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(54) Title: COMBINATION OF ORGANIC COMPOUNDS

(57) Abstract: The present invention relates to a combination of organic compounds, a pharmaceutical composition and a kit of parts comprising said combination of organic compounds and to a method of treatment or prevention of certain conditions or diseases.

Combination of Organic Compounds

The present invention relates to a combination of organic compounds that are antihypertensive agents with complementary modes of action for eliciting blood pressure-lowering, and also for attenuating the varied pathological sequelae of hypertension and several other cardiovascular disorders. Furthermore, this invention addresses the disparate responsiveness of humans to antihypertensive monotherapy, based on age and/or ethnicity *(Campo C, Segura J, Ruilope LM, J Clin Hypertens (Greenwich) 2002 Jan, 4(1):35-40).* Finally, the choice of agents and their respective dosages in the combination regimen are designed to enhance tolerability by minimizing the risk of dose-dependent adverse effects associated with individual agents.

Numerous clinical studies have shown that lowering blood pressure in hypertensive patients reduces mortality and morbidity (Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH, Lancet 1990, 335(8693):827-38). Despite the availability and use of various classes of agents in the treatment of this medical condition, adequate control of blood pressure is not always achieved (Waeber B, Brunner HR, Am J Hypertens 1997, 10(7 Pt 2):131S-137S). Using a combination of agents is one way to achieve the desired therapeutic end-point. An arbitrary selection of antihypertensive agents of different classes for inclusion in a combination therapy regimen does not necessarily help achieve target levels of blood pressure in hypertensive mammals including humans (MacGregor GA, Markandu ND, Banks RA, Bayliss J, Roulston JE, Jones JC, Br Med J (Clin Res Ed), 284(6317):693-6). Therefore, a need for further development of methods of treatment, combinations, and pharmaceutical compositions clearly exists.

Specifically, the present invention relates to pharmaceutical compositions comprising (i) an angiotensin receptor (Type 1, AT_1) blocker (ARB) selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731, and pharmaceutically acceptable salts thereof; (ii) a calcium channel blocker (CCB) selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, ryosidine, anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil, and

pharmaceutically acceptable salts thereof; and, (iii) a diuretic selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide, and pharmaceutically acceptable salts thereof where appropriate, i.e. if the diuretic compound is not already present as a pharmaceutically acceptable salt as e.g. in the case of hydrochlorothiazide; optionally in the presence of a pharmaceutically acceptable carrier. The invention further provides methods for treating hypertension and a variety of cardiovascular disorders enumerated below and their sequelae by administration of the pharmaceutical composition comprising (i) an angiotensin receptor blocker (ARB), (ii) a calcium channel blocker (CCB), (iii) and a diuretic to a mammal including humans.

Thus, the invention further relates to a pharmaceutical composition or a kit of parts, e.g. for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke which composition (or kit of part) comprises (i) an ARB selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731, or a pharmaceutically acceptable salt thereof; and (ii) a CCB selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, and ryosidine, which all belong to the group of dihydropyridines (DHPs) and the non-DHP CCBs anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil, or a pharmaceutically acceptable salt thereof; and (iii) a diuretic selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride,

spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide, or, where appropriate, a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

A further aspect of the present invention is a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, comprising administering a therapeutically effective amount of combination of (i) an ARB selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731, or a pharmaceutically acceptable salt thereof; and (ii) a CCB selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, and ryosidine, which all belong to the group of dihydropyridines (DHPs) and the non-DHP CCBs anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil, or a pharmaceutically acceptable salt thereof; and (iii) a diuretic selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide, or, where appropriate, a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

The invention also relates to combining separate pharmaceutical compositions in kit form. That is a kit combining two or three separate units: e.g. a pharmaceutical composition

comprising an ARB, an pharmaceutical composition comprising a CCB, and a pharmaceutical composition comprising a diuretic; or a pharmaceutical composition comprising an ARB and a diuretic, and a pharmaceutical composition comprising a CCB; or a pharmaceutical composition comprising a CCB and a diuretic, and a pharmaceutical composition comprising an ARB. Although the kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. parenteral valsartan formulation and oral amlodipine or hydrochlorothiazide formulations) or are administered at different dosage intervals, the administration of the single components of such a kit of parts may, without any restriction be effected simultaneously, sequentially or staggered with time.

In a preferred embodiment, the (commercial) product is a commercial package comprising as active ingredients the combination according to the present invention (in the form of two or three separate units of the components (i) to (iii)), together with instructions for its simultaneous, separate or sequential use, or any combination thereof, in the delay of progression or treatment of the diseases mentioned herein. A preferred commercial package, is where the ARB (i) and the diuretic (iii) are present in the form of Co-DIOVAN ®, or where the ACE inhibitor (i), the CCB (ii) and the diuretic (iii) are present in the form of Co-DIOVAN ® and NORVASC ®.

The pharmaceutical preparations of the present invention 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 compounds. Pharmaceutical preparations for enteral or parenteral 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, which 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 compounds 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 that are commercially available. Normally, in the case of oral administration, an approximate daily dose of from about 20 mg to about 900 mg of active agents, i.e. ARB plus CCB plus diuretic, is to be estimated e.g. for a patient of approximately 75 kg in weight.

In the present invention preferred ARBs are those agents that have been marketed, as e.g. valsartan and losartan. The same applies to the CCBs employed in the present invention, of which amlodipine and felodipine are preferred. The most preferred diuretic is hydrochlorothiazide (HCTZ).

Very surprisingly is the finding that, a combination of (i) an ARB, (ii) a CCB, and (iii) a diuretic and in particular a combination comprising valsartan, amlodipine and HCTZ achieves greater therapeutic effect than the administration of valsartan, amlodipine, or HCTZ alone or in a combination of two of these agents. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days). The aforementioned combination treatment also unexpectedly reduces blood pressure in hypertensive mammals in a smooth and sustained fashion. The trough:peak blood pressure ratio demonstrated by this combination is close to unity leading to a more homogenous blood pressure control during the inter-dosing period. The combined regimen is almost completely devoid of either orthostatic hypotension or first-dose hypotension, and incidences of rebound hypertension after cessation of treatment are very rare. It can be shown that combination therapy according to the invention results in lessening of pulse pressure in hypertensive mammals.

Furthermore, this combination therapy can ameliorate endothelial dysfunction and improve vascular compliance and distensibility in hypertensive mammals. It can also slow the progression of cardiac, renal and cerebral end-organ damage in these mammals. Further benefits 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 to diminish the incidence of side effects. Surprisingly, the combination of valsartan, amlodipine and HCTZ significantly reduce the incidences of peripheral edema relative to those observed in mammals treated with amlodipine alone. Also, the undesirable effects of HCTZ on serum lipids, glucose, and uric acid levels are surprisingly attenuated in mammals treated with the combined regimens of valsartan, amlodipine and HCTZ.

In particular the combined administration of valsartan or a pharmaceutically acceptable salt thereof, amlodipine or a pharmaceutically acceptable salt thereof, and HCTZ results in a significant response in a greater percentage of treated patients compared to monotherapy or combination therapy e.g. valsartan and HCTZ, that is, a greater responder rate results, regardless of the underlying etiology of the condition. This is in accordance with the desires and requirements of the patients to be treated. The combination treatment effectively lowers blood pressure in hypertensive patients in all age groups including pre and postmenopausal women. It can be shown that combination therapy with valsartan, amlodipine, and HCTZ results in a more effective antihypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type of hypertension) and lessening of pulse pressure through improved efficacy. The combination is also useful in the treatment or prevention of heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling. It can further be shown that a valsartan, amlodipine, and HCTZ combination therapy proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A valsartan, amlodipine, and HCTZ combination is also useful in treating atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), peripheral vascular disease, cognitive dysfunction, and stroke. Furthermore, the improvement in endothelial function with the combination therapy using valsartan, amlodipine, and HCTZ provides benefit in diseases in which normal endothelial function is disrupted such as heart failure, angina pectoris and diabetes. Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral

vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke. The combination regimen also surprisingly reduces the rate of progression of cardiac, renal and cerebral end-organ damage. By providing enhanced efficacy, safety and tolerability, the combination of drugs indicated in this invention also has the potential to promote patient compliance, a major consideration in the pharmacological treatment of hypertension.

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the herein before and hereinafter indicated therapeutic indications.

The advantages of the present combinations are, for example, demonstrated in a clinical study or in the test procedure as essentially described hereinafter. Many clinical study protocols adapted to test our combinations are known by the person skilled in the art. An example of a clinical trial useful to demonstrate the unexpected advantages of our new combinations is described by Waeber B et al. (J Hypertens. 2001 Nov;19(11):2097-104. The same protocol is performed with our preferred combinations such as a combination, preferably fixed-dose combination, of valsartan 80mg, hydrochlorothiazide 12.5 mg, and amlodipine 5 mg. This protocol is hereby incorporated into the present application by reference to this publications.

Representative studies are carried out with a combination of valsartan, amlodipine, and HCTZ applying the following methodology. Drug efficacy is assessed in various animal models including the deoxycorticosterone acetate - salt rat (DOCA-salt) and the spontaneously hypertensive rat (SHR), either maintained on a normal salt diet or with salt loading (4-8% salt in rat chow or 1% NaCl as drinking water).

The DOCA-salt test model utilizes either an acute or chronic study protocol. An acute study procedure involves assessment of the effects of various test substances over a six-hour experimental period using rats with indwelling femoral arterial and venous catheters. The Acute Study Procedure evaluates test substances for their ability to reduce blood pressure during the established phase of DOCA-salt hypertension. In contrast, the Chronic Study Procedure assesses the ability of test substances to prevent or delay the rise in blood pressure during the development phase of DOCA-salt hypertension. Therefore, blood

pressure will be monitored in the chronic study procedure by means of a radiotransmitter. The radiotransmitter is surgically implanted into the abdominal aorta of rats, prior to the initiation of DOCA-salt treatment and thus, prior to the induction of hypertension. Blood pressure is chronically monitored for periods of up 6 weeks (approximately one week prior to DOCA-salt administration and for 5 weeks thereafter).

Rats are anesthetized with 2-3% isoflurane in oxygen inhalant followed by Amytal sodium (amobarbital) 100 mg/kg, ip. The level of anesthesia is assessed by a steady rhythmic breathing pattern.

Acute study procedure:
Rats undergo a unilateral nephrectomy at the time of DOCA implantation. Hair is clipped on the left flank and the back of the neck and scrubbed with sterile alcohol swabs and povidone/iodine. During surgery rats are placed on a heating pad to maintain body temperature at 37 °C.

A 20 mm incision is made through the skin and underlying muscle to expose the left kidney. The kidney is freed of surrounding tissue, exteriorized and two ligatures (3-0 silk) are tied securely around the renal artery and vein proximal to their juncture with the aorta. The renal artery and vein are then severed and the kidney removed. The muscle and skin wounds are closed with 4-0 silk suture and stainless steel wound clips, respectively. At the same time, a 15 mm incision is made on the back of the neck and a 3-week-release pellet (Innovative Research of America, Sarasota, Florida) containing deoxycorticosterone acetate (100 mg/kg) is implanted subcutaneously. The wound is then closed with stainless-steel clips and both wounds are treated with povidone/iodine; the rats are given a post-surgical intramuscular injection of procaine penicillin G (100,000 U) and buprenorphine (0.05 – 0.1 mg/kg) s.c. The rats are immediately placed on 1% NaCl + 0.2% KCl drinking water; this treatment continues for at least 3 weeks at which time the animals have become hypertensive and available for experimentation.

Forty-eight hours prior to experimentation, animals are anesthetized with isoflurane and catheters are implanted in the femoral artery and vein for measuring arterial pressure, collection of blood, and administration of test compounds. Rats are allowed to recover for 48

hours while tethered in a Plexiglas home cage, which also serves as the experimental chamber.

Chronic study procedure:
This procedure is the same as above except that rats are implanted with a radiotransmitter, 7-10 days prior to the unilateral nephrectomy and initiation of DOCA and salt. In addition, rats do not undergo surgery for placement of femoral arterial and venous catheters. Radiotransmitters are implanted as described in M.K. Bazil, C. Krulan and R.L. Webb. Telemetric monitoring of cardiovascular parameters in conscious spontaneously hypertensive rats. J.Cardiovasc. Pharmacol. 22: 897-905, 1993.

Protocols are then set-up on the computer for measurement of blood pressure, heart rate, etc, at predetermined time points. Baseline data is collected at various time points and over various time intervals. For example, baseline or pre-dose values usually consist of data collection and averaging over 3 consecutive, 24-hour time periods prior to drug administration.

Blood pressure, heart rate and activity are determined at various pre-selected time points before, during, and after drug administration. All measurements are performed in unrestrained and undisturbed animals. The maximum study time, determined by battery life, could be as long as nine months. For studies of this duration, rats are dosed orally (1-3 ml/kg vehicle), no more than twice daily or drug is administered via the drinking water or mixed with food. For studies of a shorter duration, that is, up to 8 weeks, drugs are given via subcutaneously implanted osmotic minipumps. Osmotic minipumps are selected based on drug delivery rate and time. Valsartan dosages range from 1 to 100 mg/kg/day, amlodipine dosages range from 1 to 75 mg/kg/day, and HCTZ dosages range from 1 to 75 mg/kg/day.

Additionally, SHR are utilized to study the effects of valsartan in combination with amlodipine, and HCTZ. The hypertensive background of the SHR is modified either by chronic salt loading in an effort to suppress the RAAS or chronic salt depletion to activate the RAAS in the SHR. These manipulations will be carried out to more extensively evaluate the efficacy of the various test substances. Experiments are performed in spontaneously hypertensive rats (SHR) supplied by Taconic Farms, Germantown, New York (Tac:N(SHR)fBR). A radiotelemetric device (Data Sciences International, Inc., St. Paul,

Minnesota) is implanted into the lower abdominal aorta of all test animals between the ages of 14 to 16 weeks of age. All SHR are allowed to recover from the surgical implantation procedure for at least 2 weeks prior to the initiation of the experiments. Cardiovascular parameters are continuously monitored via the radiotransmitter and transmitted to a receiver where the digitized signal is then collected and stored using a computerized data acquisition system. Blood pressure (mean arterial, systolic and diastolic pressure) and heart rate are monitored in conscious, freely moving and undisturbed SHR in their home cages. The arterial blood pressure and heart rate are measured every 10 minutes for 10 seconds and recorded. Data reported for each rat represent the mean values averaged over a 24 hour period and are made up of the 144-10 minute samples collected each day. The baseline values for blood pressure and heart rate consist of the average of three consecutive 24 hour readings taken prior to initiating the drug treatments. All rats are individually housed in a temperature and humidity controlled room and are maintained on a 12 hour light dark cycle.

In addition to the cardiovascular parameters, weekly determinations of body weight also are recorded in all rats. Treatments are administered in the drinking water, via daily oral gavage or in osmotic minipumps as stated above. If given in drinking water, water consumption is measured five times per week. Valsartan, amlodipine, and HCTZ doses for individual rats are then calculated based on water consumption for each rat, the concentration of drug substance in the drinking water, and individual body weights. All drug solutions in the drinking water are made up fresh every three to four days. Typical dosages for valsartan in drinking water range from 1 to 100 mg/kg/day, dosages of amlodipine range from 1 to 75 mg/kg/day, and dosages of HCTZ range from 1 to 75 mg/kg/day. In most situations, a daily dose will not exceed 100 mg/kg/day when administered as the monotherapy. In combination, lower dosages of each agent are used and correspondingly, valsartan is given in the range of 1 to 30 mg/kg/day, and amlodipine and HCTZ are give in dosages below 50 mg/kg/day.

When drugs are administered by oral gavage, the dose of valsartan ranges from 1 to 50 mg/kg/day and that of amlodipine and HCTZ does not exceed 75 mg/kg/day, respectively.

Upon completion of the chronic studies, SHR or DOCA-salt rats are anesthetized, blood samples obtained for biochemical analysis and the heart rapidly removed. After separation and removal of the atrial appendages, left ventricle and left plus right ventricle (total) are

weighed and recorded. Left ventricular and total ventricular mass are then normalized to body weight and reported.

Vascular function and structure are evaluated after treatment to assess the beneficial effects of the combination. SHR are studied according to the methods described by Intengan HD, Thibault G, Li JS, Schiffrin EL, Circulation 1999, 100 (22): 2267-2275. Similarly, the methodology for assessing vascular function in DOCA-salt rats is described in Intengan HD, Park JB, Schiffrin, EL, Hypertension, 1999, 34(4 Part 2): 907-913. Assessment of vascular compliance and distensibility following treatment with the combination regimen is performed according to the methods described by Ceiler DL, Nelissen-Vrancken HJ, De Mey JG, Smits JF, J Cardiovasc Pharmacol 1998, 31(4):630-7. Amelioration of cardiac, renal, and cerebral injury secondary to hypertension is assessed after treatment with the combination regimen in salt-loaded stroke-prone spontaneously hypertensive rats according to the methods described by Nagura J, Yamamoto M, Hui C, Yasuda S, Hachisu M, Konno F, Clin Exp Pharmacol Physiol 1996, 23(3):229-35. Propensity of the combination therapy to elicit postural or orthostatic hypotension is assessed in SHRs by the methods described by Nabata H, Aono J, Ishizuka N, Sakai K, Arch Int Pharmacodyn Ther 1985, 277(1):104-18. Tendency to produce peripheral edema by the combination regimen was assessed by the methods described by Lacolley P, Poitevin P, Koen R, Levy BI, J Hypertens 1998, 16(3):349-55.

Valsartan is 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 or 640 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 or 640 mg daily. Preferably, valsartan is applied once a day or twice a day in heart failure patients 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 q.d. or b.i.d. administration in heart failure.

In case of amlodipine, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 1 mg to about 60 mg, preferably 2.5 to 20 mg, more preferably between 2.5 and 10 mg daily when administered orally.

In case of HCTZ, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 5 mg to about 200 mg preferably from about 50 mg to about 150 mg, even more preferably from about 25 mg to about 100 mg and even more preferably from about 5 mg to about 25 mg, administered orally once a day.

An example of a preferred composition, comprises an amount of Valsartan between 60 and 100 mg e.g. 80 mg, an amount of amlodipine between 2 and 12 mg e.g. 2.5 or 5 mg and an amount of HCTZ between 8 and 16 mg e.g. 12.5 mg.

Another example of a preferred composition, comprises an amount of Valsartan between 140 and 180 mg e.g. 160 mg, an amount of amlodipine between 2 and 12 mg e.g. 2.5 or 5 or 10 mg and an amount of HCTZ between 8 and 16 mg e.g. 12.5 mg.

Another example of a preferred composition comprises an amount of Valsartan between 140 and 180 mg e.g. 160 mg, an amount of amlodipine between 4 and 12 mg e.g. 5 mg or 10 mg, and an amount of HCTZ between 20 and 30 mg e.g. 25 mg.

The combination of (i) an ARB, (ii) a CCB, and (iii) a diuretic may, according to the present invention be manufactured and administered in free or fixed dose combinations of the respective pharmaceutically active agents. It may be advantageous to begin the treatment with free combinations that allow an easy adjustment of the administered dose of each individual agent. When the ideal dose regimen, which generally is dependent on the specific condition of the individual to be treated, the individuals weight, other medication administered to the individual and the like, is reached, a fixed dose combination may be administered in case where an administration once a day or e.g. twice or three times daily is possible and a sufficient control of blood pressure is achieved.

Presently it is preferred to combine two of the components (i) to (iii) and administer the third separately at the same or at a different time.

Valsartan is being marketed under the trade name Diovan®. A combination of valsartan and HCTZ is being marketed under the trade name Co-Diovan® and amlodipine is being

marketed under the trade name Norvasc®. All of these marketed products may be utilized in as such for combination therapy according to the present invention.

The following examples illustrate the invention described above and are not intended to restrict the scope of this invention in any way.

Formulation Example 1:

Composition and batch quantities for Diovan® tablets

Components	COMPOSITION PER UNIT (mg)				QUANTITY PER BATCH[1] (kg)			
Granulation	**40mg**	**80mg**	**160mg**	**320mg**	**40mg**	**80mg**	**160mg**	**320mg**
Diovan Drug Substance	40.000	80.000	160.000	320.000	144.000	144.000	144.000	144.000
Microcrystalline Cellulose(NF,Ph.Eur.) Avicel PH102	27.000	54.000	108.000	216.000	97.200	97.200	97.200	97.200
Crospovidone (NF,Ph.Eur.)	7.500	15.000	30.000	60.000	27.000	27.000	27.000	27.000
Colloidal Anhydrous Silica (Ph.Eur.)/Colloidal silicon Dioxide (NF)/Aerosil 200	0.750	1.500	3.000	6.000	2.700	2.700	2.700	2.700
Magnesium Stearate (NF,Ph.Eur.)	1.500	3.000	6.000	12.000	5.400	5.400	5.400	5.400
Blending								
Magnesium Stearate (NF,Ph.Eur.)	0.750	1.500	3.000	6.000	2.700	2.700	2.700	2.700
Coating								
DIOLACK Gelb F32892	2.800				11.090[2]			
DIOLACK Blassrot F34899		6.000				12.420[3]		
DIOLACK Hellbraun F33172			9.000				9.720[4]	
DIOLACK Braun F16711				16.000				8.640[4]
Purified Water					62.843	70.380	55.080	48.960
Total Tablet/Batch Weight	80.300	161.000	319.000	636.000	289.080	289.800	287.100	286.200

[1]A total of 2 subdivisions of granulation per batch
[2]A 10% excess of coating solution was manufactured to account for loss during coating.
[3]A 15% excess of coating solution was manufactured to account for loss during coating.
[4]A 20% excess of coating solution was manufactured to account for loss during coating.

Composition of Diolack

DIOLACK	HPMC USP/Ph.Eur (603)	PEG 8000 USP/Ph.Eur.	Titanium Dioxide (White) USP/Ph.Eur	Iron Oxide (Red) Ph.Fr./NF/ E172/CFR/ CI 77491	Iron Oxide (Yellow) Ph.Fr./NF/ E172/CFR/ CI 77492	Iron Oxide (Brown) Mixture of iron oxide red & black	Iron Oxide (Black) E172/CFR/ CI 77499
Gelb F32892	80.00 %	4.00 %	13.48 %	0.01 %	2.50 %	–	0.01 %
Blassrot F34899	80.00 %	4.00 %	15.50 %	0.40 %	0.10 %	–	–
Hellbraun F33172	80.00 %	4.00 %	9.34 %	0.25 %	6.40 %	–	0.01 %
Braun F16711	80.00 %	4.00 %	14.00 %	0.50 %	0.50 %	0.50 %	0.50 %

A mixture of Diovan drug substance, 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 sieved through a screening mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compacter and then sieved 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 tablets are coated with a film by using the appropriate composition of Diolack in a perforated pan.

Formulation Example 2:

Composition and quantities for Co-Diovan® tablets

Components	COMPOSITION PER UNIT (mg)	COMPOSITION PER UNIT (mg)	COMPOSITION PER UNIT (mg)
Granulation			
Diovan Drug Substance	80.000	160.000	160.00
Esidrex Drug Substance (micro)	12.500	12.500	25.00
Microcrystalline Cellulose (NF, Ph.Eur.)/ Avicel PH 102	31.500	75.500	63.00
Crospovidone (NF, Ph.Eur.)	20.000	40.000	40.00
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	1.500	3.00	3.00
Magnesium Stearate (NF, Ph.Eur.)	3.000	6.000	6.00
Blending			
Magnesium Stearate, NF, Ph.Eur.	1.500	3.000	3.00
Coating			
Opadry Black OOF17713	-	-	0.096
Opadry Red OOF15613	-	-	0.762
Opadry Yellow OOF12951	-	-	3.808
Opadry White OOF18296	-	-	5.334
Hydroxy propyl Methylcellulose	2.76	5.510	-
Iron Oxide Yellow	0.025	-	-
Iron Oxide Red	0.025	0.750	-
Polyethylene Glycol 8000	0.50	1.000	-
Talc	2.000	3.990	-
Titanium Dioxide	0.70	0.750	-
Total Tablet/Batch Weight	156.000	312.000	310.00

Composition of Opadry

OPADRY	HPMC USP/Ph.Eur (603)	PEG 4000 USP/Ph.Eur.	Talc USP/Ph.Eur	Titanium Dioxide USP/Ph.Eur (White)	Iron Oxide (Red) Ph.Fr./NF/ E172/CFR/ CI 77491	Iron Oxide (Yellow) Ph.Fr./NF/ E172/CFR/ CI 77492	IronOxide (Black) E172/CFR/ CI 77499
Opadry White OOF18296*	71.4 %	7.15 %	7.15 %	14.3 %	-	-	-
Opadry Red OOF15613*	71.4 %	7.15 %	7.15 %	-	14.3 %	-	-
Opadry Red OOF15613*	71.4 %	7.15 %	7.15 %	-	-	14.3 %	-
Opadry Black OOF17713*	71.4 %	7.15 %	7.15 %	-	-	-	14.3 %

A mixture of Diovan drug substance, Esidrex drug substance (micro), microcrystalline cellulose, crospovidone, colloidal anhydrous silica/Aerosil 200 and part of the magnesium stearate is premixed in a diffusion mixer and then sieve through a screening mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compacter and then sieved through a screening mill. The final blend is made in a diffusion mixer under addition of the remaining part of the magnesium stearate, which is hand screened before. The whole mixture is compressed in a rotary tabletting machine and the tablets are coated with a film by using the appropriate composition of Opadry in a perforated pan.

Formulation Example 3:

Composition and quantities for a combination of valsartan and amlodipine

Components	COMPOSITION PER UNIT (mg)	COMPOSITION (%)
Diovan Drug Substance	80.00	43.02
Amlodipine Drug Substance	6.94	3.73
Avicel 102 (I)	54.00	29.04
Avicel 102 (II)	20.00	10.76
Crospovidone (I)	15.00	8.07
Crospovidone (II)	4.0	2.15
Cab-O-Sil	1.50	0.81
Magnesium Stearate (I)	3.00	1.61
Magnesium Stearate (II)	1.50	0.81
	185.94	100.00

The tablet is manufactured e.g essentially as described in Formulation Example 1.

What is claimed is:

1. A pharmaceutical composition comprising
(i) an angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof,
(ii) a calcium channel blocker (CCB) or a pharmaceutically acceptable salt thereof, and
(iii) a diuretic or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition according to claim 1, wherein (i) the angiotensin receptor blocker (ARB) is selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731; (ii) the calcium channel blocker (CCB) is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, ryosidine, anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil; and (iii) the diuretic is selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide.

3. A pharmaceutical composition according to claim 2, wherein (i) the angiotensin receptor blocker (ARB) is valsartan; (ii) the calcium channel blocker (CCB) is amlodipine; and (iii) the diuretic is hydrochlorothiazide.

4. A pharmaceutical composition according to claim 3, wherein valsartan is contained in an amount from about 20 to about 640 mg, amlodipine is contained in an amount from about 1 mg to about 60 mg, and hydrochlorothiazide is contained in an amount from about 5 mg to about 200 mg.

5. A pharmaceutical composition according to claim 4, wherein valsartan is contained in an amount from about 40 to about 320 mg, amlodipine is contained in an amount from

about 2.5 mg to about 10 mg, and hydrochlorothiazide is contained in an amount from about 5 mg to about 25 mg.

6. A kit of parts comprising
   (i) a pharmaceutical composition of an angiotensin receptor blocker (ARB),
   (ii) a pharmaceutical composition of a calcium channel blocker (CCB), and
   (iii) a pharmaceutical composition of a diuretic
   in the form of two or three separate units of the components (i) to (iii).

7. A kit of parts according to claim 6, wherein (i) the angiotensin receptor blocker (ARB) is selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731; (ii) the calcium channel blocker (CCB) is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, ryosidine, anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil; and (iii) the diuretic is selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide.

8. A kit of parts according to claim 7, wherein (i) the angiotensin receptor blocker (ARB) is valsartan; (ii) the calcium channel blocker (CCB) is amlodipine; and (iii) the diuretic is hydrochlorothiazide.

9. A kit of parts according to claim 8, wherein valsartan is contained in an amount from about 20 to about 640 mg, amlodipine ins contained in an amount from about 1 mg to about 60 mg, and hydrochlorothiazide is contained in an amount from about 5 mg to about 200 mg.

10. A kit of parts according to claim 9, wherein valsartan is contained in an amount from about 40 to about 320 mg, amlodipine ins contained in an amount from about 2.5 mg to about 10 mg, and hydrochlorothiazide is contained in an amount from about 5 mg to about 25 mg.

11. A method of treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, comprising administering a therapeutically effective amount of combination of (i) an ARB selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, olmesartan, saprisartan, tasosartan, telmisartan, valsartan, E-4177, SC-52458, and ZD8731, or a pharmaceutically acceptable salt thereof; and (ii) a CCB selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, and ryosidine, which all belong to the group of dihydropyridines (DHPs) and the non-DHP CCBs anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil, and verapamil, or a pharmaceutically acceptable salt thereof; and (iii) a diuretic selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, metolazone, and dichlorphenamide, or, where appropriate, a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

12. A commercial package comprising

(i) a pharmaceutical composition of an angiotensin receptor blocker (ARB),

(ii) a pharmaceutical composition of a calcium channel blocker (CCB), and

(iii) a pharmaceutical composition of a diuretic,

in the form of two or three separate units of the components (i) to (iii),

together with instructions for simultaneous, separate or sequential use thereof for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke

13. A commercial package according to claim 12, wherein (i) the angiotensin receptor blocker (ARB) is valsartan; (ii) the calcium channel blocker (CCB) is amlodipine; and (iii) the diuretic is hydrochlorothiazide.

14. A commercial package according to claim 13, wherein the angiotensin receptor blocker (ARB) (i) and the diuretic (iii) are present in the form of Co-DIOVAN ® or wherein the angiotensin receptor blocker (ARB) (i), the CCB (ii) and the diuretic (iii) are present in the form of Co-DIOVAN ® and Norvasc ®.

15. The use of a combination according to any one of claims 1 to 5, or a kit of parts according to any one of claims 6 to 10, for the manufacture of a medicament for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy,

glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke.

16. The use of a combination according to any one of claims 1 to 5, or a kit of parts according to any one of claims 6 to 10, for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke.

INTERNATIONAL SEARCH REPORT

PCT/EP 03/05180

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4184 A61K31/19 C07D401/12 A61K31/44 A61K31/196

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 100 04 651 A (DIERKES JUTTA ;LULEY CLAUS (DE); WESTPHAL SABINE (DE)) 16 August 2001 (2001-08-16) claim 1 table 1 ---	1-3,6-8, 11-13, 15,16
X	DE 198 20 151 A (HEXAL AG) 11 November 1999 (1999-11-11) claims 1,5-7 page 1, line 12 - line 15 --- -/--	1,2,6,7, 11,12, 15,16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 August 2003	01/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MACGREGOR G A ET AL: "THE EFFICACY OF CANDESARTAN: AN ANGIOTENSIN II TYPE I RECEPTOR ANTAGONIST ALONE OR IN COMBINATION WITH AMLODIPINE OR IN COMBINATION WITH AMLODIPINE AND HYDROCHLOROTHIAZIDE IN PATIENTS WITH MODERATE-TO-SEVERE ESSENTIAL HYPERTENSION" AMERICAN JOURNAL OF HYPERTENSION, NEW YORK, NY, US, vol. 10, no. 4, PART 2, April 1997 (1997-04), page 112A XP000869500 * abstract * ---	1,2,6,7, 11,12, 15,16
X	MACGREGOR G A ET AL: "Efficacy of candesartan cilexetil alone or in combination with amlodipine and hydrochlorothiazide in moderate-to-severe hypertension" HYPERTENSION 2000 UNITED STATES, vol. 36, no. 3, 2000, pages 454-460, XP002251650 ISSN: 0194-911X page 455; figure 1 page 457, right-hand column, paragraph 1 * page 459, right-hand column, last paragraph * ---	1,2,6,7, 11,12, 15,16
X	OPARIL SUZANNE ET AL: "Efficacy and safety of Losartan/Hydrochlorothiazide in patients with severe hypertension." AMERICAN JOURNAL OF CARDIOLOGY, vol. 87, no. 6, 15 March 2001 (2001-03-15), pages 721-726, XP002251651 ISSN: 0002-9149 page 722, left-hand column, paragraph 2 page 726, right-hand column, paragraph 1 ---	1,2,6,7, 11,12, 15,16
X	WO 92 20342 A (DU PONT) 26 November 1992 (1992-11-26) claims 1,6 page 5, line 28 -page 6, line 17 ---	1,6,11, 12,15,16
X	US 5 656 650 A (WEINSTOCK JOSEPH) 12 August 1997 (1997-08-12) claims 1,4,17 --- -/--	1,6,11, 12,15,16

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	OPARIL SUZANNE ET AL: "Efficacy, tolerability, and effects on quality of life of losartan, alone or with hydrochlorothiazide, versus amlodipine, alone or with hydrochlorothiazide, in patients with essential hypertension." CLINICAL THERAPEUTICS, vol. 18, no. 4, 1996, pages 608-625, XP002251652 ISSN: 0149-2918 page 618, right-hand column, paragraph 2 ---	1-16
Y	OHNISHI K ET AL: "Influence of the angiotensin II receptor antagonist losartan on diuretic-induced metabolic effects in elderly hypertensive patients: Comparison with a calcium channel blocker." INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY AND THERAPEUTICS, vol. 39, no. 10, October 2001 (2001-10), pages 417-422, XP008020851 ISSN: 0946-1965 * page 417, abstract * * page 418, Study design * * page 421, left-hand column, Discussion * -----	1-16

INTERNATIONAL SEARCH REPORT

PCT/EP 03/05180

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 6, 12, 15 and 16 relate to compounds defined by reference to a desirable characteristic or property, namely "angiotensin receptor blocker", "calcium channel blocker" and "diuretic".
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely Examples and the combination of valsartan, amlodipine and hydrochlorothiazide, as described on page 7.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 10004651 A	16-08-2001	DE 10004651 A1	16-08-2001
		AU 7285800 A	14-08-2001
		WO 0156609 A1	09-08-2001
DE 19820151 A	11-11-1999	DE 19820151 A1	11-11-1999
		AU 760550 B2	15-05-2003
		AU 3931199 A	23-11-1999
		BR 9910201 A	09-01-2001
		CA 2331414 A1	11-11-1999
		WO 9956734 A2	11-11-1999
		EP 1085858 A2	28-03-2001
		JP 2002513753 T	14-05-2002
WO 9220342 A	26-11-1992	AU 664375 B2	16-11-1995
		AU 2026992 A	30-12-1992
		CA 2103276 A1	16-11-1992
		CZ 9302351 A3	16-03-1994
		EP 0584250 A1	02-03-1994
		IE 921534 A1	18-11-1992
		IL 101858 A	04-08-1996
		JP 2930252 B2	03-08-1999
		JP 6508128 T	14-09-1994
		KR 222627 B1	01-10-1999
		MX 9202243 A1	01-11-1992
		NZ 242724 A	27-09-1994
		WO 9220342 A1	26-11-1992
		US 5492904 A	20-02-1996
		ZA 9203557 A	15-11-1993
US 5656650 A	12-08-1997	AT 177634 T	15-04-1999
		AU 656551 B2	09-02-1995
		AU 9178291 A	08-07-1992
		CA 2098176 A1	14-06-1992
		DE 69131021 D1	22-04-1999
		DE 69131021 T2	12-08-1999
		DK 565634 T3	27-09-1999
		EP 0565634 A1	20-10-1993
		ES 2130170 T3	01-07-1999
		GR 3030293 T3	30-09-1999
		HK 1012209 A1	12-05-2000
		JP 3398379 B2	21-04-2003
		JP 6503834 T	28-04-1994
		KR 222252 B1	01-10-1999
		WO 9210097 A1	25-06-1992