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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING COMBINATION USEFUL FOR TREATMENT OR PREVENTION OF ARTERIOSCLEROSIS OR XANTHOMA

(57) Abrégé/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.
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.
PHARMACEUTICAL COMPOSITION COMPRISING COMBINATION USEFUL FOR TREATMENT OR PREVENTION OF ARTERIOSCLEROSIS OR XANTHOMA

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).

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 [J. Clinical Therapeutic & Medicines, 2 (Supp. 3), 39-60 (1993)].

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.


The following indicates the chemical planar structural formulae of some typical examples of angiotensin II receptor antagonists.
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-(cyclohexyloxy)carbonyloxyethyl 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-spirooxepantane-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,

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

![Temocapril](image1)
![Captopril](image2)
![Enalapril](image3)
![Lisinopril](image4)
![Cilazapril](image5)
![Delapril](image6)
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-[(S)-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.


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

\[ \text{struct1} \]

Pioglitazone

\[ \text{struct2} \]

Englitazone

\[ \text{struct3} \]

BRL-49653

\[ \text{struct4} \]

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.

Enoglitzzone 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 enoglitzzone 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, pyridazinoidazepine 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, enoglazone 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, enoglazone 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 xanthoma 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 xanthoma.

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 xanthoma in finger joints (%). Those results are shown in Tables 1 and 2.
[Table 1]

Surface Area of Aortic Lesions

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

[Table 2]

Incidence of Xanthoma in Finger Joints

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Test Compound</th>
<th>Dose (mg/kg)</th>
<th>No. of animals</th>
<th>Xanthoma incidence (%)</th>
<th>Forelimbs</th>
<th>Hindlimbs</th>
<th>Overall</th>
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<tr>
<td>1</td>
<td>CS-866</td>
<td>1</td>
<td>25</td>
<td>4</td>
<td>75</td>
<td>63</td>
<td>69</td>
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<tr>
<td></td>
<td>+ Troglitazone</td>
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<td>Troglitazone</td>
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</table>

(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 xanthoma in finger joints. Those results are shown in Tables 3 and 4.

[Table 3]

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

[Table 4]

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Test Compound</th>
<th>Dose (mg/kg)</th>
<th>No. of animals</th>
<th>Xanthoma incidence (%)</th>
<th>Fore-limbs</th>
<th>Hind-limbs</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Candesartan</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ troglitazone</td>
<td>25</td>
<td>7</td>
<td>86</td>
<td>86</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Candesartan</td>
<td>1</td>
<td>7</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Troglitazone</td>
<td>25</td>
<td>7</td>
<td>100</td>
<td>86</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>-</td>
<td>7</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
(Formulation Example 1)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td></td>
</tr>
<tr>
<td>CS-866</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>100.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>244.0</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>50.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>400 mg</td>
</tr>
</tbody>
</table>

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.
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A pharmaceutical composition comprising one or more insulin resistance improving agents in combination with one or more angiotensin II receptor antagonists, wherein the one or more insulin resistance improving agents are troglitazone, pioglitazone and/or BRL-49653 and the one or more angiotensin II receptor antagonists are CS-866 and/or candesartan.

2. A pharmaceutical composition according to claim 1, wherein the one or more angiotensin II receptor antagonists is CS-866.

3. A pharmaceutical composition according to claim 1 or 2, wherein the one or more insulin resistance improving agents are troglitazone and/or pioglitazone.

4. A pharmaceutical composition according to claim 1 or 2, wherein the one or more insulin resistance improving agents is troglitazone.

5. A pharmaceutical composition for the treatment of arteriosclerosis, comprising: a pharmaceutically-effective amount of a combination of (a) one or more insulin resistance improving agents or pharmacologically-acceptable salts thereof, with (b) one or more angiotensin II receptor antagonists or pharmacologically-acceptable salts thereof, wherein the one or more insulin resistance improving agents are troglitazone, pioglitazone and/or BRL-49653 and the one or more angiotensin II receptor antagonists are CS-866 and/or candesartan, together with a pharmaceutically-acceptable diluent or carrier therefor.

6. A pharmaceutical composition according to claim 5, wherein (b) is CS-866.

7. A pharmaceutical composition according to claim 5 or 6, wherein said one or more insulin resistance improving agents are troglitazone and/or pioglitazone.
8. A pharmaceutical composition according to claim 7, wherein said one or more insulin resistance improving agents is pioglitazone.

9. A pharmaceutical composition according to claim 7, wherein said one or more insulin resistance improving agents is troglitazone.

10. A pharmaceutical composition according to claim 5, wherein the one or more insulin resistance improving agents are troglitazone and/or pioglitazone, and the one or more angiotensin II receptor antagonists is CS-866.

11. A pharmaceutical composition according to claim 5, wherein (b) is the angiotensin II receptor antagonist CS-866, and the one or more insulin resistance improving agents is troglitazone.

12. A pharmaceutical composition according to claim 5 or 6, wherein said one or more insulin resistance improvement agents is BRL-49653.

13. A pharmaceutical composition according to any one of claims 5 to 12, wherein the amount of said (a) to the amount of said (b) is in a weight ratio of 1:200 to 200:1.

14. A kit for the treatment or prevention of arteriosclerosis or xanthoma comprising 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 the containers contains one or more insulin resistance improving agents and at least one different container contains one or more angiotensin II receptor antagonists, wherein the one or more insulin resistance improving agents are troglitazone, pioglitazone and/or BRL-49653 and the one or more angiotensin II receptor antagonists are CS-866 and/or candesartan.

15. A kit according to claim 14, wherein the one or more angiotensin II receptor antagonists is CS-866.

16. A kit according to claim 14, wherein the one or more insulin resistance improving agents are troglitazone and/or pioglitazone.
17. A kit for according to claim 16, wherein the one or more insulin resistance improving agents is troglitazone.

18. A kit for the treatment or prevention of arteriosclerosis or xanthoma comprising 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 the containers contains (a) one or more insulin resistance improving agents or pharmacologically-acceptable salts thereof, and at least one different container contains (b) one or more angiotensin II receptor antagonists or pharmacologically-acceptable salts thereof, wherein the one or more insulin resistance improving agents are troglitazone, pioglitazone and/or BRL-49653 and the one or more angiotensin II receptor antagonists are CS-866 and/or condesarten.

19. A kit according to claim 18, wherein (b) is CS-866.

20. A kit according to claim 18 or 19, wherein said one or more insulin resistance improving agents are troglitazone and/or pioglitazone.

21. A kit according to claim 20, wherein said one or more insulin resistance improving agents is troglitazone.

22. A kit according to any one of claims 18 to 21, wherein the amount of said (a) to the amount of said (b) is in a weight ratio of 1:200 to 200:1.

23. Use of one or more insulin resistance improving agents in the preparation of a medicament for use, in combination with one or more angiotensin II receptor antagonists, wherein the one or more insulin resistance improving agents are troglitazone, pioglitazone and/or BRL-49653 and the one or more angiotensin II receptor antagonists are CS-866 and/or candesartan, in the prophylaxis or treatment of arteriosclerosis.

24. Use according to claim 23, wherein the one or more angiotensin II receptor antagonists is CS-866.
25. Use according to claim 23 or 24, wherein the one or more insulin resistance improving agents are troglitazone and/or pioglitazone.

26. Use according to claim 23 or 24, wherein the one or more insulin resistance improving agents is troglitazone.

27. Use of a pharmaceutical composition as defined in any one of claims 1 to 13, in the prophylaxis or treatment of arteriosclerosis.

28. Use according to claim 27, wherein the one or more insulin resistance improving agents and the one or more angiotensin II receptor antagonists are in the form of a combination drug for administration to a mammal suffering from arteriosclerosis.

29. Use according to claim 27, wherein the one or more insulin resistance improving agents and the one or more angiotensin II receptor antagonists are in a form for administering separately but simultaneously to a mammal suffering from arteriosclerosis.

30. Use according to claim 27, wherein the one or more insulin resistance improving agents and the one or more angiotensin II receptor antagonists are in a form for administering separately and non-simultaneously to a mammal suffering from arteriosclerosis.

31. Use according to claim 28, 29 or 30, wherein said mammal is a human.

32. Use of one or more insulin resistance improving agents in the preparation of a medicament for use, in combination with one or more angiotensin II receptor antagonists, wherein the one or more insulin resistance improving agents are troglitazone, pioglitazone and/or BRL-49653 and the one or more angiotensin II receptor antagonists are CS-866 and/or candesartan, in the prophylaxis or treatment of xanthoma.

33. Use according to claim 32, wherein the one or more angiotensin II receptor antagonists is CS-866.
34. Use according to claim 32 or 33, wherein the one or more insulin resistance improving agents are troglitazone and/or pioglitazone.

35. Use according to claim 32 or 33, wherein the one or more insulin resistance improving agents is troglitazone.

36. Use of a pharmaceutical composition as defined in any one of claims 1 to 13, in the prophylaxis or treatment of xanthoma.

37. Use according to claim 36, wherein the one or more insulin resistance improving agents and the one or more angiotensin II receptor antagonists are in the form of a combination drug for administration to a mammal suffering from xanthoma.

38. Use according to claim 36, wherein the one or more insulin resistance improving agents and the one or more angiotensin II receptor antagonists are in a form for administering separately but simultaneously to a mammal suffering from xanthoma.

39. Use according to claim 36, wherein the one or more insulin resistance improving agents and the one or more angiotensin II receptor antagonists are in a form for administering separately and non-simultaneously to a mammal suffering from xanthoma.

40. Use according to claim 37, 38 or 39, wherein said mammal is a human.