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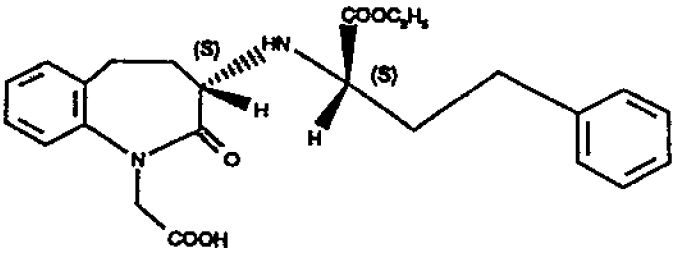
(54) **COMPOSITIONS DE COMBINAISON CONTENANT BENAZEPRILE OU BENAZEPRILAT ET VALSARTANE**

(54) **COMBINATION COMPOSITIONS CONTAINING BENAZEPRIL OR BENAZEPRILAT AND VALSARTAN**



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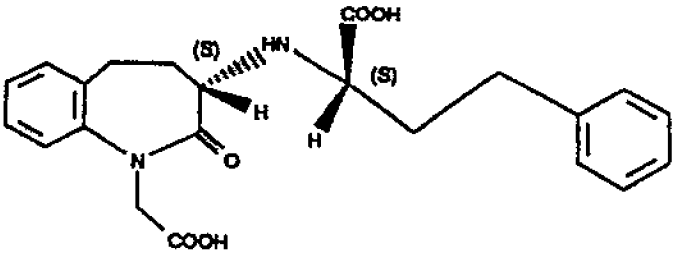

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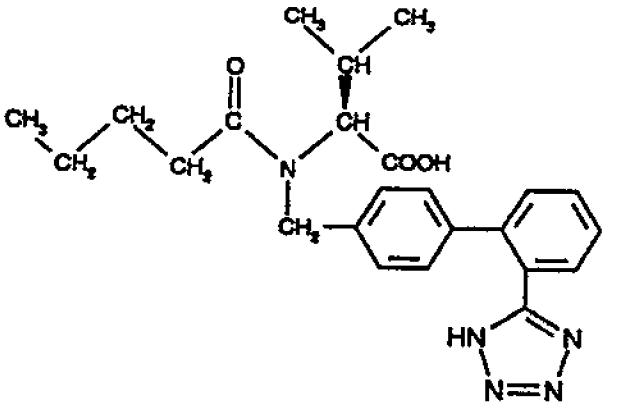

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(57) L'invention se rapporte à des compositions de combinaison pharmaceutique pour le traitement de l'hypertension, l'insuffisante cardiaque globale et l'insuffisance rénale, comportant (1) le bénazéprile inhibiteur de ACE de formule (I) ou le bénazéprilat de formule (II) ou un de leurs sels pharmaceutiquement acceptables, et la valsartane antagoniste AT_1 de formule (III) ou un de leurs sels pharmaceutiquement acceptables, ainsi que les méthodes de traitement de l'hypertension, de l'insuffisance cardiaque globale et de l'insuffisance rénale.

(57) The invention relates to pharmaceutical combination compositions for the treatment of hypertension, congestive heart failure and renal failure, comprising (1) the ACE-inhibitor benazepril of formula (I) or benazeprilat of formula (II) or a pharmaceutically acceptable salt thereof, and (2) the AT_1-antagonist valsartan of formula (III) or a pharmaceutically acceptable salt thereof, as well as to methods for the treatment of hypertension, congestive heart failure and renal failure.

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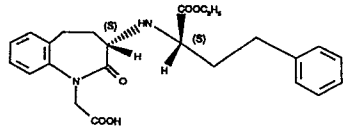

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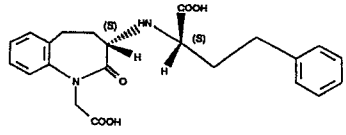

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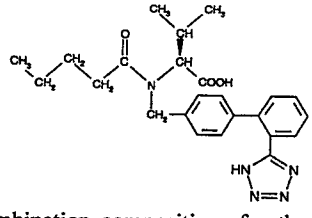


(III)

(57) Abstract

The invention relates to pharmaceutical combination compositions for the treatment of hypertension, congestive heart failure and renal failure, comprising (1) the ACE-inhibitor benazepril of formula (I) or benazeprilat of formula (II) or a pharmaceutically acceptable salt thereof, and (2) the AT_1-antagonist valsartan of formula (III) or a pharmaceutically acceptable salt thereof, as weel as to methods for the treatment of hypertension, congestive heart failure and renal failure.

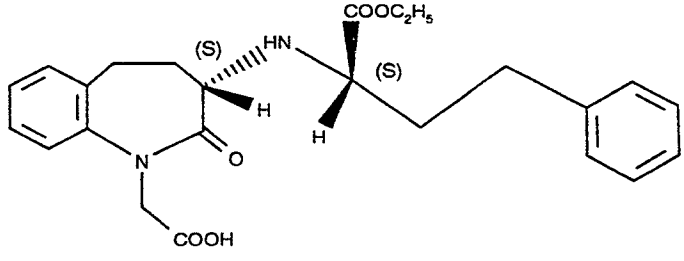
COMBINATION COMPOSITIONS CONTAINING BENAZEPRIL OR BENAZEPRILAT AND VALSARTAN

There are different approaches for intervening regulatively at different places in the renin-angiotensin cascade and for opening up possibilities to influence the regulation of blood pressure in different ways.

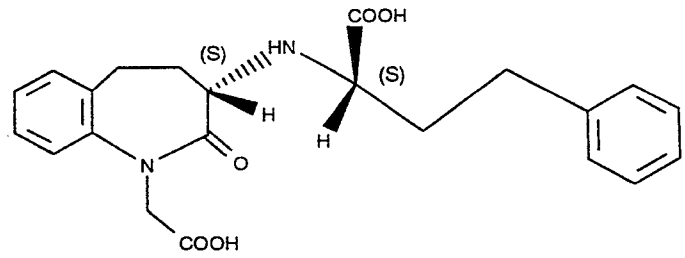
Angiotensinogen, a α2-macroglycoprotein, is split by the renin enzyme into the decapeptide angiotensin I which itself is biologically only very weakly active. The next step in the cascade is the removal of a further two amino acids by the action of the angiotensin-converting enzyme (ACE), bonded mainly in the endothelium, with formation of angiotensin II. This latter is regarded as being one of the strongest natural vasoconstrictors.

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

One known representative from among the conventional ACE-inhibitors is the active ingredient 3-[(1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl)amino]-2,3,4,5-tetra-hydro-2-oxo-1H-1-(3S)-benzazepine-1-acetic acid [benazepril] of formula



or (see EP 72352) (3S)-3-[[(1S)-(1-carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid [benazeprilat] of formula



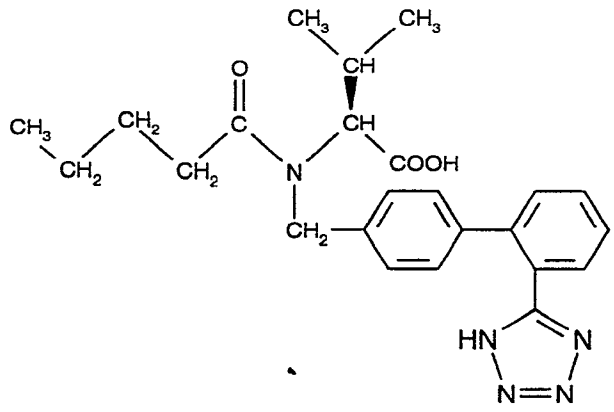
(see EP 72352) and its pharmaceutically acceptable salts. Monohydrochloride merits special mention (benazepril hydrochloride).

The vasoconstrictive effects of angiotensin II are produced by its action on the non-striated muscle cells, the stimulation of the formation of the adrenergenic hormones epinephrine and norepinephrine as well as the increase of the activity of the sympathetic nervous system as a result of the formation of norepinephrine. Angiotensin II also has an influence on the electrolytic balance, produces e.g. antinatriuretic and antidiuretic effects in the kidney and thereby promotes the release of, on the one hand, the vasopressin peptide from the pituitary gland and, on the other hand, of aldosterone from the adrenal glomerulosa. All these influences play an important part in the regulation of blood pressure.

Angiotensin II interacts with specific receptors on the surface of the target cell. It has been possible to identify receptor subtypes which are termed e.g. AT_1- and AT_2-receptors. In recent times great efforts have been made to identify substances that bind to the AT_1-receptor. Such active ingredients are often termed angiotensin II antagonists. Because of the inhibition of the AT_1-receptor such antagonists can be used e.g. as antihypertensives or for the treatment of congestive heart failure.

Angiotensin II antagonists are therefore understood to be those active ingredients which bind to the AT_1-receptor subtype. These include compounds having different structural features.

The representative selected for the AT_1-antagonists is the active ingredient (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine [valsartan] of formula



(see EP 443983) and its pharmaceutically acceptable salts.

Pharmaceutically acceptable salts of benazepril and valsartan are typically acid addition salts. These acid addition salts are formed, for example, with strong inorganic acids, typically mineral acids, such as sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic acids, typically with C_1-C_4alkanecarboxylic acids which may be substituted, e.g. by halogen, typically acetic acid, for example with dicarboxylic acids which may be unsaturated, such as oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, phthalic acid or terephthalic acid, for example with hydroxycarboxylic acids, such as ascorbic acid, glycolic acid, lactic acid, malic acid, tartaric acid or citric acid, for example with amino acids, such as aspartic acid or glutaminic acid, or e.g. benzoic acid, or with organic sulfonic acids, for example with C_1-C_4alkane acid or arylsulfonic acid which may be substituted, e.g. by halogen, for example with methane- or p-toluenesulfonic acid. Suitable salts with bases are typically metal salts, such as alkali metal salts or alkaline earth metal salts, typically sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, typically ethylamine, tert-butylamine, diethylamine, diisopropylamine, triethylamine, tributylamine or dimethylpropylamine, or a mono-, di- or trihydroxy-lower alkylamine, typically mono-, di- or triethanolamine. Corresponding internal salts can also be used.

Many assays endeavour also to develop combinations of different active ingredients for the treatment of, for example, hypertension and congestive heart failure. The advantages of such combinations are held to be, for example, that in

these combinations doses of the individual components are used which are markedly lower than the effective dose for the single component. If, for example, antihypertensives having different mechanisms of action are used in such combinations, then an additive effect is usually expected. The aim is, however, to provide such combinations that have, on the one hand, synergistic effects and, on the other hand, prolonged duration of efficacy.

PCT application WO 94/28924 discloses the combination of an ACE-inhibitor with an angiotensin-II antagonist. Clinical tests of the combination of enalapril (ACE-inhibitor) with losartan (AT_1-antagonist) in the indicated doses did not result in any significant synergistic effect of lowered blood pressure at all compared with the lowered blood pressure achieved with enalapril, only an additive effect could be ascertained. Furthermore, there is no indication in said patent application of any prolonged duration of action after treatment with a combination of losartan and enalapril. Hence it cannot be assumed per se that such a combination of a potent ACE-inhibitor with an AT_1-antagonist produces a synergistic lowering of the blood pressure in man. Accordingly, there can be no mention of class effect. Rather, the disclosure of WO 94/28924 shows that the combined application of the two indicated active ingredients effects an increase of the renal blood flow rate instead. Azizi et al., Circulation 1995; 92:825-834, likewise found additive effects of combined ACE inhibition and AT_1 antagonism (combination of captopril and losartan) on blood pressure and that the duration of the mean blood pressure fall was not prolonged by the combination of captopril and losartan.

All the more surprising is the experimental finding that the combined administration of the ACE-inhibitor benazepril or a pharmaceutically acceptable salt thereof with the AT_1-antagonist valsartan or a pharmaceutically acceptable salt thereof results not only a synergistic antihypertensive effect but that a surprising prolongation of efficacy is also observed.

The advantage of these unexpected effects is that the dosages need not only often be smaller but also less frequent. This is in accordance with the desires and requirements of the patients to be treated.

In addition, any occurrence of side-effects can thus be minimised in some patients.

The combined blocking of the angiotensin-converting enzyme and the AT_1-receptor also markedly reduces the increased circulation of vasoconstrictive angiotensin II in a favourable manner.

Synergistic effect will be understood to occur when the two active ingredients are administered together, be it, for example, together in one combined unit dose form or one after the other or separately in two separate unit dose forms, and when the combined effects of the combination are greater than the algebraic sum of the two individual effects, i.e. when a more than additive effect is achieved.

The synergistic effect can be shown experimentally, e.g. by telemetering, as follows:

For the present experiments, spontaneously hypertensive rats (SHR) are used which are 22 to 25 weeks old. Such rats are available from Taconic Farms, Germantown, New York (Tac:N(SHR)fBR). A radiotelemetric device is implanted in the lower abdominal aorta of all test animals at least one month before the experiments. The radio transmitter is fastened to the inner abdominal muscle with a silk seam. The cardiovascular parameters are continuously transmitted via the radio transmitter, allowing data to be collected without disturbing the animals in their cages. The animals are kept in their cages at controlled temperature and atmospheric humidity and at a 12-hourly alternation of light and darkness. The body weights are measured at weekly intervals. Usually groups of five rats are formed. One group of animals receives only valsartan; another group receives only benazepril; a further group receives a combination of valsartan and benazepril; the fourth group receives a combination of valsartan and benazepril which is differently dosed; and a last group, receiving only the vehicle (0.15 N NaOH), is used as control group. Minipumps are used for continuous subcutaneous drug delivery over a 14 day interval. In these experiments, the mean arterial blood pressure and the heart beat are checked by means of a computerised data detection system (Data Sciences Inter., Inc.). The mean arterial blood pressure and the heart beat are measured every 10 minutes for 10 seconds and recorded. The values for each rat are reported as mean values over 24 hours and contain 144 data points per day. The base line for the blood pressure is determined as the average from three consecutive days before the

minipump is implanted. The values during the administration of the active ingredients are 24 hour mean values. On the 14th day the minipumps are removed and observation of the effects is continued for 7 days after the administration of the active ingredients is discontinued.

These studies show that the non-combined administration of 1.5 mg/kg/day of benazepril and valsartan results in a lowering of the blood pressure of about 20 mm Hg. In contrast, the combined administration of 1.5 mg/kg/day of benazepril and 1.5 mg/kg/day of valsartan results in a potential lowering of the blood pressure of about 50 mg Hg. In addition, a prolonged constant duration of efficacy of up to 16 hours and a reduced, but still significant, duration of efficacy of at least up to 21 hours is achieved.

Additional experiments carried out with spontaneously hypertensive rats using radiotelemetry evaluating chronic effects on mean arterial blood pressure show following results:

Compound	Dose [mg/kg/day]	AUC [mmHg]	SEM
benazepril	0.5 (N=7)	- 64	6
	0.75 (N=6)	-136	11
	1.0 (N=7)	-244	30
	1.5 (N=5)	-213	28
	3.0 (N=7)	-341	20
	10.0 (N=7)	-581	18
valsartan	0.5 (N=7)	- 62	16
	0.75 (N=7)	-107	6
	1.0 (N=7)	-115	19
	1.5 (N=6)	-195	8
	3.0 (N=7)	-226	21
	10.0 (N=7)	-425	38
benazepril/ valsartan	0.5 (N=6)	-221	21
	0.75 (N=6)	-329	20
	1.0 (N=5)	-470	31
	1.5 (N=5)	-609	23
0.15N NaOH vehicle	(N=6) (N=7) (N=6) (N=7) (N=4)	1 10 -23 4 -11	11 9 16 13 14
1N $NaHCO_3$	(N=7)	-61	15

[AUC = area under the curve (mmHg) since all values are recorded over 14 days, days (time) are factored out]
[SEM = standard error of means]

These results clearly underline that the AUC values, for example, of 1 mg/kg/day for the combination of benazepril and valsartan is dramatically higher than the additive values of 0.5 mg/kg/day of both benazepril and valsartan. Correspondingly, the same effect can be taken from other values.

In the remnant kidney model in the rat, the combination of valsartan and benazepril proves to be more renal protective than either individual therapy. This model involves removal of the right kidney and ligation of 2-3 branches of the left renal artery effectively resulting in 1/6 functional renal mass. Marked proteinuria, loss of tubular electrolyte reabsorptive capacity and dramatic elevations in systolic blood pressure ensues. Drug(s) are administered subcutaneously (via osmotic minipump) one week following surgery at which time the animals are in progressive, chronic renal failure. The animals remain on treatment for 6 weeks. The combination of valsartan + benazepril (Val+Bz) is given at doses of 1.0 mg/kg/day and 3.0 mg/kg/day of each agent. Individually, benazepril or valsartan at these doses are without effect or slightly improve renal function compared to vehicle treated animals. Val+Bz almost normalizes systolic blood pressure to pre-ablation levels, reduces proteinuria and greatly improves tubular function (as indicated by changes in the fractional excretions of sodium).

Likewise, a synergistic effect of a combination of valsartan and benazepril in congestive heart failure can be manifested, for example, in an animal model in which congestive heart failure can be induced by atrial pacing. Chronic rapid heart pacing in the pig is a well-accepted model of congestive heart failure. A dose of benazeprilate (0.15 mg/kg/day) or valsartan (2.4 mg/kg/day) is selected to block the Ang I and Ang II pressure response by 50 % without altering resting blood pressure. For the combination treatment (benazeprilate/valsartan 0.04/2.4 mg/kg/day) , it is necessary to reduce the dose of benazeprilate from monotherapy in order to prevent a significant fall in resting blood pressure. For comparative purposes, age matched pigs undergo chronic pacing without treatment as well as sham controls. Following 21 days of concomitant treatment and pacing tachycardia, terminal studies are performed in which left ventricular (LV) function and geometry are performed, neurohormonal profiles, isolated myocyte contractile function, β adrenergic response and electrophysiology are examined. Chronic rapid pacing and

concomitant ACE inhibition reduce the LV and diastolic dimension, significantly improve LV pump function and reduce the levels of circulating catecholamines. Ang II receptor blockade with valsartan improves cardiac output and decreases pulmonary and systemic vascular resistence. In contrast, combined benazeprilate and valsartan significantly provide further beneficial effects on LV geometry, function and neurohormonal activation including endothelin plasma levels Moreover, such a combination reduces LV wall stress and pulmonary and vascular resistance, important indices of myocardial oxygen consumption and LV afterload, to a greater degree than that of ACE inhibition alone. There is also an enhanced myocytes β adrenergic and calcium response when compared to monotherapy with benazeprilate.

The available results indicate an unexpected beneficial effect of such a combination on blood pressure, renal blood flow and in congestive heart failure. The existence of alternative pathways responsible for the production of Ang II in the tissues may limit the effectiveness of ACE inhibitor treatment. On the other hand, ACE inhibition through an effect on bradykinin degradation, improved endothelium dependent vascular reactivity. The combination of ACE inhibition and Ang II antagonism therefore leads to a more complete blockade of the RAS and of the counter-regulatory mechanism mediated by Ang II itself. Accordingly, the reduction of the dosing and therefore of the probability of side-effects is also expected. This may be of importance in situations where renal function is extremely renin dependent.

It is the object of this invention to provide a pharmaceutical combination composition for the treatment of hypertension, congestive heart failure and renal failure, which composition comprises (1) the ACE-inhibitor benazepril or benazeprilat or a pharmaceutically acceptable salt thereof and (2) the AT_1-antagonists valsartan or a pharmaceutically acceptable salt thereof. In this composition, components (1) and (2) can be present and administered together, one after the other or separately in one combined unit dose form or in two separate unit dose forms.

Said pharmaceutical compositions are those for enteral, such as oral, and also rectal or parenteral administration to warm-blooded animals, the pharmacological active ingredient being present on its own or together with the usual pharmaceutical excipients. The pharmaceutical compositions contain, for example, from about 0.1 % to 100 %, preferably from about 1 % to about 80 %,

of the active ingredient. Pharmaceutical compositions for enteral or parenteral and also for ocular administration are typically those in unit dose forms, such as dragées, tablets, capsules or suppositories and also ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilising methods. Accordingly, pharmaceutical compositions for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary after the addition of suitable excipients, to give tablets or dragée cores.

Suitable carriers are preferably fillers, typically sugars, such as lactose, saccharose, mannitol or sorbitol, cellulose compositions and/or calcium phosphates, e.g. tricalcium phosphate or calciumhydrogen phosphate, furthermore binders, such as starch paste, typically using e.g. corn starch, wheat starch, rice starch or potato starch, gelatin, tragacanth gum, methylcellulose and/or polyvinylpyrrolidone and, if desired, disintegrants, such as the above-mentioned starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, typically sodium alginate. Excipients are primarily flow regulators and lubricants, typically silica gel, talcum, stearic acid or salts thereof, typically magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings which, if desired, are resistant to gastric juice, using, inter alia, concentrated sugar solutions which optionally contain gum arabic, talcum, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of gastric juice-resistant coatings, solutions of suitable cellulose compositions, typically acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourants or pigments may be added to the tablets or dragée coatings, for example to identify or indicate different doses of active ingredient.

Other pharmaceutical compositions for oral administration are dry-filled gelatin capsules as well as soft closed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, typically in admixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talcum or magnesium stearate. In soft capsules, the active ingredient is preferably dissolved or suspended in

suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, and stabilisers can also be added.

Suitable pharmaceutical compositions for rectal administration are typically suppositories consisting of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons and higher alkanols. Furthermore, gelatin rectal capsules containing a combination of the active ingredient with a base substance may also be used. Suitable base substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable compositions for parenteral administration are primarily aqueous solutions of an active ingredient in water-soluble form, typically a water-soluble salt, and also suspensions of the active ingredient, such as appropriate oily injection suspensions, using suitable lipophilic solvents or vehicles, typically fatty oils, e.g. sesame oil, or synthetic fatty acid esters, typically ethyl oleate or triglycerides, or aqueous injection suspensions containing viscosity-increasing substances, e.g. sodium carboxymethylcellulose, sorbitol and/or dextran and, optionally, also stabilisers.

It is preferred to use unit dose forms that can be used for oral administration, typically tablets or capsules.

The dose of the active ingredient can depend on various factors, e.g. mode of application, species of warm-blooded animal, age and/or individual state. The estimated normal dose for oral administration to a patient weighing about 75 kg is an approximate dose of the active ingredient component (1) [benazepril or a pharmaceutically acceptable salt therof] of about 5 mg to about 40 mg and of the active ingredient component (2) [valsartan or a pharmaceutically acceptable salt thereof] of about 20 mg to about 160 mg, preferably once or twice a day.

The weight ratio of the active ingredient component (1) to the active ingredient component (2) can be, for example, about 1 to 8 and also 1 to 4 or 1 to 2.

The novel combination compositions can comprise as active ingredient component (1) preferably about 10 mg to about 40 mg, more preferably 10 mg to about 20 mg and, most preferably, 10 mg.

The novel combination compositions can comprise as active ingredient component (2) preferably about 20 mg to about 80 mg, more preferably about 40 mg to about 80 and, most preferably, about 40 mg or 80 mg.

In a preferred embodiment of this invention pharmaceutically acceptable combination compositions are used consisting of benazepril monohydrochloride and valsartan in a unit dose form. The amount of ACE-inhibitor therein is preferably 10 mg and the amount of AT_1-antagonist is preferably 40 mg or 80 mg.

In the compositions of this invention the active ingredient components (1) and (2) can be obtained together, one after the other or separately in one combined unit dose form or in two separate unit dose forms. They are preferably obtained together in one combined unit dose form.

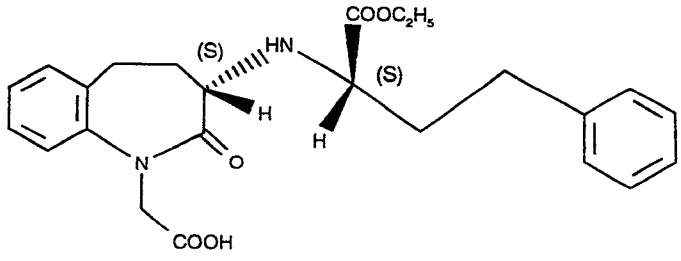
The novel pharmaceutical combination can be used for a method for the treatment of hypertension and congestive heart failure.

The method for the treatment of hypertension, congestive heart failure and renal failure comprises administering to a patient in need of such treatment a corresponding pharmaceutical combination composition according to this invention, comprising (1) the ACE-inhibitor benazepril or benazeprilat or a pharmaceutically acceptable salt thereof and (2) the AT_1-antagonists valsartan or a pharmaceutically acceptable salt thereof..

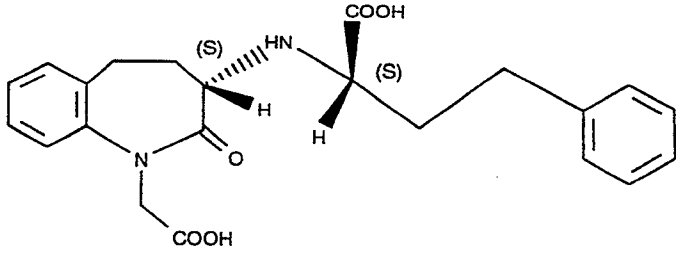
This invention also relates to the preparation of the novel pharmaceutical combination compositions.

What is claimed is

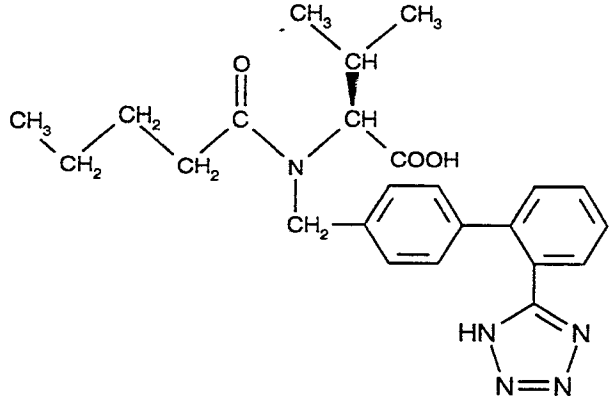
1. A pharmaceutical combination composition for the treatment of hypertension, congestive heart failure and renal failure, comprising
(1) the ACE-inhibitor benazepril of formula



or benazeprilat of formula



or a pharmaceutically acceptable salt thereof, and
(2) the AT_1-antagonist valsartan of formula



or a pharmaceutically acceptable salt thereof.

2. A composition according to claim 1, wherein the active ingredient component (1) is benazepril monohydrochloride and the active ingredient component (2) is valsartan.

3. A composition according to either claim 1 or claim 2, comprising about 5 mg to about 40 mg of the active ingredient component (1).

4. A composition according to claim 3, comprising about 10 mg to about 40 mg of the active ingredient component (1).

5. A composition according to claim 3, comprising about 10 mg or about 20 mg of the active ingredient component (1).

6. A composition according to claim 3, comprising abount 10 mg of the active ingredient component (1).

7. A composition according to any one of claims 1-6, comprising about 20 mg to about 160 mg of the active ingredient component (2).

8. A composition according to claim 7, comprising about 20 mg to about 80 mg of the active ingredient component (2).

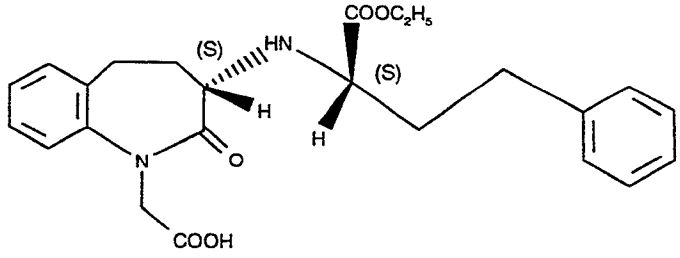
9. A composition according to claim 7, comprising about 40 mg or about 80 mg of the active ingredient component (2).

10. A composition according to any one of claims 1-9, comprising about 10 mg of the active ingredient component (2) and about 40 mg or about 80 mg of the active ingredient component (1).

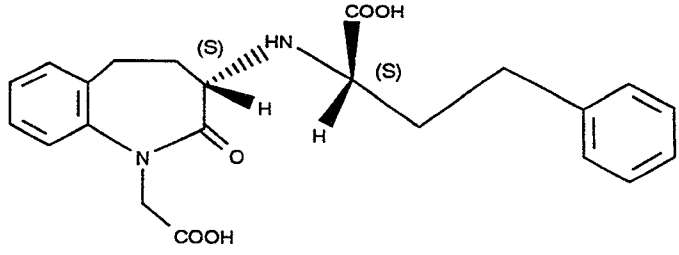
11. A composition according to claim 1, wherein components (1) and (2) are present together, one after the other or separately in one combined or in two separate unit dose forms.

12. A method for the treatment of hypertension, congestive heart failure and renal failure, which comprises administering to a patient in need of such treatment a combination of

(1) the ACE-inhibitor benazepril of formula

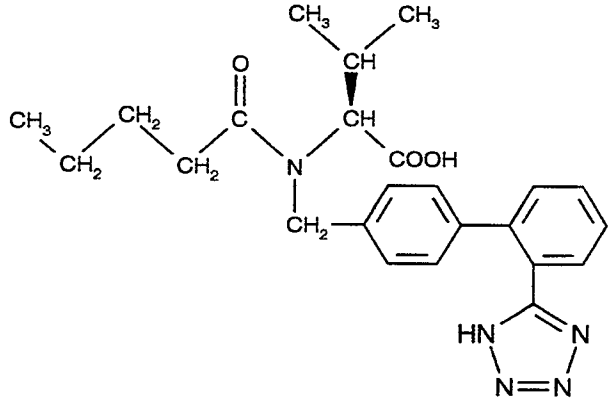


or benazeprilat of formula



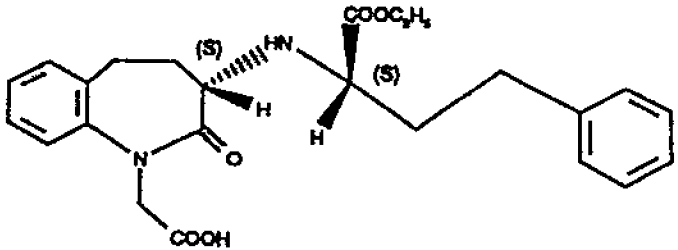
or a pharmaceutically acceptable salt thereof, and

(2) the AT_1-antagonist valsartan of formula



or a pharmaceutically acceptable salt thereof.

13. A method according to claim 12, wherein components (1) and (2) are administered together, one after the other or separately in one combined or in two separate unit dose forms.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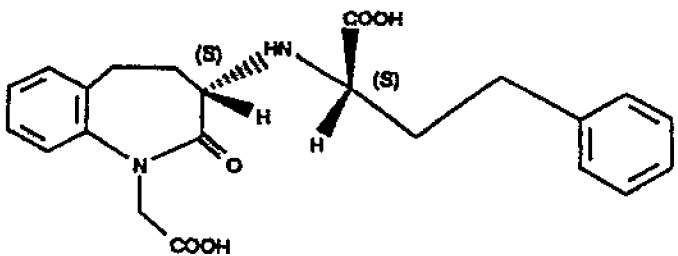
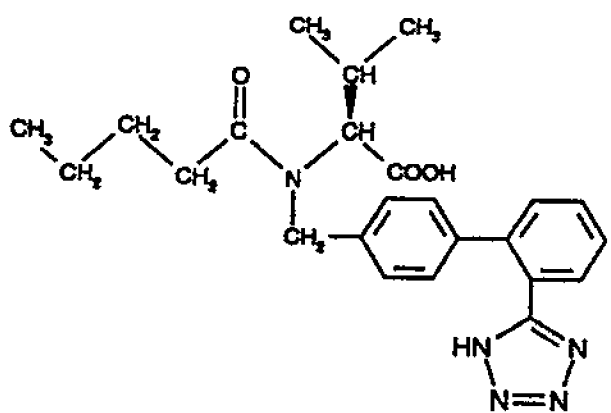
(S)
HN
(S)
H
H
O
N
COOH

(I)


COOH
(S)
HN
(S)
H
H
O
N
COOH

(II)


CH3
CH3
CH
O
C
CH
CH2
CH2
CH2
CH3
N
COOH
CH2
HN
N
N=N

(III)