

COMPLEX PHARMACEUTICAL PREPARATION, FOR PREVENTING OR TREATING CARDIOVASCULAR DISEASE, COMPRISING AMLODIPINE, LOSARTAN AND CHLORTHALIDONE IN SINGLE-LAYER TABLET

TECHNICAL FIELD

The present invention relates to a pharmaceutical complex preparation in a single-layer tablet for preventing or treating cardiovascular diseases, the pharmaceutical complex preparation comprising, as active ingredients, amlodipine, losartan, and chlorthalidone in a single-layer tablet, and more particularly, to a pharmaceutical complex preparation having improved dissolution rate, stability, and productivity, the complex preparation comprising amlodipine, losartan, and chlorthalidone in low doses in a single-layer tablet.

BACKGROUND ART

Cardiovascular diseases globally have high prevalence rates and are chronic diseases in many cases that develop over a long period of time and continue to recur, and thus proper treatment management from the beginning is important. Conventionally, a stepped care approach starting with a single drug treatment has been preferred for the treatment of cardiovascular diseases including hypertension. However, in this treatment, the following problems have been discussed: an increase in dose-dependent adverse reactions according to dose escalation of a single drug; an increase in the number of patient visits to a hospital to increase a drug dose and to add a drug; a consequent decrease in patient medication adherence, followed by a failure in blood pressure control; and treatment inertia (acceptance in despite uncontrolled blood pressure) by repeated up-titration and drug addition. Therefore, there is a clinical need for an effective method for treating cardiovascular diseases that can replace the complicated stepped care approach in the art.

A complex preparation of drugs having different action mechanisms from one another, such as a complex preparation of amlodipine and losartan, has advantages in exhibiting further excellent effect in the prevention or treatment of hypertension and cardiovascular diseases, reducing side effects of each drug used, and increasing patient adherence, compared to the existing single preparation. The complex preparation has been disclosed in Korean Patent Nos. 1160151 and 1232296, and is currently available under the trade name Amosartan. In addition, research on a complex preparation of amlodipine, losartan, and chlorthalidone has been carried out, and Korean Patent Nos. 1914930 and 1910902 suggest a method of preparing a complex preparation by separating a first mixed part comprising amlodipine and chlorthalidone from a second mixed part comprising losartan to prevent a decrease in a dissolution rate of the drugs due to gelation of losartan.

However, when a conventionally known complex preparation comprising a single preparation in a common dose is administered to patients classified to patients having an early-stage cardiovascular disease, such as mild hypertension or moderate hypertension, problems of excessive lowering in blood pressure and consequent side effects may occur. In addition, the number of reports on adverse events with cardiovascular disease medication is increasing every year. For example, calcium-channel antagonists including amlodipine are known to have more adverse reactions related to edema, such as peripheral edema, systemic edema, facial edema, and the like, than other types of drugs. In addition, the previously studied complex preparations and preparation methods thereof are not preferable as means of providing low-dose complex preparations in terms of dissolution rates, stability, or productivity. Therefore, there is a need to develop a low-dose complex preparation with improved dissolution rate, stability, and productivity to be used for the prevention or treatment of early-stage cardiovascular diseases.

DESCRIPTION OF EMBODIMENTS

TECHNICAL PROBLEM

An aspect provides a low-dose pharmaceutical complex preparation having improved dissolution rate, stability, and productivity to be used for prevention or treatment of an early-stage cardiovascular disease.

Another aspect provides a method of manufacturing the complex preparation.

Another aspect provides a method of treating cardiovascular diseases by using the complex preparation.

SOLUTION TO PROBLEM

An aspect provides a pharmaceutical complex preparation in a single-layer tablet for preventing or treating cardiovascular diseases, the pharmaceutical complex preparation comprising, as active ingredients, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in low doses.

Another aspect provides a method of manufacturing a pharmaceutical complex preparation in a single-layer tablet for preventing or treating cardiovascular diseases, wherein the pharmaceutical complex preparation in a single-layer tablet comprises, as active ingredients, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in low doses.

Another aspect provides a method of treating an early-stage cardiovascular disease by administering a pharmaceutical complex preparation in a single-layer tablet that comprises, as active ingredients, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in low doses.

ADVANTAGEOUS EFFECTS OF DISCLOSURE

A pharmaceutical complex preparation in a single-layer tablet according to an aspect may be used for prevention or treatment of an early-stage cardiovascular

disease, wherein dissolution rates of active ingredients are improved, and stability and productivity of the complex preparation are improved.

The pharmaceutical complex preparation according to an aspect comprising, as active ingredients, amlodipine or a pharmaceutically acceptable salt thereof, losartan or a pharmaceutically acceptable salt thereof, and chlorthalidone or a pharmaceutically acceptable salt thereof, in low doses exhibits an improved blood pressure-lowering effect while clinically minimizing adverse reactions following the drug administration. Thus, limitations of the existing blood pressure therapies due to excessive blood pressure-lowering or adverse reactions may be overcome, thereby having excellent benefits versus risks. In addition, when the complex preparation is administered in combination with drugs having different mechanisms from one another, the cardiovascular diseases may be effectively prevented or treated, the blood pressure-lowering effect may be maximized by inhibiting all possible mechanisms of causing hypertension at once, the complementary action mechanisms may reduce patient-specific variability of the effect, and blood pressure treatment rates for hypertension due to multifactorial mechanisms may be increased. At the same time, the complex preparation may have excellent safety as a therapeutic agent for hypertension because the complex preparation can reduce dose-dependent adverse reactions by lowering a dose of each single component as much as possible.

Accordingly, the low-dose pharmaceutical complex preparation may quickly and effectively treat the blood pressure of a subject at the beginning suffering from mild hypertension to moderate hypertension, may avoid a failure of blood pressure control according to therapeutic inertia of clinical subjects or patients by increasing the blood pressure control rates, and may ultimately improve patient adherence by quickly reaching target blood pressure.

In addition, in an embodiment, the low-dose pharmaceutical complex preparation may reduce expression of ankle edema, which is a drug-specific adverse reaction to amlodipine.

In addition, the complex preparation may help patients reduce pill burden and improve medication convenience, and may reduce patient-specific variability. Also, a simple dosing method can be applied so that patient adherence may be improved, and

due to reduced costs for drugs compared to the existing stepped-care therapy, the complex preparation is economical.

In addition, in an embodiment, the complex preparation comprises, as active ingredients, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in one identical layer, i.e., in a single-layer tablet. Thus, compared to a multi-layer tablet such as a two-layer tablet, a tableting speed during the manufacture may increase, thereby improving productivity of the manufacture of the complex preparation. In addition, the complex preparation may have an excellent yield of a tableting process, and at the same time, may have excellent preparation uniformity, thereby improving the drug quality.

In addition, the active ingredients comprised in the complex preparation, such as amlodipine, losartan, and chlorthalidone, may have excellent dissolution rates, content uniformity, and thermal stability, reduce generation of related substances, and have excellent storage stability, and thus may be usefully utilized in the pharmaceutical field. In addition, the complex preparation may reduce the patient-specific variability with respect to the effect by the complementary action mechanism. The complex preparation may maintain the drug efficacy for 24 hours, and thus may be able to reduce night-time hypertension and blood pressure variability after activity.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 illustrates a method of administering, to a clinical trial subject during a treatment period through a run-in period, an trial drugs comprising: 2.5 mg of amlodipine, 25 mg of losartan potassium, 6.25 mg of chlorthalidone; 1.67 mg of amlodipine, 16.67 mg of losartan potassium, 4.17 mg of chlorthalidone; or 1.25 mg of amlodipine, 12.5 mg of losartan potassium, and 3.13 mg of chlorthalidone, respectively, control drugs comprising: 5 mg of amlodipine; 10 mg of amlodipine; or losartan potassium 100 mg, respectively, or a placebo.

FIG. 2 shows sitSBP change from baseline at 8 weeks in a FAS.

FIG. 3 shows sitDBP change from baseline at 8 weeks in a FAS.

FIG. 4 shows percentage of subjects achieving the blood pressure control at 8 weeks in a FAS. Here, the achievement of blood pressure control is defined as sitSBP < 140 mmHg and sitDBP < 90 mmHg.

FIG. 5 shows percentage of blood pressure responders at 8 weeks in a FAS. Here, the blood pressure responders refer to trial subjects with sitSBP reduction ≥ 20 mmHg or sit DBP reduction ≥ 10 mmHg from the baseline.

FIG. 6 shows change from baseline in pulse pressure at 8 weeks in a FAS.

FIG. 7 shows sitSBP change from baseline at 8 weeks in a FAS (sitSBP < 160 mmHg).

FIG. 8 shows ankle circumference change from baseline (based on an ankle with a larger absolute value of the ankle circumference change from the baseline at 8 weeks than the other between both ankles) in the FAS at 8 weeks in the trial drug-administered groups, each comprising: 2.5 mg of amlodipine, 25 mg of losartan potassium, 6.25 mg of chlorthalidone; 1.67 mg of amlodipine, 16.67 mg of losartan potassium, 4.17 mg of chlorthalidone; or 1.25 mg of amlodipine, 12.5 mg of losartan potassium, and 3.13 mg of chlorthalidone, or in the drug-administered groups as controls, each comprising 5 mg of amlodipine and or 10 mg of amlodipine.

FIG. 9 shows time-dependent dissolution rates (%) of (a) amlodipine besylate and (b) chlorthalidone in Comparative Examples 1 and 2.

FIG. 10 shows time-dependent dissolution rates (%) of (a) amlodipine besylate and (b) chlorthalidone in Comparative Examples 3 and 4.

FIG. 11 shows time-dependent dissolution rates (%) of (a) amlodipine besylate and (b) chlorthalidone in Example 4 and Comparative Examples 5 and 6.

FIG. 12 shows contents (%) of (a) impurity B (Imp B) and (b) unknown related substance (Unknown max) of chlorthalidone in Comparative Examples 3 and 4 and Example 1.

FIG. 13 shows time-dependent dissolution rates (%) of (a) amlodipine besylate, (b) losartan potassium, and (c) chlorthalidone in Examples 1 and 2.

FIG. 14 shows time-dependent dissolution rates (%) of (a) amlodipine besylate, (b) losartan potassium, (c) chlorthalidone in Examples 2 to 6.

FIG. 15 shows content determinations (%) according to a tableting speed in each of (a) Comparative Example 3 and (b) Example 3.

MODE OF DISCLOSURE

Hereinafter, the present invention will be described in more detail.

An aspect provides a pharmaceutical complex preparation in a single-layer tablet for prevention or treatment of cardiovascular diseases, comprising, as active ingredients, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in low doses.

The term "cardiovascular diseases" as used in the present specification refers to not only direct diseases occurring due to various causes such as abnormality and dysfunction of the circulatory system in the body, damage thereto, and the like, but also secondary diseases induced by these direct diseases. For example, the cardiovascular diseases may include hypertension, dyslipidemia, angina pectoris, arteriospasm, cardiac arrhythmia, cardiomegaly, cerebral infarction, congestive heart failure, arteriosclerosis, coronary heart disease, or myocardial infarction.

The term "blood pressure" as used in the present specification refers to the pressure of blood flowing along blood vessels on the walls of the blood vessels. Blood pressure may be summarized as two measures of the highest systolic blood pressure and the lowest diastolic blood pressure in the pulse.

The term "hypertension" as used in the present specification refers to chronic diseases in which the blood pressure is higher than the normal range. Hypertension may be divided into essential hypertension (primary hypertension) and secondary hypertension. In addition, the criteria of hypertension may be, through several epidemiological investigation, defined as blood pressure that causes an increase in mortality due to cardiovascular complications. In addition, the criteria of hypertension may be defined in consideration of a risk contrast effect, i.e., based on a numerical value demonstrating that lowering the blood pressure has greater benefits than risks therefrom. For example, according to the diagnosis criteria for hypertension based on

the European Society of Hypertension (ESH) guidelines in 2018, the normal or the hypertension may be classified as follows.

[Table 1]

Classification of blood pressure	Systolic blood pressure (SBP)(mmHg)	Diastolic blood pressure (DBP)(mmHg)
Optimal	Less than 120	(and) less than 80
Normal	120 to 129	(and/or) 80 to 84
High normal BP	130 to 139	(and/or) 85 to 89
Stage 1 (Grade 1)	140 to 159	(and/or) 90 to 99
Stage 2 (Grade 2)	160 to 179	(and/or) 100 to 109
Stage 3 (Grade 3)	180 or higher	(and/or) 110 or higher
Isolated systolic hypertension	140 or higher	(and) less than 90

According to the ESH guidelines (2018), the most optimal blood pressure for humans is less than or equal to 120/80 mmHg, and a case where systolic blood pressure is from 120 mmHg to 129 mmHg and/or diastolic blood pressure is from 80 mmHg to 84 mmHg is referred to as normal. In addition, the ESH guidelines subdivide the classification according to systolic and diastolic blood pressure into high normal blood pressure (130 to 139/85 to 89 mmHg), stage 1 hypertension (140 to 159/90 to 99 mmHg), stage 2 hypertension (160 to 179/100 to 109 mmHg), stage 3 hypertension (greater than or equal to 180/110 mmHg), and isolated systolic hypertension (greater than or equal to 140 mmHg/less than 90 mmHg).

Also, in general, normal blood pressure at rest is from 100 mmHg to 140 mmHg during contraction and is from 60 mmHg to 90 mmHg during relaxation, and a case in which blood pressure is consistently greater than or equal to 140 mmHg/90 mmHg is referred to as having hypertension.

According to the guidelines of the Korean Society of Hypertension for treatment of hypertension, the reference for diastolic blood pressure (DBP) at prehypertension is lowered to 80 mmHg to encourage active prophylaxis of hypertension. Also, by introducing the concept of 'caution blood pressure (SBP of 120 to 129 mmHg and DBP

of less than 80 mmHg)', it was revised to maintain the blood pressure within the normal range as much as possible even if the blood pressure is slightly higher than normal blood pressure. It was also recommended to lower the blood pressure down to 130/80 mmHg as much as possible even if the blood pressure was adjusted to less than 140/90 mmHg.

The term "pulse pressure" as used in the present specification refers to a difference between systolic blood pressure and diastolic blood pressure (sitSBP - sitDBP). Pulse pressure is the difference in blood pressure when the heart contracts and relaxes. When the walls of blood vessels thicken and accordingly lose elasticity by aging, the systolic pressure increases. Here, the dilated arteries are difficult to return to the original state so that the diastolic blood pressure decreases, resulting in increased pulse pressure. In the Framingham study by Franklin et al. in 1999, it was reported that pulse pressure was a strong risk predictor for coronary artery diseases when age, gender, and other risk factors were corrected. In addition, in 50-year-old or older people, systolic blood pressure, rather than systolic blood pressure, and pulse pressure may show greater prediction power for cardiovascular complications (Evidence-based Recommendations for Hypertension in Primary Care, Korean Academy of Medical Sciences, Korea Disease Control and Prevention Agency).

The term "complication" as used in the present specification refers to the presence of other symptoms in a certain disease. Hypertension may be accompanied by symptoms such as dizziness, headaches, heart palpitations, dyspnea, and the like, and if the human body is in a long-term hypertensive state, it may lead to many complications such as stroke, coronary heart disease, renal failure, and the like.

The complex preparation may be used for the prevention or treatment of patients who have cardiovascular diseases including hypertension or complications thereof.

As examples of the cardiovascular treatment, drugs used for the treatment of hypertension may be largely divided into diuretics, sympathetic nerve inhibitors, and vasodilators according to action mechanisms of the drugs, and the vasodilators may be subdivided into angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and calcium channel blockers according to action mechanisms.

The term "amlodipine" is the generic drug name for 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate, and amlodipine is a calcium channel blocker that blocks calcium ion channels on the myocardial and vascular smooth muscle surfaces to relax vascular smooth muscle, and increases a glomerular filtration rate by relaxing the afferent arterioles of the kidneys, thus causing diuretic action, and thereby exhibiting a blood pressure-lowering effect. Amlodipine, by blocking calcium channels, is used to treat cardiovascular diseases such as angina pectoris, hypertension, and congestive heart attack. Amlodipine, which is a third-generation CCB, exhibits a long-term, slow blood pressure-lowering effect due to slow absorption when orally administered and a long half-life of about 35 hours to about 40 hours, alleviates side effects such as orthostatic hypotension and the like, is effective in preventing systolic hypertension and stroke, and is useful in treatment of angina pectoris since it causes dilatation of the coronary arteries.

The "chlorthalidone" is the generic drug name for benzenesulfonamide-2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl), and chlorthalidone is currently on sale under the trade name Hygroton®. Chlorthalidone is a thiazide-type diuretic that blocks Na^+/Cl^- cotransporter in the distal renal convoluted tubule to inhibit re-absorption of Na^+ and Cl^- and increase excretion of K^+ , thereby performing an action on water retention in the urine. In detail, chlorthalidone is a thiazide-type diuretic that blocks Na^+/Cl^- cotransporter in the distal renal convoluted tubule to inhibit re-absorption of Na^+ and Cl^- and increase excretion of K^+ , thereby performing an action on water retention in the urine. Chlorthalidone has a half-life of 50 hours to 60 hours and time of action of 48 hours to 72 hours. Thus, compared to hydrochlorothiazide having a half-life of 9 hours to 10 hours and time of action of 16 hours to 24 hours, chlorthalidone has longer duration and action times, and thus is more useful in control of nighttime blood pressure.

The "losartan" is the generic drug name for 2-butyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-imidazole-5-methanol, and losartan was the first developed angiotensin receptor antagonist-based component. Losartan is used to treat hypertension and heart failure by blocking the binding of angiotensin II, which is a vasoconstrictor, to receptors. Losartan is also used to treat ischemic peripheral circulatory disorder and myocardial ischemia (angina pectoris), prevent progression of

heart failure after myocardial infarction, and treat diabetic neuropathy, glaucoma, and the like. In addition, losartan has a blood pressure-lowering effect by acting as a selective and competitive antagonist against the receptor of angiotensin II, which is a potent vasoconstrictor. Losartan is useful in treating hypertension, heart failure, ischemic peripheral circulatory disorder, myocardial ischemia (angina pectoris), and the like, or preventing the progression of heart failure after myocardial infarction, and is effective in diabetic neuropathy, glaucoma, and the like.

In an embodiment, the complex preparation may comprise, as active ingredients, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in low doses.

The term "daily defined dose (DDD)" as used in the present specification refers to an average maintenance dose that an adult weighing 70 kg needs to take in one day with respect to main indications for each main component of the corresponding drug. For example, in the case of a commercially available drug, DDDs of amlodipine, losartan potassium, and chlorthalidone may be about 5 mg to about 10 mg, about 50 mg to about 100 mg, and about 12.5 mg to about 25 mg, respectively. For example, the lowest doses among the DDDs of amlodipine, losartan potassium, and chlorthalidone may be about 5 mg, 50 mg, and 12.5 mg, respectively.

The term "low dose" as used in the present specification refers to a dose that is less than the DDD of a drug. The low dose may be, compared to the DDD, about 1/6 to about 1/2 dose, about 1/5 to about 1/2 dose, or about 1/4 to about 1/2 dose.

In an embodiment, amlodipine or a pharmaceutically acceptable salt thereof may be comprised in a content of 0.5 mg to 5 mg when converted to a free base form. In an embodiment, amlodipine or a pharmaceutically acceptable salt thereof may be comprised in a content of 0.8 mg to 3 mg when converted to a free base form.

In an embodiment, chlorthalidone or a pharmaceutically acceptable salt thereof may be comprised in a content of 1 mg to 7 mg when converted to a free base form. In an embodiment, chlorthalidone or a pharmaceutically acceptable salt thereof may be comprised in a content of 2 mg to 7 mg when converted to a free base form.

In an embodiment, losartan or a pharmaceutically acceptable salt thereof may be comprised in a content of 7 mg to 30 mg when converted to a losartan free acid form.

In an embodiment, amlodipine or a pharmaceutically acceptable salt thereof may be comprised in a content of 0.5 mg to 5 mg when converted to an amlodipine free base form, chlorthalidone or a pharmaceutically acceptable salt thereof may be comprised in a content of 1 mg to 7 mg when converted to a chlorthalidone free base form, and losartan or a pharmaceutically acceptable salt thereof may be comprised in a content of 7 mg to 30 mg when converted to a losartan free acid form.

In an embodiment, amlodipine or a pharmaceutically acceptable salt thereof may be comprised in a content of 0.8 mg to 3 mg when converted to an amlodipine free base form, chlorthalidone or a pharmaceutically acceptable salt thereof may be comprised in a content of 2 mg to 7 mg when converted to a chlorthalidone free base form, and losartan or a pharmaceutically acceptable salt thereof may be comprised in a content of 7 mg to 30 mg when converted to a losartan free acid form.

In an embodiment, amlodipine or a pharmaceutically acceptable salt thereof may be comprised in a content of 1.25 mg to 3.5 mg or 1.25 mg to 2.5 mg when converted to an amlodipine free base form.

In an embodiment, when converted to a chlorthalidone free base form, a content of 3 mg to 6.25 mg may be comprised.

In an embodiment, losartan or a pharmaceutically acceptable salt thereof may be comprised in a content of 11 mg to 22 mg when converted to a losartan free acid form. In an embodiment, losartan or a pharmaceutically acceptable salt thereof may be comprised in a content of 11.5 mg to 25 mg or 11.5 mg to 23 mg when converted to a losartan free acid form.

In an embodiment, amlodipine or a pharmaceutically acceptable salt thereof may be comprised in a content of 1.25 mg to 2.5 mg when converted to an amlodipine free base form, chlorthalidone or a pharmaceutically acceptable salt thereof may be comprised in a content of 3 mg to 6.25 mg when converted to a chlorthalidone free base form, and losartan or a pharmaceutically acceptable salt thereof may be comprised in a content of 11 mg to 22 mg when converted to a losartan free acid form.

In an embodiment, amlodipine or a pharmaceutically acceptable salt thereof may be comprised in a content of 1.25 mg to 2.5 mg when converted to an amlodipine free base form, chlorthalidone or a pharmaceutically acceptable salt thereof may be comprised in a content of 3 mg to 6.25 mg when converted to a chlorthalidone free base form, and losartan or a pharmaceutically acceptable salt thereof may be comprised in a content of 11.5 mg to 23 mg when converted to a losartan free acid form.

In the low-dose pharmaceutical complex preparation, amlodipine or a pharmaceutically acceptable salt thereof may be comprised in a content of 0.5 mg to 4 mg, 0.5 mg to 3 mg, 0.8 mg to 3 mg, 0.8 mg to 2.5 mg, 0.83 mg to 2.5 mg, 1.25 mg to 2.5 mg, 1 mg to 3 mg, 1.5 mg to 3.5 mg, 1.5 mg to 2.5 mg, or 1.25 mg to 2.5 mg when converted to an amlodipine free acid form. For example, the amlodipine free base or the pharmaceutically acceptable salt of amlodipine may be comprised in a content of 0.83 mg, 1 mg, 1.25 mg, 1.5 mg, 1.67 mg, 2.5 mg, 3 mg, or 3.5 mg, or may be comprised in this range set as an upper limit or a lower limit.

The amlodipine may be comprised in the form of a pharmaceutically acceptable salt, such as amlodipine camsylate or amlodipine besylate, in a content of 1 mg to 4 mg, 1.3 mg to 3.9 mg, 1.5 mg to 4 mg, 1.8 mg to 4 mg, or 1.96 mg to 3.9 mg. For example, the pharmaceutically acceptable salt of amlodipine, such as amlodipine camsylate or amlodipine besylate, may be comprised in a content of 1.3 mg, 1.57 mg, 1.74 mg, 1.96 mg, 2.32 mg, 2.62 mg, 3.47 mg, or 3.92 mg, or may be comprised in this range set as an upper limit or a lower limit.

When converted to a chlorthalidone free base form in the low-dose pharmaceutical complex preparation, a content of 1 mg to 7 mg, 2 mg to 7 mg, 2 mg to 6.5 mg, 2.1 mg to 6.25 mg, 3 to 6.25 mg, 3.13 mg to 6.25 mg, 3 mg to 6.5 mg, or 3 mg to 7 mg may be comprised. For example, chlorthalidone may be comprised in a content of 2.08 mg, 2.5 mg, 3.13 mg, 4.17 mg, or 6.25 mg, or may be comprised in this range set as an upper limit or a lower limit.

In the low-dose pharmaceutical complex preparation, losartan or a pharmaceutically acceptable salt thereof may be comprised in a content of 5 mg to 30 mg, 7 mg to 30 mg, 7 mg to 25 mg, 7.5 mg to 23 mg, 7.6 mg to 22.9 mg, 10 mg to 30 mg, 11 mg to 23 mg, 11 mg to 22 mg, 11.4 mg to 22.95 mg, 11.47 mg to 22.93 mg, 11.5

mg to 23 mg, or 12 to 25 mg when converted to a losartan free acid form. For example, the losartan free acid may be comprised in a content of about 7.64 mg, 9.17 mg, 11.47 mg, 12.5 mg, 15.29 mg, 16.67 mg, 22.93 mg, or 25 mg, or may be comprised in this range set as an upper limit or a lower limit.

Losartan may be comprised in the form of a pharmaceutically acceptable salt, such as losartan potassium, in a content of 8 mg to 30 mg, for example, 8.3 mg to 25 mg, 10 mg to 25 mg, or 12.5 mg to 25 mg. For example, the pharmaceutically acceptable salt of losartan, such as losartan potassium, may be comprised in a content of about 8.33 mg, 10 mg, 12.5 mg, 16.67 mg, or 25 mg, or may be comprised in this range set as an upper limit or a lower limit.

In the low-dose pharmaceutical complex preparation, when converted to an amlodipine free base form, a losartan free acid form, and a chlorthalidone free base form, respectively, amlodipine or a pharmaceutically acceptable salt thereof, losartan or a pharmaceutically acceptable salt thereof, and chlorthalidone or a pharmaceutically acceptable salt thereof may be comprised in contents of: 0.5 mg to 3 mg, 5 mg to 30 mg, and 1 to 7 mg, respectively; 0.8 mg to 3 mg, 8 mg to 30 mg, and 2 mg to 7 mg, respectively; 0.62 mg to 2.5 mg, 6.25 mg to 25 mg, and 1.56 mg to 6.25 mg, respectively; 0.8 mg to 2.5 mg, 8.3 mg to 25 mg, and 2 mg to 6.5 mg, respectively; 0.8 mg to 2.5 mg, 8 mg to 25 mg, and 2 mg to 6.25 mg, respectively; 1 mg to 3 mg, 10 mg to 30 mg, and 3 mg to 7 mg, respectively; 1.25 mg to 2.5 mg, 11 mg to 23 mg, and 3.13 mg to 6.25 mg, respectively; 1.25 mg to 2.5 mg, 12 mg to 27 mg, and 3 mg to 6.5 mg, respectively; 1.25 mg to 2.5 mg, 12.5 mg to 25 mg, and 3.13 mg to 6.25 mg, respectively; or 1.5 mg to 2.5 mg, 12.5 mg to 25 mg, and 3.13 mg to 6.25 mg, respectively.

In the low-dose pharmaceutical complex preparation, when converted to an amlodipine free base form, a losartan free acid form, and a chlorthalidone free base form, respectively, amlodipine or a pharmaceutically acceptable salt thereof, losartan or a pharmaceutically acceptable salt thereof, and chlorthalidone or a pharmaceutically acceptable salt thereof may be comprised in contents of: 2.5 mg, 25 mg, and 6.25 mg, respectively; 2.5 mg, 23 mg, and 6.5 mg, respectively; 2.5 mg, 22.9 mg, and 6.25 mg, respectively; 1.7 mg, 15.3 mg, and 4.2 mg, respectively; 1.67 mg, 15.29 mg, and 4.17

mg, respectively; 1.25 mg, 11.47 mg, and 3.13 mg, respectively; 1.25 mg, 12.5 mg, and 3.13 mg, respectively; 1.67 mg, 16.67 mg, and 4.17 mg, respectively; 1 mg, 10 mg, and 2.5 mg, respectively; 1 mg, 9.2 mg, and 2.5 mg, respectively; 1 mg, 9 mg, and 3 mg, respectively; 1 mg, 9 mg, and 2.5 mg, respectively; 0.8 mg, 8 mg, and 2 mg, respectively; or 0.8 mg, 7.6 mg, and 2 mg, respectively, or may be comprised in this range set as an upper limit or a lower limit.

The dose may vary in consideration of the age, gender, body weight, severity of disease, age, and race of patients, and a drug administration route.

When referring to the clinical trial guidelines for antihypertensive agents, the efficacy of antihypertensive agents at the time of evaluating the blood pressure-lowering effect may be generally assessed based on a variation of sitting systolic blood pressure as a primary evaluation element before-after treatment as the primary evaluation item, and then, based on a variation of sitting diastolic blood pressure as a secondary evaluation item before-after treatment.

In the present specification, the degree of response to the hypertension treatment may be evaluated by a normalization percentage of blood pressure, i.e., a control rate of blood pressure control rate (e.g., a percentage of trial subjects with systolic blood pressure of less than 140 mmHg and diastolic blood pressure of less than 90 mmHg after treatment)(a percentage of trial subjects with sitSBP < 140 mmHg and sitDBP < 90 mmHg).

In addition, in the present specification, the degree of response to the hypertension treatment may be evaluated by a responder rate of blood pressure (e.g., a percentage of trial subjects having a decrease in systolic blood pressure of greater than or equal to 20 mmHg or a decrease in diastolic blood pressure of greater than or equal to 10 mmHg from baseline after treatment) (a percentage of trial subjects with sitSBP reduction $\geq$ 20 mmHg or sitDBP reduction $\geq$ 10 mmHg from baseline).

Also, in the present specification, the efficacy of the antihypertensive agent may be evaluated based on a pulse pressure variation, for example, a mean pulse pressure variation (mean sitSBP - sitDBP).

The low-dose pharmaceutical complex preparation according to an embodiment may reduce the variation of the sitting systolic blood pressure and/or the variation of the

sitting diastolic blood pressure, and may simultaneously or selectively reduce the variation of the pulse pressure.

The low-dose pharmaceutical complex preparation according to an embodiment may safely, quickly, and sufficiently inhibit elevation of blood pressure in a subject with mild hypertension to moderate hypertension, and may exhibit a blood pressure-lowering effect.

The low-dose pharmaceutical complex preparation according to an embodiment may be used as an initial therapy for the hypertension treatment.

The low-dose pharmaceutical complex preparation according to an embodiment shows a superior effect in the improvement of blood pressure to an effect of a placebo, and may exhibit a similar effect in the improvement of blood pressure with a case where 5 mg or 10 mg of amlodipine was administered or 100 mg of losartan was administered.

The low-dose pharmaceutical complex preparation according to an embodiment may be effectively used for the treatment of mild hypertension to moderate hypertension.

In the present specification, mild hypertension refers to a case where systolic blood pressure (mmHg) is greater than or equal to 140 and less than 160 and/or diastolic blood pressure (mmHg) is greater than or equal to 90 and less than 100. In the present specification, moderate hypertension refers to a case where systolic blood pressure (mmHg) is greater than or equal to 160 and less than 180 and/or diastolic blood pressure (mmHg) is greater than or equal to 100 and less than 110.

The low-dose pharmaceutical complex preparation according to an embodiment may effectively improve the blood pressure of a subject of which systolic blood pressure (mmHg) is greater than or equal to 140 and less than 180 and/or diastolic blood pressure (mmHg) is greater than or equal to 90 and less than 110, and may also have excellent benefits versus risks. For example, the complex preparation may effectively improve blood pressure of a subject of which systolic blood pressure (mmHg) is greater than or equal to 140 and less than or equal to 179 and/or diastolic blood pressure (mmHg) is greater than or equal to 90 and less than or equal to 109.

In an embodiment, mild hypertension to moderate hypertension may include stage 1 hypertension and stage 2 hypertension according to the 2018 ESH guidelines.

The low-dose pharmaceutical complex preparation according to an embodiment may be effectively used for the treatment of stage 1 hypertension (Grade 1) or stage 2 hypertension (Grade 2) according to the ESH guidelines (2018).

In the present specification, stage 1 hypertension refers to a case where systolic blood pressure (mmHg) is greater than or equal to 140 and less than or equal to 159 and/or diastolic blood pressure (mmHg) is greater than or equal to 90 and less than or equal to 99. In the present specification, stage 2 hypertension refers to a case where systolic blood pressure (mmHg) is greater than or equal to 160 and less than or equal to 179 and/or diastolic blood pressure (mmHg) is greater than or equal to 100 and less than or equal to 109.

The complex preparation according to an embodiment may effectively improve blood pressure of a subject of which systolic blood pressure (mmHg) is greater than or equal to 140 and less than or equal to 179 and/or diastolic blood pressure (mmHg) is greater than or equal to 90 and less than or equal to 109. For example, the complex preparation may effectively improve blood pressure of a subject of which systolic blood pressure (mmHg) is greater than or equal to 140 and less than or equal to 159 and/or diastolic blood pressure (mmHg) is greater than or equal to 90 and less than or equal to 99. The low-dose pharmaceutical complex preparation according to one embodiment may effectively improve blood pressure of a subject of which sitting systolic blood pressure (sitSBP) is less than 160 mmHg.

The low-dose pharmaceutical complex preparation according to an embodiment may provide an effective initial therapeutic agent for patients having mild hypertension to moderate hypertension.

The low-dose pharmaceutical complex preparation according to one embodiment may be effective for hypertension with sitting systolic blood pressure (sitSBP) of less than 160 mmHg. The complex preparation may show a reduction in blood pressure that is a proportionally elevated according to the dose in a subject having sitSBP of less than 160 mmHg.

The low-dose pharmaceutical complex preparation may be formulated into a fixed-dose combination formulation comprising amlodipine or a pharmaceutically acceptable salt thereof, losartan or a pharmaceutically acceptable salt thereof, and

chlorthalidone or a pharmaceutically acceptable salt thereof in the above-mentioned contents. The complex preparation may be administered once a day to several times a day, for example, once or three times a day, according to dosage.

In an embodiment, the low-dose pharmaceutical complex preparation may be for once-a-day administration. As the complex preparation is administered once a day, optimal pharmacological clinical effects may be provided in terms of a blood pressure-lowering effect while improving patient convenience and medication adherence. The complex preparation may be administered for at least 4 weeks or 8 weeks, or more or less, in consideration of the pathological condition and severity thereof of a subject to be administered.

In the low-dose pharmaceutical complex preparation, the pharmaceutically acceptable salt of amlodipine, losartan, or chlorthalidone refers to a salt prepared according to a method commonly known in the art, and such a preparation method is known to those of ordinary skill in the art. In detail, the pharmaceutically acceptable salt may include the following inorganic acids, organic acids, and base-derived salts that are pharmacologically or physiologically acceptable, but is not limited thereto. For example, examples of suitable acids may include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, perchloric acid, fumaric acid, maleic acid, phosphoric acid, glycolic acid, lactic acid, salicylic acid, succinic acid, toluene-p-sulfonic acid, tartaric acid, acetic acid, citric acid, methane sulfonic acid, formic acid, benzoic acid, malonic acid, naphthalene-2-sulfonic acid, benzene sulfonic acid, carboxylic acid, besylic acid, camsylic acid, and the like. Suitable base-derived salts may include an alkali metal, such as sodium or potassium, and an alkali earth metal, such as calcium or magnesium, but are not limited thereto.

The pharmaceutically acceptable salt of amlodipine is formed from an acid forming a non-toxic acid addition salt containing a pharmaceutically acceptable anion, and examples thereof may include, but are not limited to, hydrochloride, hydrobromide, sulfate, phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, besylate, camsylate, and the like. For example, amlodipine besylate or amlodipine camsylate may be used. The amlodipine includes amlodipine racemate and (S)-

amlodipine. The pharmaceutically acceptable salt of losartan may preferably include, for example, a losartan potassium salt, but is not limited thereto.

In an embodiment, the complex preparation may include amlodipine camsylate, losartan potassium, and chlorthalidone.

In an embodiment, the complex preparation may include amlodipine besylate, losartan potassium, and chlorthalidone.

The low-dose pharmaceutical complex preparation may exist in the form of, for example, powder, tablets, capsules, an aqueous or oily suspension, an emulsion, or dispersible powder or granules suitable for oral administration; in the form of an aqueous or oily sterilized solution or suspension suitable for parenteral administration, e.g., intravenous administration, subcutaneous administration, intramuscular administration, or intravascular administration; in the form of, for example, a cream, a gel, or an ointment suitable for local administration; or in the form of suppositories suitable for rectal administration.

In an embodiment, the low-dose pharmaceutical complex preparation may be formulated in the form of tablets, capsules, or caplets. In an embodiment, the complex preparation may be a single-layer tablet.

The term "tablet" as used in the present specification refers to inclusion of compressed pharmaceutical dosage forms of all shapes and sizes.

The term "double-layer tablet" as used in the present specification refers to a tablet in which two or more different components are independently present in two layers by separating compartments.

The term "single-layer tablet" as used in the present specification refers to a tablet in which two or more different components are mixed in one layer. In the complex preparation in a single-layer tablet according to an embodiment, amlodipine, chlorthalidone, and losartan may be present in one identical layer without existing by separating compartments. The term single-layer tablet is used separately from a multi-layer tablet, such as a double-layer tablet and a three-layered tablet, in which two or more components are independently present in different layers from each other by separating compartments.

The pharmaceutical complex preparation according to an embodiment is a single-layer tablet, and does not cause problems such as losartan gelation or subsequent reduction of dissolution, or generation of related substances.

When a complex preparation comprising amlodipine, chlorthalidone, and losartan is prepared, gelation of losartan may be a problem. Losartan shows a very good dissolution pattern when losartan dissolves in purified water at relatively high pH, e.g., pH 4.0 or pH 6.8. However, losartan is slowly released at low pH (e.g., pH 1.2 or pH 2.0) due to gelation of losartan. This phenomenon significantly affects the dissolution rate of the preparation because the first place where disintegration and dissolution occurs when taking an oral preparation is the stomach where the digestive fluid having low pH is secreted, and may further influence absorption of drugs into the living body. In addition, when losartan is gelated as described above, amlodipine and chlorthalidone that are mixed with losartan may be also locked in the inside of the gel, resulting in a problem of dissolution reduction.

However, in the complex preparation comprising losartan in low doses, for example, less than or equal to 30 mg, e.g., 7 mg to 30 mg, when converted to a losartan free acid form, the dissolution reduction due to the gelation of losartan may not occur.

Accordingly, the complex preparation in a single-layer tablet comprising amlodipine, chlorthalidone, and losartan at low doses may have the improved dissolution rate, stability and productivity without causing such gelation problems.

Therefore, the low-dose complex preparation in a single-layer tablet according to an embodiment may improve the dissolution rate, content uniformity, storage safety, tableting speed, and productivity of the comprised drug components.

The low-dose complex preparation in a single-layer tablet may comprise, in the form of mixed granules, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof.

The pharmaceutical complex preparation in a single-layer tablet comprises the active ingredients in mixed granules, and does not show a decrease in the dissolution rate of the active ingredients or an increase in the generation of related substances when even compared to a case where the active ingredients are comprised in

separated granules and formulated into a double-layer tablet or a single-layer tablet. Rather, the dissolution rate of amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof and the stability of the complex preparation are excellent.

In an embodiment, the total weight of the pharmaceutical complex preparation in a single-layer tablet for the prevention or treatment of cardiovascular diseases may be less than or equal to 350 mg. In an embodiment, the total weight of the complex preparation may be less than or equal to 330 mg, less than or equal to 300 mg, less than or equal to 200 mg, less than or equal to 170 mg, or less than or equal to 165 mg. When the total weight of the complex preparation is less than or equal to 330 mg, less than or equal to 300 mg, less than or equal to 200 mg, less than or equal to 170 mg, or less than or equal to 165 mg, further improved dissolution rates of amlodipine, chlorthalidone and losartan may be exhibited.

The total weight of the complex preparation may be greater than or equal to 42 mg, greater than or equal to 40 mg, greater than or equal to 50 mg, greater than or equal to 60 mg, greater than or equal to 70 mg, or greater than or equal to 80 mg.

In an embodiment, the total weight of the pharmaceutical complex preparation in a single-layer tablet for the prevention or treatment of cardiovascular diseases may be greater than or equal to 70 mg and less than or equal to 350 mg.

When the total weight of the complex preparation is within the ranges above, the dissolution rates of the active ingredients may be improved, and at the same time, the uniformity of the preparation may be secured, and the complex preparation may be prepared with excellent quality.

In an embodiment, the total weight of the active ingredients in the complex preparation, i.e., amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, may be greater than or equal to 15 mg.

When the total weight of the active ingredients in the complex preparation is within the ranges above, the dissolution rates of the active ingredients may be improved,

and at the same time, the uniformity of the preparation may be secured, and the complex preparation may be prepared with excellent quality.

In an embodiment, the active ingredients may be comprised in a content of 10 % or more of the total weight of the complex preparation.

In an embodiment, the active ingredients may be comprised in a content of 20 % or more of the total weight of the complex preparation.

When the active ingredients are comprised within the weight range above in the complex preparation, the dissolution rates of the active ingredients may be improved, and the complex preparation may be prepared with excellent quality.

In an embodiment, the pharmaceutical complex preparation may further comprise a disintegrant, wherein a content of the disintegrant may be in a range of about 1 % to about 15 % of the total weight of the complex preparation.

When the disintegrant is comprised in a content of less than 1 % of the total weight of the complex preparation, a fast dissolution pattern cannot be achieved, and when the disintegrant is comprised in a content of greater than 15 % of the total weight of the complex preparation, the stability of the preparation may be degraded. Meanwhile, when the disintegrant comprised in a content of 1 % to 15 % of the total weight of the complex preparation, desired dissolution rate and formulation stability can be achieved.

In an embodiment, the disintegrant may be further comprised, wherein a content of the disintegrant may be 2 % or more, 3 % or more, 4 % or more, or 5 % or more of the total weight of the complex preparation.

In an embodiment, the disintegrant may be further comprised, wherein a content of the disintegrant may be 4 % to 15 % of the total weight of the complex preparation.

In an embodiment, the disintegrant may be further comprised, wherein a content of the disintegrant may be 4.5 % to 10 % of the total weight of the complex preparation.

In an embodiment, the disintegrant may be further comprised, wherein a content of the disintegrant may be 9 % to 15 % of the total weight of the complex preparation.

When the disintegrant is comprised within the weight range above in the complex preparation, the dissolution rate of the disintegrant may be improved, and the complex preparation may be prepared with excellent quality.

In an embodiment, the complex preparation may further comprise a pharmaceutical additive selected from a diluent, a disintegrant, a lubricant, and a combination thereof.

In an embodiment, the diluent may be any one selected from microcrystalline cellulose, starch, pre-gelatinized starch, dicalcium phosphate, lactose, low-substituted hydroxypropyl cellulose, and a combination thereof.

In an embodiment, the disintegrant may be any one selected from croscopovidone, croscarmellose sodium, sodium starch glycolate, starch, pre-gelatinized starch, and a combination thereof.

In an embodiment, the lubricant may be any one selected from magnesium stearate, palmitic acid, talc, magnesium stearate, zinc stearate, calcium stearate, and a combination thereof.

In an embodiment, the complex preparation may further include a binder.

In an embodiment, the binder may be any one selected from hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, acacia gum, and a combination thereof.

In an embodiment, amlodipine or a pharmaceutically acceptable salt thereof in the complex preparation may be comprised in a content 0.1 wt% to 7 wt%, for example, 0.5 wt% to 3 wt%.

In an embodiment, chlorthalidone or a pharmaceutically acceptable salt thereof in the complex preparation may be comprised in a content 0.3 wt% to 9 wt%, for example, 1 wt% to 5 wt%.

In an embodiment, losartan or a pharmaceutically acceptable salt thereof in the complex preparation may be comprised in a content 1 wt% to 40 wt%, for example, 5 wt% to 20 wt%.

In an embodiment, the diluent may be comprised in a content of 40 wt% to 95 wt%, for example, 50 wt% to 90 wt%.

In an embodiment, the disintegrant may be comprised in a content of 1 wt% to 20 wt%, for example, 1.5 wt% to 15 wt%.

In an embodiment, the lubricant may be comprised in a content of 0.1 wt% to 2 wt%, for example, 0.5 wt% to 1.5 wt%.

In one embodiment, the binder may be comprised in a content 0 wt% to 10 wt%, for example, 0.1 wt% to 10 wt%, and for example, 0.5 wt% to 5 wt%.

The complex preparation may further include a pH adjusting agent, a suspending agent, a preservative, a flavoring agent, a colorant, a sweetener, an adsorbent, a solubilizer, and the like, if necessary. The content of the additive is not particularly limited in the present invention, and may be appropriately adjusted as necessary.

In an embodiment, the diluent may be comprised in so that a weight ratio of a diluent except for low-substituted hydroxypropyl cellulose to low-substituted hydroxypropyl cellulose may be 6:1 to 1:1.

In an embodiment, microcrystalline cellulose and low-substituted hydroxypropyl cellulose may be further comprised as the diluent, wherein a weight ratio of microcrystalline cellulose to low-substituted hydroxypropyl cellulose may be 2:1 to 1:1.

For example, the weight ratio may be 6:1 to 1:1, 5:1 to 1:1, 4:1 to 1:1, or 2:1 to 1.5:1.

When the low-substituted hydroxypropyl cellulose is used within the content range above, improved tableting property and dissolution rate may be exhibited. In detail, the flowability and tableting property of the tablet may be improved, and the dissolution rate of chlorthalidone may be improved.

When the content of the diluent is smaller than the content range above, problems in compressing tablets occur during a tableting process, whereas when the content of the diluent is greater than the content range above, problems occur in that a formulation is prepared in a greater dosage than necessary is prepared.

Therefore, when the weight ratio of the diluent except for low-substituted hydroxypropyl cellulose to low-substituted hydroxypropyl cellulose, for example, the weight ratio of microcrystalline cellulose to low-substituted hydroxypropyl cellulose, is within the ranges above, tablets with improved quality may be prepared.

In an embodiment, the diluent may be further comprised so that a weight ratio of the total weight of the active ingredients, i.e., amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof,

and losartan or a pharmaceutically acceptable salt thereof, to the diluent may be 1:2 to 1:9.

When the active ingredients and the diluent are comprised within the weight ratios above in the complex preparation, the dissolution rates of the active ingredients may be improved, and the complex preparation may be prepared with excellent quality.

In an embodiment, when the complex preparation in a single-layer tablet is subjected to a dissolution test according to the guidelines for setting dissolution specifications for oral drugs, dissolution rates of the active ingredients in 30 minutes may each be greater than or equal to 80 %.

In an embodiment, when the complex preparation in a single-layer tablet is subjected to a dissolution test according to the guidelines for setting dissolution specifications for oral drugs, a dissolution rate of amlodipine in 30 minutes may be greater than or equal to 80 %.

In an embodiment, when the complex preparation in a single-layer tablet is subjected to a dissolution test according to the guidelines for setting dissolution specifications for oral drugs, a dissolution rate of chlorthalidone in 30 minutes may be greater than or equal to 80 %.

In an embodiment, when the complex preparation in a single-layer tablet is subjected to a dissolution test according to the guidelines for setting dissolution specifications for oral drugs, a dissolution rate of losartan in 30 minutes may be greater than or equal to 80 %.

In an embodiment, when the complex preparation in a single-layer tablet is subjected to a dissolution test according to the paddle method of the dissolution test of the United States Pharmacopoeia under conditions of 100 ± 5 rpm, 37 ± 0.5 °C, and 900 mL of 0.01 M hydrochloric acid solution, a dissolution rate of amlodipine in 30 minutes may be greater than or equal to 80 %.

In an embodiment, when the complex preparation in a single-layer tablet is subjected to a dissolution test according to the paddle method of the dissolution test of the United States Pharmacopoeia for chlorthalidone tablets under conditions of 75 ± 2 rpm, 37 ± 0.5 °C, and 900 mL of purified water, a dissolution rate of chlorthalidone in 30 minutes may be greater than or equal to 80 %.

In an embodiment, when the complex preparation in a single-layer tablet is subjected to a dissolution test according to the paddle method of the dissolution test of the United States Pharmacopoeia for losartan potassium tablets under conditions of 75 rpm $\pm$ 2 rpm, 37 $\pm$ 0.5 °C, and 900 mL of purified water, a dissolution rate of losartan in 30 minutes may be greater than or equal to 80 %.

When the complex preparation is subjected to a dissolution test according to the paddle method of the dissolution test of the United States Pharmacopoeia, a dissolution rate of each active ingredient in 30 minutes may be greater than or equal to 85 %, and in an embodiment, a dissolution rate of each active ingredient in 15 minutes may be greater than or equal to 85 %.

In an embodiment, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof in the single-layer tablet may exist in one mixed part or one granule part.

When amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof are comprised in one mixed part or one granule part in the complex preparation, the complex preparation, the complex preparation may have a high maximum tableting speed and a high tableting process yield and excellent content uniformity compared to a case where the drugs are comprised in a separated mixed part or a separated granule part.

The complex preparation may be prepared in the form of a mixed part by mixing: amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof; and a pharmaceutical additive such as a diluent and a disintegrant. The mixed part may be compressed by after granulation by a conventional granulation method, for example, a compression granulation method. In one or more embodiments, the mixed part may be in the form of granules underwent a roller compaction process. The compressed and granulated mixed part may be mixed with a lubricant to prepare a final granule part.

When the mixed part or the final granule part is tableted into a single-layer tablet, dissolution rates of amlodipine, chlorthalidone, and losartan may be excellent, a desired dissolution pattern may be exhibited without gelation of losartan, and the complex preparation may have excellent stability.

In addition, when the complex preparation is tableted into a single-layer tablet, a maximum tableting speed and a tableting process yield may be high and content uniformity may be excellent, compared to a case where the complex preparation is tableted into a double-layered tablet.

The particle size (D90) of chlorthalidone or a pharmaceutically acceptable salt thereof in the complex preparation may be about 0.5 μm to 50 μm , for example, 0.5 μm to 25 μm , or for example, 0.5 μm to 10 μm . When particles of chlorthalidone are pulverized as described above, the dissolution rate, content uniformity, and thermal stability of the active ingredient may be improved. The particle size may be measured by using a commercially available apparatus according to a laser diffraction · scattering method based on the Mie theory. For example, the particle size may be measured by using a commercially available apparatus, such as a HELOS (Helium-neon Laser for Optical Spectrometry, Sympatec Company) laser diffraction apparatus. When a helium-neon laser beam is irradiated to particles, scattering occurs and a light scattering pattern appears on a detector of the apparatus, and this light scattering pattern is analyzed according to the Mie theory to obtain the particle size distribution.

A method of controlling the particle size in the manufacture of the complex preparation is not particularly limited, and a method known in the art may be appropriately selected. In detail, the chlorthalidone may be pulverized by using a conventional mill capable of pulverizing particles, such as a jet mill, a hammer mill, a ball mill, and a fluid energy mill. In addition, the particle size of the drugs may be subdivided by using a sieve method performed by using a sieve or by a size classification method such as air current classification.

Another aspect provides a method of manufacturing a pharmaceutical complex preparation in a single-layer tablet for preventing or treating cardiovascular diseases, wherein the pharmaceutical complex preparation in a single-layer tablet comprises

amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in low doses in a single-layer tablet.

The manufacturing method may include mixing a pharmaceutically acceptable additive. The manufacturing method may include mixing amlodipine or a pharmaceutically acceptable salt thereof in a content of 0.5 mg to 5 mg when converted into an amlodipine free base form, chlorthalidone or a pharmaceutically acceptable salt thereof in a content of 1 mg to 7 mg when converted to a chlorthalidone free base form, losartan or a pharmaceutically acceptable salt thereof in an amount of 7 mg to 30 mg when converted to a losartan free acid form, and a pharmaceutically acceptable additive.

The manufacturing method may include mixing amlodipine or a pharmaceutically acceptable salt thereof in a content of 0.8 mg to 3 mg when converted into an amlodipine free base form, chlorthalidone or a pharmaceutically acceptable salt thereof in a content of 2 mg to 7 mg when converted to a chlorthalidone free base form, losartan or a pharmaceutically acceptable salt thereof in an amount of 7 mg to 30 mg when converted to a losartan free acid form, and a pharmaceutically acceptable additive.

The manufacturing method may include mixing amlodipine or a pharmaceutically acceptable salt thereof in a content of 1 mg to 3 mg when converted into an amlodipine free base form, chlorthalidone or a pharmaceutically acceptable salt thereof in a content of 3 mg to 7 mg when converted to a chlorthalidone free base form, losartan or a pharmaceutically acceptable salt thereof in an amount of 10 mg to 30 mg when converted to a losartan free acid form, and a pharmaceutically acceptable additive.

The manufacture method may include: mixing amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive to form a mixture (step 1);

granulating the mixture to prepare a granule part (step 2);

mixing the granule part with a pharmaceutically acceptable additive to obtain a final granule part (step 3); and

tableting the final granule part to prepare a single-layer tablet (step 4).

The pharmaceutically acceptable additive mixed in step 1 may include a diluent, a disintegrant, and a combination thereof.

The pharmaceutically acceptable additive mixed in step 2 may include a lubricant.

Another aspect provides a method of treating an early-stage cardiovascular disease, the method comprising administering a pharmaceutical complex preparation in a single-layer tablet that comprises amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in low doses in a single-layer tablet.

The treatment method according to an embodiment may be effective as an initial therapy for the treatment of mild hypertension to moderate hypertension.

Amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof comprised in the complex preparation or a composition may be administered in an effective content for the treatment or prevention of a subject or patient with a disease by using various administration methods, either orally or parenterally, according to a desired purpose. For the administration methods, an administration dose for specific subjects or patients may be determined depending on several related factors, such as the body weight, age, race, gender, health conditions, and diet of patients, an administration period, an administration method, severity of diseases, and the like. It is to be understood that the administration dose may be appropriately increased or decreased by experts, and the administration dose is not intended to limit the scope of the present invention in any way. If needed, an administration dose of compounds used may be easily determined and prescribed by doctors of ordinary skill in the related art. For example, an administration dose of compounds of the present invention used for a pharmaceutical composition may be adjusted by a doctor such that the administration dose is first adjusted to be of a lower level than required to achieve a desired therapeutic effect and then is gradually increased until a desired effect is achieved.

The term "treatment" as used in the present specification may be used as a concept that includes all of treatment, improvement, amelioration, and management of

diseases. The term "treating" or "treatment" as used in the present specification refers to inhibiting a disease, for example, inhibiting a disease, pathologic condition, or disorder in a subject experiencing or exhibiting a pathologic condition or symptom of the disease, pathologic condition, or disorder, preventing further development of pathologic conditions and/or symptoms, ameliorating a disease, or reversing pathologic conditions and/or symptoms, such as reducing the severity of diseases.

The term "preventing" or "prevention" as used herein refers to preventing a disease, for example, preventing a disease, pathologic condition, or disorder in a subject who may have predisposition to the disease, pathologic condition, or disorder, but has not yet experienced or exhibited the pathology or symptoms of a disease.

The term "subject" or "patient" as used in the present specification refers to any animal including mammals, for example, mice, rats, other rodents, rabbits, dogs, cats, pigs, cows, sheep, horses, or primates, and humans.

In the treatment method according to an embodiment, the amlodipine or a pharmaceutically acceptable salt thereof, the chlorthalidone or a pharmaceutically acceptable salt thereof, and the losartan or a pharmaceutically acceptable salt thereof may be administered in a single dosage form comprising all the components, or in multiple dosage forms comprising each of the components individually. The components may exist in a single dosage form, or may each exist in separate dosage forms to be administered in combination. The single dosage form or the separate dosage form may be in the form of a tablet or a capsule. For example, when administered as a separate dosage form, the components may be administered by different routes. When the administration of the active ingredients is sequential or separate, a delay in administering a second ingredient should not preferably impair, for example, beneficial effects of the combination therapy. In this context, sequential administration may also include (but is not limited to), for example, alternate administration of the active ingredients.

In the treatment method according to an embodiment, an administration dose of the drugs vary depending on the age, gender, body weight, and pathologic conditions and severity thereof of subjects to be administered, an administration route, or determination of prescribers. A suitable dose based on these factors may be then

determined by those of ordinary skill in the art. In addition, if necessary, the drugs may be administered in combination with one or more other pharmaceuticals for preventing or treating cardiovascular diseases.

All technical terms as used in the present specification have the same meaning as commonly understood by those of ordinary skill in the relevant art, unless otherwise defined. In addition, suitable methods or samples are described in the present specification, but similar or equivalent ones are also within the scope of the present specification.

The contents of all publications referred in the present specification are incorporated herein by reference in their entirety. The numerical values set forth in the present specification are considered to include the meaning of "about" unless otherwise specified herein, and the term "about" as used herein means that the mentioned value may vary to some extent. For example, the value may vary by 10 %, 5 %, 2 %, or 1 %. For example, the expression "about 5" is construed as including a certain value between 4.5 and 5.5, between 4.75 and 5.25, between 4.9 and 5.1, or between 4.95 and 5.05. The numerical range indicated with the term "to" in the present specification refers to a range including the numerical values described before and after the term "to" as the lower limit and the upper limit, respectively. The expressions "has," "may have," "comprises," "may comprise," and the like as used in the present specification indicate the presence of the corresponding characteristic (e.g., a numerical value, or a component such as an ingredient or the like), and is not intended to exclude the presence of additional characteristics.

Hereinafter, the present invention will be described in detail based on Examples below. However, Examples below are for illustrating the present invention, and the scope of the present invention is not limited thereto.

[Examples]

Manufacture Example 1: Selection of test subjects and administration of clinical trial drugs

1. Selection of trial subjects

Trial subjects were selected based on the following selection criteria and exclusion criteria.

(1) Selection criteria

- 1) 19-year-old or older patients with essential hypertension
- 2) Trial subjects who understood clinical trial processes and signed a consent form
- 3) Patients in which mean blood pressure satisfied $140 \text{ mmHg} \leq \text{sitSBP} < 180 \text{ mmHg}$ and $\text{sitDBP} < 110 \text{ mmHg}$ when measured at the first visit (Visit 1) and the second visit (Visit 2)

However, based on the exclusion criteria exemplified below, trial subjects who were not suitable for the clinical trials according to the criteria set in the clinical trial protocol were excluded.

(2) Exclusion criteria

- 1) Patients in which a difference in mean values between the blood pressures measured in both arms at the first visit satisfied sitSBP of 20 mmHg or greater or sitDBP of 10 mmHg or greater.
- 2) Patients in which a difference in mean sitSBP between the first visit and the second visit was greater than 15 mmHg.
- 3) Patients in which mean sitSBP was greater than or equal to 180 mmHg or mean sitDBP was greater than or equal to 110 mmHg, at the first visit and the second visit.
- 4) Patients with secondary hypertension or suspected secondary hypertension (e.g., coarctation of aorta, primary aldosteronism, renal artery stenosis, renal hypertension, pheochromocytoma, Cushing's syndrome, etc.)
- 5) Patients who have taken antihypertensive drugs within 2 weeks after Visit 1 or needs to take drugs listed in contraindicated drugs during the trial period (see 82 Concomitant Drugs and Prohibited Drugs)
- 6) Patients with type 1 diabetes or uncontrolled type 2 diabetes ($\text{HbA1c} \geq 9\%$ at Visit 1), etc.

2. Preparation and administration of clinical trial drugs

(1) Preparation of trial drugs

As test drugs to be administered to the selected subject groups, trial drugs containing the following contents were prepared. To develop therapeutic agents

targeting patients with mild hypertension to moderate hypertension, there is a need to demonstrate an appropriate level of blood pressure-lowering effects. Accordingly, to develop a low-dose complex preparation in a suitable dose in consideration of both safety and efficacy, the inventors of the present invention searched for a dose by reducing the dose at a constant proportion while maintaining the proportion of main ingredients the same based on the lowest dose of Amosartan Plus™ tablet, i.e., 5 mg/50 mg/12.5 mg of amlodipine, losartan, and chlorthalidone, respectively. As a result, the inventors of the present invention suggested trial drugs with the following proportions.

1) HCP1803-2.5/25/6.25: 2.5 mg of amlodipine, 25 mg of losartan potassium, and 6.25 mg of chlorthalidone

2) HCP1803-1.67/16.67/4.17: 1.67 mg of amlodipine, 16.67 mg of losartan potassium, and 4.17 mg of chlorthalidone

3) HCP1803-1.25/12.5/3.13: 1.25 mg of amlodipine, 12.5 mg of losartan potassium, 3.13 mg of chlorthalidone

(2) Preparation of control drug (active control)

As control drugs, HGP0904 (Norvasc™ 5 mg tablet)(5 mg of amlodipine)(available from Pfizer Korea Inc.) and Cozaar™ 100 mg tablet (100 mg of losartan potassium)(available from MSD Korea Ltd.) were prepared.

(3) Preparation of placebo

1) Placebo of HGP0904 (5 mg of amlodipine) (white octagonal tablet)

2) Placebo of HCP1803-1.25/12.5/3.13 (white, round, film-coated tablet)

(4) Preparation of DB capsule for double blinding

To secure double blindness, the tablets prepared in Sections (1) to (3) were packaged in DB capsules (DB caps® size A; Capsugel, USA), and then clinical trials were conducted.

To prepare the DB capsules, which were to be taken for each drug-administered group, in similar weights, the test drugs or the control drugs filled the DB capsules with the placebo of HGP0904 or the placebo of HCP1803-1.25/12.5/3.13. However, for the group administered with 10 mg of amlodipine, 2 tablets of HGP0904 filled the DB capsule in consideration of the size of the DB capsule.

(5) Administration method

All the trial subjects took 1 tablet of single-blind placebo of Novask 5 mg tablet during 2 weeks of a run-in period, and then 1 capsule of the trial drug was orally administered to a randomly allocated group once a day in the morning with or without food during 8 weeks of a treatment period.

3. Plans and methods for clinical trial

The present clinical trial was designed as a multicenter, randomized, double-blinded, and parallel-way clinical trial.

Subjects who met the selection/exclusion criteria at the first visit (Visit 1) went through a 2-week run-in period, and were requested to control a diet (salt intake), smoking, drinking alcohol, body weight, amount of exercise, and the like. Patients who met the inclusion/exclusion criteria at the second visit (Visit 2) were stratified and divided into 7 groups based on sitSBP of 160 mmHg, randomized at a ratio of 1:1:1:1:1:1:1, and then administered with the corresponding trial drugs for 8 weeks. During a treatment period, the subjects visited a trial institution at 0 week (Visit 2), 4 weeks (Visit 3), and 8 weeks (Visit 4) for the evaluation of efficacy and safety. During this test period, the same treatment method was maintained without adjusting a dose of the clinical trial drugs. In addition, all the subjects were requested to maintain regular lifestyle habits that could affect blood pressure measurement results, such as a diet (salt intake), smoking, drinking alcohol, body weight, an amount of exercise, and the like throughout the clinical trial period.

FIG. 1 illustrates a method of administering, to a clinical trial subject during a treatment period through a run-in period according to the above-described clinical trial plan, the above-described trial drug (2.5 mg of amlodipine, 25 mg of losartan potassium, 6.25 mg of chlorthalidone; 1.67 mg of amlodipine, 16.67 mg of losartan potassium, 4.17 mg of chlorthalidone; or 1.25 mg of amlodipine, 12.5 mg of losartan potassium, and 3.13 mg of chlorthalidone) the control drug (5 mg of amlodipine; 10 mg of amlodipine; or 100 mg of losartan potassium), or the placebo.

4. Evaluation criteria for clinical trial results

The clinical trial results were evaluated based on the following entries for the efficacy and safety evaluations.

(1) Efficacy evaluation

1) Entries for primary efficacy evaluation

- ① Mean deviation from baseline in sitSBP after 8 weeks

1) Entries for secondary efficacy evaluation

- ① Mean deviation from baseline in sitSBP after 4 weeks

- ② Mean deviation from baseline in sitSBP after 4 weeks and 8 weeks

③ Blood pressure control rate at 4 and 8 weeks (ratio for trial subject was sitSBP/sitDBP < 140/90 mmHg)

④ Blood pressure responder rate at 4 weeks and 8 weeks (ratio for trial subject was reduction of sitSBP/sitDBP from baseline $\geq$ 20/10 mmHg)

⑤ Mean deviation from baseline in pulse pressure after 4 weeks and 8 weeks (mean sitSBP - sitDBP)

(2) Safety evaluation

1) Adverse events

2) Vital signs, clinical laboratory tests, physical examination, electrocardiogram (ECG)

(3) Dose selection

A suitable dose for confirmatory Phase III clinical trial was selected by comprehensively evaluating the efficacy and safety of each drug-administered group.

5. Statistical analysis method

The result values obtained based on the clinical trial evaluation entries were statistically analyzed in the following way. For the analysis of the efficacy evaluation, a full analysis set (FA set or FAS) (among trial subjects who took the clinical trial drugs at least one time after random allocation, those who have measured sitSBP at least one time until the end of the clinical trial after being administered with the clinical trial drugs) was used as a main analysis target, and a per-protocol set (PP set or PPS) was used as a second analysis target.

(1) Analysis of efficacy evaluation

1) Primary efficacy evaluation

- ① Mean deviation from baseline in sitSBP after 8 weeks

To examine whether changes from baseline in sitSBP after 8 weeks in the test group were superior to those in the placebo control group, analysis of covariance (ANCOVA) was performed by using a baseline value as a covariate.

2) Secondary efficacy evaluation

① Mean deviation from baseline in sitSBP after 8 weeks

To compare the test groups with the control group for the changes from baseline in sitSBP after 8 weeks, the ANCOVA was performed by using a baseline value as a covariate (wherein the comparison between the test drugs and placebo that were primary evaluation variables was excluded)

② Mean deviation from baseline in sitSBP after week 4

To compare the test group with the control group for the changes from baseline in sitSBP after 4 weeks, the ANCOVA was performed by using a baseline value as a covariate.

③ Mean deviation from baseline in sitSBP after 4 weeks and 8 weeks

To compare the test group with the control group for the changes from baseline in sitDBP after 4 weeks and 8 weeks, the ANCOVA was performed by using baseline values and stratified variables as covariates.

④ Blood pressure control rate at 4 weeks and 8 weeks (ratio for trial subject was sitSBP < 140 mmHg and sitDBP < 90 mmHg)

To compare the blood pressure control rates between the test group and the control group at 4 weeks and 8 weeks, the Pearson's chi-square test or the Fisher's exact test was performed for the comparison among the drug-administered groups.

⑤ Blood pressure responder rate at 4 and 8 weeks (percentage of trial subjects with sitSBP reduction ≥ 20 mmHg or sitDBP reduction ≥ 10 mmHg from baseline)

To compare the blood pressure responder rates between the test group and the control group at 4 and 8 weeks, Pearson's chi-square test or Fisher's exact test was performed for the comparison among the drug-administered groups.

⑥ Changes from base line in pulse pressure at 4 and 8 weeks (mean sitSBP-sitDBP)

To compare the test group with the control group for the changes from baseline in pulse pressure at 4 and 8 weeks, the ANCOVA was performed by using baseline values and stratified variables as covariates.

(2) Analysis of safety evaluation

The safety analysis was carried out on test subjects who have verified the safety-related data at least once until the end of the clinical trial after administration of the trial drug, among test subjects who have administered the trial drug at least once after being randomly allocated.

1) Adverse events

Adverse events refer to any noxious and unintended signs (abnormalities in laboratory test values), symptoms, or diseases that occur in trial subjects who have administered the clinical trial drug, do not necessarily have to have a cause-and-effect relationship with the corresponding clinical trial drug. An investigator recorded and evaluated all adverse events that occurred during the trial.

Adverse events (AEs) that occurred prior to randomization (referred to as pre-existing AEs) were presented in a list, and for comparative evaluation, adverse events that occurred after randomization (referred to as treatment emergent AEs (TEAEs)) were presented for each drug-administered group and with the number of trial subjects and incidence (%) in terms of the presence and severity of serious AEs and the correlation with the clinical trial drug.

2) Vital signs, clinical laboratory test, physical examination, electrocardiogram (ECG)

For each drug-administered group, a shift table was presented for normality, not clinically significant (NCS) abnormality, and clinically significant (CS) abnormality according to the time point, and the McNemar's test was performed to conduct a statistical significance test for changes in each drug-administered group before/after administration. In the case of continuous variables, the descriptive statistics (e.g., number of trial subjects, an arithmetic mean, a standard deviation, a median, minimum and maximum values) were presented for each time point of the measurement.

Clinical Trial Example 1: Observation of SAEs and adverse drug reaction following administration of low-dose therapeutic agent for hypotension in trial subject group

An adverse drug reaction, as any noxious and unintended reaction that occurs at any dose of a clinical trial drug, refers to a case where a cause-and-effect relationship with the clinical trial drug cannot be excluded. In the present clinical trial, an adverse event evaluated as having a cause-and-effect was classified as an adverse drug reaction.

The serious AE or ADR refers to a case corresponding to any one of the following AEs or ADRs occurring at any dose of the clinical trial drug:

- 1) a case where death or menace to life occurs;
- 2) a case requiring hospitalization or extension of hospitalization period;
- 3) a case where permanent or significant disability and functional decline occurs;
- 4) a case where malformation or abnormality occurs in fetus; and/or
- 5) a case other than cases 1) to 4), where medically important situations, such occurrence of drug dependency or drug abuse, blood diseases, and the like, occur.

The administration of the low-dose therapeutic agent for hypertension among the clinical trial drugs according to the present clinical trial (amlodipine 2.5 mg, losartan potassium 25 mg, and chlorthalidone 6.25 mg; amlodipine 1.67 mg, losartan potassium 16.67 mg, and chlorthalidone 4.17 mg; or amlodipine 1.25 mg, losartan potassium 12.5 mg, and chlorthalidone 3.13 mg) did not show any clinically significant AE or ADR.

Clinical Trial Example 2: Blood pressure improvement effect by administration of low-dose therapeutic agent for hypertension in patients with mild hypertension to moderate hypertension

(1) Measurement of blood pressure before drug administration in target groups

Systolic blood pressure and diastolic blood pressure of trial subject groups were measured before administration of the trial drugs.

(2) Blood pressure improvement effect by administration of low-dose therapeutic agent for hypertension

Systolic blood pressure and diastolic blood pressure according to the administration of the trial drugs were measured in the trial subject group, and then compared with results of administration of the control drug or the placebo. As a result, the low-dose therapeutic agents for hypertension prepared as the clinical drugs (HCP1803-2.5/25/6.25, HCP1803-1.67/16.67/4.17, and HCP1803-1.25/12.5/3.13) showed superior effects on the blood pressure improvement to the effects of the placebo, and exhibited similar effects on the blood pressure improvement with the effects by the administration of amlodipine 5 mg or 10 mg or losartan 100 mg. The trial drugs did not show an excessive decrease in blood pressure in patients with mild hypertension to moderate hypertension, and at the same time, showed an average blood pressure lowering effect sufficient to control the blood pressure, and thus the trial drugs were confirmed to have excellent safety and drug tolerance. In addition, in the trial subject group rather than in the control drug or the placebo, the trial drugs were confirmed to have excellent benefits versus risks for mild or moderate hypertension, such as Stage 1 or 2 hypotension, according to the ESH guidelines (2018).

Clinical Trial Example 3: Measurement of blood pressure normalization rate

When the low-dose therapeutic agents for hypertension as the clinical trial drugs (i.e., amlodipine 2.5 mg, losartan potassium 25 mg, and chlorthalidone 6.25 mg; amlodipine 1.67 mg, losartan potassium 16.67 mg, chlorthalidone 4.17 mg; or amlodipine 1.25 mg, losartan potassium 12.5 mg; chlorthalidone 3.13 mg) were administered, superior effects on the blood pressure improvement were shown in patient groups with mild or moderate hypertension, including Stage 1 or 2 hypertension according to the ESH guidelines (2018), compared to the effects by the placebo administration. In spite of low-dose administration, the effects of the therapeutic agents were similar to the effects in cases where usual dose of amlodipine or usual dose of losartan was administered. In detail, compared to a case where amlodipine 5 mg or 10 mg or losartan 100 mg was administered as a control drug, a reference drug, the low-dose therapeutic agents for hypertension prepared as the trial drugs (i.e., HCP1803-2.5/25/6.25, HCP1803-1.67/16.67/4.17, and HCP1803-1.25/12.5/3.13) exhibited improved blood pressure normalization rates in mild hypertension to moderate

hypertension including Stage 1 or 2 hypertension according to the ESH guidelines (2018).

<Primary efficacy evaluation results>

Clinical Trial Example 4: Changes from baseline in mean sitSBP after 8 weeks

For comparison of the sitSBP change from baseline after 8 week treatment between each of the test drug groups and the placebo control group, the analysis of covariance (ANCOVA) in which mean sitSBP at the baseline was corrected with a covariate was performed.

For least mean square $\pm$ standard error (LS Mean $\pm$ SE) of the sitSBP variation from baseline after 8 weeks as being estimated as a result of the ANCOVA, each trial drug group and the active control group were compared based on an FAS, and results are as follows.

The LS mean $\pm$ SE of the sitSBP variation from baseline after 8 weeks as the variables of the primary efficacy evaluation was larger in the group administered with amlodipine/losartan potassium/chlorthalidone 1.25/12.5/3.13 mg (hereinafter referred to as A/L/C-1.25/12.5/3.13), the group administered with amlodipine/losartan potassium/chlorthalidone 1.67/16.67/4.17 mg (hereinafter referred to as A/L/C-1.67/16.67/4.17), and the group administered with amlodipine/losartan potassium/chlorthalidone 2.5/25/6.25 mg (hereafter referred to as A/L/C-2.5/25/6.25) with -14.91 ± 3.89 mmHg, -19.49 ± 4.36 mmHg, and -17.21 ± 3.60 mmHg, respectively, as compared to the group administered with placebo, and the difference of change among the groups was statistically significant ($p=0.0003$, $p<0.0001$, and $p<0.0001$). Accordingly, it was statistically demonstrated that, for all doses of trial drug HCP1803, the sitSBP change from baseline after 8 weeks was superior to placebo.

<Secondary efficacy evaluation results>

Clinical Trial Example 5: Mean sitSBP variation from baseline after 8 week treatment

- Measurement of sitSBP change from baseline in FAS

For comparison of the sitSBP change from baseline after 8 week treatment between the test group and the active control group, the ANCOVA in which mean sitSBP at the baseline was corrected with a covariate was performed.

For the sitSBP variation (LS Mean $\pm$ SE) from baseline after 8 week treatment as being estimated as a result of the ANCOVA, each of the test groups was compared with the active control group based on the FAS, and the comparison results are shown in Table 2.

[Table 2]

sitSBP (mmHg)	A/L/C 1.25/12.5/3.13 (N=35)	A/L/C 1.67/16.67/4.17 (N=33)	A/L/C 2.5/25/6.25 (N=36)	A5 (N=34)	A10 (N=33)	L100 (N=34)	P (N=33)
Baseline							
N	35	33	36	34	33	34	33
MEAN (SD)	154.36(10.30)	153.71(10.05)	155.32(8.67)	154.65(10.31)	154.32(7.43)	154.57(9.75)	153.62(8.86)
MEDIAN	152.50	151.50	153.50	152.75	152.00	153.50	154.00
MIN, MAX	140.50,178.50	140.00,177.00	140.00,177.00	141.00,178.00	141.50,171.00	140.50,178.00	140.50,171.00
Week 8							
N	35	33	36	34	33	34	33
MEAN (SD)	138.23(13.61)	133.15(15.38)	137.21(13.95)	142.25(15.77)	134.77(12.11)	143.47(16.02)	152.59(20.73)
MEDIAN	136.00	132.00	134.75	140.50	135.00	140.75	148.50
MIN, MAX	115.50,175.00	112.00,168.50	121.50,184.00	103.00,175.50	107.50,162.00	114.00,191.50	117.00,212.00
Week 8 - Baseline							
N	35	33	36	34	33	34	33
MEAN (SD)	-16.13(13.62)	-20.56(17.87)	-18.11(10.44)	-12.40(13.13)	-19.55(10.67)	-11.10(15.89)	-1.03(18.38)
MEDIAN	-16.50	-22.50	-20.50	-12.50	-19.50	-14.75	-2.50
MIN, MAX	-46.50, 22.00	-57.00, 20.50	-33.00, 7.00	-43.50, 22.00	-44.50, -3.00	-39.00, 21.00	-31.50, 41.00
ANCOVA Result ^{a)}							-1.13(2.79)
LS Mean (SE)	-16.04(2.71)						
LS Mean difference (SE)	-14.91(3.89)						
95% C.I for LS Mean difference	(-22.68,-7.13)						
p-value	0.0003						
ANCOVA Result ^{a)}							-1.05(3.08)
LS Mean (SE)		-20.54(3.08)					
LS Mean difference (SE)		-19.49(4.36)					

sitSBP (mmHg)	A/L/C (N=35)	A/L/C 1.67/16.67/4.17 (N=33)	A/L/C 2.5/25/6.25 (N=36)	A5 (N=34)	A10 (N=33)	L100 (N=34)	P (N=33)
95% C.I for LS Mean difference	1.25/12.5/3.13 (N=35)	(-28.19,-10.8)					
p-value		<0.0001					
ANCOVA Result ^{a)}							
LS Mean (SE)			-18.17(2.48)				-0.96(2.60)
LS Mean difference (SE)			-17.21(3.60)				
95% C.I for LS Mean difference			(-24.40,-10.0)				
p-value			<0.0001				
ANCOVA Result ^{a)}							
LS Mean (SE)				-12.37(2.75)			-1.05(2.80)
LS Mean difference (SE)				-11.32(3.93)			
95% C.I for LS Mean difference				(-19.17,-3.47)			
p-value				0.0054			
ANCOVA Result ^{a)}							
LS Mean (SE)					-19.53(2.64)		-1.04(2.64)
LS Mean difference (SE)					-18.49(3.73)		
95% C.I for LS Mean difference					(-25.95,-11.0)		
p-value					<0.0001		
ANCOVA Result ^{a)}							
LS Mean (SE)						-11.00(2.95)	-1.14(2.99)
LS Mean difference (SE)						-9.86(4.20)	

sitSBP (mmHg)	A/L/C 1.25/12.5/3.13 (N=35)	A/L/C 1.67/16.67/4.17 (N=33)	A/L/C 2.5/25/6.25 (N=36)	A5 (N=34)	A10 (N=33)	L100 (N=34) (-18.25,-1.47)	P (N=33)
95% C.I for LS Mean difference p-value						0.0220	
ANCOVA Result ^{b)}							
LS Mean (SE)	-16.18(2.37)					-11.05(2.41)	
LS Mean difference (SE)	-5.13(3.38)						
95% C.I for LS Mean difference p-value	(-11.88, 1.62) 0.1339						
ANCOVA Result ^{b)}							
LS Mean (SE)		-20.87(2.71)				-10.81(2.67)	
LS Mean difference (SE)		-10.06(3.80)					
95% C.I for LS Mean difference p-value		(-17.65,-2.47) 0.0102					
ANCOVA Result ^{b)}							
LS Mean (SE)			-18.03(2.22)			-11.19(2.28)	
LS Mean difference (SE)			-6.84(3.18)				
95% C.I for LS Mean difference p-value			(-13.19,-0.49) 0.0353				
ANCOVA Result ^{b)}							
LS Mean (SE)				-12.39(2.46)		-11.11(2.46)	
LS Mean difference (SE)				-1.27(3.49)			

sitSBP (mmHg)	A/L/C 1.25/12.5/3.13 (N=35)	A/L/C 1.67/16.67/4.17 (N=33)	A/L/C 2.5/25/6.25 (N=36)	A5 (N=34) (-8.23, 5.69)	A10 (N=33)	L100 (N=34)	P (N=33)
95% C.I for LS Mean difference p-value							
ANCOVA Result ^{b)}							
LS Mean (SE)					-19.59(2.31)	-11.06(2.28)	
LS Mean difference (SE)					-8.54(3.24)		
95% C.I for LS Mean difference p-value					(-15.02,-2.06)		
ANCOVA Result ^{c)}					0.0106		
LS Mean (SE)					-19.55(2.06)		
LS Mean difference (SE)							
95% C.I for LS Mean difference p-value							
ANCOVA Result ^{c)}							
LS Mean (SE)					-19.35(2.37)		
LS Mean difference (SE)							
95% C.I for LS Mean difference p-value							
ANCOVA Result ^{c)}							
LS Mean (SE)					-18.09(1.77)		
LS Mean difference (SE)					1.48(2.57)		

sitSBP (mmHg)	A/L/C (N=35)	A/L/C 1.25/12.5/3.13	A/L/C (N=33)	A/L/C 1.67/16.67/4.17	A/L/C (N=36)	A5 (N=34)	A10 (N=33)	L100 (N=34)	P (N=33)
95% C.I for LS Mean difference					(-3.65, 6.60)				
p-value					0.5673				
ANCOVA Result ^{e)}									
LS Mean (SE)									
LS Mean difference (SE)									
95% C.I for LS Mean difference									
p-value									
ANCOVA Result ^{d)}									
LS Mean (SE)									
LS Mean difference (SE)									
95% C.I for LS Mean difference									
p-value									
ANCOVA Result ^{d)}									
LS Mean (SE)									
LS Mean difference (SE)									
95% C.I for LS Mean difference									
p-value									
ANCOVA Result ^{d)}									
LS Mean (SE)									
LS Mean difference (SE)									
95% C.I for LS Mean difference									
p-value									
ANCOVA Result ^{d)}									
LS Mean (SE)									
LS Mean difference (SE)									
95% C.I for LS Mean difference									
p-value									

sitSBP (mmHg)	A/L/C 1.25/12.5/3.13 (N=35)	A/L/C 1.67/16.67/4.17 (N=33)	A/L/C 2.5/25/6.25 (N=36)	A5 (N=34)	A10 (N=33)	L100 (N=34)	P (N=33)
95% C.I for LS Mean difference p-value			(-11.36, 0.01)				
ANCOVA Result ^{e)}			0.0502				
LS Mean (SE)	-16.26(2.02)		-17.99(1.99)				
LS Mean difference (SE)	1.73(2.84)						
95% C.I for LS Mean difference p-value	(-3.93, 7.40)						
ANCOVA Result ^{e)}	0.5441						
LS Mean (SE)							
LS Mean difference (SE)		-20.96(2.42)	-17.75(2.32)				
95% C.I for LS Mean difference p-value		(-9.91, 3.50)					
ANCOVA Result ^{f)}		0.3434					
LS Mean (SE)	-15.91(2.41)						
LS Mean difference (SE)	4.88(3.46)	-20.79(2.48)					
95% C.I for LS Mean difference	(-2.03, 11.80)						

sitSBP (mmHg)	A/L/C (N=35)	A/L/C 1.67/16.67/4.17 (N=33)	A/L/C 2.5/25/6.25 (N=36)	A5 (N=34)	A10 (N=33)	L100 (N=34)	P (N=33)
p-value	0.1635						
Treatments:							
A/L/C 1.25/12.5/3.13: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg							
A/L/C 1.67/16.67/4.17: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg							
A/L/C 2.5/25/6.25: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg							
A5: amlodipine 5mg; A10: amlodipine 10mg; L100: losartan 100mg; P: placebo							
Compared with:							
a) Placebo; b) L100; c) A10; d) A5; e) A/L/C 2.5/25/6.25; f) A/L/C 1.67/16.67/4.17							
Report Generated by Program : Table 10.2.3. Change from Baseline in sitSBP at Week 8-FAS.SAS							

FIG. 2 shows sitSBP change from baseline at 8 weeks in a FAS.

When the sitSBP variation from baseline after 8 week treatment in the group administered with A/L/C-1.25/12.5/3.13 was compared with the group administered with 5 mg of amlodipine (hereinafter referred to as A5), the group administered with 10 mg of

amlodipine (hereinafter referred to as A10), and the group administered with 100 mg of losartan potassium (hereinafter referred to as L100), the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-1.25/12.5/3.13 and each of the drug-administered groups was -3.83 ± 3.14 mmHg, 3.43 ± 2.87 mmHg, and -5.13 ± 3.38 mmHg, respectively, and the group administered with A/L/C-1.25/12.5/3.13 showed a statistically significant difference with the active control group ($p=0.2280$, $p=0.2355$, and $p=0.1339$).

When the sitSBP variation from baseline after 8 week treatment in the group administered with A/L/C-1.67/16.67/4.17 was compared with each of the A5-administered group, the A10-administered group, and the L100-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-1.67/16.67/4.17 and each of the drug-administered groups was -8.64 ± 3.64 mmHg, -1.42 ± 3.35 mmHg, and -10.06 ± 3.80 mmHg, respectively, and the group administered with A/L/C-1.67/16.67/4.17 showed a statistically significant difference with the A5-administered group and the L100-administered group ($p=0.0205$, $p=0.6745$, and $p=0.0102$).

When the sitSBP variation from baseline after 8 week treatment in the group administered with A/L/C-2.5/25/6.25 was compared with each of the A5-administered group, the A10-administered group, and the L100-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-2.5/25/6.25 and each of the drug-administered groups was -5.68 ± 2.85 mmHg, 1.48 ± 2.57 mmHg, and -6.84 ± 3.18 mmHg, respectively, and the group administered with A/L/C-2.5/25/6.25 showed a statistically significant difference with the L100-administered group ($p=0.0502$, $p=0.5673$, $p=0.0353$).

There was no statistically significant difference among the test groups.

Clinical Trial Example 6: Mean sitSBP variation from baseline after 8 week treatment

For comparison of the sitDBP change from baseline after 8 week treatment between the test group and the placebo control group, the ANCOVA in which mean sitDBP at the baseline and stratification variables were corrected with covariates was performed.

- Measurement of sitDBP change from baseline in FAS

For the sitDBP variation of LS Mean $\pm$ SE from baseline after 8 week treatment as being estimated as a result of the ANCOVA, each of the test groups was compared with the control group based on a FAS, and the comparison results are shown in FIG. 3.

FIG. 3 shows sitDBP change from baseline at 8 weeks in a FAS.

When the sitDBP variation from baseline after 8 week treatment in the group administered with A/L/C-1.25/12.5/3.13 was compared with each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-1.25/12.5/3.13 and each of the drug-administered groups was 0.44 ± 1.77 mmHg, 4.07 ± 1.87 mmHg, -4.12 ± 1.93 mmHg, and -8.17 ± 2.27 mmHg, respectively, and the group administered with A/L/C-1.25/12.5/3.13 showed a statistically significant difference with the A10-administered group, the L100-administered group, and the placebo-administered group ($p=0.8033$, $p=0.0333$, $p=0.0362$, $p=0.0006$).

When the sitDBP variation from baseline after 8 week treatment in the group administered with A/L/C-1.67/16.67/4.17 was compared with each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-1.67/16.67/4.17 and each of the drug-administered groups was -1.59 ± 1.66 mmHg, 1.63 ± 1.74 mmHg, -6.02 ± 1.73 mmHg, and -10.03 ± 2.16 mmHg, respectively, and the group administered with A/L/C-1.67/16.67/4.17 showed a statistically significant difference with the L100-administered group and the placebo-administered group ($p=0.3415$, $p=0.3533$, $p=0.0009$, $p<0.0001$).

When the sitDBP variation from baseline after 8 week treatment in the group administered with A/L/C-2.5/25/6.25 was compared with each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-2.5/25/6.25 and each of the drug-administered groups was -0.69 ± 1.58 mmHg, 2.62 ± 1.68 mmHg, -5.52 ± 1.69 mmHg, and -9.36 ± 2.06 mmHg, respectively, and the group administered with A/L/C-2.5/25/6.25 showed a statistically

significant difference with the L100-administered group and the placebo-administered group ($p=0.6620$, $p=0.1253$, $p=0.0018$, $p<0.0001$).

There was no statistically significant difference among the test groups.

Clinical Trial Example 7: Blood pressure control rate at 8 weeks

For comparison of percentage of the trial subjects with sitSBP adjusted to less than 140 mmHg and sitDBP adjusted to less than 90 mmHg after 8 weeks of the administration of the clinical trial drugs among the drug-administered groups, Pearson's chi-square test or Fisher's exact test was performed. Results of comparing each test group with the control group on the FAS basis are as follows.

FIG. 4 shows percentage of subjects achieving the blood pressure control at 8 weeks in FAS. Here, the achievement of the blood pressure control is defined as sitSBP<140 mmHg and sitDBP<90 mmHg.

The percentage of the trial subjects with sitSBP adjusted to less than 140 mmHg and sitDBP adjusted to less than 90 mmHg after 8 weeks of the administration of the trial drugs was 57.14 % (20/35 subjects) in the group administered with A/L/C-1.25/12.5/3.13, 69.70 % (23/33 subjects) in the group administered with A/L/C-1.67/16.67/4.17, 63.89 % (23/36 subjects) in the group administered with A/L/C-2.5/25/6.25, 44.12 % (15/34 subjects) in the A5-administered group, 66.67 % (22/33 subjects) in the A10-administered group, 41.18 % (14/34 subjects) in the L100-administered group, and 18.18 % (6/33 subjects) in the placebo-administered group.

When the blood pressure control rate in the group administered with A/L/C-1.25/12.5/3.13 after 8 weeks of the administration of the trial drugs was compared with the blood pressure control rate in each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the group administered with A/L/C-1.25/12.5/3.13 showed a statistically significant difference with the placebo-administered group ($p=0.0010$).

When the blood pressure control rate in the group administered with A/L/C-1.67/16.67/4.17 after 8 weeks of the administration of the trial drugs was compared with the blood pressure control rate in each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the group administered with A/L/C-1.67/16.67/4.17 showed a statistically significant

difference with the A5-administered group, the L100-administered group, and the placebo-administered group ($p=0.0346$, $p=0.0189$, $p=0.0000$).

When the blood pressure control rate in the group administered with A/L/C-2.5/25/6.25 after 8 weeks of the administration of the trial drugs was compared with the blood pressure control rate in each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the group administered with A/L/C-2.5/25/6.25 showed a statistically significant difference with the placebo-administered group ($p=0.0001$).

There was no statistically significant difference among the test groups.

Clinical Trial Example 8: blood pressure responder rate at 8 weeks

For comparison of percentage of the trial subjects with sitSBP reduction of greater than or equal to 20 mmHg or sitDBP reduction of greater than or equal to 10 mmHg after 8 weeks of the administration of the clinical trial drugs among the drug-administered groups, Pearson's chi-square test or Fisher's exact test was performed. Results of comparing each test group with the control group on the FAS basis are as follows.

FIG. 5 shows percentage of blood pressure responders at 8 weeks in FAS. Here, the blood pressure responders refer to trial subjects with sitSBP reduction ≥ 20 mmHg or sit DBP reduction ≥ 10 mmHg from the baseline.

The percentage of the trial subjects with sitSBP reduction ≥ 20 mmHg or sitDBP reduction ≥ 10 mmHg after 8 weeks of the administration of the trial drugs was 51.43 % (18/35 subjects) in the group administered with A/L/C-1.25/12.5/3.13, 60.61 % (20/33 subjects) in the group administered with A/L/C-1.67/16.67/4.17, 58.33 % (21/36 subjects) in the group administered with A/L/C-2.5/25/6.25, 47.06 % (16/34 subjects) in the A5-administered group, 63.64 % (21/33 subjects) in the A10-administered group, 32.35 % (11/34 subjects) in the L100-administered group, and 21.21 % (7/33 subjects) in the placebo-administered group.

When the blood pressure responder rate in the group administered with A/L/C-1.25/12.5/3.13 after 8 weeks of the administration of the trial drugs was compared with the blood pressure control rate in each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group,

the group administered with A/L/C-1.25/12.5/3.13 showed a statistically significant difference with the placebo-administered group ($p=0.0098$).

When the blood pressure responder rate in the group administered with A/L/C-1.67/16.67/4.17 after 8 weeks of the administration of the trial drugs was compared with the blood pressure control rate in each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the group administered with A/L/C-1.67/16.67/4.17 showed a statistically significant difference with the L100-administered group and the placebo-administered group ($p=0.0204$, $p=0.0011$).

When the blood pressure responder rate in the group administered with A/L/C-2.5/25/6.25 after 8 weeks of the administration of the trial drugs was compared with the blood pressure control rate in each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the group administered with A/L/C-2.5/25/6.25 showed a statistically significant difference with the L100-administered group and the placebo-administered group ($p=0.0292$, $p=0.0017$).

There was no statistically significant difference among the test groups.

Clinical Trial Example 9: Mean pulse pressure variation from baseline after 8 week treatment (mean sitSBP-sitDBP)

For comparison of the pulse pressure change (sitSBP-sitDBP) from baseline after 8 week treatment between the test groups and the control groups, the ANCOVA in which the mean pulse pressure (mean sitSBP-sitDBP) at the baseline and stratification variables were corrected with covariates was performed.

- Measurement of mean pulse pressure variation from baseline after 8 week treatment in FAS

For the pulse pressure variations of LS Mean $\pm$ SE from baseline after 8 week treatment as being estimated as a result of the ANCOVA, each of the test groups was compared with the control group based on a FAS, and the comparison results are shown in FIG. 6.

FIG. 6 shows change from baseline in pulse pressure at 8 weeks in a FAS.

When the pulse pressure variation from baseline after 8 week treatment in the group administered with A/L/C-1.25/12.5/3.13 was compared with each of the A5-

administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-1.25/12.5/3.13 and each of the drug-administered groups was -4.23 ± 2.10 mmHg, 0.05 ± 1.93 mmHg, -0.92 ± 2.31 mmHg, and -6.85 ± 2.82 mmHg, respectively, and the group administered with A/L/C-1.25/12.5/3.13 showed a statistically significant difference with the A5-administered group and the placebo-administered group ($p=0.0483$, $p=0.9801$, $p=0.6910$, $p=0.0180$).

When the pulse pressure variation from baseline after 8 week treatment in the group administered with A/L/C-1.67/16.67/4.17 was compared with each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-1.67/16.67/4.17 and each of the drug-administered groups was -6.71 ± 2.54 mmHg, -2.67 ± 2.40 mmHg, -3.86 ± 2.65 mmHg, and -9.43 ± 3.18 mmHg, respectively, and the group administered with A/L/C-1.67/16.67/4.17 showed a statistically significant difference with the A5-administered group and the placebo-administered group ($p=0.0104$, $p=0.02710$, $p=0.1503$, $p=0.0043$).

When the pulse pressure variation from baseline after 8 week treatment in the group administered with A/L/C-2.5/25/6.25 was compared with each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-2.5/25/6.25 and each of the drug-administered groups was -4.88 ± 1.91 mmHg, -0.73 ± 1.80 mmHg, -1.88 ± 2.27 mmHg, and -7.54 ± 2.71 mmHg, respectively, and the group administered with A/L/C-2.5/25/6.25 showed a statistically significant difference with the A5-administered group and the placebo-administered group ($p=0.0157$, $p=0.6855$, $p=0.4109$, $p=0.0071$).

There was no statistically significant difference among the test groups.

Clinical Trial Example 10: Subgroup analysis: Measurement of mean sitSBP variation from baseline after 8 week treatment (baseline blood pressure of sitSBP<160 mmHg)

For the mean sitSBP variation from baseline after 8 week treatment, subjects with the baseline blood pressure of sitSBP<160 mmHg (178 subjects) were further analyzed according to stratification variables of the FAS subjects.

For comparison of the sitSBP change from baseline after 8 week treatment of the subjects with the baseline blood pressure of sitSBP<160 mmHg between each of the test groups and the control group, the ANCOVA in which mean sitSBP at the baseline was corrected with a covariate was performed.

For the sitSBP variation (LS Mean $\pm$ SE) from baseline after 8 week treatment as being estimated as a result of the ANCOVA, each of the test groups was compared with the active control group based on a FAS, and the comparison results are shown in Table 3 and FIG. 7.

FIG. 7 shows sitSBP change from baseline at 8 weeks in a FAS (sitSBP<160 mmHg).

When the sitSBP variation from baseline after 8 week treatment in the group administered with A/L/C-1.25/12.5/3.13 was compared with each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-1.25/12.5/3.13 and each of the drug-administered groups was -1.40 $\pm$ 3.74 mmHg, 5.44 $\pm$ 3.25 mmHg, and -7.02 $\pm$ 3.62 mmHg, -13.13 $\pm$ 4.06 mmHg, respectively, and the group administered with A/L/C-1.25/12.5/3.13 showed a statistically significant difference with the placebo-administered group (p=0.7100, p=0.1013, p=0.0586, p=0.0022).

When the sitSBP variation from baseline after 8 week treatment in the group administered with A/L/C-1.67/16.67/4.17 was compared with each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-1.67/16.67/4.17 and each of the drug-administered groups was -4.42 $\pm$ 4.27 mmHg, 1.17 $\pm$ 3.78 mmHg, -9.94 $\pm$ 4.19 mmHg, and -16.11 $\pm$ 4.59 mmHg, respectively, and the group administered with A/L/C-1.67/16.67/4.17 showed a statistically significant difference with the L100-administered group and the placebo-administered group (p=0.3503, p=0.6524, p=0.0220, p=0.0010).

When the sitSBP variation from baseline after 8 week treatment in the group administered with A/L/C-2.5/25/6.25 was compared with each of the A5-administered group, the A10-administered group, the L100-administered group, and the placebo-administered group, the variation difference (LS Mean $\pm$ SE) between the group administered with A/L/C-2.5/25/6.25 and each of the drug-administered groups was -6.07 $\pm$ 3.40 mmHg, 1.29 $\pm$ 2.77 mmHg, -11.94 $\pm$ 3.26 mmHg, and -17.77 $\pm$ 3.71 mmHg, respectively, and the group administered with A/L/C-2.5/25/6.25 showed a statistically significant difference with the L100-administered group and the placebo-administered group ($p=0.0806$, $p=0.6427$, $p=-0.0006$, $p<0.0001$).

There was no statistically significant difference among the test groups.

[Table 3]

sitSBP (mmHg)	A/L/C (N=26)	A/L/C 1.67/16.67/4.17 (N=24)	A/L/C 2.5/25/6.25 (N=27)	A5 (N=26)	A10 (N=25)	L100 (N=25)	P (N=25)
Baseline							
N	26	24	27	26	25	25	25
MEAN (SD)	149.23(5.42)	148.71(5.73)	151.31(5.06)	149.81(5.20)	151.02(4.90)	149.70(5.24)	149.92(6.42)
MEDIAN	148.50	148.25	152.00	149.25	151.50	149.50	148.50
MIN, MAX	140.50,159.50	140.00,158.50	140.00,158.50	141.00,159.00	141.50,159.00	140.50,159.50	140.50,159.50
Week 8							
N	26	24	27	26	25	25	25
MEAN (SD)	135.88(12.91)	132.92(15.02)	132.85(10.31)	137.73(14.92)	131.40(10.17)	143.32(14.36)	149.54(16.91)
MEDIAN	134.50	130.75	129.50	137.00	132.50	144.00	147.00
MIN, MAX	115.50,175.00	112.00,168.50	121.50,158.00	103.00,175.50	107.50,149.50	114.00,173.00	117.00,192.50
Week 8 - Baseline							
N	26	24	27	26	25	25	25
MEAN (SD)	-13.35(12.51)	-15.79(16.31)	-18.46(9.82)	-12.08(14.21)	-19.62(10.52)	-6.38(13.09)	-0.38(16.09)
MEDIAN	-14.75	-18.75	-20.00	-11.25	-18.50	-10.00	-1.50
MIN, MAX	-38.50, 22.00	-45.00, 20.50	-32.00, 6.00	-43.50, 22.00	-44.50, -4.00	-27.50, 21.00	-31.50, 33.00
ANCOVA Result ^{a)}							
LS Mean (SE)	-13.43(2.84)						-0.30(2.89)
LS Mean difference (SE)	-13.13(4.06)						
95% C.I for LS Mean difference	(-21.28, -4.97)						
p-value	0.0022						
ANCOVA Result ^{a)}							
LS Mean (SE)		-16.15(3.27)					-0.04(3.20)
LS Mean difference (SE)		-16.11(4.59)					

sitSBP (mmHg)	A/L/C 1.25/12.5/3.13 (N=26)	A/L/C 1.67/16.67/4.17 (N=24)	A/L/C 2.5/25/6.25 (N=27)	A5 (N=26)	A10 (N=25)	L100 (N=25)	P (N=25)
95% C.I for LS Mean difference p-value	(-25.35,-6.88) 0.0010						
ANCOVA Result ^{a)}							
LS Mean (SE)							
LS Mean difference (SE)							
95% C.I for LS Mean difference p-value	-18.31(2.56) -17.77(3.71) (-25.23,-10.3) <0.0001						-0.54(2.67)
ANCOVA Result ^{a)}							
LS Mean (SE)							
LS Mean difference (SE)							
95% C.I for LS Mean difference p-value	-12.09(3.00) -11.71(4.28) (-20.33,-3.10) 0.0087						-0.37(3.06)
ANCOVA Result ^{a)}							
LS Mean (SE)							
LS Mean difference (SE)							
95% C.I for LS Mean difference p-value	-19.43(2.72) -18.86(3.86) (-26.63,-11.1) <0.0001						-0.57(2.72)
ANCOVA Result ^{a)}							
LS Mean (SE)							
LS Mean difference (SE)							
95% C.I for LS Mean difference p-value	-6.39(2.96) -6.01(4.19) (-14.44, 2.42) 0.1582						-0.37(2.96)

sitSBP (mmHg)	A/L/C (N=26)	A/L/C (N=24)	A/L/C (N=27)	A5 (N=26)	A10 (N=25)	L100 (N=25)	P (N=25)
ANCOVA Result ^{b)}							
LS Mean (SE)	-13.37(2.53)					-6.35(2.58)	
LS Mean difference (SE)	-7.02(3.62)						
95% C.I for LS Mean difference	(-14.30, 0.26)						
p-value	0.0586						
ANCOVA Result ^{b)}							
LS Mean (SE)		-16.06(2.99)				-6.12(2.93)	
LS Mean difference (SE)		-9.94(4.19)					
95% C.I for LS Mean difference		(-18.38,-1.50)					
p-value		0.0220					
ANCOVA Result ^{b)}							
LS Mean (SE)			-18.40(2.25)			-6.45(2.34)	
LS Mean difference (SE)			-11.94(3.26)				
95% C.I for LS Mean difference			(-18.50,-5.38)				
p-value			0.0006				
ANCOVA Result ^{b)}							
LS Mean (SE)				-12.08(2.71)		-6.38(2.76)	
LS Mean difference (SE)				-5.70(3.87)			
95% C.I for LS Mean difference				(-13.48, 2.08)			
p-value				0.1474			
ANCOVA Result ^{b)}							
LS Mean (SE)				-19.47(2.40)		-6.53(2.40)	

sitSBP (mmHg)	A/L/C (N=26)	A/L/C 1.67/16.67/4.17 (N=24)	A/L/C 2.5/25/6.25 (N=27)	A5 (N=26)	A10 (N=25)	L100 (N=25)	P (N=25)
LS Mean difference (SE)	1.25/12.5/3.13	1.67/16.67/4.17	2.5/25/6.25		-12.93(3.41)		
95% C.I for LS Mean difference					(-19.79,-6.08)		
p-value					0.0004		
ANCOVA Result ^{e)}							
LS Mean (SE)	-13.76(2.26)				-19.19(2.31)		
LS Mean difference (SE)	5.44(3.25)						
95% C.I for LS Mean difference	(-1.11,11.98)						
p-value	0.1013						
ANCOVA Result ^{e)}							
LS Mean (SE)		-16.87(2.67)			-18.58(2.61)		
LS Mean difference (SE)		1.71(3.78)					
95% C.I for LS Mean difference		(-5.89, 9.32)					
p-value		0.6524					
ANCOVA Result ^{e)}							
LS Mean (SE)			-18.40(1.92)		-19.69(2.00)		
LS Mean difference (SE)			1.29(2.77)				
95% C.I for LS Mean difference			(-4.28, 6.87)				
p-value			0.6427				
ANCOVA Result ^{e)}							
LS Mean (SE)				-12.29(2.47)	-19.40(2.52)		
LS Mean difference (SE)				7.10(3.54)			
95% C.I for LS Mean difference				(-0.01,14.21)			

sitSBP (mmHg)	A/L/C (N=26)	A/L/C (N=24)	A/L/C (N=27)	A5 (N=26)	A10 (N=25)	L100 (N=25)	P (N=25)
p-value	1.25/12.5/3.13	1.67/16.67/4.17	2.5/25/6.25	0.0503			
ANCOVA Result ^{d)}							
LS Mean (SE)	-13.41(2.64)			-12.01(2.64)			
LS Mean difference (SE)	-1.40(3.74)						
95% C.I for LS Mean difference	(-8.92, 6.12)						
p-value	0.7100						
ANCOVA Result ^{d)}							
LS Mean (SE)		-16.16(3.07)		-11.74(2.95)			
LS Mean difference (SE)		-4.42(4.27)					
95% C.I for LS Mean difference		(-13.01, 4.16)					
p-value		0.3053					
ANCOVA Result ^{d)}							
LS Mean (SE)			-18.31(2.37)	-12.24(2.42)			
LS Mean difference (SE)			-6.07(3.40)				
95% C.I for LS Mean difference			(-12.90, 0.77)				
p-value			0.0806				
ANCOVA Result ^{e)}							
LS Mean (SE)	-13.68(2.22)		-18.14(2.18)				
LS Mean difference (SE)	4.46(3.14)						
95% C.I for LS Mean difference	(-1.86,10.77)						
p-value	0.1624						
ANCOVA Result ^{e)}							

sitSBP (mmHg)	A/L/C (N=26)	A/L/C 1.25/12.5/3.13 (N=24)	A/L/C 1.67/16.67/4.17 (N=27)	A5 (N=26)	A10 (N=25)	L100 (N=25)	P (N=25)
LS Mean (SE)		-16.81(2.65)	-17.56(2.50)				
LS Mean difference (SE)		0.75(3.70)					
95% C.I for LS Mean difference		(-6.68, 8.18)					
p-value		0.8407					
ANCOVA Result ^{†)}							
LS Mean (SE)		-13.16(2.75)	-15.99(2.86)				
LS Mean difference (SE)		2.83(3.97)					
95% C.I for LS Mean difference		(-5.17, 10.82)					
p-value		0.4807					
Treatments:							
A/L/C 1.25/12.5/3.13: amlodipine/losartan/chlorthalidone 1.25/12.5/3.13mg							
A/L/C 1.67/16.67/4.17: amlodipine/losartan/chlorthalidone 1.67/16.67/4.17mg							
A/L/C 2.5/25/6.25: amlodipine/losartan/chlorthalidone 2.5/25/6.25mg							
A5: amlodipine 5mg; A10: amlodipine 10mg; L100: losartan 100mg; P: placebo							
Compared with:							
a) Placebo; b) L100; c) A10; d) A5; e) A/L/C 2.5/25/6.25; f) A/L/C 1.67/16.67/4.17							
Report Generated by Program : Table 4-2. Change from Baseline in sitSBP at Week 8-FAS(SBP160) SAS							

Clinical Trial Example 11: Mean ankle circumference variation from baseline after 8 week treatment through edema test

The edema test was performed by measuring the ankle circumference for each of the clinical trial drug-administered groups. For comparison of the ankle circumference

change from baseline after 8 week treatment between the trial drug-administered group and an amlodipine single agent-administered group, the Wilcoxon rank sum test was performed, and for confirmation of statistical significance within each group, the Wilcoxon signed-rank test was performed. In the analysis, an ankle with a larger absolute value of the ankle circumference change after 8 week treatment than the other between both ankles of each subject was selected. In the case of having the same absolute value of the ankle circumference change in both ankles, an ankle with an increased ankle circumference was selected, and results of the comparison are shown in FIG. 8.

FIG. 8 shows ankle circumference change from baseline (based on an ankle with a larger absolute value of the ankle circumference change from the baseline at 8 weeks than the other between both ankles) in the FAS at 8 weeks in the trial drug-administered groups, each comprising: 2.5 mg of amlodipine, 25 mg of losartan potassium, 6.25 mg of chlorthalidone; 1.67 mg of amlodipine, 16.67 mg of losartan potassium, 4.17 mg of chlorthalidone; or 1.25 mg of amlodipine, 12.5 mg of losartan potassium, and 3.13 mg of chlorthalidone, or in the drug-administered groups as controls, each comprising 5 mg of amlodipine and or 10 mg of amlodipine.

As shown in FIG. 8, the ankle circumference variation (Mean $\pm$ SD) from the baseline after 8 week treatment was -0.76 ± 6.33 mm in the trial drug-administered group and 2.48 ± 8.79 mm in the amlodipine single agent-administered group. The ankle circumference increased by 3.23 mm more in the amlodipine single agent-administered group than in the trial drug-administered group, also showing a statistically significant difference ($p=0.0033$). In addition, the trial drug-administered group did not show a statistically significant difference with the ankle circumference change from the baseline after 8 week treatment ($p=0.2668$), whereas the amlodipine single agent-administered group showed a statistically significant increase in the ankle circumference from the baseline after 8 week treatment ($p=0.0150$).

[Description of abbreviations]

A2.5, A1.67, A1.25: 2.5 (mg), 1.67 (mg), and 1.25 (mg) of amlodipine (A), respectively

L25, L16.67, L12.5: 25 (mg), 16.67 (mg), and 12.5 (mg) of losartan potassium (L), respectively

C6.25, C4.17, C3.13: 6.25 (mg), 4.17 (mg), and 3.13 (mg) of chlorthalidone (C), respectively

DBP: Diastolic blood pressure

SBP: Systolic blood pressure

sitDBP: Sitting diastolic blood pressure

sitSBP: Sitting systolic blood pressure

HbA_{1c}: Hemoglobin A_{1c}

ANCOVA: Analysis of covariance

<Preparation of complex preparation>

Examples 1 to 6: Preparation of single-layer tablet containing amlodipine, chlorthalidone and losartan

According to the compositions shown in Table 4 below, amlodipine, chlorthalidone, losartan, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and crospovidone were used and mixed for 10 minutes. After the mixture was compacted into a slug, the slug was sieved through 1.0 mm sieve to prepare a granule part. Magnesium stearate is added thereto and mixed for 5 minutes to prepare a final granule part. Then, the final granule part was used to product a single-layer tablet complex.

The components of pharmaceutical complex preparations according to Examples 1 to 6 are shown in Table 4 below.

[Table 4]

Ingredient (mg)		Example 1	Example 2	Example 3	Example 4	Example 5	Example 6
Compacting	Amlodipine besylate	3.47	3.47	3.47	3.47	1.74	2.32
	Chlorthalidone	6.25	6.25	6.25	6.25	3.13	4.17
	Losartan potassium	25.00	25.00	25.00	25.00	12.50	16.67
	MCC PH101	190.08	83.86	78.39	70.19	35.09	46.79
	L-HPC (LH-11)	96.00	42.36	42.36	42.36	21.18	28.24
	Crospovidone (XL-10)	6.20	2.74	8.21	16.41	8.21	10.94
Final	Magnesium	3.00	1.32	1.32	1.31	0.66	0.87

mixing	stearate						
Total tablet weight		330.0	165.0	165.0	165.0	82.5	110.0

Comparative Examples 1 to 4: Preparation of double-layer tablet or single-layer tablet, comprising granule part I comprising amlodipine and chlorthalidone and granule part II comprising losartan

According to components shown in Table 5 below, amlodipine, chlorthalidone, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and crospovidone were used and mixed for 10 minutes. After the mixture was compacted into a slug, the slug was sieved through 1.0 mm sieve to prepare granules. Magnesium stearate was added thereto and mixed for 5 minutes to prepare Granule part I.

In addition, losartan, microcrystalline cellulose, and crospovidone were used and mixed for 10 minutes. After the mixture was compacted into a slug, the slug was sieved through 1.0 mm sieve to prepare granules. The granules were mixed with magnesium stearate for 5 minutes to prepare Granule part II.

Comparative Examples 1 and 3: A double-layer tablet was produced by using granule part I as an upper granule part and granule part II as a lower granule part.

Comparative Examples 2 and 4: A single-layer tablet was produced by finally mixing granule part I and granule part II.

[Table 5]

Ingredient (mg)		Comparative Example 1	Comparative Example 2	Comparative Example 3	Comparative Example 4
Compacting	Amlodipine besylate	6.94	6.94	3.47	3.47
	Chlorthalidone	12.5	12.5	6.25	6.25
	MCC (PH101)	114.56	114.56	57.28	57.28
	L-HPC (LH-11)	186	186	93	93
	Crospovidone (XL-10)	6	6	3	3
Post-mixture	Magnesium stearate	4	-	2	-
Granule part I		330	326	165	163
Compacting	Losartan potassium	50	50	25	25
	MCC (PH101)	271.6	271.6	135.8	135.8
	Crospovidone (XL-10)	6.4	6.4	3.2	3.2
Post-	Magnesium stearate	2	-	1	-

mixing					
Granule part II		330	328	165	164
Post-mixing	Magnesium stearate	-	6	-	3
Total tablet weight		660.0	660.0	330.0	330.0

Comparative Examples 5 to 8: Preparation of a single-layer tablet comprising granule part I comprising amlodipine and chlorthalidone and granule part II comprising losartan

According to components shown in Table 6 below, amlodipine, chlorthalidone, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and crospovidone were used and mixed for 10 minutes. After the mixture was compacted into a slug, the slug was sieved through 1.0 mm sieve to prepare granules. Magnesium stearate was added thereto and mixed for 5 minutes to prepare granule part I.

In addition, losartan, microcrystalline cellulose, and crospovidone were used and mixed for 10 minutes. After the mixture was compacted into a slug, the slug was sieved through 1.0 mm sieve to prepare granules. The granules were mixed with magnesium stearate for 5 minutes to prepare granule part II.

The components of pharmaceutical complex preparations according to Comparative Examples 5 to 8 are shown in Table 6 below.

[Table 6]

Ingredient (mg)		Comparative Example 5	Comparative Example 6	Comparative Example 7	Comparative Example 8
Compacting	Amlodipine besylate	6.94	4.63	1.39	1.16
	Chlorthalidone	12.5	8.33	2.50	2.08
	Losartan potassium	50.0	33.33	10.0	8.33
	MCC PH101	156.78	104.52	31.36	26.13
	L-HPC (LH-11)	84.72	56.48	16.94	14.12
	Crospovidone (XL-10)	16.42	10.95	3.28	2.74
Final mixing	Magnesium stearate	2.64	1.76	0.53	0.44
Total tablet weight		330.0	220.0	66.0	55.0

Test Examples

Test Example 1: Dissolution test of amlodipine and chlorthalidone according to gelling by losartan content

By using the tablets of Comparative Examples 1 to 6, dissolution rates of amlodipine and chlorthalidone were confirmed under the following conditions. Conditions for dissolution and HPLC analysis are as follows:

[Dissolution conditions]

Apparatus: USP <711> Dissolution Apparatus 2 (paddle method)

Test solution: 0.01 M hydrochloric acid solution, 900 mL

Dissolution temperature: 37 ± 0.5 °C

Number of revolutions: 100 ± 5 rpm

[Analysis conditions]

Detector: UV absorbance spectrophotometer (measured wavelength: 240 nm)

Column: Inertsil ODS-4, 4.6 x 250 mm, 5 μ m or equivalent column

Mobile phase: 10 mM hexanesulfonic acid sodium hydrate (pH 2.5): ACN = 64:36 (v/v)

Column temperature: 35 °C

Analysis time: 25 minutes

Flow rate: 1.3 mL/min

Injection volume: 40 μ L

The results of the dissolution test on amlodipine and chlorthalidone are shown in FIGS. 9 to 11.

FIG. 9 shows time-dependent dissolution rate (%) of (a) amlodipine besylate and (b) chlorthalidone of Comparative Examples 1 and 2.

FIG. 10 shows time-dependent dissolution rate (%) of (a) amlodipine besylate and (b) chlorthalidone of Example 1 and Comparative Examples 3 and 4.

FIG. 11 shows time-dependent dissolution rate (%) of (a) amlodipine besylate and (b) chlorthalidone of Example 4 and Comparative Examples 5 and 6.

As shown in FIG. 9, the double-layer tablet of Comparative Example 1 in which a high dose (50 mg) of losartan was comprised in a granule part separated from amlodipine or chlorthalidone showed high dissolution rates of amlodipine and

chlorthalidone, compared to the single-layer tablet of Comparative Example 2 prepared under the same condition.

However, as shown in FIG. 10, the double-layer tablet of Comparative Example 3 in which a low dose (25 mg) of losartan was comprised in a granule part separated from amlodipine or chlorthalidone showed no significant difference in the dissolution rates of amlodipine and chlorthalidone, compared to the single-layer tablet of Comparative Example 4 prepared under the same condition.

In addition, as shown in FIG. 10, the single-layer tablet of Comparative Example 4 in which a low dose (25 mg) of losartan was comprised in separated granules from amlodipine and chlorthalidone showed similar dissolution rates with the single-layer tablet of Example 1 in which a low dose (25 mg) of losartan was comprised in mixed granules of amlodipine and chlorthalidone.

In addition, as shown in FIG. 11, the single-layer tablets Comparative Examples 5 and 6 in which a high dose (50 mg or 33.33 mg, respectively) of losartan was comprised in a granule part mixed amlodipine and chlorthalidone showed low dissolution rates, compared to the single-layer tablet of Example 4 in which a low dose (25 mg) of losartan was comprised in a granule part mixed with amlodipine and chlorthalidone.

Accordingly, it was confirmed that the dissolution rates of amlodipine and chlorthalidone were affected due to the degree of gelation according to the dose of losartan in the complex preparation, and that, especially in the case of a high dose of losartan, the dissolution rates of amlodipine and chlorthalidone was decreased due to the gelation.

In addition, it was confirmed that, when losartan was comprised in a high dose, the dissolution rates of amlodipine and chlorthalidone were affected by the form of tablets (single-layer tablet or double-layer tablet) (FIG. 9), whereas when losartan was included in low doses, the dissolution rates of amlodipine and chlorthalidone were not significantly affected by the form of tablets (single-layer tablet or double-layer tablet) or the form of granules (mixed granules or separated granules) in the complex preparation (FIGS. 10 and 11).

Test Example 2: Stability test according to form of tablets and granules

- Test for related substances in double-layer tablet with separated granules, single-layer tablet with separated granules, and single-layered tablet with mixed granules

Regarding the double-layer tablet with separated granules of Comparative Example 3, the single-layer tablet with separated granules of Comparative Example 4, and the single-layered tablet with mixed granules of Example 1, the stability of the tablets was evaluated by measuring changes in contents of related substances of amlodipine, chlorthalidone, and losartan under the following stress conditions for storage.

[Stress test condition for storage]

Storage conditions: Packed in HDPE (high density polyethylene) bottle at 60 °C

Test conditions: Initial, 1 week, 2 weeks

Subject of analysis: Amlodipine, chlorthalidone, losartan

[Analysis conditions]

[Table 7]

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0.0	77	23
11.0	77	23
65	50	50
90	30	70
90.1	77	23
110.0	77	23

Detector: UV absorbance spectrophotometer (measured wavelength: 239 nm)

Column: Zorbax SB-C18 column, 4.6 x 250 mm, 5 µm or equivalent level

Mobile phase:

A - 17 mM sodium hexanesulfonate/0.05% (v/v) phosphoric acid

B - 17 mM sodium hexanesulfonate/0.05 % (v/v) phosphoric acid: ACN = 10: 90

(v/v)

Column temperature: 35 °C

Analysis time: 110 minutes

Flow rate: 1.0 mL/min

Injection volume: 40 µL

FIG. 12 shows a result of confirming generation of related substances by measuring contents (%) of (a) impurity B (Imp B) and (b) unknown related substance (Unknown max) of chlorthalidone in Comparative Examples 3 and 4 and Example 1.

As shown in FIG. 12, the contents (%) of the related substances in Comparative Examples 3 and 4 and Example 1 were as (a) Imp B (1.00 %) and (b) Unknown max (0.3 %) for 2 weeks under the stress conditions, and thus it was confirmed that the complex preparations exhibited a very stable pattern without an increase in the contents of the related substances.

In addition, the related substances of amlodipine and losartan were not detected in all of the double-layer tablet with separated granules of Comparative Example 3, the single-layer tablet with separated granules of Comparative Example 4, and the single-layered tablet with mixed granules of Example 1. As shown in FIG. 12, it was confirmed that, due to almost no generation of (a) Imp B and (b) Unknown max related substances of chlorthalidone, the complex preparation was stable.

Accordingly, it was confirmed that, when losartan was comprised in low doses (25 mg) in the complex preparation, the form of tablets (single-layer tablet, double-layer tablet) or granules (mixed granule part, separated granule part) of the complex preparation had little effect on the generation of the related substances from the complex preparation.

Test Example 3: Dissolution test of amlodipine, losartan, chlorthalidone

- Dissolution test according to a content of active ingredient or disintegrant in the complex preparation or a total weight of the complex preparation

A dissolution test was performed by using the tablets obtained in Examples 1 to 6. Conditions for dissolution and HPLC analysis are as follows:

[Dissolution conditions - Amlodipine]

Apparatus: USP <711> Dissolution Apparatus 2 (paddle method)

Test solution: 0.01 M hydrochloric acid solution, 900 mL

Dissolution temperature: 37 ± 0.5 °C

Number of revolutions: 100 ± 5 rpm

Determination conditions: Dissolution rate of 80 % or more after 30 minutes

[Dissolution conditions - Losartan, chlorthalidone]

Apparatus: USP <711> Dissolution Apparatus 2 (paddle method)

Test solution: Purified water, 900 mL

Dissolution temperature: 37 ± 0.5 °C

Number of revolutions: 75 ± 2 rpm

Determination conditions: Dissolution rate of 80 % or more after 30 minutes

[Analysis conditions]

Detector: UV absorbance spectrophotometer (measured wavelength: 240 nm)

Column: Inertsil ODS-4 column, 4.6 x 250 mm, 5 μ m or equivalent level

Mobile phase: 10 mM hexanesulfonic acid sodium hydrate (pH 2.5): ACN = 64:36 (v/v)

Column temperature: 35 °C

Analysis time: 25 minutes

Flow rate: 1.3 mL/min

Injection volume: 40 μ L

FIGS. 13 and 14 show results of dissolution rates of amlodipine, chlorthalidone, and losartan.

FIG. 13 shows time-dependent dissolution rates (%) of (a) amlodipine besylate, (b) losartan potassium, (c) chlorthalidone in Examples 1 and 2.

FIG. 14 shows time-dependent dissolution rates (%) of (a) amlodipine besylate, (b) losartan potassium, (c) chlorthalidone in Examples 2 to 6.

As shown in FIG. 13, as a result of measuring the dissolution rates in Examples 1 and 2, the dissolution rates of amlodipine, chlorthalidone, and losartan were higher in Example 2 in which the total tablet weight was reduced by 50 %, compared to Example 1.

As shown in FIG. 14, in Examples 3 and 4 in which the content of a disintegrant increased compared to Example 2, the dissolution rate was high as the content of disintegrant increased (tablet hardness of 18 kp in Examples 2 to 4).

In addition, as shown in FIG. 14, each of Example 5 in which the tablet total weight and the content of each component of Example 4 were reduced by 1/2 and Example 6 in which the tablet total weight and the content of each component of Example 4 were reduced by 2/3 showed a similar dissolution rate to Example 4 (tablet

hardness of 16 kp of Examples 5 and 6). In addition, all the tablets of Examples 4 to 6 satisfied the conditions for determining uniformity of the preparations (Test Example 4).

Test Example 4: Preparation uniformity test on amlodipine, chlorthalidone, and losartan

Preparation uniformity of amlodipine, chlorthalidone, and losartan in one tablet was confirmed by using the tablets of Examples 4 and 5 and Comparative Examples 7 and 8.

[Analysis conditions]

Detector: UV absorbance spectrophotometer (measured wavelength: 240 nm)

Column: Inertsil ODS-4 column, 4.6 x 250 mm, 5 µm or equivalent level

Mobile phase: 10 mM hexanesulfonic acid sodium hydrate (pH 2.5): ACN = 64:36 (v/v)

Column temperature: 35 °C

Analysis time: 25 minutes

Flow rate: 1.3 mL/min

Injection volume: 10 µL

Results of the preparation uniformity of amlodipine, chlorthalidone, and losartan are shown in Table 8.

[Table 8]

Preparation uniformity	Example 4	Example 5	Example 6	Comparative Example 7	Comparative Example 8
Amlodipine besylate	99.8 ± 0.3 %	99.3 ± 0.7 %	100.3 ± 1.2 %	97.1 ± 2.8 %	94.5 ± 3.7 %
Chlorthalidone	99.1 ± 0.1 %	100.0 ± 0.9 %	100.3 ± 1.6 %	97.9 ± 5.1 %	96.0 ± 8.1 %
Losartan potassium	101.1 ± 0.5 %	99.9 ± 0.8 %	100.8 ± 1.4 %	98.3 ± 3.9 %	98.0 ± 4.1 %

As shown in Table 8, the result value from the determination of the preparation uniformity was within 98.0 % to 102.0 % in Examples 4 to 6 in which the contents of the main components were high, and the deviation was less than or equal to 2.0 %, thereby satisfying the determination conditions.

However, in the case of Comparative Examples 7 and 8 in which the contents of the main components were low, the deviation of the values for each sample was greater than or equal to 2.0 % which was very large. On this bases, the smaller contents of the main components refer to main components not uniform in a certain content in the preparations of one tablet.

Test Example 5: productivity (tableting speed) and quality (content uniformity) test

When the double-layer tablet of Comparative Example 3 and the single-layer tablet of Example 1 having the same weight were produced, productibility (tableting speed) and quality (content uniformity) according to the tableting speed were tested.

[Table 9]

	Producible maximum tableting speed	Tableting process yield
Two-layer tablet of Comparative Example 3	50,000 T/h	About 92 %
Single layer tablet of Example 1	180,000 T/h	About 98 %

As shown in Table 9, in the production of the tables having the same contents, the double-layer tablet of Comparative Example 3 was produced at a tableting speed of up to 50,000 T/h, whereas the single-layer tablet of Example 1 was produced at a speed of 180,000 T/h, which enabled the tablet production 3.6 times faster than Comparative Example 3.

That is, compared to the double-layer tablet produced by tableting separated granules into upper and lower layers (Comparative Example 3), the single-layer tablet produced by tableting the mixed granule part (Example 1) showed high productivity. In addition, compared to the single-layer tablet comprising the separated granule part, the single-layer tablet produced by tableting the mixed granule part showed high productivity.

In addition, in terms of a yield of the tableting process in Table 9, a large content was consumed to adjust the weight of each layer and the residual content in a hopper was high in the double-layer tablet compared to the single-layer tablet. In this regard,

the single-layer tablet of Example 1 was confirmed to have a higher production yield than the double-layer tablet of Comparative Example 3.

FIG. 15 shows the content determination (%) according to the tableting speed in each of (a) Comparative Example 3 and (b) Example 1.

As shown in FIG. 15, in the case of the double-layer tablet of Comparative Example 3, the content uniformity was not even as the tableting speed increased. However, in the case of the single-layer tablet of Example 1, the content uniformity was shown evenly although the tableting speed increased. This is because the content uniformity of each active ingredient is difficult to appear evenly when separated in a two-layer tablet, the weight of each layer is low.

So far, the present invention was examined with respect to the preferred embodiments. Those of ordinary skill in the art to which the present invention pertains will understand that the present invention may be implemented in a modified form without departing from the essential characteristics of the present invention. Therefore, the disclosed embodiments are to be considered in a descriptive point of view rather than a restrictive sense. The scope of the present invention is indicated in the claims rather than the above description, and differences within the scope equivalent thereto should be construed as being included in the invention.

CLAIMS

1. A pharmaceutical complex preparation in a single-layer tablet for preventing or treating cardiovascular diseases, the pharmaceutical complex preparation comprising, as active ingredients, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in low doses.

2. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein amlodipine or a pharmaceutically acceptable salt thereof is comprised in an amount of 0.5 mg to 5 mg when converted to an amlodipine free base form.

3. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein chlorthalidone or a pharmaceutically acceptable salt thereof is comprised in an amount of 1 mg to 7 mg when converted to a chlorthalidone free base form.

4. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein losartan or a pharmaceutically acceptable salt thereof is comprised in an amount of 7 mg to 30 mg when converted to a losartan free acid form.

5. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof are comprised in a mixed granular part.

6. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein a total weight of the pharmaceutical complex preparation in a single-layer tablet for preventing or treating cardiovascular diseases is less than or equal to 350 mg.

7. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein a total weight of the pharmaceutical complex preparation in a single-layer

tablet for preventing or treating cardiovascular diseases is greater than or equal to 70 mg and less than or equal to 350 mg.

8. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein a total weight of the active ingredients, such as amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and losartan or a pharmaceutically acceptable salt thereof, in the complex preparation is greater than or equal to 15 mg.

9. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein the active ingredients are comprised in an amount of 10 % or more of the total weight of the complex preparation.

10. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein the active ingredients are comprised in an amount of 20 % or more of the total weight of the complex preparation.

11. The pharmaceutical complex preparation in a single-layer tablet of claim 1, further comprising a disintegrant, wherein an amount of the disintegrant is 1 % to 15 % of the total weight of the complex preparation.

12. The pharmaceutical complex preparation in a single-layer tablet of claim 1, further comprising a disintegrant, wherein an amount of the disintegrant is 4 % to 15 % of the total weight of the complex preparation.

13. The pharmaceutical complex preparation in a single-layer tablet of claim 1, further comprising a disintegrant, wherein an amount of the disintegrant is 9 % to 15 % of the total weight of the complex preparation.

14. The pharmaceutical complex preparation in a single-layer tablet of claim 1, further comprising a pharmaceutical additive selected from a diluent, a disintegrant, a lubricant, and a combination thereof.

15. The pharmaceutical complex preparation in a single-layer tablet of claim 14, wherein the diluent is any one selected from microcrystalline cellulose, starch, pre-gelatinized starch, dicalcium phosphate (DCP), lactose, low-substituted hydroxypropyl cellulose, and a combination thereof.

16. The pharmaceutical complex preparation in a single-layer tablet of claim 14, wherein the disintegrant is any one selected from crospovidone, croscarmellose sodium, sodium starch glycolate, starch, pre-gelatinized starch, and a combination thereof.

17. The pharmaceutical complex preparation in a single-layer tablet of claim 14, wherein the lubricant is any one selected from magnesium stearate, palmitic acid, talc, magnesium stearate, zinc stearate, calcium stearate, and a combination thereof.

18. The pharmaceutical complex preparation in a single-layer tablet of claim 1, further comprising, as diluents, microcrystalline cellulose and low-substituted hydroxypropyl cellulose, wherein a weight ratio of microcrystalline cellulose to low-substituted hydroxypropyl cellulose is 2:1 to 1:1.

19. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein a dissolution rate of amlodipine in 30 minutes is greater than or equal to 80 % when a dissolution test is performed on the complex preparation according to the guidelines for setting dissolution specifications for oral drugs.

20. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein a dissolution rate of chlorthalidone in 30 minutes is greater than or equal to

80 % when a dissolution test is performed on the complex preparation according to the guidelines for setting dissolution specifications for oral drugs.

21. The pharmaceutical complex preparation in a single-layer tablet of claim 1, wherein a dissolution rate of losartan in 30 minutes is greater than or equal to 80 % when a dissolution test is performed on the complex preparation according to the guidelines for setting dissolution specifications for oral drugs.