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国際調査報告書

(54)Title: MEDICINAL COMPOSITIONS

(54)発明の名称 医薬組成物

(57) Abstract

Medicinal compositions comprising as the active ingredient one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and one or more drugs selected from the group consisting of insulin resistance improving agents. Because of showing excellent effects of inhibiting the progression of arteriosclerosis, these compositions are useful as drugs, in particular, preventives or remedies for arteriosclerosis.

（５７）要約

アンジオテンシンＩＩ受容体拮抗剤及びアンジオテンシン変換酵素阻害剤から成る群の薬剤から選択される１種又は２種以上の薬剤とインスリン抵抗性改善性剤の１種又は２種以上の薬剤を有効成分として含有する組成物は、優れた動脈硬化進展抑制作用を示し、医薬、特に、動脈硬化症の予防剤又は治療剤として有用である。

Abstract

A pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents exhibits excellent arteriosclerotic progress inhibitory effects, and is useful as a drug, particularly as a drug for the prevention or treatment of arteriosclerosis.

SPECIFICATION

Pharmaceutical Composition

[Technical Field of the Invention]

The present invention relates to a pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis), the use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents for preparing a pharmaceutical composition (particularly a composition for prevention or treatment of arteriosclerosis), and a method which comprises administering in combination effective amounts of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to warm-blooded animals for preventing or treating diseases (particularly arteriosclerosis).

[Background of the Invention]

The occurrence of atherosclerosis is increasing with the adoption of Western-style diet and the growth of the aged population. This disease is the main cause of such disorders as myocardial infarction, cerebral infarction and cerebral apoplexy, and there is a need for its effective prevention and treatment. Examples of risk factors which cause atherosclerosis include hyperlipemia (particularly hypercholesterolemia), hypertension and saccharometabolism disorders based on insulin resistance. In addition, there are many cases in which these risk factors occur in the form of complications (Syndrome X), and are considered to be mutually interrelated [Diabetes, 37, 1595-1607 (1988)].

Efforts have been made for the purpose of preventing and treating atherosclerosis by suppression of various risk factors such as hyperlipemia, hypertension and insulin resistance. Although HMG-CoA reductase inhibitors like pravastatin improve hyperlipemia, their inhibitory activity on arteriosclerosis in a case of administration alone is not enough [Biochim. Biophys. Acta, 960, 294-302 (1988)].

In addition, even insulin resistance improving agents like troglitazone do not exhibit sufficient atherosclerosis inhibitory activity in a case of administration alone (Japanese Patent Application (Kokai) No. Hei 7-41423).

On the other hand, among drugs for the treatment of hypertension, it has been reported that atherosclerotic lesions are suppressed when angiotensin converting enzyme (ACE) inhibitors that inhibit the renin-angiotensin system [Hypertension, 15, 327-331 (1990)] or angiotensin II receptor antagonists [Jpn. Circ. J., 60 (Suppl. I), 332 (1996)] are administered to animals having normal blood pressure and hypercholesterolemia. Angiotensin II not only exhibits vasoconstrictive activity, but also activity that stimulates the production of growth factors such as PDGF [Hypertension, 13, 706-711 (1989)] and activity that stimulates migration of neutrophils and macrophages [Eur. Heart J., 11, 100-107 (1990)]. Although the mechanism in which renin-angiotensin system inhibitors suppress atherosclerosis is not clear at the present time, there is a possibility that the mechanism for suppressing atherosclerosis may be a function at the site of the lesion which is different from their blood pressure lowering action. However, since inhibitors of renin-angiotensin system are unable to lower serum lipids [J. Cardiovasc. Pharmacol., 15, S65-S72 (1990)], their administration alone has limitations on the treatment of arteriosclerosis.

In addition, although troglitazone, glibenclamide and captopril are administered concomitantly to diabetes patients, there is no suggestion indicated whatsoever relating to the prevention and treatment of arteriosclerosis [Clin. Pharm., 9 (Supp. 3), 39-60 (1993)].

[Disclosure of the Invention]

As a result of earnestly conducting various research in consideration of the importance of the prevention and treatment of arteriosclerosis, the inventors of the present invention found a method to solve the above-mentioned problems involved in the prior art and to obtain a preventive and/or therapeutic effect on arteriosclerosis by using the combination of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of one or more of insulin resistance improving agents.

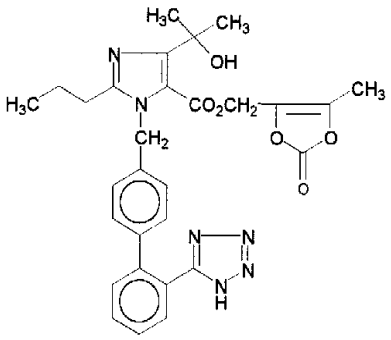
The present invention provides a pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more

insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis), the use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents for preparing a pharmaceutical composition (particularly a composition for prevention or treatment of arteriosclerosis), a method which comprises administering in combination effective amounts of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to warm-blooded animals for prevention or treatment of diseases (particularly arteriosclerosis), or a pharmaceutical composition for administering at the same time or at the different time one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis).

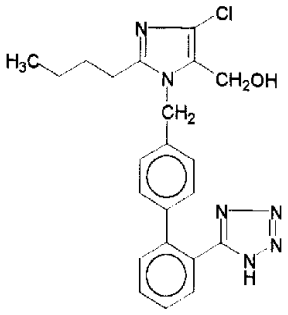
The active ingredients of the pharmaceutical composition of the present invention (particularly a pharmaceutical composition for the prevention or treatment of arteriosclerosis), or the active ingredients of a method for preventing or treating diseases (particularly arteriosclerosis) include one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents.

Representative examples of angiotensin II receptor antagonists as an active ingredient of the present invention include biphenyltetrazole compounds and biphenylcarboxylic acid compounds described in Japanese Patent Application (Kokai) No. Hei 5-78328, Japanese Patent Application (Kokai) No. Sho 63-23868, Japanese Patent Application (Kokai) No. Hei 4-364171, Japanese Patent Application (Kokai) No. Hei 4-159718 or Japanese PCT Application (Kokai) No. Hei 4-506222, preferably biphenyltetrazole compounds, more preferably CS-866, losartan, candesartan, valsartan or irbesartan, still more preferably CS-866, losartan or candesartan, and most preferably CS-866.

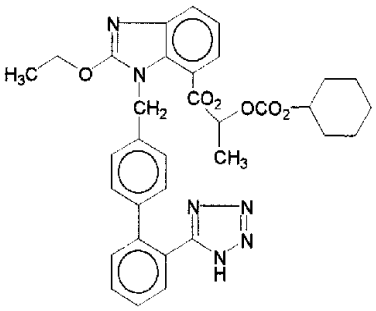
The following indicates the chemical planar structural formulae of some typical examples of angiotensin II receptor antagonists.



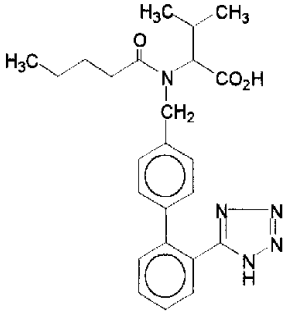
CS-866



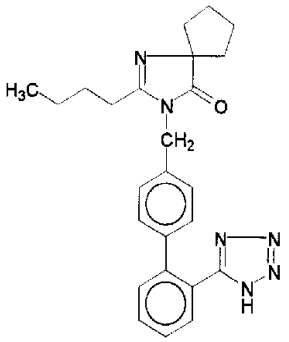
Losartan



Candesartan



Valsartan



Irbesartan

CS-866 is described in Japanese Patent Application No. (Kokai) No. Hei 5-78328 and the like, and its chemical name is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazole-5-carboxylate. The CS-866 of the present application includes its carboxylic acid derivative, pharmacologically acceptable esters of its carboxylic acid derivative (such as CS-866) and their pharmacologically acceptable salts.

Losartan (DUP-753) is described in Japanese Patent Application (Kokai) No. Sho 63-23868, U.S. Patent No. 5,138,069 and the like, and its chemical name is 2-butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-imidazole-5-methanol. The losartan of the present application includes its pharmacologically acceptable salts (such as losartan potassium salt).

Candesartan (TCV-116) is described in Japanese Patent Application (Kokai) No. Hei 4-364171, EP-459136, U.S. Patent No. 5,354,766 and the like, and its chemical name is 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-benzimidazole-7-carboxylate. The candesartan of the present application includes its carboxylic acid derivative, pharmacologically acceptable esters of its carboxylic acid derivative (such as TCV-116) and their pharmacologically acceptable salts.

Valsartan (CGP-48933) is described in Japanese Patent Application (Kokai) No. Hei 4-159718, EP-433983 and the like, and its chemical name is (S)-N-valeryl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)valine. The valsartan of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

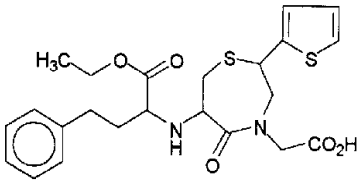
Irbesartan (SR-47436) is described in Japanese PCT Application (Kokai) No. Hei 4-506222, WO91-14679 and the like, and its chemical name is 2-N-butyl-4-spirocyclopentane-1-[2'-(tetrazol-5-yl)biphenyl-4-ylmethyl]-2-imidazolin-5-one. The irbesartan of the present application includes its pharmacologically acceptable salts.

In addition, where the above-mentioned compounds have asymmetric carbons, the angiotensin II receptor antagonists of the present invention also include optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included.

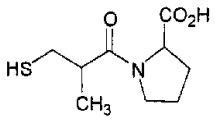
Representative examples of the angiotensin converting enzyme inhibitors as an active ingredient of the present invention include tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds,

imidazolidine compounds and isoquinoline compounds described in Japanese Patent Application (Kokai) No. Sho 61-267579, Japanese Patent Application (Kokai) No. Sho 52-116457, U.S. Patent No. 4,374,829, Japanese Patent Application (Kokai) No. Sho 58-126851, Japanese Patent Application (Kokai) No. Sho 58-206591, Japanese Patent Application (Kokai) No. Sho 57-77651, Japanese Patent Application (Kokai) No. Sho 55-9058, Japanese Patent Application (Kokai) No. Sho 58-203971 and Japanese Patent Application (Kokai) No. Sho 63-258459, preferably temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril or quinapril, more preferably temocapril, captopril or enalapril, and most preferably temocapril.

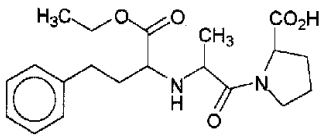
The following indicates the chemical planar structural formulae of some typical examples of angiotensin converting enzyme inhibitors.



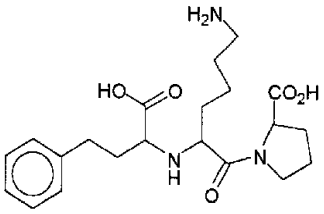
Temocapril



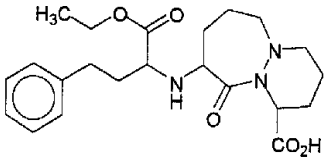
Captopril



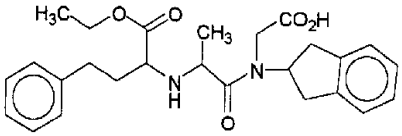
Enalapril



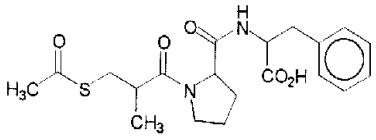
Lisinopril



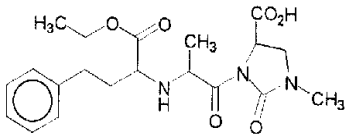
Cilazapril



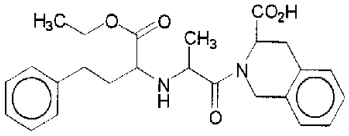
Delapril



Alacepril



Imidapril



Quinapril

Temocapril is described in Japanese Patent Application (Kokai) No. Sho 61-267579, U.S. Patent No. 4,699,905 and the like, and its chemical name is (+)-(2S,6R)-[6-(1S)-1-ethoxycarbonyl-3-phenylpropylamino]-5-oxo-2-(2-thienyl)perhydro-1,4-thiazepin-4-yl acetic acid. The temocapril of the present application includes its dicarboxylic acid derivatives, its pharmacologically acceptable salts, its pharmacologically acceptable monoesters and its pharmacologically acceptable salts (such as temocapril hydrochloride).

Captopril is described in Japanese Patent Application (Kokai) No. Sho 52-116457, U.S. Patent No. 4,046,889 and the like, and its chemical name is 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline. The captopril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

Enalapril is described in U.S. Patent No. 4,374,829 and the like, and its chemical name is N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline. The enalapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts (such as enalapril maleate).

Lisinopril is described in Japanese Patent Application (Kokai) No. Sho 58-126851, U.S. Patent No. 4,555,502 and the like, and its chemical name is (S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline. The lisinopril of the present

application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

Cilazapril is described in Japanese Patent Application (Kokai) No. Sho 58-206591, U.S. Patent No. 4,512,924 and the like, and its chemical name is (1S,9S)-9-[(S)-1-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-oxo-6H-pyridazino[1,2-α][1,2]diazepine-1-carboxylic acid. The cilazapril of the present application includes its pharmacologically acceptable esters and pharmacologically acceptable salts.

Delapril is described in Japanese Patent Application (Kokai) No. Sho 57-77651, U.S. Patent No. 4,385,051 and the like, and its chemical name is (S)-N-(2,3-dihydro-1H-inden-2-yl)-N-[N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]glycine. The delapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

Alacepril is described in Japanese Patent Application (Kokai) No. Sho 55-9058, U.S. Patent No. 4,248,883 and the like, and its chemical name is 1-(D-3-acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine. The alacepril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

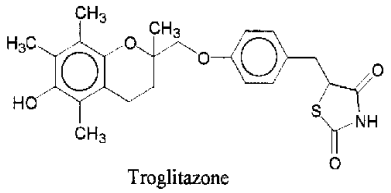
Imidapril is described in Japanese Patent Application (Kokai) No. Sho 58-203971, U.S. Patent No. 4,508,727 and the like, and its chemical name is (4S)-3-[(2S)-2-[(1S)-1-ethoxycarbonyl-3-phenylpropylamino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic acid. The imidapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

Quinapril is described in Japanese Patent Application (Kokai) No. Sho 63-258459, U.S. Patent No. 4,761,479 and the like, and its chemical name is (S)-2-[(2S)-2-(1S)-1-ethoxycarbonyl-3-phenylpropylamino)propionyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid. The quinapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

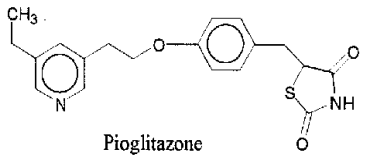
Where the above-mentioned angiotensin converting enzyme inhibitors of the present invention have asymmetric carbons, said angiotensin converting enzyme inhibitors of the present invention also include their optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included in the present invention.

The insulin resistance improving agents as another active ingredient of the present invention are inherently used for the prevention and treatment of diabetes. Representative examples include thiazolidinedione compounds, oxazolidinedione compounds or oxadiazolidinedione compounds described in Japanese Patent Application (Kokai) No. Hei 4-69383, WO 89/08651, WO 91/07107, WO 92/02520, WO 94/01433, USP-4287200, USP-4340605, USP-4438141, USP-4444779, USP-4461902, USP-4572912, USP-4687777, USP-4703052, USP-4725610, USP-4873255, USP-4897393, USP-4897405, USP-4918091, USP-4948900, USP-5002953, USP-5061717, USP-5120754, USP-5132317, USP-5194443, USP-5223522, USP-5232925 and USP-5260445, preferably thiazolidinedione compounds, more preferably troglitazone, pioglitazone, englitazone or BRL-49653, still more preferably troglitazone or pioglitazone, and most preferably troglitazone.

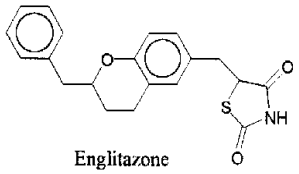
The following indicates the chemical planar structural formulae of some typical examples of insulin resistance improving agents.



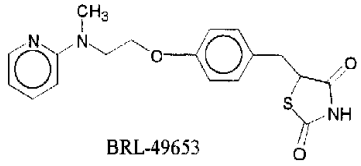
Troglitazone



Pioglitazone



Englitazone



BRL-49653

Troglitazone is described in Japanese Patent Application (Kokai) No. Sho 60-51189, U.S. Patent No. 4,572,912 and the like, and its chemical name is 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-thiazolidinedione. The troglitazone of the present application includes its pharmacologically acceptable salts.

Pioglitazone is described in Japanese Patent Application (Kokai) No. Sho 55-22636, U.S. Patent No. 4,287,200 and the like, and its chemical name is 5-[4-[2-(5-ethyl-pyridin-2-yl)ethoxy]phenylmethyl]-2,4-thiazolidinedione. The pioglitazone of the present application includes its pharmacologically acceptable salts.

Englitazone is described in Japanese Patent Application (Kokai) No. Sho 61-271287, U.S. Patent No. 4,703,052 and the like, and its chemical name is 5-(3,4-dihydro-2-benzyl-2H-benzopyran-6-ylmethyl)-2,4-thiazolidinedione. The englitazone of the present application includes its pharmacologically acceptable salts.

BRL-49653 is described in Japanese Patent Application (Kokai) No. Hei 1-131169, U.S. Patent No. 5,002,953 and the like, and its chemical name is 5-[4-[2-[N-methyl-N-(pyridin-2-yl)amino]ethoxy]phenylmethyl]-2,4-thiazolidinedione. The BRL-49653 of the present application includes its pharmacologically acceptable salts.

Where the above-mentioned insulin resistance improving agents of the present invention have asymmetric carbons, said resistance improving agents the present invention also include their optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included in the present invention.

In the present invention, one or more drugs are selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors (preferably the group consisting of angiotensin II receptor antagonists), and one or more insulin resistance improving agents are selected; and preferably the one drug is selected from angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and the other drug is selected from insulin resistance improving agents to use in combination.

Preferable examples of the pharmaceutical composition of the present invention are as follows:

(1) a pharmaceutical composition wherein as active ingredients, the angiotensin II receptor antagonists are chosen from biphenyltetrazole compounds and biphenylcarboxylic acid compounds and the angiotensin converting enzyme inhibitors are chosen from tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds;

(2) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme

inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril;

(3) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril;

(4) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril;

(5) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan;

(6) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866;

(7) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are angiotensin II receptor antagonists;

(8) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan and irbesartan;

(9) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from angiotensin converting enzyme inhibitors;

(10) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is temocapril;

(11) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds;

(12) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;

(13) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone and pioglitazone; and,

(14) a pharmaceutical composition wherein as an active ingredient, the insulin resistance improving agent is troglitazone.

In addition, a pharmaceutical composition obtained by selecting as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors from the group (1) to (10), by selecting as active ingredients, insulin resistance improving agents from the group (11) to (14) and by combining these groups in an arbitrary manner is also preferable, examples of which are as follows:

(15) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;

(16) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;

(17) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone;

(18) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone;

(19) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme

inhibitors is CS-866, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone;

(20) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and as the other active ingredient, the insulin resistance improving agent is troglitazone;

(21) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and as the other active ingredient, the insulin resistance improving agent is troglitazone; and,

(22) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril, and as the other active ingredient, the insulin resistance improving agent is troglitazone.

[Effect of the Invention]

A drug comprising one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents, which are the active ingredients of the pharmaceutical composition of the present invention (particularly a composition for prevention or treatment of arteriosclerosis), has excellent inhibitory action on aortosclerosis and excellent inhibitory action against onset of xanthochromia occurring in limb joints, and low toxicity. Consequently, it is useful as a drug for the prevention and treatment (particularly for treatment) of arteriosclerosis or xanthochromia.

According to the present invention, drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and insulin resistance improving agents exhibit excellent effects by using two of these agents in combination as compared with being used alone. In addition, these effects can be achieved without requiring that both types of agents be present in the body simultaneously.

Namely, such effects can be obtained even if both types of agents do not simultaneously have certain concentrations in the blood. According to hypothesis, if two types of agents used in the present invention are both incorporated in vivo and

reach the receptors, they have the effect of turning on a switch in vivo. Thus, even if it appears that such effects are not demonstrated at their blood concentrations in course of time after their administration, the switch is actually still on, thereby allowing demonstration of preventive or therapeutic effects on arterial sclerosis possessed by the one type of substance. When the other type of agent is administered in this state, in addition to the preventive or therapeutic effects on arterial sclerosis possessed by that agent, the effects of the drug initially administered are combined to obtain excellent effects. Naturally, since it is convenient clinically to administer two types of agents simultaneously, drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and an insulin resistance improving agent can be administered in the form of a combination drug. In cases where it is undesirable to physically mix both agents simultaneously in consideration of pharmaceutical formulation technology, each individual agent may be administered simultaneously. In addition, as was stated above, since excellent effects are demonstrated even if the two types of agents are not administered simultaneously, each individual agent can also be administered at a suitable interval in succession. The maximum administration interval of the two types of agents to demonstrate the excellent effects brought about by said two types of agents can be determined by clinical or animal studies.

[Industrial Applicability]

The administration route of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of the insulin resistance improving agents used in the present invention is typically the oral administration route. Thus, the two types of agents can either be prepared in the form of two separate administrations or in the form of a single administration by physically mixing the two types of agents. The administration form can be, for example, a powder, granules, tablet or capsule and the like, and can be prepared by using conventional pharmaceutical formulation techniques.

The dose and administration ratio of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of the insulin resistance improving agents used in the present invention can be changed over a wide range according to various conditions such as the individual activity of each agent, the patient's symptoms, age and body weight, and the like. For example, in the case of

insulin resistance improving agents, since the in vivo activities of troglitazone and BRL-49653 by using a diabetic animal model are different, the dose of these two agents may be different by a factor of ten or more. In addition, for both agents consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and insulin resistance improving agents, their doses in the case used for prevention or treatment of arteriosclerosis in the present invention can be lower than their dose for use as hypotensive agents and diabetes therapeutic agents respectively, which are their well-known applications. In addition, their doses can be made even lower due to the excellent effects resulting from combined use of both types of agents. For example, in the case of using CS-866 and troglitazone for the object of the present invention, their doses are lower than the approximately 5 to 100 mg and approximately 10 to 2000 mg, respectively, which are the doses for adults (mg/day) for use as a hypotensive agent and diabetes therapeutic agent in their well-known applications, being able to be approximately 1 to 80 mg and approximately 1 to 1000 mg, respectively.

As has been described above, the doses of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and of the insulin resistance improving agents can be varied over a wide range, in general, and their doses for adults (mg/day) are approximately 0.5 to 100 mg and approximately 0.05 to 1,500 mg, respectively.

The ratio of the doses of these two types of agents can also be varied over a wide range, in general, and the dose ratio of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors to the insulin resistance improving agents can be, in terms of weight ratio, within the range from 1:200 to 200:1.

In the present invention, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and the insulin resistance improving agents are administered at the respective doses described above once a day or divided among several times per day, and may be administered simultaneously or separately at respectively different times.

[Best Mode for Carrying Out the Invention]

The present invention will be described more specifically by way of Examples and Preparation examples, but the scope of the present invention is not limited to them.

(Example 1)

Arterial sclerosis Progress Inhibitory Effect

A certain amount of an agent was administered orally for 32 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: supra (Biochimica et Biophysica Acta), etc.] in groups of 4 to 7 animals each. Incidentally, food consumption was restricted to 120 g/day per animal. Blood samples were collected immediately before administration of the agent and 4, 8, 12, 16, 20, 24, 28 and 32 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. The test animals were subjected to autopsy in the 32nd week to investigate the surface area of aortic lesions (%) and the incidence of xanthochromia in finger joints (%). Those results are shown in Tables 1 and 2.

[Table 1]

Surface Area of Aortic Lesions

Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%) Arcuate region	Thoracic part	Abdominal region	Overall
1	CS-866 + Troglitazone	1 + 25	5	52 10	9 3	13 2	21 4
	CS-866	1	6	68 10	26 8	19 5	34 7
	Troglitazone	25	7	80 7	57 12	32 8	54 9
	Control	-	7	83 6	59 7	39 4	56 4

[Table 2]

Incidence of Xanthochromia in Finger Joints

Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%) Forelimbs	Hindlimbs	Overall
1	CS-866 + Troglitazone	1 + 25	4	75	63	69
	CS-866	1	6	100	100	100
	Troglitazone	25	7	93	86	89
	Control	-	7	100	100	100

(Example 2)

Arterial sclerosis Progress Inhibitory Effect

A certain amount of an agent was administered orally for 31 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: described supra (Biochimica et Biophysica Acta), etc.] in groups of 5 to 7 animals each. Incidentally, food consumption was restricted to 100 g/day per animal. Blood

samples were collected immediately before administration of the agent and 8, 16, 24 and 31 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. In addition, the test animals were subjected to autopsy in the 31st week to investigate the surface area of aortic lesions (%) and the incidence of xanthochromia in finger joints. Those results are shown in Tables 3 and 4.

[Table 3]

Surface Area of Aortic Lesions

Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%)			
				Arcuate region	Thoracic part	Abdominal region	Overall
2	CS-866 + pioglitazone	0.5 + 20	6	62±8	29±10	24±6	36±7
3	CS-866 + BRL-49653	0.5 + 2.5	5	52±5	32±7	25±5	34±5
	CS-866	0.5	7	66±5	41±10	32±8	44±7
	Pioglitazone	20	7	65±6	62±12	32±6	52±8
	BRL-49653	2.5	6	83±2	54±12	29±4	52±5
	Control	-	7	84±5	59±9	32±11	54±8

[Table 4]

Incidence of Xanthochromia in Finger Joints

Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%)		
				Fore-limbs	Hind-limbs	Overall
4	Candesartan + troglitazone	1 + 25	7	86	86	86
	Candesartan	1	7	100	100	100
	Troglitazone	25	7	100	86	93
	Control	-	7	100	100	100

(Formulation Example 1)

Tablets

CS-866	4.0 mg
Troglitazone	100.0
Lactose	244.0
Cornstarch	50.0
Magnesium stearate	2.0
	---
	400 mg

The above-mentioned prescriptions are mixed and formed into tablets with a tablet-making machine to obtain tablets containing 400 mg per tablet.

These tablets can be provided with a sugar-coating if necessary.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS

1. A pharmaceutical composition comprising as its active ingredients one or more insulin resistance improving agents in synergistic combination with one or more drugs chosen from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, provided that said composition does not contain a combination of troglitazone, glibenclamide and captopril.

2. A pharmaceutical composition according to Claim 1, wherein the angiotensin II receptor antagonists are chosen from biphenyl tetrazole compounds and biphenylcarboxylic acid compounds, and the angiotensin converting enzyme inhibitors are chosen from tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds.

3. A pharmaceutical composition according to Claim 1, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril.

4. A pharmaceutical composition according to Claim 1, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril.

5. A pharmaceutical composition according to Claim 1, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril.

6. A pharmaceutical composition according to Claim 1, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan.

7. A pharmaceutical composition according to Claim 1, wherein the drug chosen from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866.

8. A pharmaceutical composition according to Claim 1, wherein the insulin resistance improving agent or agents are in combination with one or more angiotensin II receptor antagonists.

9. A pharmaceutical composition according to Claim 8, wherein the angiotensin II receptor antagonists are chosen from CS-866, losartan, candesartan, valsartan and irbesartan.

10. A pharmaceutical composition according to Claim 1, wherein the insulin resistance improving agent or agents are in combination with one or more angiotensin converting enzyme inhibitors.

11. A pharmaceutical composition according to Claim 10, wherein the insulin resistance improving agent or agents are in combination with temocapril.

12. A pharmaceutical composition according to any one of Claims 1 to 11, wherein the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds.

13. A pharmaceutical composition according to any one of Claims 1 to 11, wherein the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

14. A pharmaceutical composition according to any one of Claims 1 to 11, wherein the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

15. A pharmaceutical composition according to any one of Claims 1 to 11, wherein the insulin resistance improving agent is troglitazone.

16. A kit when used in the treatment or prophylaxis of arteriosclerosis by administering a synergistic combination of an effective amount of one or more drugs selected from the group consisting of insulin resistance improving agents and one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, said kit including a plurality of containers, the contents of at least two containers differing from each other in whole or in part, in which at least one of said containers contains at least one insulin resistance improving agent and at least one different container contains at least one drug chosen from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, the anti-arteriosclerosis activity of the administered combination being greater than the additive effect of the activities of each of said drugs administered alone, provided that said kit does not provide at least one container containing captopril and either at least one further container containing troglitazone and glibenclamide or at least two further containers one of which contains troglitazone and the other of which contains glibenclamide.

17. A kit according to Claim 16, wherein the angiotensin II receptor antagonists are chosen from biphenyl tetrazole compounds and biphenylcarboxylic acid compounds, and the angiotensin converting enzyme inhibitors are chosen from tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds.

18. A kit according to Claim 16, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril, and quinapril.

19. A kit according to Claim 16, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril.

20. A kit according to Claim 16, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril.

21. A kit according to Claim 16, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan.

22. A kit according to Claim 16, wherein the drug chosen from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866.

23. A kit according to Claim 16, in which at least one of said containers contains at least one insulin resistance improving agent and at least one different container contains at least one angiotensin II receptor antagonist.

24. A kit according to Claim 23, wherein the angiotensin II receptor antagonists are chosen from CS-866, losartan, candesartan, valsartan and irbesartan.

25. A kit according to Claim 16, in which at least one of said containers contains at least one insulin resistance improving agent and at least one different container contains at least one angiotensin converting enzyme inhibitor.

26. A kit according to Claim 25, wherein at least one of said containers contains at least one insulin resistance improving agent and at least one different container contains temocapril.

27. A kit according to any one of Claims 16 to 26, wherein the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds.

28. A kit according to any one of Claims 16 to 26, wherein the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

29. A kit according to any one of Claims 16 to 26, wherein the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

30. A kit according to any one of Claims 16 to 26, wherein the insulin resistance improving agent is troglitazone.

31. The use of at least one insulin resistance improving agent in the preparation of a medicament for use, in synergistic combination with at least one drug chosen from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, in the prophylaxis or treatment of arteriosclerosis.

32. A use according to Claim 31, wherein the angiotensin II receptor antagonists are chosen from biphenyl tetrazole compounds and biphenylcarboxylic acid compounds, and the angiotensin converting enzyme inhibitors are chosen from tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds.

33. A use according to Claim 31, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril.

34. A use according to Claim 31, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril.

35. A use according to Claim 31, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril.

36. A use according to Claim 31, wherein the angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan.

37. A use according to Claim 31, wherein the drug chosen from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866.

38. A use according to Claim 31 of at least one insulin resistance improving agent in the preparation of a medicament for use, in combination with at least one angiotensin II receptor antagonist, in the prophylaxis or treatment of arteriosclerosis.

39. A use according to Claim 38, wherein the angiotensin II receptor antagonists are chosen from CS-866, losartan, candesartan, valsartan and irbesartan.

40. A use according to Claim 31 of at least one insulin resistance improving agent in the preparation of a medicament for use, in combination with at least one angiotensin converting enzyme inhibitor, in the prophylaxis or treatment of arteriosclerosis.

41. A use according to Claim 40, wherein the angiotensin converting enzyme inhibitor is temocapril.

42. A use according to any one of Claims 31 to 41, wherein the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds.

43. A use according to any one of Claims 31 to 41, wherein the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

44. A use according to any one of Claims 31 to 41, wherein the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

45. A use according to any one of Claims 31 to 41, wherein the insulin resistance improving agent is troglitazone.

46. The use of a composition as defined in any one of Claims 1 to 15 in the preparation of a medicament for use in the prophylaxis or treatment of arteriosclerosis.

47. A method for the treatment or prophylaxis of arteriosclerosis, which method comprises administering in synergistic combination an effective amount of one or more drugs selected from the group consisting of insulin resistance improving agents and one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors to a mammal suffering from or susceptible to arteriosclerosis.

48. A method according to Claim 47, wherein said angiotensin II receptor antagonists are selected from the group consisting of biphenyl tetrazole compounds and biphenylcarboxylic acid compounds, and said angiotensin converting enzyme inhibitors are selected from the group consisting of tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds.

49. A method according to Claim 47, wherein said group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors consists of CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril.

50. A method according to Claim 47, wherein said group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors consists of CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril.

51. A method according to Claim 47, wherein said group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors consists of CS-866, losartan, candesartan and temocapril.

52. A method according to Claim 47, wherein said group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors consists of CS-866, losartan and candesartan.

53. A method according to Claim 47, wherein said drug chosen from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866.

54. A method according to Claim 47, wherein one or more drugs selected from said group consisting of insulin resistance improving agents are administered in combination with one or more drugs selected from the group consisting of angiotensin II receptor antagonists.

55. A method according to Claim 54, wherein one or more drugs selected from said group consisting of insulin resistance improving agents are administered in combination with one or more drugs selected from the group consisting of the angiotensin II receptor antagonists CS-866, losartan, candesartan, valsartan and irbesartan.

56. A method according to Claim 47, wherein one or more drugs selected from said group consisting of insulin resistance improving agents are administered in combination with one or more drugs selected from the group consisting of angiotensin converting enzyme inhibitors.

57. A method according to Claim 56, wherein one or more drugs selected from said group consisting of insulin resistance improving agents are administered in combination with the angiotensin converting enzyme inhibitor temocapril.

58. A method according to any one of Claims 47 to 57, wherein said insulin resistance improving agents are selected from the group consisting of thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds.

59. A method according to any one of Claims 47 to 57, wherein said insulin resistance improving agents are selected from the group consisting of troglitazone, pioglitazone, englitazone and BRL-49653.

60. A method according to any one of Claims 47 to 57, wherein said insulin resistance improving agents are selected from the group consisting of troglitazone and pioglitazone.

61. A method according to any one of Claims 47 to 57, wherein said insulin resistance improving agent is troglitazone.

62. A method according to Claim 47, wherein said synergistic combination of one or more drugs selected from the group consisting of insulin resistance improving agents and one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is administered in the form of a combination drug to a mammal suffering from or susceptible to arteriosclerosis.

63. A method according to Claim 47, wherein said one or more drugs selected from the group consisting of insulin resistance improving agents and one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are administered separately but simultaneously to a mammal suffering from or susceptible to arteriosclerosis.

64. A method according to Claim 47, wherein said one or more drugs selected from the group consisting of insulin resistance improving agents and one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors to a mammal suffering from or susceptible to arteriosclerosis are administered separately and non-simultaneously to a mammal suffering from or susceptible to arteriosclerosis, the time interval between the administration of said one or more drugs selected from the group consisting of insulin resistance improving agents and said one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors being such that the anti-arteriosclerosis activity of the thus administered combination is greater than the additive effect of the activities of each of said drugs administered alone.

65. A pharmaceutical composition comprising a synergistic combination substantially as hereinbefore described with reference to the Examples.

66. A kit according to claim 16 substantially as hereinbefore described with reference to the Examples.

67. A method substantially as hereinbefore described with reference to the Examples.

68. A use substantially as hereinbefore described with reference to the Examples.

DATED this 8th day of November 1999
Sankyo Company Limited.
By its Patent Attorneys
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