate even a short course of such treatment), eligible patients will be randomized in a parallel group design with 1000 patients assigned active treatment and 1000 assigned to matching placebo. The decision to use embusartan alone or the combination of embusartan and acarbose would be based in part upon the result of Phase I. Treatment and follow-up would be scheduled to continue for an average of 3 years after randomization.

<table>
<thead>
<tr>
<th>Embusartan alone or composition of embusartan plus acarbose</th>
<th>vs</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1000</td>
<td></td>
<td>N=1000</td>
</tr>
</tbody>
</table>

Outcomes

20 Efficacy: Difference in incidence of new-onset diabetes (90% power to detect 25% reduction with p=0.05)
Difference in incidence of new-onset diabetes or major cardiovascular event (90% power to detect 20% reduction with \( p=0.05 \))

Difference in blood glucose, blood pressure, plasma lipids and lipoproteins, new onset micro and macro albuminurea

5 Tolerability: Proportion of patients experiencing suspected side-effects including but not limited to flatulence, diarrhoea, abdominal pain, dizziness and headache

Safety: All serious adverse events

10 Example 9

Amount of embusartan and acarbose in a composition (such as a tablet) according to the invention.

Embubstaran in a dosage of 50 mg and acarbose in a dosage of 50 mg.

Example 10

15 Amount of embusartan and acarbose in a composition (such as a tablet) according to the invention.

Embubstaran in a dosage of 50 mg and acarbose in a dosage of 100 mg.

Example 11

Amount of embusartan and acarbose in a composition (such as a tablet) according to the invention

Embubstaran in a dosage of 100 mg and acarbose in a dosage of 50 mg.
Example 12

Amount of embusartan and acarbose in a composition (such as a tablet) according to the invention

Embusartan in a dosage of 100 mg and acarbose in a dosage of 100 mg.

Example 13

Determination of PPARγ agonistic activity in vitro - assay description

A cell-based assay was used to identify peroxisome-proliferator-activated receptor gamma (PPARγ) agonists.

Since mammalian cells express different endogenous nuclear receptors, which may complicate the interpretation of experimental results, a chimeric system was used, in which the ligand binding domain of the human PPARγ protein was fused to the DNA binding domain of the yeast transcription factor GAL4. The GAL4-PPARγ fusion construct plus a reporter construct, containing GAL4 binding sites in front of the luciferase gene, were co-transfected and stably expressed in CHO (Chinese hamster ovary) cells.

Cloning

The human GAL4-PPARγ expression construct contains the ligand binding domain of PPARγ (aa 203-506). This part has been amplified by PCR and cloned into the pcDNA3.1 vector. This vector contains the GAL4 DNA binding domain (aa 1-147) of the pFC2-dbax vector (Stratagene). The reporter construct pFRLuc (Stratagene), which contains five copies of the GAL4 binding site in front of the thymidine kinase promoter leads to the expression of the firefly luciferase (Photinus pyralis) after activation of the bound GAL4-PPARγ fusion protein.
Transactivation-Assay

Stably transfected CHO (Chinese hamster ovary) cells were seeded in DMEM/ F12 media (BioWhittaker) containing 10 % FCS and 1 % penicillin/ streptomycin (GIBCO). 2 x 10^3 cells per well were seeded on a 384 well plate format (Greiner). After cultivation for 48h at 37°C, cells were stimulated.

Compounds were solved in CHO-A-SFM media (GIBCO) containing 2,5 % FCS, 1 % penicillin/ streptomycin (GIBCO) and added to the cells. After 24h of incubation luciferase activity was measured with a video camera system. The measured RLUs led to a sigmoidal dose response curve with increasing compound concentrations. EC_{50}s were calculated using the computer program GraphPad PRISM® (Version 3.02). The results are shown in Figure 1.
Claims

1. A use of embusartan for controlling blood glucose in an individual.

2. A use of embusartan for treating an individual for diabetes mellitus.

3. A use of embusartan for preventing the new onset of diabetes mellitus in an individual.

4. A use of embusartan for treating an individual having a condition characterised by abnormal PPARγ function selected from the group of diseases consisting of metabolic, endocrine, proliferative, autoimmune, immunomodulatory, inflammatory and infective diseases.

5. A use of embusartan for controlling blood pressure in an individual.

6. The use according to any one of the preceding claims wherein the individual does not have hypertension.

7. A use of embusartan for controlling blood triglycerides in an individual.

8. The use according to any one of the preceding claims wherein embusartan is provided to the individual in an amount of between about 50 to 400 mg daily.

9. The use according to any one of the preceding claims, further including providing a further compound for controlling blood glucose level.

10. The use according to claim 9 wherein the further compound is an α glucosidase inhibitor.

11. The use according to claim 10 wherein the α glucosidase inhibitor is acarbose.

12. The use according to claim 11 wherein the acarbose is provided to the individual in an amount of about 25 to 300 mg daily.
13. The use according to claim 11 wherein embusartan and acarbose are provided by providing a composition including embusartan and acarbose.

14. The use according to any one of the preceding claims, further including providing a compound for preventing diabetes to the individual, provided that the compound is not a dual PPARα/γ agonist.

15. The use according to claim 14 wherein the compound is metformin or rosiglitazone.

16. The use according to any one of the preceding claims, further including providing a compound for lowering blood pressure, provided that the compound is not a dual PPARα/γ agonist.

17. The use according to claim 16 wherein the compound is a diuretic, calcium channel blocker or an angiotensin converting enzyme inhibitor.

18. The use according to claim 17 wherein the compound is hydrochlorothiazide, amlodipine, and ramipril.

19. The use according to any one of the preceding claims, further including providing a compound for inhibiting co-enzyme A reductase.

20. The use according to claim 19 wherein the compound is selected from the group consisting of simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvasatin and lovastatin.

21. A method of preventing the development of new onset diabetes mellitus in an individual including:

- selecting an individual having a pre-diabetic state; and

- administering embusartan to a selected individual.
22. The method according to claim 21 wherein the pre-diabetic state consists of one or more of metabolic syndrome, impaired glucose tolerance, impaired fasting glucose and insulin resistance.

23. The method according to claim 21 wherein the selected individual does not have hypertension.

24. A composition for preventing the development of new onset diabetes mellitus in an individual, the composition including embusartan and an \( \alpha \)-glucosidase inhibitor, the composition being further characterised in that it does not contain a dual PPAR\( \alpha / \gamma \) agonist.

25. A composition for preventing the development of new onset diabetes mellitus in an individual, the composition consisting essentially of embusartan and an \( \alpha \)-glucosidase inhibitor.

26. The composition according to claim 25 further including a pharmaceutically acceptable carrier, excipient, diluent, lubricant or like component for assisting in the manufacture, stability or half life of the composition.

27. A composition for preventing the development of new onset diabetes mellitus in an individual, the composition consisting of embusartan and an \( \alpha \)-glucosidase inhibitor.

28. A composition according to any one of the preceding claims wherein the \( \alpha \)-glucosidase inhibitor is acarbose.

29. A kit for preventing the development of new onset diabetes mellitus in an individual including:

- an amount of embusartan effective for preventing the development of new onset diabetes mellitus in an individual; and
-instructions for using the embusartan to prevent the development of new onset diabetes mellitus in an individual.

30. The kit according to claim 29 wherein the instructions include directions to administer embusartan to an individual at risk for new onset diabetes mellitus in an amount of between about 50 to 400 mg daily.
Activation of PPARγ receptor 24 h after compound stimulation in stably transfected CHO cells (Gal4 system)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

Int. Ci.
A61K 31/4439 (2006.01) A61P 3/08 (2006.01) A61P 9/12 (2006.01)
A61P 3/06 (2006.01) A61P 3/10 (2006.01)

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)

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)
DWPI and Medline. Keywords: enbusarten, PPAR, diabetes, hypertension, hypotension, blood lipids, tumour, inflammation, glucosidase inhibitor and acarbose and related words.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>WO 2004/017896 A (MERCK &amp; Co., INC.) 4 March 2004 Pg 6, line 26 to Pg 8, Pg 9, lines 9 to 17, Pg 20 to Pg 22, Claims 5 and 13.</td>
<td>1-30</td>
</tr>
<tr>
<td>X</td>
<td>US 5596006 A (DRESSEL et al.) 21 January 1997 See abstract and Example 28.</td>
<td>4-5</td>
</tr>
</tbody>
</table>

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

A* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claims(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search
26 June 2006

Date of mailing of the international search report
11 JUL 2006

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Facsimile No. (02) 6285 3929

Authorized officer

Steven Chew
Telephone No.: (02) 6283 2248
<table>
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<td>YAMAGISHI et al. Telmisartan is a promising cardiometabolic sartan due to its unique PPAR-γ-inducing property. Medical Hypotheses, 2005, vol 64, pages 476-478. See whole article.</td>
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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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