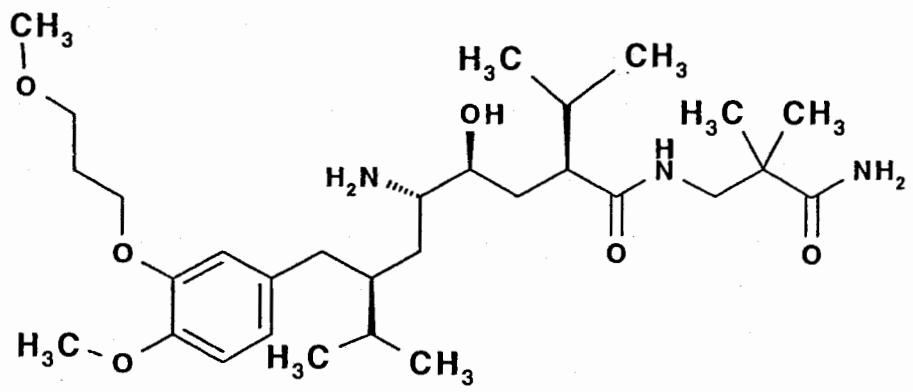
SYNERGISTIC COMBINATIONS COMPRISING A RENIN INHIBITOR FOR CARDIOVASCULAR DISEASES

The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, comprising the renin inhibitor of formula (I)



(I)

or a pharmaceutically acceptable salt thereof.

The invention especially relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, comprising the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof and at least one therapeutic agent selected from the group consisting of

(i) an AT_1-receptor antagonist or a pharmaceutically acceptable salt thereof,

(ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,

(iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,

(iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,

(v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,

(vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,

(vii) an dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,

(viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and

(ix) a diuretic or a pharmaceutically acceptable salt thereof.

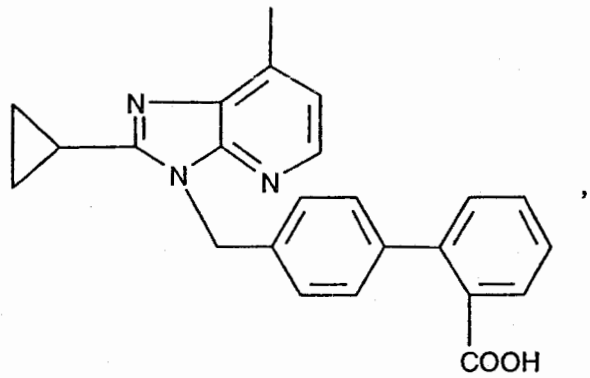
The term "at least one therapeutic agent" shall mean that in addition to the compound of formula (I) one or more, for example two, furthermore three, active ingredients as specified according to the present invention can be combined.

Renin inhibit the action of the natural enzyme renin. The latter passes from the kidneys into the blood where it effects the cleavage of angiotensinogen, releasing the decapeptide angiotensin I which is then cleaved in the lungs, the kidneys and other organs to form the octapeptide angiotensinogen II. The octapeptide increases blood pressure both directly by arterial vasoconstriction and indirectly by liberating from the adrenal glands the sodium-ion--retaining hormone aldosterone, accompanied by an increase in extracellular fluid volume. That increase can be attributed to the action of angiotensin II. Inhibitors of the enzymatic activity of renin bring about a reduction in the formation of angiotensin I. As a result a smaller amount of angiotensin II is produced. The reduced concentration of that active peptide hormone is the direct cause of e.g. the hypotensive effect of renin inhibitors.

The renin inhibitor of formula (I), chemically defined as 2(S),4(S),5(S),7(S)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-di(1-methylethyl)-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxy-propoxy)phenyl]-octanamide, is specifically disclosed in EP 678503 A. Especially preferred is the hemi-fumarate salt thereof.

AT_1-receptor antagonists (also called angiotensin II receptor antagonists) are understood to be those active ingredients that bind to the AT_1-receptor subtype of angiotensin II receptor but do not result in activation of the receptor. As a consequence of the inhibition of the AT_1 receptor, these antagonists can, for example, be employed as antihypertensives or for treating congestive heart failure.

The class of AT_1 receptor antagonists comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds that are selected from the group consisting of valsartan (cf. EP 443983), losartan (cf. EP253310), candesartan (cf. 459136), eprosartan (cf. EP 403159), irbesartan (cf. EP454511), olmesartan (cf. EP 503785), tasosartan (cf. EP539086), telmisartan (cf. EP 522314), the compound with the designation E-1477 of the following formula



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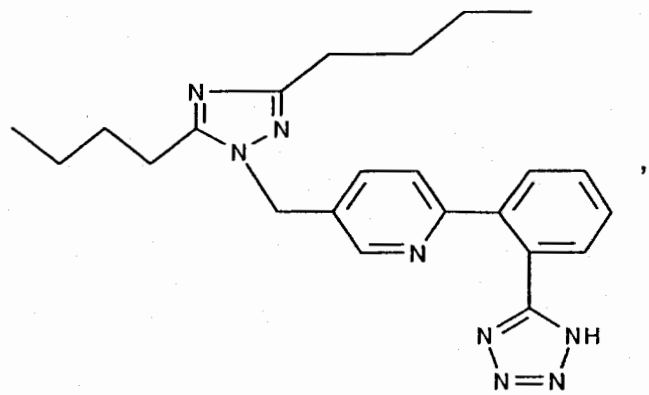
the compound with the designation SC-52458 of the following formula



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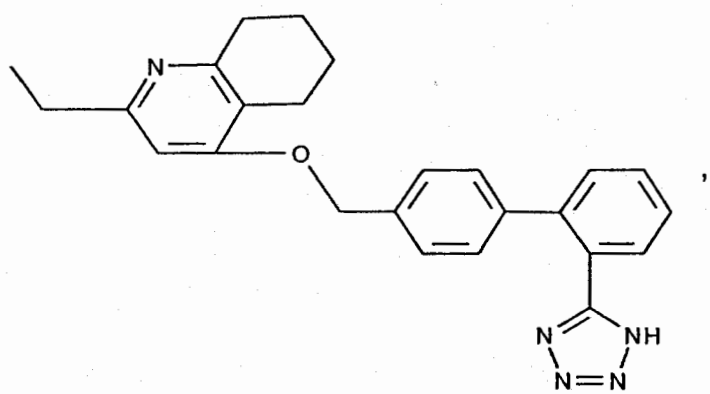
and the compound with the designation the compound ZD-8731 of the following formula



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or, in each case, a pharmaceutically acceptable salt thereof.

Preferred AT_1-receptor antagonist are those agents that have been marketed, most preferred is valsartan or a pharmaceutically acceptable salt thereof.

HMG-Co-A reductase inhibitors (also called β-hydroxy-β-methylglutaryl-co-enzyme-A reductase inhibitors) are understood to be those active agents that may be used to lower the lipid levels including cholesterol in blood.

The class of HMG-Co-A reductase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds that are selected from the group consisting of atorvastatin, cerivastatin, compactin, dalvastatin, dihydrocompactin, fluindostatin, fluvastatin, lovastatin, pitavastatin, mevastatin, pravastatin, rivastatin, simvastatin, and velostatin, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred HMG-Co-A reductase inhibitors are those agents which have been marketed, most preferred is fluvastatin and pitavastatin and also atorvastatin or, in each case, a pharmaceutically acceptable salt thereof.

The interruption of the enzymatic degradation of angiotensin I to angiotensin II with so-called ACE-inhibitors (also called angiotensin converting enzyme inhibitors) is a successful variant for the regulation of blood pressure and thus also makes available a therapeutic method for the treatment of congestive heart failure.

The class of ACE inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, in each case, a pharmaceutically acceptable salt thereof.

Preferred ACE inhibitors are those agents that have been marketed, most preferred are benazepril and enalapril.

The class of CCBs essentially comprises dihydropyridines (DHPs) and non-DHPs such as diltiazem-type and verapamil-type CCBs.

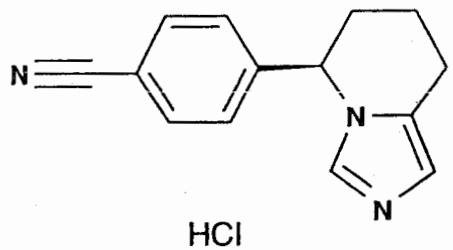
A CCB useful in said combination is preferably a DHP representative selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, and in each case, a pharmaceutically acceptable salt thereof. All these CCBs are therapeutically used, e.g. as anti-hypertensive, anti-angina pectoris or anti-arrhythmic drugs. Preferred CCBs comprise amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and verapamil, or, e.g. dependent on the specific CCB, a pharmaceutically acceptable salt thereof. Especially preferred as DHP is amlodipine or a pharmaceutically acceptable salt, especially the besylate, thereof. An especially preferred representative of non-DHPs is verapamil or a pharmaceutically acceptable salt, especially the hydrochloride, thereof.

Aldosterone synthase inhibitor is an enzyme that converts corticosterone to aldosterone by hydroxylating cortocosterone to form 18-OH-corticosterone and 18-OH-corticosterone to aldosterone. The class of aldosterone synthase inhibitors is known to be applied for the treatment of hypertension and primary aldosteronism comprises both steroidal and non-steroidal aldosterone synthase inhibitors, the later being most preferred.

Preference is given to commercially available aldosterone synthase inhibitors or those aldosterone synthase inhibitors that have been approved by the health authorities.

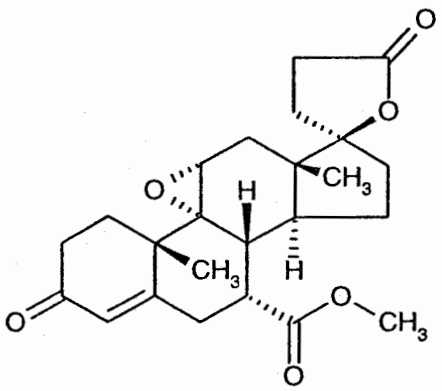
The class of aldosterone synthase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting of the non-steroidal aromatase inhibitors anastrozole, fadrozole (including the (+)-enantiomer thereof), as well as the steroidal aromatase inhibitor exemestane, or, in each case where applicable, a pharmaceutically acceptable salt thereof.

The most preferred non-steroidal aldosterone synthase inhibitor is the (+)-enantiomer of the hydrochloride of fadrozole (US patents 4617307 and 4889861) of formula



HCl

A preferred steroidal aldosterone antagonist is eplerenone (cf. EP 122232 A) of the formula



or

spironolactone.

Compounds having an inhibitory effects on both angiotensin converting enzyme and neutral endopetidase, so-called dual ACE/NEP inhibitors, can be used for the treatment of cardiovascular pathologies.

A preferred dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor is, for example, omapatrilate (cf. EP 629627), fasidotril or fasidotrilate, or Z 13752A (cf. WO 97/24342) or, if appropriable, a pharmaceutically acceptable salt thereof.

Endothelin (ET) is a highly potent vasoconstrictor peptided synthesized and released by the vascular endotleium. Endothelin exists in three isoforms (ET-1, ET-2 and ET-3). (ET shall meand any or all othe isoforms of ET). Elevated levels of ET have been reported in plasma fomr patients with e.g. essential hypertension. Endothelin receptor antagonist can be used to inhibit the vasoconstrictive effects induced by ET.

A preferred endothelin antagonist is, for example, bosentan (cf. EP 526708 A), enrasentan (cf. WO 94/25013), atrasentan (cf. WO 96/06095), especially atrasentan hydrochloride, darusentan (cf. EP 785926 A), BMS 193884 (cf. EP 702012 A), sitaxentan (cf. US

5594021), especially sitaxsentan sodium, YM 598 (cf. EP 882719 A), S 0139 (cf. WO 97/27314), J 104132 (cf. EP 714897 A or WO 97/37665), furthermore, tezosentan (cf. WO 96/19459), or in each case, a pharmaceutically acceptable salt thereof.

A diuretic is, for example, a thiazide derivative selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon. The most preferred is hydrochlorothiazide.

Preferred are combinations, such as a combined preparations or pharmaceutical compositions, respectively, comprising the renin inhibitor of formula (I) or a pharmaceutically accepted salt thereof and as second active agent an active agent selected from the group consisting of valsartan, fluvastatin, atorvastatin, pitavastatin, benzepril, enalapril, amlodipine, especially the besylate thereof, the (+) enantiomer of fadrozole, eplerenone, omapatrilate, Z 13752A, sitaxsentan, especially sitaxsentan sodium, darusentan and hydrochlorothiazide.

Furthermore preferred are combinations, such as a combined preparations or pharmaceutical compositions, respectively, comprising the renin inhibitor of formula (I) or a pharmaceutically accepted salt thereof and one active agent selected from the group consisting of valsartan, fluvastatin, atorvastatin, pitavastatin, benzepril, enalapril, amlodipine, especially the besylate thereof, the (+) enantiomer of fadrozole, eplerenone, omapatrilate, Z 13752A, sitaxsentan, especially sitaxsentan sodium, and darusentan, furthermore comprising as third active agent hydrochlorothiazide.

The structure of the active agents identified by generic or tradenames may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The corresponding active ingredients or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example COOH) can also form salts with bases.

All the more surprising is the experimental finding that the combined administration of the renin inhibitor of formula (I) or a salt thereof with a therapeutic agent selected from the group consisting of (i) to (ix) results not only in a beneficial, especially a synergistic, therapeutic effect, but also in additional benefits resulting from the combined treatment and further surprising beneficial effects compared to a monotherapy applying only one of the pharmaceutically active compounds used in the combinations disclosed herein.

In particular, all the more surprising is the experimental finding that the combination of the present invention results not only in a beneficial, especially a synergistic, therapeutic effect but also in additional benefits resulting from combined treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions as specified hereinafter.

It can be shown by established test models and especially those test models described herein that the combination of the renin inhibitor of formula (I) with with a therapeutic agent selected from the group consisting of (i) to (ix) results in a more effective prevention or preferably treatment of diseases specified in the following. In particular, it can be shown by established test models and especially those test models described herein that the combination of the present invention results in a more effective prevention or preferably treatment of diseases specified hereinafter.

If taken simultaneously, this results not only in a further enhanced beneficial, especially a synergistic, therapeutic effect, but also in additional benefits resulting from the simultaneous treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects, e.g. less increase of weight, on diseases and conditions associated with diabetes mellitus, for a number of combinations as described herein. Moreover, for a human patient, especially for elderly people, it is more convenient and easier to remember to take two tablets at the same time, e.g. before a meal, than

staggered in time, i.e. according to a more complicated treatment schedule. More preferably, both active ingredients are administered as a fixed combination, i.e. as a single tablet, in all cases desribed herein. Taking a single tablet is even easier to handle than taking two tablets at the same time. Furthermore, the packaging can be accomplished with less effort.

The term "synergistic" as used herein means that the effect achieved with the methods and compositions of the present invention is greater than the sum of the effects that result from methods and compositions comprising the active ingredients of this invention separately.

The person skilled in the pertinent art is fully enabled to select a relevant and standart animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The pharmaceutical activities as effected by administration of representatives of the class of AT_1-receptor antagonists or ACE inhibitors, respectively, or of the combination of active agents used according to the present invention can be demonstrated e.g. by using corresponding pharmacological models known in the pertinent art. The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The beneficial effects on blood pressure can, for example, be demonstrated in the test model as disclosed in R.L. Webb et al., in J. Hypertension, 16:843-852, 1998.
Methods:
The combination according to the present invention comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof can be administered by various routes of administration but are tested in this example using a continuous infusion via subcutaneously-implanted osmotic minipumps. Each agent can be tested over a wide-range of dosages to determine the optimal drug level for each agent in combination to elicit the maximal response. For these studies, it is preferred to use treatment groups consisting of at least 6 animals per group. Each study is best performed in which the effects of the combination treatment group are determined at the same time as the individual components are evaluated. Although drug effects may be observed with acute administration (such as 1 day), it is preferable to observe responses in a chronic setting as shown below in which experiments were done over a two to three week observation period. The long-term study is

of sufficient duration to allow for the full development of compensatory responses to occur and therefore, the observed effect will most likely depict the actual responses of the test system representing sustained or persistent effects. The effects on blood pressure depicted below represent a synergistic antihypertensive effect when the two agents are used in combination.

Statistical Analysis:

The combination therapy can be compared to that of the monotherapy groups by determining the maximum change in blood pressure or the area under the curve (AUC) for change in blood pressure over time in each of the treatment groups. All values are represented as the group mean $\pm$ SEM. Statistical significance is obtained when $p < 0.05$. The AUC values for each of the treatment groups can be compared statistically using a one-way ANOVA followed by the appropriate post-hoc analysis, for example by performing a Tukey's test.

Results:

Blood pressure can be reduced to a similar degree using lower dosages of each of the components when given in combination than when the individual monotherapies are administered. An additional unexpected finding is that the blood pressure can be lowered to a greater extent with the combination than when the individual compound of formulat (I) or a pharmaceutically acceptable salt thereof is given alone at a higher dosage.

These beneficial effects can, for example, be demonstrated in the test model as disclosed by G. Jeremic et al. in J. Cardovasc. Pharmacol. 27:347-354, 1996.

For example, the valuable potential of the combination of the present invention for the prevention and treatment of myocardial infarction (including the post-myocardial infarction indication to delay the progression to congestive heart failure) can be found using the following test model.

Study design

In the study to be performed, permanent coronary artery occlusion (CAO) in rats is used as a model of acute myocardial infarction. The experiments are carried out with 5 treatment groups characterized by following features:

- sham-operated animals

• CAO + vehicle
• CAO + compound of formula (I) or a pharmaceutically accetable salt, especially the hemi-fumarate, thereof,
• CAO + aldosterone synthase inhibitor
• CAO + compound of formula (I) or a pharmaceutically accetable salt, especially the hemi-fumarate, thereof, + aldosterone synthase inhibitor.

Following doses and routes of administration can be applied:
For the (+)-enantioner of the hydrochloride of fadrozole
Alza osmotic minipumps 0.4 mg/kg/d.

During the study following variables are measured:
• infarct size
• LV chamber volume
• interstitial and perivascular collagen density in spared LV myocardium
• COL-I and COL-III protein content in spared LV myocardium by Western blot
• cardiomyocytes cross-sectional area and length in sections of LV myocardium
• plasma concentrations of renin and aldosterone
• urine concentration of sodium, potassium and aldosterone
• blood pressure in conscious animals
• LV and carotid blood pressure in anesthetized animals.

Methodology

Infarct size: Six µm-thick transverse histological sections of the left ventricle are stained with nitroblue tetrazolium and acquired by a B/W XC-77CE CCD video camera (Sony). The resulting image is processed on a KS 300 image analysis system (Carl Zeiss Vision) using a software specifically developed (Porzio *et al.,* 1995). A single operator blinded to treatment interactively defines the boundaries of the interventricular septum, and the infarcted area on each section is semiautomatically identified as the area of unstained ventricular tissue. The software automatically calculates for each component of the ventricular section defined as the chamber, septum, infarcted area, infarcted LV wall and viable LV wall, a set of geometric parameters (Porzio *et al.,* 1995).

Histology: Hearts are fixed in situ, by retrograde perfusion with buffered 4% formaldehyde after arrest in diastole by i.v. injection of 0.5 M KCl. After fixation, the left ventricle (LV) and

the free wall of the right ventricle are separately weighed; LV longer diameter is measured with a caliper. LV histological sections are stained with hematoxylin & eosin for qualitative examination and to quantify cardiomyocytes cross-sectional area with a semi-automated image analysis routine. Interstitial collagen deposition in LV is evaluated on Sirius red stained sections with a semi-automated image analysis routine (Masson *et al.*, 1998).

Collagen content in LV spared myocardium: LV tissue in the spared myocardium is homogenized, subjected to PAGE-SDS electrophoresis and electroblotted onto nitrocellulose membrane. The blots are exposed to primary antibodies, i.e. rabbit anti-rat collagen type I or type III antiserum (Chemicon). The primary antibodies are recognized by secondary antibodies conjugated to alkaline phosphatase (for colagen type I) or peroxidase (collagen type III).

Left ventricular chamber volume: LV chamber volume is determined in hearts arrested in diastole (KCl) and fixed in formalin under a hydrostatic pressure equivalent to the measured LV end-diastolic pressure. A metric rod is inserted into the LV to measure LV inner length. The transverse diameters of the LV chamber are measured in two 1-mm thick transverse sections near to the base and the apex of the ventricle (Jeremic *et al.*, 1996). The chamber volume is computed from an equation integrating transverse diameters and inner length.

Systemic and Left ventricular hemodynamics: A microtip pressure transducer (Millar SPC-320) connected to a recorder (Windograf, Gould Electronics) is inserted into the right carotid artery to record systolic and diastolic blood pressures. The pressure transducer is advanced into the LV to measure LV systolic (LVSP) and end-diastolic (LVEDP) pressures, the first derivative of LV pressure over time (+dP/dt) and heart rate.

Non-invasive blood pressure: Systolic blood pressure and heart rate are measured by the tail-cuff method (Letica LE 5002) in conscious rats.

Urine electrolytes, hormones: Rats are individually housed in metabolic cages and 24-h urine collected on 1 ml HCl 6N. Water intake is measured. Urine catecholamines are extracted on Bondelut C_{18} columns (Varian), separated by HPLC (Apex-II C18, 3 µm, 50x4.5 mm analytical column, Jones Chromatography) and quantified with an electrochemical detector (Coulochem II, ESA) (Goldstein *et al.*, 1981). Plasma and urine aldosterone, and plasma angiotensin II are determined with specific radioimmunoassays

(Aldoctk-2, DiaSorin and Angiotensin II, Nichols Diagnostics). Urine sodium and potassium are measured by flame photometry.

Sample size

10 animals analyzable in each treatment groups are sufficient to detect biologically significant differences. Only rats with an infarct size of at least 10% of the LV section area are included in the final analysis.

Endothelial dysfunction is being acknowledged as a critical factor in vascular diseases. The endothelium plays a bimodal role as the source of various hormones or by-products with opposing effects: vasodilation and vasoconstriction, inhibition or promotion of growth, fibrinolysis or thrombogenesis, production of anti-oxidants or oxidising agents. Genetically predisposed hypertensive animals with endothelial dysfunction constitute a valid model for assessing the efficacy of a cardiovascular therapy.

Endothelial disfunction is characterized by, for example, increased oxidative stress, causing decreased nitric oxide, increased factors involved in coagulation or fibrinolysis such as plasminogen activating inhibitor-1 (PAI-1), tissue factor (TF), tissue plasminogen activator (tPA), increased adhesion molecules such as ICAM and VCAM, increased growth factors such as bFGF, TGFb, PDGF, VEGF, all factors causing cell growth inflammation and fibrosis.

The treatment e.g. of endothelial dysfunction can be demonstrated in the following pharmacological test:

Material and methods

Male 20-24 week-old SHR, purchased from RCC Ldt (Fullingsdorf, Switzerland), are maintained in a temperature- and light-controlled room with free access to rat chow (Nafag 9331, Gossau, Switzerland) and tap water. The experiment is performed in accordance with the NIH guidelines and approved by the Canton Veterinary office (Bew 161, Kantonales Veterinäramt, Liestal, Switzerland). All rats are treated with the NO synthesis inhibitor L-NAME (Sigma Chemicals) administered in drinking water (50 mg/l) for 12 weeks. The average daily dose of L-NAME calculated from the water consumed was 2.5 mg/kg/d (range 2.1-2.7).

The rats can be divided into 5 groups: group 1, control (n = 40); Group 2, the compound of formula (I) in form of the hemi-fumarate (ren1; n = 40); Group 3, enalapril (ena1; n = 30); Group 4, a combination (ena1ren1) of enalapril and the compound of formula (I) in form of the hemi-fumarate;(n = 30) and Group 5, the compound of formula (I) in form of the hemi-fumarate (ren2 – higher dose; n = 30). The drugs are administered in drinking fluid. The dose of enalapril is selected from the work of Sweet et al. (1987) indicating significantly increased survival in rats with healed myocardial infarction. The pressor effect of Ang II at 1 mg/kg obtained in controls normotensive rats can be reducted after treatment with the compound of formula (I) in form of the hemi-fumarate (Gervais et al. 1999).

Body weight is measured every week. Systolic blood pressure and heart rate are recorded by tail cuff plethysmography 3 and 2 weeks before starting the study and at 2 weeks after drug administration. Urine is collected over a 24 hour period from rats kept in individual (metabolic) cages the week before starting treatment and at weeks 4 and 12 for volume measurement and protein, creatinine, sodium and potassium determination using standard laboratory methods. At the same time points, blood samples are withdrawn from the retro-orbital plexus (maximum 1 ml) for creatinine, Na^+ and K^+ assays.

Ten rats from each group are sacrificed at 4 weeks for collection of kidney and heart for morphological analysis. The remaining rats are sacrificed at 12 weeks. Cardiac and kidney weight is recorded. Terminal blood sampling is performed in 5 % EDTA at 4 (morphometry study) and 12 (end of the study) weeks for aldosterone, determination by radioimmunoassay using a DPC coat-a-count aldosterone-RIA kit (Bühlmann, Switzerland).

Statistical analysis:

All data are expressed as mean ± SEM. Statistical analysis is performed using a one-way ANOVA, followed by a Duncan's multiple range test and a Newman-Keuls test, 7for comparison between the different groups. Results with a probability value of less than 0.05 are deemed statistically significant.

Results:

Even at non-blood pressure reducing doses, both the compound of formula (I) in form of the hemi-fumarate and enalapril treatment lead to significant improvements in survival rates.

The surprising observation is that, in this model, blockade of the RAS with low doses of the renin inhibitor of formula (I) and, for example, and enalapril improved survival despite persistent kidney dysfunction and high blood pressure. There is no decrease in proteinuria and no reduction of kidney lesions. Kidney and heart sections show glomeruloslerosis, fibrinoid necrosis and fibrosis. These results clearly demonstrate that survival of SHR with endothelial dysfunction is independent of the blood-pressure lowering effect of the treatment and may be related to a direct effect on the endothelium.

An improvement of regression of artherosclerosis without effecting the serum lipid levels can, for exmple, be demonstrated by using the animal model as disclosed by H. Kano et al. in Biochemical and Biophysical Research Communications 259, 414-419 (1999).

That the compounds or combinations according to the present invention can be used for the regression of a cholesterol diet-induced atherosclerosis, can be demonstrated using the test model described, e.g., by C. Jiang et al. in Br. J. Pharmacol. (1991), 104, 1033-1037.

That the compounds or combinations according to the present invention can be used for the treatment of renal failure, especially chronic renal failure, can be demonstrated using the test model described, e.g., by D. Cohen et al. in Journal of Cardiovascular Pharmacology, 32: 87-95 (1998).

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The pharmaceutical composition according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, for separate use or as a fixed combination.

Accordingly, the invention furthermore relates to a method for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension,

(d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia, (e) glaucoma; furthermore

(f) isolated systolic hypertension (ISH),

(g) diabetic retinopathy, and

(h) peripheral vascular disease;

comprising administering to a warm-blooded animal, including man, in need thereof a jointly effective amount of a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent selected from the group consisting of

(i) an AT_1-receptor antagonist or a pharmaceutically acceptable salt thereof,

(ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,

(iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,

(iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,

(v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,

(vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,

(vii) an dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,

(viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and

(ix) a diuretic or a pharmaceutically acceptable salt thereof.

Furthermore, the present inveniton relates to the use of a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent selected from the group consisting of

(i) an AT_1-receptor antagonist or a pharmaceutically acceptable salt thereof,

(ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,

(iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,

(iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,

(v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,

(vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,

(vii) an dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof, and

(viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and

(ix) a diuretic or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, or treatment of a disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention;

(d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia;

(e) glaucoma; furthermore

(f) isolated systolic hypertension (ISH),

(g) diabetic retinopathy, and

(h) peripheral vascular disease.

The invention furthermore relates to a pharmaceutical composition for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention;

(d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia;

(e) glaucoma; furthermore

(f) isolated systolic hypertension (ISH),

(g) diabetic retinopathy, and

(h) peripheral vascular disease;

comprising a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at leat one therapeutic agent selected from the group consisting of

(i) an AT_1-receptor antagonist or a pharmaceutically acceptable salt thereof,

(ii) a HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof,

(iii) an angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable salt thereof,

(iv) an Calcium channel blocker or a pharmaceutically acceptable salt thereof,

(v) an aldosterone synthase inhibitor or a pharmaceutically acceptable salt thereof,

(vi) an aldosterone antagonist or a pharmaceutically acceptable salt thereof,

(vii) an dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof,

(viii) an endothelin antagonist or a pharmaceutically acceptable salt thereof, and

(ix) a diuretic or a pharmaceutically acceptable salt thereof;
and a pharmaceutically acceptable carrier.

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The pharmaceutical composition according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, for separate use or as a fixed combination.

A further aspect of the present invention is a kit for the prevention of, delay of progression of, treatment of a disease or condition according to the present invention comprising
(a) an amount of the renin inhibitor of formula (I) or a pharmaceutically accetable salt thereof in a first unit dosage form;
(b) an amount of at least one therapeutic agent selected from the group consisting of components (i) to (ix), or, in each case, where approriate, a pharmaceutically acceptable salt thereof in a second etc. unit dosage form; and
(c) a container for containing said first, second etc. unit forms.

In a variation thereof, the present invention likewise relates to a "kit-of-parts", for example, in the sense that the components to be combined according to the present invention can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or at different time points. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or

condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components.

The invention furthermore relates to a commercial package comprising the combination according to the present invention together with instructions for simultaneous, separate or sequential use.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 %, preferably of from about 1 % to about 80 %, of the active compound. Pharmaceutical preparations for enteral or parenteral, and also for ocular, administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner that is known per se, for example using conventional mixing, granulation, coating, solubulizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compound with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commerically available.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated e.g. for a patient of approximately 75 kg in weight.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

The pharmaceutical preparation will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising an amount, being together with the further component(s) jointly effective, e.g.

The doses of renin inhibitor of formula (I) to be administered to warm-blooded animals, for example human beings, of, for example, approximately 70kg body weight, especially the doses effective in the inhibition of the enzyme renin, e.g. in lowering blood pressure and/or in improving the symptoms of glaucoma, are from approximately 3mg to approximately 3g, preferably from approximately 10mg to approximately 1 g, for example approximately from 20mg to 200mg, per person per day, divided preferably into 1 to 4 single doses which may, for example, be of the same size. Usually, children receive about half of the adult dose. The dose necessary for each individual can be monitored, for example by measuring the serum concentration of the active ingredient, and adjusted to an optimum level. Single doses comprise, for example, 10, 40 or 100 mg per adult patient.

Valsartan, as a representative of the class of AT_1-receptor antagonists, will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 to about 320 mg, of valsartan which may be applied to patients. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. Preferably, valsartan is applied twice a day with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is b.i.d. administration.

In case of HMG-Co-A reductase inhibitors, preferred dosage unit forms of HMG-Co-A reductase inhibitors are, for example, tablets or capsules comprising e.g. from about 5 mg to about 120 mg, preferably, when using fluvastatin, for example, 20 mg, 40 mg or 80 mg (equivalent to the free acid) of fluvastatin, for example, administered once a day.

In case of ACE inhibitors, preferred dosage unit forms of ACE inhibitors are, for example, tablets or capsules comprising e.g. from about 5 mg to about 20 mg, preferably 5 mg, 10 mg, 20 mg or 40 mg, of benazepril; from about 6.5 mg to 100 mg, preferably 6.25 mg, 12.5 mg, 25 mg, 50 mg, 75 mg or 100 mg, of captopril; from about 2.5 mg to about 20 mg, preferably 2.5 mg, 5 mg, 10 mg or 20 mg, of enalapril; from about 10 mg to about 20 mg,

preferably 10 mg or 20 mg, of fosinopril; from about 2.5 mg to about 4 mg, preferably 2 mg or 4 mg, of perindopril; from about 5 mg to about 20 mg, preferably 5 mg, 10 mg or 20 mg, of quinapril; or from about 1.25 mg to about 5 mg, preferably 1.25 mg, 2.5 mg, or 5 mg, of ramipril. Preferred is t.i.d. administration.

Especially preferred are low dose combinations.

The following examples illustrate the above-described invention; however, it is not intended to restrict the scope of this invention in any manner.

Formulation Example 1:

Film-Coated Tablets:

Components	Compostion Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	80.00	
Microcrystalline cellulose/ Avicel PH 102	54.00	NF, Ph. Eur
Crospovidone	20.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.5	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.00	NF, Ph. Eur
Coating		
Purified water *)	-	
DIOLACK pale red 00F34899	7.00	
Total tablet mass	167.00	

*) Removed during processing.

The film-coated tablet is manufactured e.g. as follows:

A mixture of valsartan, microcrystalline cellulose, crospovidone, part of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200, silicon dioxide and magnesium stearate is premixed in a diffusion mixer and then sieve through a screnning mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compacter and then sieve through a screening mill. To the resulting mixture, the rest of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200 are added and the final blend is made in a diffusion mixer. The whole mixture is compressed in a rotary tabletting machine and the tabletts are coated with a film by using Diolack pale red in a perforated pan.

Formulation Example 2:

Film-coated tablets:

Components	Compostion Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	160.00	
Microcrystalline cellulose/ Avicel PH 102	108.00	NF, Ph. Eur
Crospovidone	40.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	5.00	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	4.00	NF, Ph. Eur
Coating		
Opadry Light Brown 00F33172	10.00	
Total tablet mass	330.00	

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 3:

Film-Coated Tablets:

Components	Compostion Per Unit (mg)	Standards
Core: Internal phase		
Valsartan [= active ingredient]	40.00	
Silica, colloidal anhydrous (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= Lubricant]	2.00	USP/NF
Crospovidone [Disintegrant]	20.00	Ph. Eur
Microcrystalline cellulose [= Binding agent]	124.00	USP/NF
External phase		
Silica, colloidal anhydrous, (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [Lubricant]	2.00	USP/NF
Film coating		
Opadry® brown OOF 16711*)	9.40	
Purified Water**)	-	
Total tablet mass	199.44	

*) The composition of the Opadry® brown OOF16711 coloring agent is tabulated below.

**) Removed during processing

Opadry® Composition:

Ingredient	Approximate % Composition
Iron oxide, black (C.I. No. 77499, E 172)	0.50
Iron oxide, brown (C.I. No. 77499, E 172	0.50
Iron oxide, red (C.I. No. 77491, E 172)	0.50

Iron oxide, yellow (C.I. No. 77492, E 172)	0.50
Macrogolum (Ph. Eur)	4.00
Titanium dioxide (C.I. No. 77891, E 171)	14.00
Hypromellose (Ph. Eur)	80.00

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 4:

Capsules:

Components	Compostion Per Unit (mg)
Valsartan [= active ingredient]	80.00
Microcrystalline cellulose	25.10
Crospovidone	13.00
Povidone	12.50
Magnesium stearate	1.30
Sodium lauryl sulphate	0.60
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total tablet mass	209.50

The tablet is manufactured e.g. as follows:

Granulation/Drying

Valsartan and microcrystallin cellulose are spray-granulated in a fluidised bed granulator with a granulating solution consisting of povidone and sodium lauryl sulphate dissolved in purified water. The granulate obtained is dried in a fluidiesd bed dryer.

Milling/Blending

The dried granulate is milled together with crospovidone and magnesium stearate. The mass is then blended in a conical srew type mixer for approximately 10 minutes.

Encapsulation

Teh empty hard gelatin capsules are filled with the blended bulk granules under controlled temperature and humidity conditions. The filed capsules are dedustee, visually inspected, weightchecked and quarantied until by Quality assurance department.

Formulation Example 5:

Capsules:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	160.00
Microcrystalline cellulose	50.20
Crospovidone	26.00
Povidone	25.00
Magnesium stearate	2.60
Sodium lauryl sulphate	1.20
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total tablet mass	342.00

The formulation is manufactured e.g. as described in Formulation Example 4.

Formulation Example 6:

Hard Gelatine Capsule:

Components	Compostion Per Unit (mg)
Valsartan [= active ingredient]	80.00
Sodium laurylsulphate	0.60
Magnesium stearate	1.30
Povidone	12.50
Crospovidone	13.00
Microcrystalline cellulose	21.10
Total tablet mass	130.00

Examples 7 to 11:

Example	7	8	9	10	11
Components	Amount per Unit (mg)	Amount per Unit (mg)	Amount per Unit (mg)	Amount per Unit (mg)	Amount per Unit (mg)
Granulation					
Valsartan Drug Substance	80.000	160.000	40.000	320.000	320.000
Microcrystalline Cellulose (NF, Ph.Eur.)/ Avicel PH 102	54.000	108.000	27.000	216.000	216.000
Crospovidone (NF, Ph.Eur.)	15.000	30.000	7.500	80.000	60.000
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	1.500	3.000	0.750	3.000	6.000
Magnesium Stearate (NF, Ph.Eur.)	3.000	6.000	1.500	10.000	12.000
Blending					
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	---	---	---	3.000	-
Magnesium Stearate, NF, Ph.Eur.	1.500	3.000	0.750	8.000	6.000
Core Weight/mg	155.000	310.000	77.500	640.000	620.000
Coating	-	-	3.800	15.000	16.000

Example 12:

Hard gelatin capsule:

Component	Amount per unit [mg]
Capsule	
Fluvastatin Sodium [1)]	21.481 [2)]
Calcium Carbonate	62.840
Sodium Bicarbonate	2.000
Microcrystalline Cellulose	57.220
Pregelatinized Starch	41.900
Purified Water [3)]	Q.S.
Magnesium Stearate	1.050
Talc	9.430
Target Capsule Fill Weight	195.92
Capsule Shell	
Hard gelatin Capsule Shell	48.500
Branding Ink (pre-printed)	
White Ink	Trace
Red Ink	Trace
Target Capsule Weight	244.42

[1)] includes a 2% overage for moisture

[2)] 20 mg of free acid is equivalent to 21.06 mg Na salt

[3)] partially removed during processing

Example 13:

Hard gelatin capsule

Component	Amount per unit [mg]
Fluvastatin Sodium	42.962 [1) 2)]
Calcium Carbonate	125.680
Sodium Bicarbonate	4.000
Microcrystalline Cellulose	114.440
Pregelatinized Starch	83.800
Purified Water [3)]	Q.S.
Magnesium Stearate	2.100
Talc	18.860
Target Capsule Fill Weight	391.840
Capsule Shell	
Hard gelatin Capsule Shell	76.500
Branding Ink (pre-printed)	
White Ink	Trace
Red Ink	Trace
Target Capsule Weight	468.34

[1)] includes a 2% overage for moisture

[2)] 20 mg of free acid equivalent to 21.06 mg Na salt

[3)] partially removed during processing

Example 14:

Round, slightly bi-convex, film-coated tablets with beleved edges:

Component	Amount per unit [mg]
Table Core	
Fluvastatin Sodium [1)]	84.24 [2)]
Cellulose Microcrystalline / Micro-crystalline cellulose fine powder	111.27
Hypromellose / Hydroxypropyl methyl cellulose (Methocel K100LVP CR; HPMC100 cps)	97.50
Hydroxypropyl cellulose (Klucel HXF)	16.25
Potassium hydrogen carbonate / Potassium bicarbonate	8.42
Povidone	4.88
Magnesium stearate	2.44
Core Tablet Weight	325.00
Coating	
Coating premix - Opadry Yellow (00F22737)	9.75
Total Weight	334.75
Water, purified [3)]	Q.S.

[1)] 84.24 mg of the sodium salt of fluvastatin is equivalent to 80 mg of fluvastatin free acid

[2)] to be adjusted for moisture (LOD)

[3)] removed during processing

Example 15 :

Round, biconvex, beveled-edged, film-coated tablets

Component	Unit wt./Vol. [mg]	Unit wt./Vol. [mg]	Unit wt./Vol. [mg]	Unit wt./Vol. [mg]
Benazepril Hydrochloride	5.00	10.00	20.00	40.00
Lactose Monohydrate, NF	142.00	132.00	117.00	97.00
Pregelatinized Starch, NF	8.00	8.00	8.00	8.00
Colloidial Silicon Dioxide, NF (Cab-O-Sil, M-5)	1.00	1.00	1.00	1.00
Crospovidone, NF	3.00	3.00	3.00	3.00
Microcrystalline Cellulose, NF	18.00	18.00	18.00	24.25
Hydrogenated Castor Oil, NF	8.00	8.00		
Magnesium Stearate, NF			8.00	1.75
Color:	-			0.50
Yellow-Brown (suspension)		2.00		
Red-Brown (suspension)			0.50	
Purified Water, USP	trace	trace	trace	trace
Opadry Color:				
Yellow	8.38	8.38		
Pink			8.38	8.38
Total	193.38	190.38	183.88	183.88

Example 16:

Film-coated tablets

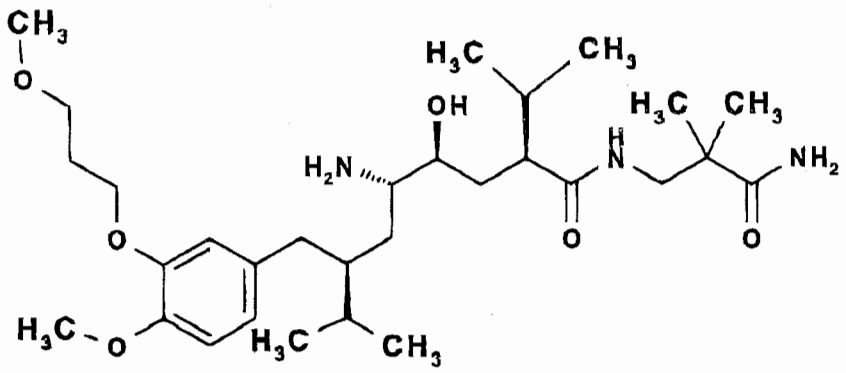
The following constituents are processed for the preparation of 10 000 tablets each containing 100 mg of active ingredient:

hemi-fumarate of the compound of formula (I)	1000 g
corn starch	680 g
colloidal silicic acid	200 g
magnesium stearate	20 g
stearic acid	50 g
sodium carboxymethyl starch	250 g
water	quantum satis

A mixture of one of the compounds of formula I mentioned in the preceding Examples as active ingredient, 50 g of corn starch and the colloidal silicic acid is processed into a moist mass with starch paste prepared from 250 g of corn starch and 2.2 kg of demineralised water. The mass is forced through a sieve having a mesh size of 3 mm and dried at 45° for 30 minutes in a fluidised bed drier. The dried granules are pressed through a sieve having a mesh size of 1 mm, mixed with a previously sieved mixture (1 mm sieve) of 330 g of corn starch, the magnesium stearate, the stearic acid and the sodium carboxymethyl starch, and compressed to form slightly biconvex tablets.

What is claimed is

1. A pharmaceutical composition comprising the renin inhibitor of formula (I)



(I),

or a pharmaceutically acceptable salt thereof, and at least one therapeutic agent selected from the group consisting of

(i) an AT_1-receptor antagonist, or a pharmaceutically acceptable salt thereof; and

(ii) an angiotensin converting enzyme (ACE) inhibitor, or a pharmaceutically acceptable salt thereof; and a carrier.

2. A composition according to claim 1 wherein the renin inhibitor of formula (I) is present in form of the hemi-fumarate salt thereof.

3. A composition according to claims 1 or 2 wherein, independent of one another, the AT_1-receptor antagonist is valsartan, or a pharmaceutically acceptable salt thereof; and the angiotensin converting enzyme (ACE) inhibitor is benazepril or enalapril, or a pharmaceutically acceptable salt thereof.

4. A composition according to any one of claims 1 to 3 for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial

infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension, all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension;

(d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia; and

(e) glaucoma.

5. A composition according to any one of claims 1 to 3 for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

(f) isolated systolic hypertension (ISH);

(g) diabetic retinopathy; and

(h) peripheral vascular disease.

6. A composition according to any one of claims 1 to 5 comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, and valsartan, or a pharmaceutically acceptable salt thereof.

7. A composition according to claim 6 comprising the compound of formula (I) in form of the hemi-fumarate salt thereof and valsartan.

8. A composition according to any one of claims 1 to 7 for simultaneous, separate or sequential use.

9. A kit for the prevention, delay of progression, or treatment according to claim 4 or 5 comprising

(a) an amount of the renin inhibitor of formula (I), or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

(b) an amount of at least one therapeutic agent selected from the group consisting of components (i) and (ii), or in each case, where appropriate, a pharmaceutically acceptable salt thereof, in a second etc. unit dosage form; and

(c) a container for containing said first, second etc. unit forms.

10. Use of a combination of the renin inhibitor of formula (I), or a pharmaceutically acceptable salt thereof, in combination with at least one therapeutic agent selected from the group consisting of

(i) an AT_1-receptor antagonist, or a pharmaceutically acceptable salt thereof; and

(ii) an angiotensin converting enzyme (ACE) inhibitor, or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, or treatment of a disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, renal failure, especially chronic renal failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal failure, e.g. chronic renal failure, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension, all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention;

(d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia; and

(e) glaucoma.

11. Use of a combination of the renin inhibitor of formula (I), or a pharmaceutically acceptable salt thereof, with at least one therapeutic agent selected from the group consisting of

(I) an AT_1-receptor antagonist, or a pharmaceutically acceptable salt thereof; and

(ii) an angiotensin converting enzyme (ACE) inhibitor, or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, or treatment of a disease or condition selected from the group consisting of

(f) isolated systolic hypertension (ISH);

(g) diabetic retinopathy; and

(h) peripheral vascular disease.

12. Use according to claim 10 or 11 wherein the compound of formula (I) is the hemi-fumarate salt thereof, and wherein the AT_1-receptor antagonist is valsartan.