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(71) Applicant *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GmbH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WEBB, Randy, Lee** [US/US]; 17 Honeyman Drive, Flemington, New Jersey 08822 (US). **SHETTY, Suraj, Shivappa** [US/US]; 20 Stoneybrook Circle, Andover, Massachusetts 01810 (US).

(74) Agent: **ZHANG, Cynthia H.**; NOVARTIS, Corporate Intellectual Property, One Health Plaza, Building 104, East Hanover, New Jersey 07936 (US).

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(54) Title: COMBINATION OF ORGANIC COMPOUNDS

(57) Abstract: The present invention relates to a product comprising at least two antihypertensive agents and a cholesterol-lowering agent wherein at least one of the antihypertensive agents is a neutral endopeptidase inhibitor, and the other antihypertensive agent is typically but not necessarily an angiotensin II receptor antagonist. The invention further relates to the use of said product in treatment of relevant conditions, or diseases, or disorders such as cardiovascular conditions.

Combination of Organic Compounds

FIELD OF THE DISCLOSURE

The invention relates to products, methods and uses which are useful in relation to the treatment of patients having or believed to be susceptible to developing an undesirable disorder or condition, for example a cardiovascular condition, particularly hypertension, hypercholesterolemia or atherosclerosis, for example.

BACKGROUND

The renin-angiotensin-aldosterone system (RAAS) is one of the hormonal mechanisms involved in regulating blood pressure/volume and also in the development of hypertension. Activation of the renin-angiotensin-aldosterone system begins with renin secretion from cells in the kidney and culminates in the formation of angiotensin II, the primary active species of this system. Angiotensin II has a strong vasoconstrictive action, aldosterone-synthesising action and cell propagating action and has been considered as one of the mediators of various circulatory diseases.

The vasoconstrictive effects of angiotensin II are produced by its action on the non-striated smooth muscle cells, the stimulation of the formation of the adrenergenic hormones epi-nephrine 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, in increasing both circulating volume and peripheral resistance. Angiotensin II is also involved in cell growth and migration and in extracellular matrix formation.

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 but do not result in activation of the receptor.

Angiotensin-converting enzyme ("ACE") inhibitors act by inhibiting the production of angiotensin II, a substance that both induces constriction of blood vessels and retention of sodium, which leads to water retention and increased blood volume.

The angiotensin II receptor antagonists losartan (Cozaar®), candesartan (Atacand®), irbesartan (Avapro®), telmisartan (Micardis®), valsartan (Diovan®) and eprosartan (Teveten®) directly inhibit the effects of angiotensin II rather than blocking its production (like the ACE inhibitors).

Natriuretic peptides are a group of peptides that act to decrease blood pressure in response to volume expansion by promoting natriuresis and diuresis, inhibiting the renin angiotensin aldosterone system (RAAS), and promoting vasodilation. The natriuretic peptides therefore play pivotal roles in the maintenance blood pressure and volume homeostasis.

Natriuretic peptides include atrial natriuretic peptide (ANP), brain-derived natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendraspis natriuretic peptide (DNP). ANP is released in the atria in response to stretching of the myocardium. BNP is released from the ventricles in response to the stretching of increased ventricular volume and pressure. ANP and BNP exhibit beneficial effects in chronic heart failure (CHF) patients such as dilation of vessels, sodium excretion (natriuresis), and excretion of large volumes of urine (diuresis). ANP also inhibits production of renin, aldosterone, and norepinephrine and has been hypothesized to inhibit production of endothelin, a vasoconstrictor.

CNP is found in the brain, kidney, heart, lungs, and vascular endothelium and can be released in response to shear stress. CNP possesses potent vasodilatory properties but has minimal natriuretic and diuretic effects. Thus, the presence of circulating natriuretic peptides promotes vasodilation and reduces blood pressure and volume.

Neutral endopeptidase (NEP), which is also known as enkephalinase, neprilysin, and atriopeptidase, is a membrane-bound zinc metalloendopeptidase found in many tissues including the brain, kidney, lungs, gastrointestinal tract, heart, and peripheral vasculature. NEP plays a major role in the clearance of natriuretic peptides by degrading circulating natriuretic peptides, thus preventing their effects on vasodilation, blood pressure and volume.

In addition to degrading circulating natriuretic peptides, NEP also degrades other vasodilating substances including circulating bradykinins; adrenomedullin, renal vasodilating and natriuretic-diuretic peptide; and/or urodilatin, a renal form of ANP.

NEP is also involved in the degradation of endothelin isoform ET-1, a vasoconstrictor, and may be involved in the formation of ET-1 (Brunner-La Rocca et al., Cardiovascular Research 51 (2001) 510-520). NEP also degrades angiotensin II.

WO2004082636 discloses a composition containing an aldosterone receptor antagonist and a neutral endopeptidase inhibitor optionally together with an ACE inhibitor, and its use in the treatment of cardiovascular disorders and hypertension.

WO02087621 discloses a composition having an ACE inhibitor, a neutral endopeptidase inhibitor and a bioavailability enhancer such as an organic acid e.g ascorbic acid. Such compositions are described as useful in the treatment of heart failure and hypertension.

EP0726072 discloses combination treatments for diseases involving cell proliferation such as atherosclerosis and restenosis. The combination treatments includes a natiuretic peptide alone or together with a neutral endopeptidase inhibitor. ACE inhibitors may also be included in the treatments.

Despite the large numbers of drugs available in various pharmacological categories, including vasodilators, beta blockers and diuretics, there remains a need for further combination therapies for treating and/or preventing conditions such as vascular disease and hypertension.

SUMMARY OF THE DISCLOSURE

According to a first aspect of the present invention there is a provided a product comprising at least two antihypertensive agents and a cholesterol-lowering agent wherein at least one of the antihypertensive agents is a neutral endopeptidase inhibitor. The other antihypertensive agent is typically but not necessarily an angiotensin II receptor antagonist.

Also provided is a product comprising at least two antihypertensive agents and an 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitor wherein at least one of the antihypertensive agents is a neutral endopeptidase inhibitor. The other antihypertensive agent is typically but not necessarily an angiotensin II receptor antagonist.

The invention therefore provides a method for treating a disorder described herein, particularly a cardiovascular condition, by prophylaxis or therapy, comprising the sequential or combined administration in a therapeutically effective amount of:

- a first antihypertensive agent, e.g. an angiotensin II receptor antagonist;
- a second antihypertensive agent different from the first one and is a neutral endopeptidase inhibitor; and
- a cholesterol-lowering agent.

The above mentioned active agents may be administered as free or fixed combinations. Free combinations may be provided as combination packages containing all the active agents in free combinations. Fixed combinations are often tablets or capsules. Also included are products comprising two of the active agents in fixed combination and a third active agent in free combination therewith.

The products of the invention may therefore be fixed combinations, particularly combined formulations for oral administration, packages comprising the agents in free combination or packages including both a fixed combination and a formulation in free combination therewith.

Included in the invention is the use in the manufacture of a medicament for the treatment of a disorder described herein, particularly a cardiovascular condition, by prophylaxis or therapy of the combinations of active agents outlined above.

The products of the invention have the advantage that they may be more efficacious, be less toxic, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, be more easily absorbed than, or that they may have other useful pharmacological properties over, compositions known in the prior art. Advantageously, the products of the invention can provide one or more of the following benefits or effects:

1. By including active ingredients that act by different physiological mechanisms or pathways, it is anticipated that the composition of the invention will provide medicaments with superior properties to those currently available. Advantageously, effects, e.g. synergistic effects, are provided giving rise to unexpected therapeutic benefits, including one or more of:

- anti-hypertensive activity
- control of heart failure including cardiac remodelling
- control of collagen synthesis in cardiac fibroblasts
- control of renal function
- control of anti-inflammatory activity
- control of endothelial dysfunction
- control of atherosclerosis
- regulating development and/or stability of atherosclerotic plaques
- control of oxidative stress.

"Synergy", as used herein, may describe the action of the three or more agents of the product of the invention working together to produce an effect greater than the expected combined effect of the agents used separately.

2. In particular the use of a neutral endopeptidase inhibitor may counter the effects of reflex up-regulation of the renin-angiotensin-aldosterone system caused by the body's own hypertensive compensatory reaction to the angiotensin II receptor antagonist, and/or the cholesterol-lowering agent. The releasing of this physiological barrier may result in a synergistic effect of the three agents. This synergy may be a more-than additive acute effect or a reduced propensity to the development of tolerance following repeated dosing.

3. The combination of three or more active ingredients in the composition of the invention provides the additional advantage of reducing the dosage of some or all of the active

ingredients, or reducing the frequency of administration of a dosage, thereby increasing the safety of the therapy, for example, by prolonging the efficacy of the active ingredients. Moreover, by reducing the dependency on any one active ingredient in the product, any possible side effects caused by that ingredient would also be reduced.

4. In any population there will be patients who benefit from treatments using a single active ingredient and/or a combination therapy. The combination of three or more active ingredients within a composition provides the additional advantage of targeting a broader spectrum of the population to include those patients who fail to respond, or responded poorly, to the administration of a product having only one or two of the active ingredients.

5. Non-response or poor response to a drug may be treated. For example, drug response may be enhanced by counter-action of a drug side-effect which tends to negate the desired therapeutic activity. Increased potency through administration of the drug combination may be achieved.

6. By including the combination of three or more active ingredients with different physiological mechanisms, it is expected that a broader variety of diseases or conditions will be treatable.

7. It has, surprisingly, been found that the inclusion of a neutral endopeptidase inhibitor in the products of the invention provides a medicament with superior properties since it allows for simultaneous targeting of at least three separate mechanisms for the control of blood pressure, thereby reducing the reliance on a single mechanism, and in this way, reducing the possibility of problems associated with prolonged use.

8. A reduction of blood pressure and/or blood cholesterol levels to target levels, e.g. those set by medical standards are, surprisingly, reached following treatment, for example they may unexpectedly be reached at lower than predicted dosages.

The compounds mentioned in this specification can exist in different forms, such as free acids, free bases, esters and other prodrugs, salts and tautomers, for example, and the invention includes all variant forms of the compounds.

The extent of protection includes counterfeit or fraudulent products which contain or purport to contain a product of the invention irrespective of whether they do in fact contain such a product and irrespective of whether any or all of the components are contained in a therapeutically effective amount. Included in the scope of protection therefore are packages which include a description or instructions which indicate that the package contains a combination of active agents as described herein and product (e.g. a plurality of formulations in free combination or a fixed combination) which is or comprises, or purports to be or comprise, such a combination of active agents.

Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprises", mean "including but not limited to", and are not intended to (and do not) exclude other moieties, additives, components, integers or steps.

Further aspects and embodiments of the invention are set forth in the following description and claims.

DETAILED DESCRIPTION

The following terms and abbreviations are used in this specification:

The term "agent" as used herein is used broadly to refer to active substances, whether a chemical compound (whether an active principle or a prodrug), salt thereof or otherwise.

The term "antihypertensive agent" is intended to include compounds or agents having the ability to lower blood pressure, or at least prevent increases in blood pressure.

The term "angiotensin II receptor antagonist" is intended to include compounds or agents having the ability to interact with an angiotensin receptor but which do not result in the activation of the receptor.

The term "neutral endopeptidase inhibitor" is intended to include compounds or agents having the ability to inhibit the activity of a neutral endopeptidase (NEP).

The term "dual NEP inhibitor/ACE inhibitor" is intended to include compounds or agents that inhibit both ACE and NEP.

The term "cholesterol lowering agent" includes compounds or agents that lower the levels of lipids, including triglycerides and cholesterol, in the blood.

The above-mentioned agents and inhibitor often comprise a single active species; however, the option of having a plurality of active substances in any one class of agent is not excluded.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings or, as the case may be, an animal without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

By an "effective" amount or "therapeutically effective amount" is meant an amount of one or more active substances which, within the scope of sound medical judgment, is sufficient to provide a desired effect without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Non-limiting examples of the desired effect include but are not limited to, at least partially inhibiting or inactivating the AT1 receptor, or the neutral endopeptidase, or the HMG Co-A reductase; or controlling the blood pressure; or lowering the cholesterol level; or treating the

cardiovascular or metabolic conditions or diseases, for example, those diseases or conditions described in this application.

The compounds of the invention may be administered in the form of pharmaceutically acceptable salts. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 20th ed., Mack Publishing Company, Easton, Pa., US, 2000, the disclosure of which is hereby incorporated by reference; see also Stahl et al, Eds, *"Handbook of Pharmaceutical Salts Properties Selection and Use"*, Verlag Helvetica Chimica Acta and Wiley-VCH, 2002.

The invention thus includes pharmaceutically-acceptable salts of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof for example the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

The invention includes prodrugs for the active pharmaceutical species of the described compounds, for example in which one or more functional groups are protected or derivatised but can be converted *in vivo* to the functional group, as in the case of esters of carboxylic acids convertible *in vivo* to the free acid, or in the case of protected amines, to the free amino group. The term "prodrug," as used herein, represents in particular compounds which are rapidly transformed *in vivo* to the parent compound, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; H Bundgaard, ed, Design of Prodrugs, Elsevier, 1985; and Judkins, et al. Synthetic Communications, 26(23), 4351-4367 (1996), each of which is incorporated herein by reference.

Prodrugs therefore include drugs having a functional group which has been transformed into a reversible derivative thereof. Typically, such prodrugs are transformed to the active drug by hydrolysis. As examples may be mentioned the following:

Functional Group	**Reversible derivative**
Carboxylic acid	Esters, including e.g. acyloxyalkyl esters, amides
Alcohol	Esters, including e.g. sulfates and phosphates as well as carboxylic acid esters
Amine	Amides, carbamates, imines, enamines,
Boronic acid	Diol ester
Carbonyl (aldehyde, ketone)	Imines, oximes, acetals/ketals, enol esters, oxazolidines and thiazoxolidines

Prodrugs also include compounds convertible to the active drug by an oxidative or reductive reaction. As examples may be mentioned:

Oxidative activation

- N- and O- dealkylation
- Oxidative deamination
- N-oxidation

- Epoxidation

Reductive activation

- Azo reduction
- Sulfoxide reduction
- Disulfide reduction
- Bioreductive alkylation
- Nitro reduction.

Also to be mentioned as metabolic activations of prodrugs are nucleotide activation, phosphorylation activation and decarboxylation activation. For additional information, see "The Organic Chemistry of Drug Design and Drug Action", R B Silverman (particularly Chapter 8, pages 497 to 546), incorporated herein by reference.

The use of protecting groups is fully described in `Protective Groups in Organic Chemistry`, edited by J W F McOmie, Plenum Press (1973), and `Protective Groups in Organic Synthesis`, 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

Thus, it will be appreciated by those skilled in the art that, although protected derivatives of the described compounds may not possess pharmacological activity as such, they may be administered, for example parenterally or orally, and thereafter metabolised in the body to form compounds which are pharmacologically active. Such derivatives are therefore examples of "prodrugs". All prodrugs of the described compounds are included within the scope of the invention.

Many of the groups referred to or featured herein (especially those containing heteroatoms and conjugated bonds) can exist in tautomeric forms and all these tautomers are included in the scope of the invention. More generally, many species may exist in equilibrium, as for example in the case of organic acids and their counterpart anions; a reference herein to a species accordingly includes reference to all equilibrium forms thereof.

The invention therefore includes all variant forms of the defined compounds, for example any tautomer or any pharmaceutically acceptable salt, ester, acid or other variant of the defined compounds and their tautomers as well as substances which, upon administration, are

capable of providing directly or indirectly a compound as defined above or providing a species which is capable of existing in equilibrium with such a compound.

The invention therefore includes pharmaceutical products comprising at least:

- a first antihypertensive agent;
- a second antihypertensive agent different from the first one and is a neutral endopeptidase inhibitor; and
- a third active agent selected from cholesterol lowering agents and HMG Co-A reductase inhibitors.

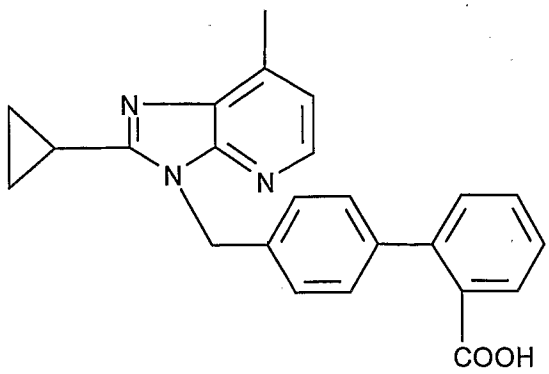
The First Antihypertensive Agent

The first antihypertensive agent may be an agent that regulates the RAAS, for example an agent which inhibits the production or activity of angiotensin II, in the latter for example by blocking the angiotensin II receptor. In particular, the first antihypertensive agent may be selected from the group consisting of angiotensin II receptor antagonists or ACE inhibitors.

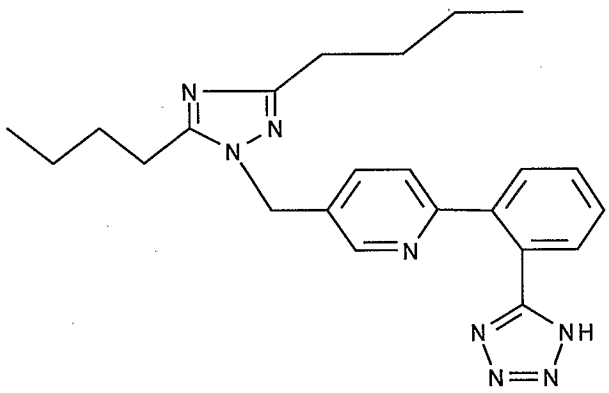
The angiotensin receptor antagonist may be an AT_1- or AT_2-angiotensin receptor subtype antagonist. In particular, the angiotensin receptor antagonist is an antagonist of the AT_1-receptor angiotensin receptor subtype.

The angiotensin II receptor antagonist may comprise compounds having differing structural features, for example the angiotensin II receptor antagonist may be a peptidic or non-peptidic compound. Preferred are the non-peptidic compounds.

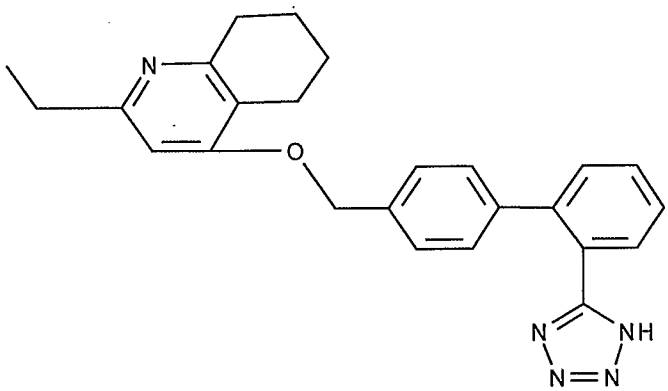
The angiotensin II receptor antagonist may be selected from the group consisting of valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, the compound with the designation E-1477 of the following formula



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



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



or, in each case, a salt or prodrug thereof.

Particularly exemplary is valsartan, sold by Novartis AG under the registered trade mark Diovan. Valsartan is *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine.

The angiotensin II receptor antagonist may be selected from the group consisting of saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007, PD-123177, A-81988, BMS-180560, CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-3I5995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, saralasin, Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017, LY-301875, XH-148, XR-510, zolasartan and PD-123319.

Examples of angiotensin II receptor antagonists include losartan potassium, valsartan, irbesartan, candesartan cliexetil, telmisartan, eprosartan mesylate, and olmesartan medoxomil. The scope of the present invention includes all those angiotensin receptor antagonists now known and all those angiotensin receptor antagonists to be discovered in the future.

The structure of the agents identified hereinbefore or hereinafter by generic or trade names 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*.

In a preferred aspect of the invention the angiotensin receptor antagonist is valsartan or a salt thereof.

The Second Antihypertensive Agent

The second antihypertensive agent may be an NEP inhibitor. The NEP inhibitor may be selected from the group consisting of candoxatrilat, candoxatril (a pro-drug of candoxatrilat), thiorphan, ecadotril (a pro-drug of thiorphan), racecadotril and phosphoramidon, CGS 24128, CGS 24592 (see *J Med Chem.* 1994 Feb 18;37(4):498-511), CGS 25155, CGS 25155, CGS 25462, CGS 26303, CGS 26393 (diphenyl [(*S*)-2-biphenyl-4-yl-1-(1H-tetrazol-5-yl)-ethylamino-methyl] phosphonate, a prodrug of CGS 26303; see Trapani, A.J. et al. (1995) *J. Cardiovasc. Pharmacol.* **26** (Suppl. 3), S69–S71) and CGS 31447.

The second antihypertensive agent may be a dual NEP/ACE inhibitors, for example mapatrilat, fasidotril, mixanpril, sampatrilat, gemopatrilat (BMS-189921), MDL-100240 or 752A (GW660511).

The Cholesterol-Lowering Agent

Cholesterol lowering agents may lower serum low density lipoprotein cholesterol levels, or inhibit oxidation of LDL cholesterol, whereas high density lipoprotein (HDL) serum cholesterol levels may be lowered, remain the same, or be increased. Preferably, the cholesterol-lowering agent brings the serum levels of LDL cholesterol and HDL cholesterol (and, more preferably, triglyceride levels) to normal or nearly normal levels.

The cholesterol lowering agent may comprise HMG-Co-A reductase inhibitors (also called β-hydroxy-β-methylglutaryl-co-enzyme-A reductase inhibitors), which are used to lower the lipid levels including cholesterol in blood. As with other active agents described herein, the HMG-Co-A reductase inhibitors may be in the form of the active principle, or alternatively in the form of a substance that releases the active principle *in vivo*, for example a salt or prodrug.

The HMG-Co-A reductase inhibitor

The invention is not limited as to the identity of the HMG-Co-A reductase inhibitor: it may be selected from the group of statins including atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin (formerly itavastatin), pravastatin, rosuvastatin, and simvastatin, or, in each case, a salt or prodrug thereof.

Particular HMG-Co-A reductase inhibitors are selected from the group consisting of fluvastatin, atorvastatin, pitavastatin or simvastatin, or the salts or prodrugs thereof.

The Products of the Invention

A preferred product comprises an angiotensin II receptor antagonist, a neutral peptidase inhibitor and a cholesterol-lowering agent.

Another preferred product comprises an angiotensin II receptor antagonist, a neutral peptidase inhibitor and an HMG Co-A reductase inhibitor.

Preferably the angiotensin II receptor antagonist is valsartan or a salt or prodrug thereof.

In a class of products, the HMG-Co A reductase inhibitor is selected from the group consisting of fluvastatin, atorvastatin, pitavastatin and simvastatin, for example it is pitavastatin or simvastatin.

The product of the invention may further comprise a diuretic.

Examples of diuretics include thiazide derivatives selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon. Other diuretics may include bendroflumethazide, benazepril, enalapril, and trandolapril. The scope of the present invention includes all those diuretics now known and all those diuretics to be discovered in the future. Preferably the diuretic is hydrochlorothiazide, i.e. 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide.

The product of the invention may be provided as a free combination. Free combinations may be provided as combination packages containing all the active agents. For example, a package may comprise separate oral unit dosage forms containing respective ones of the active agent; in some instances one or more individual blister sheets are provided for each active ingredient but in other instances the separate units containing their respective active agents are all included in the same blister sheet or sheets.

The active agents may be administered simultaneously, sequentially or separately. Thus the combination package may contain the product of the invention together with instructions for simultaneous, separate or sequential administration of each of the active agents. For sequential administration, the active agents can be administered in any order. It is generally preferred that such administration is simultaneous and oral.

The product of the invention may be administered as a fixed combination. Alternatively, at least one of the active agents may be administered separately from the other(s). The invention therefore includes:

- administration in a single fixed combination (e.g. in a combined oral formulation, for example a tablet or capsule) of all of the first and second antihypertensive agents and the third active agent selected from cholesterol lowering agents and HMG Co-A reductase inhibitors, including any diuretic or other additional active agent(s)
- administration of the first antihypertensive agent and second antihypertensive agent in fixed combination and separate administration of the cholesterol-lowering agent
- administration of the first antihypertensive agent and the cholesterol-lowering agent in fixed combination and separate administration of second antihypertensive agent
- administration of the second antihypertensive agent and the cholesterol-lowering agent in fixed combination and separate administration of first antihypertensive agent.

Where two or more agents are administered separately from one another, they may be administered concomitantly (in the same "session") or, in other instances, at spaced apart times.

The administration of a product of the invention may therefore comprise the administration, whether sequential, combined or part-sequential and part-combined, in a therapeutically effective amount of:

- a first antihypertensive agent, e.g. an angiotensin II receptor antagonist;
- a second antihypertensive agent which is different from the first one and is a neutral endopeptidase inhibitor; and
- a cholesterol-lowering agent
- optionally one or more additional active agents, e.g. a diuretic.

The invention includes an article of manufacture comprising packaging material and, within the same packaging material, one or more pharmaceutical compositions, which single composition or plural compositions in combination comprise:

(i) a first antihypertensive agent;

(ii) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral peptidase inhibitor; and

(iii) a cholesterol-lowering agent,

the article further includes a label or instructions which indicates that the pharmaceutical composition(s) be used for treating a cardiovascular or metabolic disease. For example, the packaging may carry such a label or instructions.

The active agents of the product of the invention may be provided as pharmaceutical compositions additionally containing one or more pharmaceutically acceptable diluents, excipients and/or carriers. This applies to both fixed and free combinations.

Oral administration is a preferred route being the most convenient. A product for oral administration can take the form of solutions, suspensions, tablets, pills, gels, elixirs, capsules, powders, and the like, and may be for immediate-, delayed-, modified-, sustained-, pulsed-, or controlled-release applications. Suitable products may be in coated or uncoated form as desired.

The term "delayed release" refers to a product in which there is a time delay provided between oral administration of the product and release of the active agents(s) therefrom.

The term "sustained release" refers to a product that provides for gradual release of an active ingredient(s) over an extended period of time and that may result in substantially constant blood levels of an active ingredient over an extended time period.

The term "controlled release" is intended to refer to any composition in which release of the active ingredient(s) is not immediate i.e. with a controlled release composition, oral administration does not result in immediate release of the drug into the blood. The term "controlled release" may include sustained release, delayed release and pulsatile release compositions.

In such solid dosage forms, the active compound or agent is typically mixed with at least one inert, pharmaceutically acceptable diluent, excipient or carrier such as sodium citrate or dicalcium phosphate, for example, and/or one or more: a) fillers or extenders for example starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders for example carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants for example glycerol; d) disintegrating agents for example agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents for example paraffin; f) absorption accelerators for example quaternary ammonium compounds; g) wetting agents for example cetyl alcohol and glycerol monostearate; h) absorbents for example kaolin and bentonite clay and i) lubricants for example talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycol, for example.

Suitably, oral formulations contain a dissolution aid. The dissolution aid is not limited as to its identity so long as it is pharmaceutically acceptable. Examples include nonionic surface active agents, for example sucrose fatty acid esters, glycerol fatty acid esters, sorbitan fatty acid esters (e.g., sorbitan trioleate), polyethylene glycol, polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, methoxypolyoxyethylene alkyl ethers, polyoxyethylene alkylphenyl ethers, polyethylene glycol fatty acid esters, polyoxyethylene alkylamines, polyoxyethylene alkyl thioethers, polyoxyethylene polyoxypropylene copolymers, polyoxyethylene glycerol fatty acid esters, pentaerythritol fatty acid esters, propylene glycol monofatty acid esters, polyoxyethylene propylene glycol monofatty acid esters, polyoxyethylene sorbitol fatty acid esters, fatty acid alkylolamides, and alkylamine oxides; bile acid and salts thereof (e.g., chenodeoxycholic acid, cholic acid, deoxycholic acid, dehydrocholic acid and salts thereof, and glycine or taurine conjugate thereof); ionic surface active agents, for example sodium laurylsulfate, fatty acid soaps, alkylsulfonates, alkylphosphates, ether phosphates, fatty acid salts of basic amino acids; triethanolamine soap, and alkyl quaternary ammonium salts; and amphoteric surface active agents, for example betaines and aminocarboxylic acid salts.

Solid compositions of a similar type may be employed as fillers in soft and hard-filled gelatin capsules; suitable materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols.

When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavouring agents colouring agents, emulsifying agents and/or suspending agents, as well as such diluents for example water, ethanol, propylene glycol, glycerin and various like combinations thereof.

Tablets are typically manufactured by a standard process, for example, direct compression or a wet or dry granulation process.

Modified release and pulsatile release dosage forms may contain additional excipients that act as release rate modifiers, these being coated on or included in the composition. Release rate modifiers include, but are not limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, Xanthan gum, Carbomer, ammonio methacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof. Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients.

When two or more active agents are combined in a single pharmaceutical product, possible interactions among the active agents, and among the active agents and the excipients, must be considered. The present invention thus encompasses products wherein two or more of the active agents are separated from each other within the product by, for example, separating potentially interacting compounds from each other as in separate flat layers of a tablet (e.g a bilayer or trilayer tablet), concentric layers, coated beads or granules (which may be incorporated into a compressed tablet or into a capsule) and/or by using buffers (see for example US 6,235,311). Moreover, where two or more active agents are physically separated from the other active agent(s), the products can be manufactured so that different active agents will have different release profiles e.g. if one active ingredient is formulated with an enteric coating, another active ingredient is formulated in a sustained release matrix.

For purposes of parenteral administration ("parenteral" as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion of which intravenous is most preferred), solutions in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

The products of the invention may contain from about 0.1% to about 90%, preferably from about 1% to about 80%, of the active agents.

For parenteral administration, the products of the invention may contain from about 0.1% to about 90%, preferably from about 1% to about 80%, of the active agents.

The dosage of the active ingredients can depend on a variety of factors, for example mode of administration, homeothermic species, age and/or individual condition.

Valsartan, as a representative of the class of angiotensin II receptor antagonists, may 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 valsartan 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.

In the 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.

The active agents may be administered in synergistically effective amounts. The invention therefore includes: the use of synergistically effective amounts of (i) a first antihypertensive agent, (ii) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor, and (iii) a cholesterol-lowering agent for the manufacture of a product for simultaneous, separate or sequential administration of said agents in the treatment of a cardiovascular or metabolic disease.

Further included is the use of a synergistically effective amount of a first antihypertensive agent with a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor, and a cholesterol-lowering agent, for the manufacture of a product, e.g. a medicament, for simultaneous, separate or sequential administration of said agents in the treatment of a cardiovascular or metabolic disease.

An aspect of the invention is the use of a synergistically effective amount of a cholesterol-lowering agent with a first antihypertensive agent and a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor, for the manufacture of a product, e.g. a medicament, for simultaneous, separate or sequential administration of said agents in the treatment of a cardiovascular or metabolic disease.

Another aspect of the invention is the use of a synergistically effective amount of a combination of a first antihypertensive agent and cholesterol-lowering agent with a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor, for the manufacture of a product, e.g. a medicament, for simultaneous, separate or sequential administration of said agents in the treatment of a cardiovascular or metabolic disease.

The invention also provides the use of a synergistically effective amount of a combination of a first antihypertensive agent and a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor with a cholesterol-lowering agent, for the manufacture of a product, e.g. a medicament, for simultaneous, separate or sequential administration of said agents in the treatment of a cardiovascular or metabolic disease.

The products of the invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser, nebuliser, with or without the use of a suitable propellant.

Alternatively the products of the invention can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or powder. The products of the invention may be dermally or transdermally administered, for example, by use of a skin patch, depot or subcutaneous injection. They may also be administered by pulmonary or rectal routes.

Methods of preparing various pharmaceutical products with a certain amount of active ingredient are known, or will be apparent in light of this invention, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 20th Edition (2000).

The products of the invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances.

Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired

Use

The product of the invention may be used in the treatment of diseases including cardiovascular and metabolic conditions or diseases and may in particular be useful in the treatment of hyperlipidaemia or hypertension, or both.

Preferably the cardiovascular condition to be treated is hypertension, heart failure, angina, arrhythmia, myocardial infarction, hyperlipidemia, dyslipidemia, vascular disease, vascular damage, cardiac hypertrophy including left ventricular hypertrophy, vascular hypertrophy, atherosclerosis, endothelial dysfunction, restenosis (e.g restenoisis after angioplasty or bypass surgery), stroke, fibrosis (myocardial or vascular) or renal dysfunction (e.g chronic renal failure). The cardiovascular condition may be hypertension associated with diabetes, hypertension associated with atherosclerosis or renovascular hypertension.

Preferably the metabolic disease to be treated is impaired glucose tolerance or diabetes, including complications thereof such as diabetic retinopathy and diabetic neuropathy. More preferably the metabolic disorder is impaired glucose tolerance, type-1 diabetes mellitus, type-2 diabetes mellitus, syndrome X.

Another aspect of the invention resides in methods of treating, preventing or delaying the progression of a disease or condition in a mammal, especially a human, having a cardiovascular or metabolic condition, e.g. as described herein, by administering a therapeutically effective amount of a product of the invention to the mammal.

Thus the product of the invention may be useful in the prevention of, delay of progression of, or treatment of a disease or condition selected from the group consisting of hyperlipidaemia, dyslipidemia, hypercholesterolemia, atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, renal dysfunction, e.g. chronic renal failure, liver disease, hypothyroidism, hyperthyroidism, thrombosis, arthritis, edema (e.g pulmonary edema), baroreceptor dysfunction, reducing post myocardial infarction (MI) damage, left ventricular hypertrophy, vascular hypertrophy, ischemia, coronary heart diseases, hypertension (including hypertension in the elderly and familial dyslipidemic hypertension), stroke, erectile dysfunction and vascular disease. Also to be mentioned are the prevention of cardiac arrest, myocardial infarction, stroke or angina (e.g worsening angina) for example in a patient with an increased cardiovascular risk for example due to coronary heart disease, a history of ischaemic attacks or stroke or due to a history of vascular disease.

The present inventive method includes the administration to an animal, such as a mammal, particularly a human, in need of treatment of a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for treating cardiovascular diseases comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for treating hypertension comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for treating hyperlipidemia comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for treating hypercholesterolemia comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for treating atherosclerosis comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for treating angina comprising administering to a mammal a therapeutically effective amount of a product of the invention

Another aspect of this invention is directed to methods for treating cardiac hypertrophy comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for treating post myocardial infarction comprising administering to a mammal a therapeutically effective amount of a product of the invention

Another aspect of this invention is directed to methods for treating renal diseases comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for treating diabetes mellitus or associated diabetic complications comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for treating vascular disease comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Another aspect of this invention is directed to methods for reducing collagen synthesis in cardiac fibroblasts comprising administering to a mammal a therapeutically effective amount of a product of the invention.

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.

There is compelling evidence for endothelial dysfunction in both type 1 and type 2 diabetics (See e.g., Taylor, A A. Endocrinol Metab Clin North Am 2001 December; 30(4):983-97). This dysfunction is manifest as blunting of the biological effect of a potent endothelium-derived vasodilator, nitric oxide (NO), and increased production of vasoconstrictors such as angiotensin II, ET-1, and cyclooxygenase and lipoxygenase products of arachidonic acid metabolism. These agents and other cytokines and growth factors whose production they stimulate cause acute increases in vascular tone, resulting in increases in blood pressure, and vascular and cardiac remodeling that contributes to the microvascular, macrovascular, and renal complications in diabetes. Reactive oxygen species, overproduced in diabetics, may serve as signaling molecules that mediate many of the cellular biochemical reactions that result in these deleterious effects. Adverse vascular consequences associated with endothelial dysfunction in diabetes mellitus include: decreased NO formation, release, and action; increased formation of reactive oxygen species; decreased prostacyclin formation and release; increased formation of vasoconstrictor prostanoids; increased formation and release of ET-1; increased lipid oxidation; increased cytokine and growth factor production;

increased adhesion molecule expression; hypertension; changes in heart and vessel wall structure; and acceleration of the atherosclerotic process. Treatment with antioxidants and ACE inhibitors may reverse some of the pathologic vascular changes associated with endothelial dysfunction.

Thus another aspect of this invention is directed to methods for treating endothelial dysfunction, and diseases or conditions associated therewith, comprising administering to a mammal a therapeutically effective amount of a product of the invention.

Diseases or conditions associated with endothelial dysfunction may include vascular diseases, hypertension, diabetes (Type 1 or Type 2) and renal failure.

The invention also includes methods of treatment in which a product of the invention is administered to a mammal together with one or more other therapeutic agents. Said other therapeutic agent may include agents having a cardioavascular effect, for example ACE inhibitors, β-blockers, calcium channel blockers, potassium channel blockers etc.

The products of the invention may be administered therapeutically or prophylactically.

The following examples illustrate the above-described invention; however, it is not intended to restrict the scope of this invention in any manner. In the examples, the active ingredients comprise a combination of valsartan, fluvastatin and CGS 24592 or CGS 26393.

EXAMPLES

The products or the combinations described in the examples below provide medicaments with unexpected therapeutic benefits, or superior or more efficient properties to those of individual monotherapies.

Formulation Example 1:

Film-Coated Tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Active ingredients	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	Composition Per Unit (mg)	Standards
Granulation		
Active ingredients	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	Composition Per Unit (mg)	Standards
Core: Internal phase		
Active ingredients	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	Composition Per Unit (mg)
Active ingredients	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 fluidised bed dryer.

Milling/Blending

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

Encapsulation

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

Formulation Example 5:

Capsules:

Components	Composition Per Unit (mg)
Active ingredients	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	Composition Per Unit (mg)
Active ingredients	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					
Active ingredients	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	
Active ingredients	21.481
Calcium Carbonate	62.840
Sodium Bicarbonate	2.000
Microcrystalline Cellulose	57.220
Pregelatinized Starch	41.900
Purified Water [1)]	Q.S.
Magnesium Stearate	1.050
Talc	9.430
Target Capsule Fill Weight	195.92
Capsule Shell	
Hard gelatine Capsule Shell	48.500
Branding Ink (pre-printed)	
White Ink	Trace
Red Ink	Trace
Target Capsule Weight	244.42

[1)] partially removed during processing

Example 13:

Hard gelatin capsule

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

[1)] partially removed during processing

Example 14:

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

Component	Amount per unit [mg]
Table Core	
Active ingredients	84.24
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 [1)]	Q.S.

[1)] removed during processing

CLAIMS

1. A product comprising

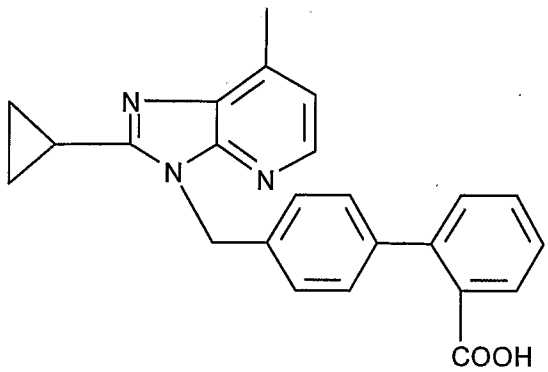
i.) a first antihypertensive agent;

ii.) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor;

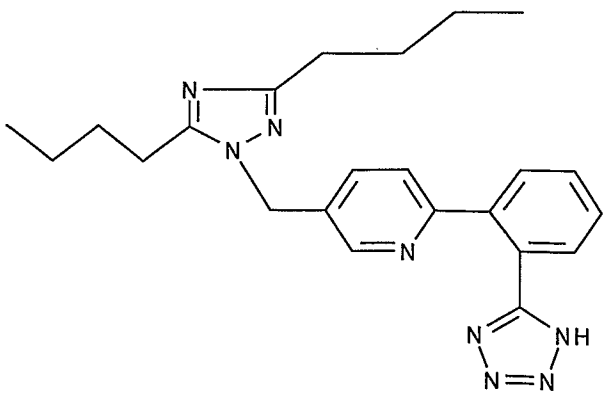
iii.) a cholesterol-lowering agent.

2. A product as claimed in claim 1 wherein the first antihypertensive agent is an angiotensin II receptor antagonist.

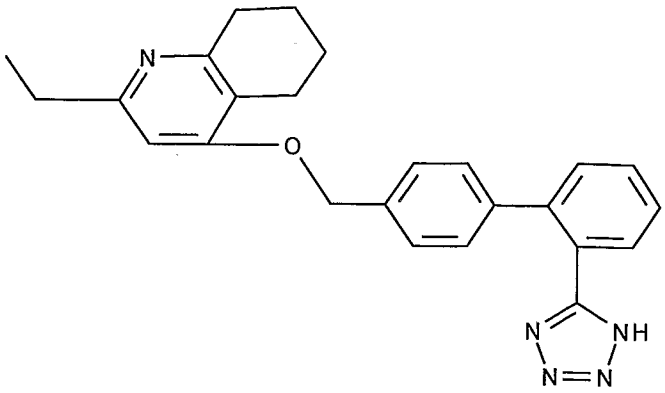
3. A product as claimed in claim 2 wherein the angiotensin II receptor antagonist is selected from the group consisting of valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, the compound with the designation E-1477 of the following formula



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



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



or a pharmaceutically acceptable salt or prodrug thereof.

4. A product as claimed in claim 2 wherein the angiotensin II receptor antagonist is selected from the group consisting of saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007, PD-123177, A-81988, BMS-180560, CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-3I5995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, saralasin, Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017, LY-301875, XH-148, XR-510, zolasartan and PD-123319, eprosartan mesylate, and olmesartan medoxomil, and pharmaceutically acceptable salts and prodrugs thereof.

5. A product as claimed in any of claims 2 to 5 wherein the angiotensin receptor antagonist is valsartan or a pharmaceutically acceptable salt or prodrug thereof.

6. A product as claimed in any preceding claim wherein the neutral endopeptidase inhibitor is selected from the group consisting of candoxatrilat, candoxatril, thiorphan, ecadotril, racecadotril and phosphoramidon, CGS 24128, CGS 24592, CGS 25155, CGS

25155, CGS 25462, CGS 26303, CGS 26393 and CGS 31447, and pharmaceutically acceptable salts and prodrugs thereof.

7. A product as claimed in any preceding claim wherein the cholesterol lowering agent is a HMG-Co-A reductase inhibitor.

8. A product as claimed in claim 7 wherein the HMG-Co-A reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, and pharmaceutically acceptable salts and prodrugs thereof.

9. A product as claimed in claim 8 wherein the HMG-Co-A reductase inhibitor is selected from the group consisting of fluvastatin, atorvastatin, pitavastatin and simvastatin, and pharmaceutically acceptable salts and prodrugs thereof.

10. A product as claimed in any preceding claim which further comprises a diuretic.

11. A product as claimed in claim 10 wherein the diuretic is a thiazide derivative selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon, and pharmaceutically acceptable salts and prodrugs thereof.

12. A product as claimed in claim 10 wherein the diuretic is selected from the group consisting of bendroflumethazide, benazepril, enalapril, and trandolapril, and pharmaceutically acceptable salts and prodrugs thereof.

13. A product as claimed in claim 1 wherein each active agent is included in a pharmaceutical composition, which may be the same composition which contains one or more other active agents or a different composition and which further contains a pharmaceutically acceptable excipient, diluent or carrier.

14. A product as claimed in any preceding claim wherein the product comprises a package containing each of the agents (i), (ii) and (iii) as a free combination.

15. A product as claimed in any preceding claim wherein the product comprises a composition containing each of the agents (i), (ii) and (iii) as a fixed combination.

16. A product as claimed in claim 15 wherein the composition is in the form of a tablet or capsule

17. A method for treating a cardiovascular or metabolic condition by prophylaxis or therapy, comprising the sequential or combined administration in a therapeutically effective amount of

i.) a first antihypertensive agent;

ii.) a second antihypertensive agent which is different from the first antihypertensive agent and is neutral endopeptidase inhibitor; and

iii.) a cholesterol-lowering agent.

18. A method as claimed in claim 17 wherein the cardiovascular condition is selected from the group consisting of hypertension, heart failure, angina, arrhythmia, myocardial infarction, hyperlipidemia, dyslipidemia, vascular disease, vascular damage, vascular hypertrophy, atherosclerosis, endothelial dysfunction, cardiac hypertrophy, angina, hyperlipidemia, dyslipidemia, hypercholesterolemia, atherosclerosis, vascular disease, restenosis, stroke, fibrosis or renal failure.

19. A method as claimed in claim 18 wherein the hypertension is hypertension associated with diabetes, hypertension associated with atherosclerosis or renovascular hypertension.

20. A method as claimed in claim 17 wherein the metabolic condition is selected from the group consisting of impaired glucose tolerance, diabetes mellitus, diabetic retinopathy and diabetic neuropathy.

21. A method as claimed in claim 20 wherein the diabetes is type-1 diabetes mellitus or type-2 diabetes mellitus.

22. A method for treating arteriosclerosis comprising administering to a mammal in combination or separately a therapeutically effective amount of the active agents of a product as claimed in any of claims 1 to 16.

23. A method for treating hypertension comprising administering to a mammal in combination or separately a therapeutically effective amount of the active agents of a product as claimed in any of claims 1 to 16.

24. A method for treating hyperlipidemia comprising administering to a mammal in combination or separately a therapeutically effective amount of the active agents of a product as claimed in any of claims 1 to 16.

25. A method for treating hypercholesterolemia comprising administering to a mammal in combination or separately a therapeutically effective amount of the active agents of a product as claimed in any of claims 1 to 16.

26. A method for treating atherosclerosis comprising administering to a mammal in combination or separately a therapeutically effective amount of the active agents of a product as claimed in any of claims 1 to 16.

27. A method for treating renal diseases comprising administering to a mammal in combination or separately a therapeutically effective amount of the active agents of a product as claimed in any of claims 1 to 16.

28. A method for treating diabetes comprising administering to a mammal in combination or separately a therapeutically effective amount of the active agents of a product as claimed in any of claims 1 to 16.

29. A method for treating vascular disease comprising administering to a mammal in combination or separately a therapeutically effective amount of the active agents of a product as claimed in any of claims 1 to 16.

30. A method for treating endothelial dysfunction comprising administering to a mammal in combination or separately a therapeutically effective amount of the active agents of a product as claimed in any of claims 1 to 16.

31. The use, for the manufacture of a medicament for the treatment of a cardiovascular or metabolic condition, of

i.) a first antihypertensive agent;

ii.) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor; and

iii.) a cholesterol-lowering agent.

32. The use of claim 31 wherein a diuretic is further used for the manufacture of the medicament.

33. The use of a first antihypertensive agent for the manufacture of a medicament for the treatment of a cardiovascular or metabolic condition, in combination with:

a.) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor; and

b.) a cholesterol-lowering agent.

34. The use of a cholesterol-lowering agent for the manufacture of a medicament for the treatment of a cardiovascular or metabolic condition, in combination with:

a.) a. first antihypertensive agent; and

b.) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor.

35. The use of claim 33 or claim 34 wherein a diuretic is further used for the manufacture of the medicament.

36. A combination comprising (i) a first antihypertensive agent, (ii) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor, and (iii) a cholesterol-lowering agent, which together comprise a therapeutically effective amount of (i), (ii) and (iii).

37. A combination comprising (i) a first antihypertensive agent, (ii) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor, (iii) a cholesterol-lowering agent, and (iv) an diuretic, which together comprise a therapeutically effective amount of (i), (ii), (iii) and (iv).

38. The use of synergistically effective amounts of (i) a first antihypertensive agent, (ii) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor, and (iii) a cholesterol-lowering agent for the manufacture of a medicament for simultaneous, separate or sequential administration of said agents in the treatment of a cardiovascular or metabolic disease.

39. A pharmaceutical product comprising (i) a first antihypertensive agent, (ii) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor, and (iii) a cholesterol-lowering agent as a combined preparation for simultaneous, separate or sequential use in the treatment of a cardiovascular or metabolic disease.

40. An article of manufacture comprising packaging material and, within the same packaging material, one or more pharmaceutical compositions, which single composition or plural compositions in combination comprise:

(i) a first antihypertensive agent,

(ii) a second antihypertensive agent which is different from the first antihypertensive agent and is a neutral endopeptidase inhibitor,

(iii) a cholesterol-lowering agent,

the article further including a label or instructions which indicates that the pharmaceutical composition(s) be used for treating a cardiovascular or metabolic disease.