Description

Title of Invention: ANTIHYPERTENSIVE PHARMACEUTICAL COMPOSITION

Technical Field

[1] The present invention relates to an antihypertensive pharmaceutical composition.

Background Art

[2] Hypertension is one of the most common cardiovascular diseases. Typically, a person is diagnosed with hypertension when his/her blood pressure is in a range of 140/90 mmHg. Recently, the incidence of lifestyle-related diseases such as hypertension has rapidly increased. As hypertension may result in the occurrence of acute heart diseases or myocardial infarction, there is a continued need for development of a more effective antihypertensive agent.

[3] According to various clinical trials of antihypertensive agents, it was found that lowering of blood pressure of hypertensive patients leads to a decrease in mortality and morbidity of heart diseases or myocardial infarction (Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH, Lancet 1990, 335(8693):827-38). Although a variety of drugs have been used and administered for the purpose of treating such a clinical condition, suitable control of blood pressure is not always successful (Waeber B, Brunner HR, Am. J. Hypertens 1997. 10(7 Pt 2):131S-137S).

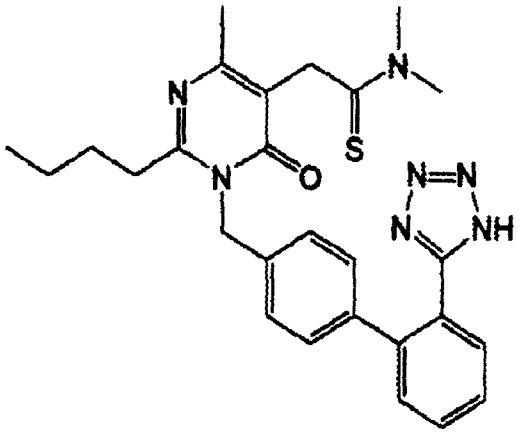
[4] Among various applicable administration modes of antihypertensive drugs, a combination preparation or combination therapy of drugs is one method for achieving desired therapeutic results. On the other hand, arbitrary selection of various classes of antihypertensive agents for application of drugs to combination therapy prescription does not always provide help to achieve a desired blood pressure level in a hypertensive mammal including a human (MacGregor GA, Markandu ND, Banks RA, Bayliss J. Roulston JE, Jones JC, Br Med J (Clin Res Ed), 284 (6317): 693-6).

[5] To this end, there is an obvious need for further development of therapeutic methods, combination preparations and pharmaceutical compositions against hypertension.

[6] Fimasartan, which is chemically defined as 2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]pyrimidin-4(3H)-one and has the following structural formula, is an antihypertensive agent of the angiotensin II receptor blocker (ARB) class and has currently been approved as a pharmaceutical product under brand name of KANARB.

[7] [Fimasartan]

[8]



[9] According to the randomized double-blind clinical testing conducted for the comparison of antihypertensive effects in patients with mild to moderate essential hypertension, at a dose of 60 mg to 120 mg of drugs between Fimasartan potassium and Losartan which is a representative compound of the ARB class, it was demonstrated that antihypertensive effects in terms of changes in diastolic blood pressure (DBP) in the sitting position at Week 12 of drug administration were respectively -11.26±7.53 mmHg for the Fimasartan-treated group and -8.56±7.72 mmHg for the Losartan-treated group, relative to a baseline, thus showing that antihypertensive effects after 12- or 24-week administration were higher in Fimasartan than Losartan (A Randomized, Double-blind, Losartan-controlled, Parallel Group Comparison Dose Titration Clinical Study to Evaluate the Antihypertensive Efficacy and Safety of Fimasartan (BR-A-657 · K) 60mg ~ 120mg in Patients with Mild to Moderate Essential Hypertension (Phase III)).

[10] Amlodipine is a calcium channel blocker (CCB), and blocks an inflow of calcium ions to cell membranes of cardiac and peripheral vascular smooth muscles and therefore directly relaxes vascular smooth muscles to exhibit antihypertensive effects. Although the action mechanism by which Amlodipine mitigates angina pectoris has not been fully understood, it was found that the following two action mechanisms function to relieve ischemic symptoms.

[11] First, Amlodipine dilates peripheral arteries to decrease the total peripheral resistance (after-load), thus leading to decreased cardiac work, and stabilizes a heart rate to decrease cardiac energy consumption and oxygen demand.

[12] Second, it is believed that Amlodipine dilates main coronary arteries and other coronary arterioles of ischemic lesions and normal regions. Such vasodilation plays a role to increase delivery of oxygen to myocardial ischemic lesions of patients with coronary artery convulsion.

[13] Although active research for the treatment of hypertension has recently been focused

on a combination preparation of Amlodipine, which is a calcium channel blocker, with a compound belonging to the ARB class, such a combination preparation may present additional problems in some cases, such as by causing drug-to-drug interaction and increased adverse side effects of individual drugs.

[14] To this end, the inventors of the present invention have recognized problems of simple combination preparations of Amlodipine and ARB class compounds and conducted a variety of extensive and intensive studies to address the foregoing problems. As a result, the present invention has been completed.

[15]

[16] [Related technique]

[17] 1. KR 1989-0011854 A 1989.08.22.,

[18] 2. WO 00/16773 1999.09.08.,

[19] 3. KR 2001-0013626 A 2001.02.26.,

[20] 4. KR 2001-0079517 A 2001.08.22.,

[21] 5. KR 2001-0090193 A 2001.10.18.,

[22] 6. KR 2004-0032639 2004.04.17.,

[23] 7. KR 2010-0048137 2010.05.11.,

[24] 8. Yoo SD et.al., Simultaneous determination of fimasartan, a novel antihypertensive agent, and its active metabolite in rat plasma by liquid chromatography-tandem mass spectrometry, Biomed Chromatogr. 2011 Jan 26. doi:10.1002/bmc. 1592. Epub ahead of print

[25] 9. Yu KS, et.al., Effect of multiple doses of fimasartan, an angiotensin II receptor antagonist, on the steady-state pharmacokinetics of digoxin in healthy volunteers. Int J Clin Pharmacol Ther. 2011 May;49(5):321-7

[26] 10. Yu KS et.al., The Effect of the Newly Developed Angiotensin Receptor II Antagonist Fimasartan on the Pharmacokinetics of Atorvastatin in relation to OATP1B1 in Healthy Male Volunteers. J Cardiovasc Pharmacol. 2011 Jul 14. Epub ahead of print

Disclosure of Invention

Technical Problem

[27] Therefore, the present invention is intended to provide an antihypertensive pharmaceutical composition which is effective not only for the prevention, alleviation and treatment of hypertension, but also for the prevention, alleviation or treatment of complications of hypertension and/or hyperlipidemia.

Solution to Problem

[28] The present invention provides an antihypertensive pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer

thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

[29] In the present invention, Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof may be crystalline or amorphous. Crystalline and/or amorphous forms thereof also fall within the scope of the present invention.

[30] In the present invention, Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof may be crystalline or amorphous. Crystalline and/or amorphous forms thereof also fall within the scope of the present invention.

[31] As used herein, the term "pharmaceutically acceptable salt" refers to a salt with an inorganic acid, organic acid or metal, which has been conventionally used in the preparation of pharmaceutical products by pharmaceutical manufacturers. Examples of the inorganic acid include hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid. Examples of the organic acid include citric acid, acetic acid, lactic acid, tartaric acid, fumaric acid, formic acid, propionic acid, oxalic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid(besylate), maleic acid, benzoic acid, gluconic acid, glycolic acid, succinic acid, 4-morpholineethanesulfonic acid, camphorsulfonic acid(camsylate), 4-nitrobenzenesulfonic acid, hydroxy-o-sulfonic acid, 4-toluenesulfonic acid, galacturonic acid, embonic acid, glutamic acid, aspartic acid and adipic acid(adipate). Examples of the metal include sodium, potassium, calcium and magnesium.

[32] In the present invention, the angiotensin II receptor blocker is preferably a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate, and more preferably a Fimasartan potassium salt or Fimasartan potassium trihydrate. These materials are commercially available or otherwise may be prepared by using a known method (for example, see Korean Patent Nos. 0354654 and 0521980).

[33] In the present invention, the calcium channel blocker is preferably an Amlodipine besylate, sulfate, camsylate, hydrochloride, potassium salt, calcium salt or adipate, and more preferably Amlodipine besylate. These materials are commercially available or otherwise may be prepared by using a known method (for example, see US Patent No. 4572909).

[34] In the present invention, the solvent in the "solvate" refers to a common organic solvent which has been used in the preparation of organic compounds. Examples of the solvent include, but are not limited to, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-acetate, acetone, acetic acid, anisole, tetrahydrofuran, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, isobutyl acetate, n-butyl acetate, dimethyl sulfoxide, pentane, and heptane.

[35] In the present invention, the content of "hydrate" and "solvate" may be in a range of 0.25 to 10 moles relative to 1 mole of Fimasartan or Amlodipine, for example, 0.5 moles, 1 mole, 1.5 moles, 2 moles, 2.5 moles, 3 moles or 5 moles, but the present invention is not limited thereto.

[36] The composition of the present invention may contain an angiotensin II receptor blocker in an amount of 0.5 to 240 mg, preferably 50 to 180 mg, and more preferably 60 to 120 mg.

[37] Further, the composition of the present invention may contain a calcium channel blocker in an amount of 0.1 to 20 mg, preferably 5 to 15 mg, and more preferably 5 to 10 mg.

[38] On the other hand, it is known that a conventional high dose (that is, pharmaceutically acceptable high dose/administration) of these drugs contained in a pharmaceutical composition is a maximum of 240 mg or less for Fimasartan and a maximum of 20 mg or less for Amlodipine, for an ordinary adult weighing 60 kg.

[39] Throughout the specification, unless otherwise specifically indicated, the term "pharmaceutical composition" is intended to generally cover not only a single dosage form which is taken or administered at one single dose, such as tablet, capsule or injection, but also plural dosage forms which are administered at two or more divided doses. For example, the term "pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker" is interpreted to designate not only a single dosage form containing these two active ingredients all together, but also two dosage forms in which each contains one active ingredient. That is, where these two dosage forms are simultaneously administered or are consecutively administered at regular intervals and therefore effective amounts of two active ingredients contained in each of these dosage forms coexist in vivo to bring about synergistic effects, these two dosage forms also fall within the scope of the "pharmaceutical composition containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker".

[40] The composition of the present invention may further contain one or more pharmaceutically acceptable carriers besides the aforesaid ingredients, to be formulated into a variety of dosage forms for desired applications. Examples of the pharmaceutically acceptable carrier include saline, sterile water, Ringer's solution, buffered physiological saline, dextrose solution, maltodextrin solution, glycerol, and ethanol. These materials may be used alone or in any combination thereof. If necessary, other conventional

additives may be added such as antioxidants, buffers and bacteriostatic agents.

[41] Further, diluents, dispersants, surfactants, binders and lubricants may be additionally added to prepare injectable formulations such as aqueous solutions, suspensions, and emulsions, or oral formulations such as pills, capsules, granules, and tablets. Furthermore, the agent may be preferably formulated into a desired dosage form, depending on diseases to be treated and ingredients, using any appropriate method known in the art, or the method as disclosed in "Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

[42] The composition of the present invention may be administered via oral routes or parenteral routes (for example, intravenously, subcutaneously, intraperitoneally, or locally), depending on desired applications. The dose of the composition may vary depending on weight, age, gender, health status, and dietary habits of patients, administration times and routes, excretion rates, and severity of disease. The composition of the present invention may be administered once or several times a day.

[43] The composition of the present invention may be an injectable formulation such as aqueous solution, suspension or emulsion, or an oral formulation such as pill, capsule, granule or tablet or in the form of a kit. An oral dosage form is preferable and a single tablet is more preferable.

[44] Further, the composition of the present invention, due to having an enhanced antihypertensive effect, may be used for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis.

[45] Therefore, the present invention provides a pharmaceutical composition for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis, containing Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

[46] Further, the present invention provides a method for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis, including administering a composition containing an effective amount of Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and an effective amount of Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a

hydrate thereof as a calcium channel blocker to a mammal, including a human, in need thereof.

[47] The present invention provides a method for preventing or treating a hypertension, comprising administering the antihypertensive pharmaceutical composition of the present invention to a mammal including a human.

[48] In the method for preventing or treating a hypertension of the present invention, the antihypertensive pharmaceutical composition is comprised Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

[49] In the method for preventing or treating a hypertension of the present invention, the sort or content of each of the angiotensin II receptor blocker and the calcium channel blocker is the same as described above regarding the antihypertensive pharmaceutical composition of present invention.

[50] In the method for preventing or treating a hypertension of the present invention, the angiotensin II receptor blocker is preferably a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate and more preferably is a Fimasartan potassium salt.

[51] In the method for preventing or treating a hypertension of the present invention, the calcium channel blocker is preferably an Amlodipine besylate.

[52] In the method for preventing or treating a hypertension of the present invention, the content of the angiotensin II receptor blocker is preferably in the range of 0.5 to 240 mg, and the content of the calcium channel blocker is in the range of 0.1 to 20 mg.

[53] Further, the present invention provides a use of a composition containing an effective amount of Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and an effective amount of Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker, for manufacturing a pharmaceutical preparation for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis.

Advantageous Effects of Invention

[54] The composition of the present invention exhibits an enhanced antihypertensive effect greater than the simple sum of antihypertensive values of the same doses of individual active ingredients. Accordingly, the composition of the present invention enables the use of individual active ingredients at a content or dose lower than that

upon separate use thereof, and thus can provide more effective treatment or prevention of hypertension or the like while reducing adverse side effects due to an overdose of individual active ingredients.

Mode for the Invention

[55] Now, the present invention will be described in more detail with reference to the following Examples. These examples are provided only for illustrating the present invention and should not be construed as limiting the scope and spirit of the present invention.

[56] **Experimental Example: antihypertensive effects of inventive composition**

[57] This study is intended to examine antihypertensive action of individual drugs. For this purpose, test drugs, i.e., Fimasartan potassium trihydrate, Losartan potassium salt, Valsartan, Amlodipine besylate, a combination of Fimasartan potassium trihydrate with Amlodipine besylate, a combination of Losartan potassium salt with Amlodipine besylate, and a combination of Valsartan with Amlodipine besylate were repeatedly and orally administered for 4 weeks to rats with essential hypertension. Changes in blood pressure, heart rate and body weight of animals were measured to investigate the antihypertensive action by long-term administration of individual drugs, confirm the maintenance degree of effective and stable blood pressure, and examine the difference between single administration and combined administration of drugs. In this manner, the antihypertensive action was compared and evaluated between the individual drugs.

[58]

[59] **(1) Test material and method**

[60] **① Experimental animals**

[61] 8-week old male spontaneously hypertensive rats (SHR), weighing 230 to 250 g, were purchased from Charles River Japan (CRJ). The animals were used in the test, after being subjected to an acclimation period until the animals were 18 to 19-week old (340 to 380 g) to reach a mean blood pressure of 160 to 170 mmHg. Animals with a good condition were selected by minute observation over the acclimation period prior to the test, and divided into individual test groups, each consisting of 8 animals (n=8). Only the selected animals, from which a rise in blood pressure was confirmed using a non-invasive blood pressure monitoring system (CODA-6), were assigned to the test group. Through the measurement of SHR blood pressure prior to application of the main test, SHR individuals having blood pressure outside a blood pressure range (individuals exhibiting a mean blood pressure below 140 mmHg or above 220 mmHg as measured) of normal SHR were excluded from the test.

[62]

[63] **② Establishment of drug-treated groups and administration method**

[64] A suitable dose capable of exhibiting a significant antihypertensive effect through a basic test and a preliminary test was taken as a final dose of drugs administered to experimental rats in this test. Low, medium and high doses of the drugs according to individual drugs were established in the preliminary test. Then, based on the test results, a dose capable of achieving significant lowering of a blood pressure from the blood pressure of hypertensive rats prior to administration of the drugs to a range of 20 to 50 mmHg after administration of the drugs (a dose corresponding to 20 to 25% of a usual clinical dose) was taken as an optimal dose of the single administration group. On the other hand, based on the review results from the literature, a dose capable of showing a stable antihypertensive action without causing toxicity at 4-week administration was set for the combination preparation-administered group. All the doses referred to those used in the already performed test. Doses and drug-administered groups used in the final main test are as follows.

[65] As an ARB compound, Losartan potassium salt, Valsartan and Fimasartan potassium trihydrate were respectively purchased and used from Zhejiang Huahai Pharmaceutical Co., Ltd. 10 mg/kg of Losartan potassium salt was taken as an L group, and 10 mg/kg of Valsartan was taken as a V group. With regard to Fimasartan potassium trihydrate, 3 mg/kg was taken as an F1 group, and 10 mg/kg was taken as an F2 group.

[66] As a calcium channel blocker, Amlodipine besylate (home-made by the method described in US Patent No. 4572909) was used. 0.5 mg/kg of Amlodipine besylate was taken as an A1 group, and a dose of 1.6 mg/kg was taken as an A2 group. The test materials and the comparative drugs were each suspended in 0.5% carboxymethylcellulose sodium salt (CMC-Na, Sigma) prior to using. As a control group, 0.5% CMC alone was administered.

[67]

[68] **③ Test method**

[69] - **Administration:** Upon carrying out the administration, the drug preparation was heated to a suitable temperature of 35℃ in a water bath, followed by forced oral administration of 5 mL/kg via a stomach sonde.

[70] - **Measurement of blood pressure:** Blood pressure of rats was measured as follows. Rats were restrained and placed in a heating device which was then heated to a temperature of about 40℃ (based on the temperature of 37℃ in a restraining cage) over 13 minutes, such that the tail blood vessels were engorged, and the blood pressure of rats was measured using CODA-6 equipment that monitors a blood pressure by means of the software of the main body through a pair of cuffs attached to the tail. The non-invasive blood pressure measuring method via CODA-6 (Kent Scientific Corporation) enables a long-term blood pressure measuring test that should involve repeated administration of test materials, which is not feasible with a direct blood pressure measuring

method through arterial cannulation, such as conventionally used physiograph or power lab. In order to confirm a disappearance pattern in response to doses of drugs by 4-week repeated administration and a degree of recovery to initial blood pressure, the blood pressure was measured once a day for 1 week after the final administration was completed.

[71] Changes in blood pressure were confirmed with focusing on changes in mean arterial pressure (MAP), and changes in diastolic and systolic blood pressure, heart rate, and body weight were used as references for other changes in the experimental results.

[72]

[73] **(2) Results processing and statistical analysis**

[74] Statistical analysis of the measurement values obtained in this experiment was carried out using a statistical program SPSS. For items where a significant F value is observed in one-way ANOVA, the comparison was made at significant levels of $p<0.001$, 0.01 and 0.05 between the control group and the experimental groups with a different dose of drugs.

[75] In the 4-week repeated administration efficacy test, all of the groups including the control group exhibited a slight increase in body weight. The body weight tended to decrease at the early stage of the test, but the maintenance of the body weight was confirmed after the middle stage of the test. This was believed to be a symptom resulting from exposure to stress during the indirect blood pressure measurement, such as heating and restraint, not direct effects due to drugs.

[76] Based on the measured results, kinds and doses of the drugs administered to the individual drug-administered groups, in conjunction with antihypertensive values obtained in the individual drug-administered groups, that is, the antihypertensive degree over 4 weeks in response to the drug administration, as calculated based on the blood pressure prior to administration of drugs, are given in Table 1 below.

[77] [Table 1]

[78]

Antihypertensive degree (mmHg) with consecutive 4-week administration of drugs, as compared to blood pressure prior to administration		
Drug-administered groups (kinds and doses of drugs)	Mean	Standard error
Example 1 (F1+A1)	-55	2.255
Example 2 (F2+A2)	-75	2.536
Comparative Example 1 (F1)	-35	1.375
Comparative Example 2 (F2)	-50	2.135
Comparative Example 3 (L)	-20	1.256
Comparative Example 4 (V)	-32	2.862
Comparative Example 5 (A1)	-13	1.105
Comparative Example 6 (A2)	-20	1.325
Comparative Example 7 (L+A2)	-32	2.268
Comparative Example 8 (V+A2)	-46	2.675

[79] As shown in Table 1 above, it can be seen that Comparative Example 1 exhibited a superior antihypertensive effect even with administration of a dose lower than a usual clinical dose (usual clinical dose of Fimasartan potassium trihydrate = 60 mg, usual clinical dose of Losartan potassium salt = 50 mg, and usual clinical dose of Valsartan = 80 mg), as compared to Comparative Example 3 and Comparative Example 4.

[80] Further, Examples 1 and 2, which use a combination preparation of Fimasartan and Amlodipine that is the composition of the present invention, exhibited an antihypertensive effect greater than a simple sum of antihypertensive effects obtained when each ingredient alone was administered. For example, as compared to an antihypertensive value of -13 mmHg for single administration of 0.5 mg/Kg of Amlodipine besylate (Comparative Example 5) and an antihypertensive value of -35 mmHg for single administration of 3 mg/Kg of Fimasartan potassium trihydrate (Comparative Example 1), Example 1 corresponding to a combination preparation of both drugs (Amlodipine besylate and Fimasartan potassium trihydrate) exhibited an antihypertensive value of -55 mmHg which corresponds to an enhanced antihypertensive effect greater than a simple sum of antihypertensive values of two drugs. This effect is a significant numerical value even upon taking into consideration a standard error. Further, as compared to an antihypertensive value of -20 mmHg for single administration of 1.6 mg/Kg of Amlodipine besylate (Comparative Example 6) and an antihypertensive value of -50 mmHg for single administration of 10 mg/Kg of Fimasartan potassium trihydrate (Comparative Example 2), Example 2 corresponding to a combination preparation of both drugs exhibited an antihypertensive value of -75 mmHg which corresponds to an enhanced antihypertensive effect greater than a simple sum of antihypertensive values of two drugs. This effect is confirmed to be an unexpected remarkable effect, when compared with the foregoing results (Comparative Examples 7 and 8) wherein a combination preparation of another ARB compound and Amlodipine

exhibited an antihypertensive value smaller than a simple sum of antihypertensive values of individual ingredients of the combination preparation.

[81] As described above, since the composition of the present invention exhibits an antihypertensive effect greater than the sum of antihypertensive effects obtained when each active ingredient alone was administered (synergistic effect), the risk of adverse side effects due to an overdose of individual active ingredients can also be greatly reduced by further decreasing the content of each active ingredient, and inconveniences associated with medication of patients upon performing combination therapy of individual active ingredients can be solved.

[82] **Preparation Example: Preparation of composition (tablet) of the present invention**

[83] The composition of the present invention was formulated into tablets containing ingredients and contents thereof as described in Table 2 below, each of which is expressed as Preparation Examples 1 to 4.

[84] [Table 2]

[85]

Ingredients	Preparation Example 1 (mg/tablet)	Preparation Example 2 (mg/tablet)	Preparation Example 3 (mg/tablet)	Preparation Example 4 (mg/tablet)
Fimasartan potassium trihydrate	66.01	132.02	66.01	132.02
Amlodipine besylate	6.99	6.99	13.98	13.98
Corn starch	46	98.99	39.01	92
Microcrystalline cellulose	16	32	16	32
Crospovidone	10	20	10	20
Hydroxypropylcellulose	3.5	7	3.5	7
Magnesium stearate	1.5	3	1.5	3
Total weight/tablet (mg)	150	300	150	300

[86] **<Preparation of tablets>**

[87] Fimasartan potassium trihydrate, Amlodipine besylate, corn starch, microcrystalline cellulose and crospovidone were placed in a high-speed mixer, followed by mixing. In addition, hydroxypropylcellulose and purified water (q.s.) were mixed to prepare a binding solution which was then added to the high-speed mixer where the pre-mixed powder was placed, followed by granulation. The resulting granules were dried in a drier. The dried granules were sieved through a No. 20 sieve and magnesium stearate was added thereto, followed by mixing to obtain a final mixture. The final mixture was compressed into tablets corresponding to Preparation Examples 1 to 4, using a rotary tablet press.

MCSLLP

CLAIMS

[Claim 1] An antihypertensive pharmaceutical composition, comprising:
Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and
Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.

[Claim 2] The antihypertensive pharmaceutical composition according to claim 1, wherein the angiotensin II receptor blocker is a Fimasartan potassium salt, hydrochloride, calcium salt, sulfate, adipate, camsylate or besylate.

[Claim 3] The antihypertensive pharmaceutical composition according to claim 2, wherein the angiotensin II receptor blocker is a Fimasartan potassium salt.

[Claim 4] The antihypertensive pharmaceutical composition according to claim 1, wherein the angiotensin II receptor blocker is a Fimasartan potassium trihydrate.

[Claim 5] The antihypertensive pharmaceutical composition according to claim 1, wherein the calcium channel blocker is an Amlodipine besylate, sulfate, camsylate, hydrochloride, potassium salt, calcium salt or adipate.

[Claim 6] The antihypertensive pharmaceutical composition according to claim 5, wherein the calcium channel blocker is an Amlodipine besylate.

[Claim 7] The antihypertensive pharmaceutical composition according to any one of claims 1 to 3, wherein the content of the angiotensin II receptor blocker is in the range of 0.5 to 240 mg, and the content of the calcium channel blocker is in the range of 0.1 to 20 mg.

[Claim 8] The antihypertensive pharmaceutical composition according to claim 7,
wherein the content of the angiotensin II receptor blocker is in the range of 50 to 180 mg.

[Claim 9] The antihypertensive pharmaceutical composition according to claim 8,
wherein the content of the angiotensin II receptor blocker is in the range of 60 to 120 mg.

[Claim 10] The antihypertensive pharmaceutical composition according to claim 7,
wherein the content of the calcium channel blocker is in the range of 5 to 15 mg.

[Claim 11] The antihypertensive pharmaceutical composition according to claim 10, wherein the content of the calcium channel blocker is in the range of 5 to 10 mg.

[Claim 12] The antihypertensive pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is an oral dosage form.

[Claim 13] The antihypertensive pharmaceutical composition according to claim 12, wherein the dosage form is a single tablet.

[Claim 14] A pharmaceutical composition for the prevention, alleviation or treatment of hypertension, heart failure, coronary heart disease, ischemic heart disease, ischemic peripheral vascular disease, hypertensive renal failure, cerebral apoplexy or arteriosclerosis, comprising Fimasartan, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as an angiotensin II receptor blocker; and Amlodipine, an isomer thereof, a pharmaceutically acceptable salt thereof, a solvate thereof or a hydrate thereof as a calcium channel blocker.