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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF CARDIOVASCULAR AND OTHER ASSOCIATED DISORDERS

(57) Abstract: Pharmaceutical compositions comprising at least one endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor in combination with at least one another active agent optionally with other pharmaceutically acceptable excipients useful in the prophylaxis, treatment and/or amelioration of cardiovascular and other associated disorders such as one or more of coronary artery disease, congestive heart failure, angina, atherosclerosis, hyperlipidemia, diabetes, neurodegenerative disorders or the like are provided. Also described are process for preparation of such compositions and method of using such compositions.

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**PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF
CARDIOVASCULAR AND OTHER ASSOCIATED DISORDERS**

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising at least one
5 endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP)
inhibitor in combination with at least one another active agent optionally with other
pharmaceutically acceptable excipients useful in the prophylaxis, treatment and/or
amelioration of cardiovascular and other associated disorders such as one or more of
10 coronary artery disease, congestive heart failure, angina, atherosclerosis,
hyperlipidemia, diabetes, neurodegenerative disorders or the like. The present invention
also describes process for preparation of such compositions and method of using such
compositions for the prophylaxis, treatment and/or amelioration of cardiovascular and
other associated disorders in a subject which comprises the administration of an
effective amount of such composition in need thereof.

15

BACKGROUND OF THE INVENTION

Cardiovascular disorders such as Coronary artery disease (CAD) and Congestive heart
failure (CHF) are the leading cause of mortality in the developed world, and are
associated with substantial morbidity as well. Coronary heart disease is a multifactorial
20 disease in which the incidence and severity are affected by the lipid profile, the
presence of diabetes and the sex of the subject. Typically, the patient with CAD has
several concomitant conditions, including hypertension, diabetes, and hyperlipidemia,
increasing overall risk for poor outcomes and complicating treatment. A therapeutic
goal for the treatment of such patients is the development of pharmaceutical
25 compositions that can simultaneously target multiple underlying disease processes.

Hypertension is a major risk factor for cardiovascular disease and is poorly controlled
worldwide. Both systolic and diastolic blood pressure (SBP/DBP) has been shown to be
related to cardiovascular disease leading to morbidity and mortality. Hypertension
30 frequently coexists with hyperlipidemia and both are considered to be major risk factors
for developing cardiac disease ultimately resulting in adverse cardiac events. This
clustering of risk factors is potentially due to a common mechanism. Further, patient
compliance with the management of hypertension is generally better than patient

compliance with hyperlipidemia. It would therefore be advantageous for patients to have a single therapy which treats both of these conditions.

Cardiovascular disorder such as Angina pectoris is a severe constricting pain in the chest, often radiating from the precordium to the left shoulder and down the left arm. Often angina pectoris is due to ischemia of the heart and is usually caused by coronary disease. The symptomatic management of angina pectoris involves the use of a number of drugs, frequently as a combination of two or more of the following classes: beta-blockers, nitrates and calcium channel blockers. Most, if not all, of these patients require therapy with a lipid-lowering agent as well.

Atherosclerosis is a condition characterized by irregularly distributed lipid deposits in the intima of arteries, including coronary, carotid and peripheral arteries. It has been demonstrated in animal model that in cardiovascular disorders such as atherosclerosis, the cholesterol content of membranes associated with vascular smooth muscle and macrophage foam cells becomes elevated, resulting in the formation of discrete domains which serve as nucleating sites for the formation of extracellular crystals. Preventing crystal formation is an important goal as cholesterol in this state is practically inert and does not respond well to pharmacologic interventions that promote lesion regression. In addition, the normal production of NO by the endothelium is critical for maintaining vascular function. During atherosclerosis, however, endothelial dysfunction effects a significant reduction in NO production, resulting in increased monocyte and LDL infiltration, loss of smooth muscle cell function and abnormal proliferation, increased oxidative stress, and increased platelet aggregation. Pharmacologic interventions that restore endothelial function and NO metabolism have demonstrated benefit in the treatment of various cardiovascular disorders, including coronary artery disease.

Many individuals are at an elevated risk of suffering serious to life-threatening cardiovascular events, such as myocardial infarction (heart attack), cardiac arrest, congestive heart failure, stroke, peripheral vascular disease and/or claudication. The risk factors are numerous and widespread throughout the world population. They include cigarette smoking, diabetes, hypercholesterolemia (high serum cholesterol), hypertension, angina, systemic lupus erythematosus, prior heart attacks or strokes,

hemodialysis, hyperhomocysteine levels, obesity, sedentary lifestyle, receiving an organ transplant, atherosclerosis, and others. There is a need for a safe and convenient pharmaceutical formulation that would effectively reduce the risk of incurring a cardiovascular event in individuals who have these risk factors.

5. Endothelin (ET) is a peptide which is composed of 21 amino acids that is synthesized and released by the vascular endothelium. Endothelin is produced by enzymatic cleavage of a Trp-Val bond in the precursor peptide big endothelin (Big ET). This cleavage is caused by an endothelin converting enzyme (ECE). Endothelin exists as
- 10 three isoforms, ET-1, ET-2 and ET-3 (hereinafter, unless otherwise stated, 'endothelin' shall mean any or all of the isoforms of endothelin). Endothelin acts on two pharmacologically distinct subtypes of receptors, termed ET.sub.A and ET.sub.B that are expressed on a wide variety of vascular and non-vascular target cells, eliciting, for example, contraction and proliferation of vascular smooth muscle cells and release of
- 15 nitric oxide from endothelial cells. Endothelin is associated with smooth muscle contraction which is involved in the pathogenesis of, inter alia, cardiovascular, cerebrovascular, respiratory and renal pathophysiology. It has been shown, among other things, to constrict arteries and veins, increase mean arterial blood pressure, decrease cardiac output, increase cardiac contractility in vitro, stimulate mitogenesis in
- 20 vascular smooth muscle cells in vitro, stimulate release of atrial natriuretic factor in vitro and in vivo, increase plasma levels of vasopressin, aldosterone and catecholamines, inhibit release of renin in vitro and stimulate release of gonadotropins in vitro. An agent which suppresses endothelin production, such as an ECE inhibitor, or which inhibits the binding of endothelin to an endothelin receptor, such as an
- 25 endothelin receptor antagonist, antagonizes various physiological effects of endothelin and produces beneficial effects in a variety of therapeutic areas. Endothelin receptor antagonists and ECE inhibitors are therefore useful in treating a variety of diseases affected by endothelin. A non-exhaustive list of such diseases includes chronic heart failure, myocardial infarction, cardiogenic shock, systemic and pulmonary
- 30 hypertension, ischemia-reperfusion injury, atherosclerosis, coronary and systemic vasospastic disorders, cerebral vasospasm, and subarachnoid hemorrhage and the like.

Neutral Endopeptidase (NEP) is a cell surface enzyme that cleaves and inactivates neuropeptides. It is well established that the natriuretic peptide system is intimately

involved in the control and regulation of blood pressure and plasma volume in the body. In humans, this peptide family consists of atrial natriuretic peptide (ANP), brain natriuretic peptide and C-type natriuretic peptide. ANP is produced in the atria and its production is stimulated by endothelin, arginine vasopressin and catecholamines. Atrial wall tension, which can occur as a result of intravascular volume expansion, can also stimulate ANP production. The hemodynamic actions of natriuretic peptides within the cardiovascular system occur at many levels and include reducing preload and sympathetic tone, and increasing venous capacitance. Natriuretic peptides can also have antimitogenic actions within the cardiovascular tree. Natriuretic peptides are degraded by the metallopeptidase neutral endopeptidase enzyme (NEP). Thus NEP inhibitors primarily increase the levels of vasodilatory peptides including atrial natriuretic peptide and brain natriuretic peptide and also increase the half-life of other vasodilator peptides, including bradykinin and adrenomedullin thus enhancing vasodilation, thereby decreasing vascular tone and lowering blood pressure.

SLV-306 (Daglutril) is an orally active inhibitor of neutral endopeptidase (NEP) and endothelin conversion enzyme (ECE). It is a Benzazepine-N-acetic acid derivative which contains an oxo group in alpha position to the nitrogen atom and is substituted in position 3 by a 1-(carboxyalkyl) cyclopentyl-carbonylamino radical, and their salts and biolabile esters fall under the scope of protection of the benzazepine, benzoxazepine and benzothiazepine-N-acetic acid derivatives which contain an oxo group in the alpha position to the nitrogen atom and are substituted in position 3 by a 1-(carboxyalkyl) cyclopentyl-carbonylamino radical and have NEP-inhibitory effects on the heart, as described in US patent no. 5,677,297. The benzazepine-N-acetic acid compounds specifically SLV-306 used in the present invention are known from EP 0733642, EP 0830863, WO00/48601 and WO01/03699, and can be produced by the methods described in said US patent no. 5,677,297. SLV-306 is a poorly bio-available drug due to the poor solubility in the gastric fluid. Even when this drug is applied in the form of a salt and when they are dissolved in a buffer, it precipitates in the gastric fluid. The precipitate formed is very difficult to solubilize again, leading to a low overall bioavailability. EP 0733642 is related to these compounds and their physiologically acceptable salts as such and to the use of the compound in heart insufficiency. EP 0830863, WO00/48601 and WO01/03699 are related to the use of the aforementioned

- compounds in the improvement of gastrointestinal blood flow, in the treatment of hypertension and in the treatment and prophylaxis of cardiac damages induced by adriamycin and comparable anti-cancer drugs, respectively.
- 5 PCT publication no. WO2004062692 discloses a formulation with enhanced bioavailability consisting of a thermodynamically stable liquid or semisolid solution of the poorly water-soluble biologically active substance i.e. SLV-306. US publication no. 20040186083 describes a method for the prophylaxis or treatment of a pathological condition, the method comprising administering to a subject susceptible to or afflicted
- 10 with such condition an aldosterone receptor antagonist such as eplerenone and spironolactone and an endothelin receptor antagonist such as bosentan, sitaxsentan, darusentan and tezosentan, further comprising administering a third amount of an ECE inhibitor such as SLV-306. US publication no. 2004063719 pertains to a method for treating a vascular condition by a combination of at least two agents selected from an
- 15 antipressor agent (ACE inhibitor, an angiotensin-II receptor antagonist, an endothelin antagonist, a non-peptidal endothelin antagonist), and an ECE inhibitor, and a sex hormone such as testosterone-like compound. PCT publication no. WO200124827 describes the use of an endothelin blocker such as SLV-306 in combination with an integrin receptor antagonist such as abciximab for the manufacture of medicaments for
- 20 the treatment or prevention of diseases. PCT publication no. WO9635453 relates to a composition comprising an endothelin antagonist and/or an endothelin synthase (ECE) inhibitor, in combination with at least one of a progestin, an estrogen, a cyclooxygenase inhibitor, a nitric oxide (NO) donor and/or an NO substrate.
- 25 Kramsch et al, Journal of Human Hypertension (1995) Supp. 1, 53-59 discloses the use of calcium channel blockers, including amlodipine, to treat atherosclerosis. This reference further suggests that atherosclerosis can be treated with a combination of amlodipine and a lipid-lowering agent. Human trials have shown that calcium channel blockers have beneficial effects in the treatment of early atherosclerotic lesions (see, for
- 30 example, Lichtlen et al, Retardation of angiographic progression of coronary artery disease by nifedipine, Lancet (1990), 335, 1109-13; and Waters et al, A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis, Circulation (1990), 82, 1940-53). European Patent No. 0247633 discloses that certain statins, including atorvastatin, are hypolipidaemic agents

and as such are useful in treating atherosclerosis. Jukema et al (Circulation (1995) Supp. 1, 1-197) discloses that there is evidence that calcium channel blockers act synergistically in combination with lipid-lowering agents, for example, HMG-CoA reductase inhibitors, specifically pravastatin. Orekhov et al (Cardiovascular Drugs and
5 Therapy (1997), 11, 350) discloses the use of amlodipine in combination with lovastatin for the treatment of atherosclerosis.

Improved drug therapies for the treatment of subjects suffering from or susceptible to life-threatening cardiovascular and other associated disorders are highly desirable.
10 However, still there exists a need for a patient compliant, safe and effective compositions that are useful in the management of cardiovascular and other associated disorders.

SUMMARY OF THE INVENTION

15 It is an objective of the present invention to provide pharmaceutical compositions comprising at least one endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor as active agent in combination with at least one another active agent optionally with one or more pharmaceutically acceptable excipients.

20 It is an objective of the present invention to provide pharmaceutical compositions comprising at least one endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor as active agent in combination with at least one another active agent selected from a group comprising antihypertensives such as calcium
25 blockers, ACE Inhibitors, angiotensin antagonists, alpha-adrenergic receptor blockers, beta-adrenergic receptor blockers, diuretics, vasodilators; antidiabetics such as biguanide, sulfonylurea or glitazone; lipid lowering agents such as cholesterol absorption inhibitors; platelet function altering agent such as platelet aggregation inhibitors; serum homocysteine lowering agent; and the like or mixtures thereof optionally with one or more pharmaceutically acceptable excipients.

30 It is an objective of the present invention to provide pharmaceutical compositions comprising at least one endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor as active agent in combination with a lipid lowering agent such as ezetimibe, niacin, or policosanol or its pharmaceutically acceptable salts,

polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof optionally with one or more pharmaceutically acceptable excipients.

5 It is an objective of the present invention to provide pharmaceutical compositions comprising at least one endothelin conversion enzyme (ECE) inhibitor and neutral endopeptidase (NEP) inhibitor which is preferably SLV-306 or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof as active agent in combination with at least one another active agent optionally with one or more pharmaceutically acceptable excipients.

10 It is a further objective of the present invention to provide process for the preparation of such pharmaceutical composition, which comprises optionally treating the active agent(s) with one or more pharmaceutically acceptable excipients and formulating into a suitable dosage form.

15 It is yet another objective of the present invention to provide a method of using such composition which comprises administering to a subject in need thereof an effective amount of the composition. The compositions of the present invention are useful for the prophylaxis, treatment and/or amelioration of cardiovascular and other associated disorders.

20 It is still further objective of the present invention to provide pharmaceutical compositions useful in the prophylaxis, treatment and/or amelioration of cardiovascular and other associated disorders such as chronic heart failure, coronary artery disease, congestive heart failure, angina, atherosclerosis, hyperlipidemia, diabetes, myocardial infarction, cardiogenic shock, systemic and pulmonary hypertension, ischemia-reperfusion injury, coronary and systemic vasospastic disorders, cerebral vasospasm, and subarachnoid hemorrhage, hyperglycemia, hyperlipidemia, metabolic disorders, renal disorders, neurodegenerative disorders, and the like or a combination of such disorders.

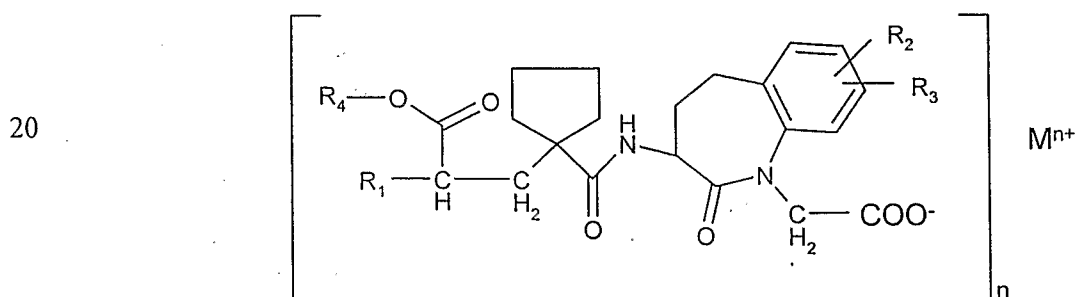
30 DETAILED DESCRIPTION OF THE INVENTION

The present invention describes pharmaceutical compositions comprising at least one endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor as active agent or its pharmaceutically acceptable salts, esters, hydrates, 35 solvates, polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms,

prodrugs or mixtures thereof in combination with at least one another active agent optionally with one or more pharmaceutically acceptable excipients.

In an embodiment of the present invention, the endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor is selected from but not limited to group comprising CGS 26303, CGS 25462, phosphoramidon, candoxatril, sinorphan, omapatrilat, FR901533, TMC-66, SM-19712, SLV-306, KC-12615, KC-90095-1-AC, CGS-26303, CGS-30440, CGS-31447, CGS-26670, Sch-54470 or pharmaceutically acceptable salts, esters, hydrates, solvates, polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms, prodrugs or mixtures thereof. In a preferred embodiment, the endothelin conversion enzyme (ECE) inhibitor and neutral endopeptidase (NEP) inhibitor is SLV-306 (also known as Daglutril) or its pharmaceutically acceptable salts, esters, hydrates, solvates, polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms, prodrugs or mixtures thereof.

In an embodiment, the endothelin conversion enzyme (ECE) and neutral endopeptidase (NEP) inhibitor of the present invention has the general formula (Formula-1):



Formula-1

Wherein:

R_1 is a selected from the group consisting of (C₁-C₆) alkoxy (C₁-C₆) alkyl which may be substituted by a (C₁-C₆) alkoxy, phenyl-(C₁-C₆)-alkyl and phenyloxy-(C₁-C₆)-alkyl, wherein the phenyl group may be substituted with (C₁-C₆) alkyl, (C₁-C₆) alkoxy or halogen, and naphthyl-(C₁-C₆)-alkyl,

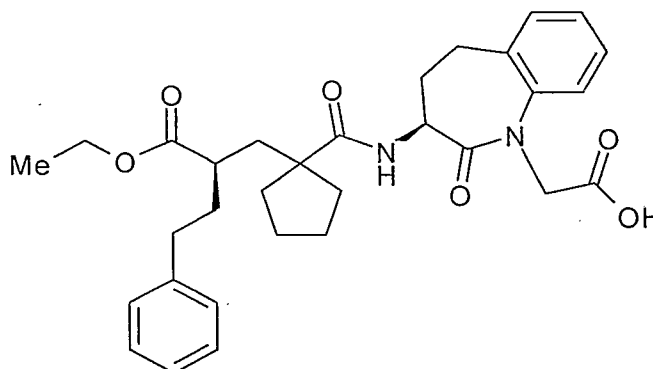
R_2 and R_3 are both independently hydrogen or halogen,

R_4 is a biolabile ester forming group,

M is hydrogen or a metal ion, preferably a bivalent metal ion, and

n is 1, 2 or 3.

More preferably the endothelin conversion enzyme (ECE) and neutral endopeptidase (NEP) inhibitor is SLV-306 having the formula (Formula-2):



Formula-2

- 5 In an embodiment of the present invention, the pharmaceutical compositions comprise endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor preferably SLV-306 in combination with at least one another active agent(s) selected from a group comprising antihypertensives such as calcium channel blockers, ACE Inhibitors, angiotensin antagonists, alpha-adrenergic receptor blockers, beta-adrenergic receptor blockers, diuretics, vasodilators or mixtures thereof; antidiabetics
- 10 such as biguanide, sulfonylurea or glitazone; lipid lowering agents such as cholesterol absorption inhibitors; platelet function altering agent such as platelet aggregation inhibitors; serum homocysteine lowering agent; and the like or mixtures thereof optionally with one or more pharmaceutically acceptable excipients.
- 15 In an embodiment of the present invention, the pharmaceutical compositions comprise ECE inhibitor and/or NEP inhibitor preferably SLV-306 in combination with at least one guanidine derivative selected from but not limited to a group comprising bethanidine, debrisoquin, guanabenz, guanadrel, guanethidine, guanfacine, guanoxaben-
- 20 z, guanoxan; hydrazines/phthalazines such as dihydralazine, endralazine, hydralazine, pheniprazine, pildralazine; imidazole derivatives such as clonidine, lofexidine, moxonidine, phentolamine, tiamenidine; or pharmaceutically acceptable salts, esters, hydrates, solvates, polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms, prodrugs, or mixtures thereof.
- 25 In an embodiment, the present invention provides pharmaceutical compositions comprising SLV-306 or its pharmaceutically acceptable salts, esters, hydrates, solvates,

polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms, prodrugs, or mixtures thereof as active agent in combination with a lipid lowering agent selected from but not limited to a group comprising ezetimibe, niacin, or policosanol or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof optionally with one or more pharmaceutically acceptable excipients.

Calcium channel blockers within the scope of the present invention include but are not limited to amlodipine, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone or perhexiline or mixtures thereof. Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) according to the present invention include but are not limited to alacepril, benazepril, captopril, ceronapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moveltipril, perindopril, quinapril, ramipril, spirapril, temocapril ortrandolapril or mixtures thereof. Angiotensin-II receptor antagonists (A-II antagonists) of this invention include but are not limited to candesartan, eprosartan, irbesartan, losartan, or valsartan or mixtures thereof. Beta-Blockers which are within the scope of this invention include but are not limited to acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantalol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butidrine hydrochloride, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, or xibenolol or mixtures thereof. Alpha-Blockers which are within the scope of the present invention include but are not limited to amosulalol, arotinolol, dapiprazole, doxazosin, fenspiride, indoramin, labetolol, naftopidil, nicergoline, prazosin, tamsulosin, tolazoline, trimazosin or yohimbine, or mixtures thereof.

The term 'vasodilator' used herein unless otherwise stated is meant to include cerebral vasodilators, coronary vasodilators or peripheral vasodilators. Cerebral vasodilators

within the scope of this invention include but are not limited to bencyclane, cinnarizine, citicoline, cyclandelate, ciclonicate, diisopropylamine dichloroacetate, eburnamonine, fasudil, fenoxedil, flunarizine, ibudilast, ifenprodil, lomerizine, nafronyl, nicametate, nicergoline, nimodipine, papaverine, pentifylline, tinofedrine, vincamine, vinpocetine, 5 or viquidil or mixtures thereof. Coronary vasodilators of this invention include but are not limited to amotriphene, bendazol, benfurodil hemisuccinate, benziodarone, chloracizine, chromonar, clobenfuril, clonitrate, cloricromen, dilazep, dipyridamole, droprenilamine, efloxate, erythrityl tetranitrate, fendiline, floredil, ganglefene, hexestrol bis(β -diethylaminoethyl)ether, hexobendine, itramin tosylate, khellin, lidoflazine, 10 mannitol hexanitate, medibazine, nitroglycerin, pentaerythritol tetranitrate, pentrinitrol, perhexiline, pimefylline, prenylamine, propatyl nitrate, trapidil, tricromyl, trimetazidine, trolnitrate phosphate or visnadine or mixtures thereof. Peripheral vasodilators within the scope of this invention include, but are not limited to aluminium nicotinate, bamethan, bencyclane, betahistine, bradykinin, brovincamine, bufeniode, buflomedil, butalamine, 15 cetiedil, ciclonicate, cinepazide, cinnarizine, cyclandelate, diisopropylamine dichloroacetate, eledoisin, fenoxedil, flunarizine, hepronicate, ifenprodil, iloprost, inositol niacinate, isoxsuprine, kallidin, kallikrein, moxisylyte, nafronyl, nicametate, nicergoline, nicofuranose, nyldrin, pentifylline, pentoxifylline, piribedil, prostaglandin E₁, suloctidil, tolazoline or xanthinol niacinate or mixtures thereof.

20 The term 'diuretic' according to the present invention includes but is not limited to diuretic benzothiadiazine derivatives, diuretic organomercurials, diuretic purines, diuretic steroids, diuretic sulfonamide derivatives, diuretic uracils and other diuretics such as amanozine, amiloride, arbutin, chlorazanyl, ethacrynic acid, etozolin, 25 hydracarbazine, isosorbide, mannitol, metochalcone, muzolimine, perhexiline, ticrynafene, triamterene, theobromine or urea or mixtures thereof. Diuretic benzothiadiazine derivatives of the present invention include but are not limited to althiazide, bendroflumethiazide, benzthiazide, benzylhydrochlorothiazide, buthiazide, chlorothiazide, chlorthalidone, cyclopenthiazide, cyclothiazide, epithiazide, ethiazide, 30 fenquizone, indapamide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, meticrane, metolazone, paraflutizide, polythiazide, quinethazone, teclothiazide, or trichlormethiazide or mixtures thereof. Diuretic sulfonamide derivatives of this invention include but are not limited to acetazolamide, ambuside, azosemide,

- bumetanide, butazolamide, chloraminophenamide, clofenamide, clopamide, clorexolone, disulfamide, ethozolamide, furosemide, mefruside, methazolamide, piretanide, torsemide, tripamide or xipamide or mixtures thereof.
- 5 Anti-diabetic or anti-hyperglycemic agents according to the present invention include but are not limited to biguanides such as metformin; thiazolidinediones such as pioglitazone, rosiglitazone or troglitazone; sulfonylureas such as acetohexamide, chlorpropamide, tolazimide, tolbutamide, gliclazide, glipizide, glyburide, or glimeperide; benzoic acid derivatives and glucosidase inhibitors such as acarbose or
- 10 miglitol or mixtures thereof. Preferred lipid lowering agents within the scope of the present invention include but are not limited to cholesterol absorption inhibitors such as ezetimibe; bile acid sequestrants; probucol; niacin; policosanol; or fibric acid agents, or their pharmaceutically acceptable salts, esters, hydrates, solvates, polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms, prodrugs or mixtures thereof.
- 15 Platelet function altering agent according to the present invention is selected from but not limited to a group comprising aspirin, ticlopidine, dipyridamole, clopidogrel, policosanol, a glycoprotein IIb/IIIa receptor inhibitor, or a non-steroidal anti-inflammatory drug. Serum homocysteine lowering agent useful in the present invention
- 20 is selected from but not limited to a group comprising folic acid, vitamin B6 or vitamin B12. In another embodiment, the composition comprises an ECE and/or NEP inhibitor in combination with an antihistaminic active agent such as chlorpheniramine, chlorphenoxamine, or the like or mixtures thereof.
- 25 In one embodiment the ECE and/or NEP inhibitor can be administered in combination with another antihypertensive or blood pressure regulating agent for the effective prophylaxis, treatment and/or amelioration of hypertension and associated cardiovascular disorder(s). In another embodiment the ECE and/or NEP inhibitor can be administered in combination with a lipid lowering agent or anti-hyperlipidemic
- 30 agent for the prophylaxis, treatment and/or amelioration of hypertension and associated hyperlipidemia. In another embodiment the ECE and/or NEP inhibitor can be administered in combination with antidiabetics, platelet function altering agent, and/or serum homocysteine lowering agent or the like or mixtures thereof for the prophylaxis, treatment and/or amelioration of cardiovascular and associated disorders.

In one embodiment, a combination comprising ECE and/or NEP inhibitor and an antihypertensive agent is used in the prophylaxis, treatment and/or amelioration of cardiovascular and other associated disorders selected from but not limited to a group comprising chronic heart failure, coronary artery disease, congestive heart failure, angina, atherosclerosis, hyperlipidemia, diabetes, myocardial infarction, cardiogenic shock, systemic and pulmonary hypertension, ischemia-reperfusion injury, ischaemic heart disease, stroke or transient ischaemic attack, coronary and systemic vasospastic disorders, cerebral vasospasm, and subarachnoid hemorrhage, aneurysm, angina pectoris, angioneurotic edema, aortic valve stenosis, arrhythmia, arrhythmogenic right ventricular dysplasia, arteriosclerosis, arteriovenous malformations, atrial fibrillation, Behcet syndrome, bradycardia, cardiac tamponade, cardiomegaly, cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiovascular diseases, carotid stenosis, cerebral hemorrhage, Churg-Strauss syndrome, Ebstein's anomaly, Eisenmenger complex, embolism, endocarditis, bacterial fibromuscular dysplasia, heart block, congenital heart diseases, congestive heart failure, heart valve diseases, hematoma, subdural Hippel-Lindau disease, hyperemia, hypertension, hypertrophy, hypoplastic syndrome, intermittent claudication, Klippel-Trenaunay-Weber syndrome, lateral medullary syndrome, long QT syndrome, microvascular angina, mitral valve prolapse, moyamoya disease, mucocutaneous lymph node syndrome, myocardial infarction, myocardial ischemia, myocarditis, pericarditis, peripheral vascular diseases, Phlebitis, polyarteritis nodosa, pulmonary atresia, Raynaud disease, Sneddon syndrome, superior vena cava syndrome, tachycardia, Takayasu's arteritis, telangiectasia, hereditary hemorrhagic, temporal arteritis, tetralogy of fallot, thromboangiitis obliterans, thrombosis, tricuspid atresia, varicose veins, vascular diseases, vasculitis, vasospasm, intracranial, ventricular fibrillation, Williams syndrome, Wolff-Parkinson-White syndrome or the like, or combinations thereof.

In an embodiment, the compositions of the present invention comprising an ECE and/or NEP inhibitor and at least one active agent selected from a group comprising dopamine agonists/COMT inhibitors; anticholinergics; selegiline; deprenyl; NDA antagonists; beta interferons; monoclonal antibodies; glutamate inhibitors; cholinesterase inhibitors such as galantamine, rivastigmine, donepezil or tacrine; glatiramer acetate; mitoxantrone, corticosteroids; muscle relaxants; anticonvulsants such as topiramate,

lamotrigine, levetiracetam; aldose reductase inhibitors such as thioctic acid; NMDA antagonists; dopamine antagonists or the like or mixtures thereof, are useful for the prophylaxis, treatment and/or amelioration of one or more neurodegenerative disorder such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, neuropathies, 5 Huntington's disease, Amyotrophic lateral sclerosis (ALS), or the like.

The combinations of the present invention also can be formulated with one or more pharmaceutically acceptable excipient(s) in the form of a pharmaceutical composition. The excipient(s) may be used as a carrier and must be acceptable in the sense of being 10 compatible with the other ingredients of the composition or must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and preferably is formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from about 0.05% to 95% by weight of the active compounds. Other pharmacologically active agents can also be present, including other compounds useful in the present 15 invention. The compositions can be formulated as powders, pellets, tablets, capsules, solutions, suspensions, emulsions, patches, topical preparations, parenterals, etc. The pharmaceutical compositions of the invention can be prepared by any of the formulation techniques known to a person skilled in art, such as by admixing the components and formulating it into a suitable dosage form, for example, mixing the combination of an ECE and/or NEP inhibitor and another active agent with 20 pharmaceutically acceptable excipients and compressing the same into a tablet. The combinations and compositions of the present invention can be administered by any conventional means available for use in conjunction with pharmaceuticals. Oral delivery of the ECE and/or NEP inhibitors, more preferably SLV-306 and at least one active agent 25 useful in the management of cardiovascular and other associated disorders is preferred.

Oral delivery of the ECE and/or NEP inhibitor and at least one active agent useful in the prophylaxis, treatment and/or amelioration of cardiovascular and other associated disorders of the present invention can include formulations to provide immediate delivery and/or 30 controlled or prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. Compositions for immediate delivery of active agent(s) include but are not limited to solutions, suspensions, emulsions, fast-dissolving tablets or capsules, disintegrating tablets, Self Microemulsifying Drug Delivery Systems (SMEDDS) or the like. Prolonged or sustained delivery formulations include but are not limited to pH

independent drug release systems or pH sensitive drug release system based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the composition achieved by floatation or bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. Dosage forms intended to deliver a fraction of active agent(s) in an immediate release form and the other fraction as a modified release or pulsatile release form as multiple units are also within the scope of the present invention. The intended effect is to extend the time period over which the active agent(s) are delivered to the site of action by manipulation of the dosage form such as enteric-coated compositions. Suitable polymers for enteric coating include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester. In an embodiment, the composition comprising the combination of the present invention can be formulated into a controlled release system by using a suitable rate controlling polymer such as cellulosic polymers, alginates, methacrylate polymers, gums, or the like or the mixtures thereof.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of active ingredients of the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid or as an oil-in-water or water-in-oil emulsion. Compressed tablets can be prepared by compressing, in a suitable machine, the material in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made, for example, by molding the powdered compound in a suitable machine. In a preferred embodiment, the compositions of the present invention are formulated as solid oral dosage form compositions possessing good bioavailability comprising one or more alkaline substance and/or surfactants. In another preferred embodiment, the solid oral dosage form composition preferably as capsule is formulated as SMEDDS. Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise excipients such as wetting agents, emulsifying and suspending agents, or sweetening, flavoring, or perfuming agents. Pharmaceutical

compositions suitable for buccal or sublingual administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the drugs in an inert base such as gelatin and glycerin or sucrose and acacia.

5 In an embodiment of the present invention, the amount of ECE and/or NEP inhibitor and at least one active agent(s) useful in the management of cardiovascular and other associated disorders that can be combined with pharmaceutically acceptable excipients to produce a dosage form to be administered varies depending upon the host treated and
10 the particular mode of administration. The excipients that can be used for preparation of such compositions are selected from but not limited to diluents, disintegrants, binders, fillers, bulking agents, anti-adherents, anti-oxidants, buffering agents, colorants, flavoring agents, coating agents, plasticizers, organic solvents, stabilizers, preservatives, lubricants, glidants, chelating agents, and the like known to the art used
15 either alone or in combination thereof. In an embodiment, the filler(s) used in the present invention is selected from but not limited to a group comprising lactose, mannitol, sorbitol, starch, microcrystalline cellulose, xylitol, fructose, sucrose, dextrose, dicalcium phosphate, calcium sulphate and the like or mixtures thereof. The disintegrants used in the present invention include but not limited to starch or its
20 derivatives, partially pregelatinized maize starch, croscarmellose sodium, sodium starch glycollate, and the like used either alone or in combination thereof. The lubricants used in the present invention include but not limited to talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil and the like used either alone or in combination thereof. The tablets may be coated with a material such as glyceryl
25 monostearate, glyceryl distearate, cellulose acetate phthalate, hydroxypropylcellulose phthalate, polyvinylacetate phthalate, methylmethacrylate polymer, a polymer mixture such as Eudragit®, cellulosic polymers, carbomers, zein, wax or similar material, or any other dissolvable coat, to delay absorption in the gastrointestinal tract. Capsules for oral use include hard gelatin capsules in which the components are mixed with a solid
30 diluent or soft gelatin capsules wherein the fill material exist as aqueous or hydroalcoholic or oily systems.

The compositions of the present invention may be in the form of tablets such as layered or monolithic tablet, mini-tablets such as such as layered or monolithic mini-tablets,

capsules, pellets, granules, patches, powders and other dosage forms suitable for oral administration. In a preferred embodiment, the composition of the present invention is in the form of layered or monolithic tablets/mini-tablets. The composition can be prepared by either direct compression, dry compression (slugging) or by granulation. In

5 a preferred embodiment of the present invention, the oral composition is prepared by direct compression or compaction granulation. The composition prepared by granulation technique is either by aqueous or non-aqueous technique or melt granulation technique. The non-aqueous solvent used is selected from a group comprising dehydrated alcohol, isopropyl alcohol, methylene chloride or acetone. In an

10 embodiment, the compositions of the present invention are in the form of granules, beads or pellets that may be further compacted, compressed, or moulded, or made into capsules. The compositions may be coated with a functional coating. By the term 'functional coating' it is herein implied that the coating composition comprises a part of the active agent(s) and/or the composition comprises excipients which aid in

15 controlling the rate of release of the active agent(s) and/or the composition comprises additionally another active agent which is different from the active agent present in the core composition. The composition may be formulated as layered tablets comprising at least two layers wherein the same active agent is present in all the layers exhibiting different release profiles or one or more additional active agent(s) is present in the

20 layers exhibiting different release profiles. The coating composition employed in the present invention may be an aqueous, non-aqueous or a hydro-alcoholic system. The solvents used to prepare a non-aqueous coating composition is selected from but not limited to a group comprising dehydrated alcohol, isopropyl alcohol, methylene chloride, acetone or any other solvent known to the art for such use, or mixtures thereof. In an embodiment, the compositions of the present invention comprises of at

25 least two fractions wherein one fraction comprises the active agent(s) optionally with one or more pharmaceutically acceptable excipients in such quantities so as to provide an immediate release of the active agent(s) and the other fraction comprises the active agent(s) optionally with one or more pharmaceutically acceptable excipients in such

30 quantities so as to provide a sustained release of the active agent(s).

In another embodiment of the present invention is provided a process for the preparation of such pharmaceutical composition, which comprises treating the

combination of active agents optionally with one or more pharmaceutically acceptable excipients and formulating into a suitable dosage form.

It is another embodiment of the present invention to provide a composition comprising
5 a combination of ECE and/or NEP inhibitor and at least one active agent useful in the management of cardiovascular and other associated disorders with increased bioavailability that provides an effective concentration of active agent(s) to obtain the desired therapeutic effect. In another embodiment of the present invention, the combination of the ECE and/or NEP inhibitor with at least one active agent may lead to
10 a synergistic effect and/or reduction in the dose required for one or both of the active agent(s) and/or lead to the reduction in the adverse effect associated with the administration of the composition of the present invention.

In another embodiment is provided a method of using such composition which
15 comprises administering to a subject in need thereof an effective amount of the composition. The compositions of the present invention are useful for the prophylaxis, treatment and/or amelioration of cardiovascular and other associated disorders.

In yet another embodiment, the present invention provides the use of the combination
20 comprising an ECE and/or NEP inhibitor with at least one active agent for the manufacture of a medicament for the prevention treatment and/or amelioration of cardiovascular disease and/or for the reduction in the risk of cardiovascular disease and other associated disorders. In a further embodiment, the cardiovascular and other associated disorders are selected from but not limited to a group comprising chronic
25 heart failure, coronary artery disease, congestive heart failure, angina, atherosclerosis, hyperlipidemia, diabetes, myocardial infarction, cardiogenic shock, systemic and pulmonary hypertension, ischemia-reperfusion injury, coronary and systemic vasospastic disorders, cerebral vasospasm, and subarachnoid hemorrhage, hyperglycemia, hyperlipidemia, metabolic disorders, renal disorders, neurodegenerative
30 disorders, and the like or a combination of such disorders.

The examples given below serve to illustrate embodiments of the present invention. However they do not intend to limit the scope of present invention.

EXAMPLES**Example-1: Immediate release Tablets**

S. No. Ingredient		Quantity (mg/tablet)
	1. SLV-306	150.0
5	2. Atenolol	50.0
	3. Sodium bicarbonate	150.0
	4. Microcrystalline cellulose	105.0
	5. Sodium starch glycollate	20.0
	6. Povidone K-30	10.0
10	7. Magnesium stearate	5.0
	8. Sodium starch glycollate	20.0
	9. Colloidal silicon dioxide	5.0
	10. Magnesium Stearate	5.0

Procedure:

- 15 i) Sift and mix ingredients 1, 2, 3, 4, 5, 6 & 7.
- ii) Pass the ingredients of step (i) through roller compactor to obtain compacts.
Pass the compacts through sieve #16 and retain on sieve #60 to get granules.
- iii) Mix the granules of step (ii) with ingredients 8, 9 & 10.
- iv) Compress the granules of step (iii) into tablets.

20

Example-2: Extended release Tablets

S. No. Ingredient		Quantity (mg/tablet)
	1. SLV-306 calcium	75.0
	2. Metformin hydrochloride	500.0
25	3. Sodium bicarbonate	170.0
	4. Hydroxypropyl methylcellulose	90.0
	5. Povidone K-90	30.0
	6. Croscarmellose Sodium	18.0
	7. Magnesium Stearate	9.0
30	8. Purified talc	4.0
	9. Colloidal silicon dioxide	4.0

Procedure:

- i) Sift and mix ingredients 1, 2, 3, 4, 5 & 6.

- ii) Pass the ingredients of step (i) through roller compactor to obtain compacts.
Pass the compacts through sieve #16 and retain on sieve #60 to get granules.
- iii) Mix the granules of step (ii) with ingredients 7, 8 & 9.
- iv) Compress the granules of step (iii) into tablets.

5

Example-3: Dual release Capsule**A) Immediate release fraction**

S. No.	Ingredient	Quantity (mg/capsule)
1.	SLV-306	75.0
10 2.	Policosanol	40.0
3.	Sodium bicarbonate	75.0
4.	Sodium starch glycollate	5.0
5.	Microcrystalline cellulose	37.0
6.	Povidone K-30	5.0
15 7.	Sodium lauryl sulfate	3.0
8.	Magnesium stearate	2.5
9.	Sodium starch glycollate	5.0
10.	Magnesium stearate	2.5

Procedure:

- 20 i) Mix ingredients 1 to 8 together and sift through mesh #30 sieve.
- ii) Pass the ingredients of step (i) through roller compactor to obtain compacts.
Pass the compacts through sieve #22 and retain on sieve #60 to get granules.
- iii) Mix the granules of step (ii) with ingredients 9 & 10.

B) Sustained release fraction

S. No.	Ingredient	Quantity (mg/capsule)
1.	SLV-306	75.0
2.	Ezetimibe	10.0
3.	Sodium bicarbonate	75.0
4.	Methacrylate polymer (Eudragit® L100-55)	38.0
30 5.	Hydroxypropyl methylcellulose	15.0
6.	Povidone K-90	15.0
7.	Colloidal silicon dioxide	2.0

Procedure:

- i) Mix ingredients 1 to 7 together and sift through mesh #30 sieve.
- ii) Pass the ingredients of step (i) through roller compactor to obtain compacts.
Pass the compacts through sieve #22 and retain on sieve #60 to get granules.

5 **C) Preparation of capsule:**

Mix the material in step (A) (iii) and the material in step (B) (ii) and fill into hard gelatin capsule.

Example-4: Tablet

10	S. No. Ingredient	Quantity (mg/tablet)
	1. SLV-306	75.0
	2. Amlodipine besylate	13.9
	3. Lactose	200.0
	4. Microcrystalline cellulose	121.0
15	5. Sodium lauryl sulfate	5.0
	6. Colloidal silicon dioxide	5.0
	7. Sodium bicarbonate	75.1
	8. Glyceryl behenate	3.0

Procedure:

- 20 i) Mix ingredients 1, 2, 3 & 4 and sift through mesh #30 sieve.
- ii) Mix ingredients 5, 6 & 7 and sift through mesh #60 sieve.
- iii) Mix the material of step (i) with the material of step (ii).
- iv) Compress the material of step (iii) into tablets.

25 **Example-5: Tablet**

	S. No. Ingredient	Quantity (mg/tablet)
	1. SLV-306	600.0
	2. Eprosartan	100.0
	3. Effer soda TM	200.0
30	4. Croscarmellose sodium	40.0
	5. Magnesium stearate	5.0
	6. Croscarmellose sodium	40.0
	7. Magnesium stearate	10.10
	8. Colloidal silicon dioxide	5.0

Procedure:

- i) Sift and mix ingredients 1, 2, 3, 4 & 5.
- ii) Pass the ingredients of step (i) through roller compactor to obtain compacts.
Pass the compacts through sieve #16 and retain on sieve #60 to get granules.
- 5 iii) Mix the granules of step (ii) with ingredients 6, 7 & 8 and sift through mesh #40 sieve.
- iv) Compress the granules of step (iii) into tablets.

Example-6: Tablet

10	S. No. Ingredient	Quantity (mg/tablet)
	1. SLV-306	150.00
	2. Captopril	12.50
	3. Sodium carbonate	200.00
	4. Microcrystalline cellulose	187.50
15	5. Crospovidone	30.00
	6. Povidone K-30	25.00
	7. Purified water	q.s.
	8. Crospovidone	30.00
	9. Magnesium stearate	8.00
20	10. Colloidal silicon dioxide	4.00
	11. Talc	3.00

Procedure:

- i) Sift and mix ingredients 1, 2, 3, 4 & 5.
- ii) Dissolve ingredient 6 in 7 and granulate with the mixture of step (i).
- 25 iii) Dry the granules of step (ii) followed by sifting through mesh #20 sieve and blending with ingredients 8, 9, 10 & 11.
- iv) Compress the material of step (iii) into tablets.

Example-7: Tablet

30	S. No. Ingredient	Quantity (mg/tablet)
	1. SLV-306	300.0
	2. Hydrochlorothiazide	25.0
	3. Docusate sodium	10.0
	4. Calcium carbonate	250.0

	5.	Microcrystalline cellulose	147.0
	6.	Croscarmellose sodium	20.0
	7.	Starch	35.0
	8.	Purified water	q.s.
5	9.	Croscarmellose sodium	28.0
	10.	Magnesium stearate	10.0

Procedure:

- i) Sift and mix ingredients 1, 2, 3, 4, 5 & 6.
- ii) Granulate the mixture of step (i) with starch mucilage prepared by dispersing ingredient 7 in 8.
- iii) Dry the granules of step (ii) followed by sifting and blending with ingredients 9 & 10.
- iv) Compress the material of step (iii) into tablets.

15 **Example-8: Tablet**

	S. No.	Ingredient	Quantity (mg/tablet)
	1.	SLV-306	300.0
	2.	Amiloride	5.0
	3.	Docusate sodium	10.0
20	4.	Calcium carbonate	250.0
	5.	Microcrystalline cellulose	147.0
	6.	Croscarmellose sodium	20.0
	7.	Starch	35.0
	8.	Purified water	q.s.
25	9.	Croscarmellose sodium	28.0
	10.	Magnesium stearate	10.0

Procedure:

- i) Sift and mix ingredients 1, 2, 3, 4, 5 & 6.
- ii) Granulate the mixture of step (i) with starch mucilage prepared by dispersing ingredient 7 in 8.
- iii) Dry the granules of step (ii) followed by sifting and blending with ingredients 9 & 10.
- iv) Compress the material of step (iii) into tablets.

Example-9: Sustained release Bilayered tablet**A) Immediate release layer**

	S. No. Ingredient	Quantity (mg/tablet)
5	1. SLV-306	300.0
	2. Crospovidone	15.0
	3. Sodium lauryl sulfate	5.0
	4. Starch	3.0
	5. Purified water	q.s.
10	6. Crospovidone	15.0
	7. Magnesium stearate	7.0
	8. Colloidal silicon dioxide	3.0

Procedure:

- i) Mix ingredients 1, 2 & 3.
- 15 ii) Granulate the mixture of step (i) with starch mucilage prepared from ingredients 4 & 5.
- iii) Dry the granules; sift and blend with ingredients 6, 7 & 8.

B) Extended release layer

	S. No. Ingredient	Quantity (mg/tablet)
20	1. Metformin hydrochloride	500.0
	2. Povidone K-90	60.0
	3. Methacrylic polymer	90.0
	4. Microcrystalline cellulose	30.0
	5. Povidone K-30	70.0
25	6. Purified water	q.s.
	7. Microcrystalline cellulose	31.0
	8. Talc	6.0
	9. Colloidal silicon dioxide	3.0

Procedure:

- 30 i) Mix ingredients 1, 2, 3 & 4.
- ii) Dissolve ingredient 5 in 6 and granulate with the mixture of step (i).
- iii) Dry the granules, sift and blend with ingredients 7, 8 & 9.

C) Preparation of bilayered tablet:

Compress the granules of step (A) (iii) and step (B) (iii) into bilayered tablet.

Example-10: Tablet in tablet**5 A) Preparation of mini-tablets:**

S. No.	Ingredient	Quantity (mg/tablet)
1.	Captopril	12.50
2.	Microcrystalline cellulose	48.0
3.	Crospovidone	2.0
10 4.	Starch	4.0
5.	Purified water	q.s.
6.	Crospovidone	2.0
7.	Purified talc	4.0
8.	Stearic acid	1.0

15 Procedure:

- i) Sift and mix ingredients 1, 2 & 3.
- ii) Dissolve ingredient 4 in 5 to form the binder solution.
- iii) Granulate the ingredients of step (i) with the binder solution of step (ii).
- iv) Dry the granules of step (iii) and mix with ingredients 6, 7 & 8.
- 20 v) Compress the granules of step (iv) to obtain mini-tablets.

B) Preparation of tablet in tablet:

S. No.	Ingredient	Quantity (mg/tablet)
1.	SLV-306	75.0
2.	Calcium carbonate	300.0
25 3.	Microcrystalline cellulose	155.0
4.	Crospovidone	20.0
5.	Povidone K-30	18.0
6.	Purified water	q.s.
7.	Crospovidone	6.0
30 8.	Microcrystalline cellulose	6.0
9.	Magnesium stearate	6.0

Procedure:

- i) Sift and mix ingredients 1, 2, 3 & 4.

- ii) Dissolve ingredient 5 in 6 to form the binder solution.
 iii) Granulate the ingredients of step (i) with the binder solution of step (ii).
 iv) Dry the granules of step (iii) and mix with ingredients 7, 8 & 9.
 v) Compress the mini-tablets of step (A) (v) with the granules of step (B) (iv) to
 5 obtain tablet in tablet.

C) Coating of tablet in tablet:

S. No.	Ingredient	Quantity (mg/tablet)
1.	Opadry® yellow	25.0
2.	Purified water	q.s.

10 Procedure:

i) Dissolve Opadry® yellow in sufficient quantity of water.
 ii) Coat the tablet in tablet of step (B) (v) with the coating solution of step (C) (i)

Example-11: Tablet in tablet

15 **A) Preparation of mini-tablet:**

S. No.	Ingredient	Quantity (mg/tablet)
1.	Policosanol	40.0
2.	Ezetimibe	10.0
3.	Microcrystalline cellulose	12.0
20 4.	Lactose	9.2
5.	Sodium starch glycollate	1.6
6.	Starch	4.0
7.	Purified water	q.s.
8.	Sodium starch glycollate	1.6
25 9.	Magnesium stearate	0.8
10.	Talc	0.8

Procedure:

- i) Sift and mix ingredients 1, 2, 3, 4 & 5.
 ii) Dissolve ingredient 6 in 7 to form the binder solution.
 30 iii) Granulate the ingredients of step (i) with the binder solution of step (ii).
 iv) Dry the granules of step (iii) and mix with ingredients 8, 9 & 10.
 v) Compress the granules of step (iv) to obtain mini-tablets.

B) Coating of mini-tablets:

S. No.	Ingredient	Quantity (mg/tablet)
1.	Opadry® white	3.0
2.	Purified water	q.s.

5 **Procedure:**

- i) Dissolve Opadry® white in sufficient quantity of water.
- ii) Coat the mini-tablets in step (A) (v) with the coating solution of step (B) (i)

C) Preparation of granules to be filled into Capsule:

S. No.	Ingredient	Quantity (mg/capsule)
10 1.	SLV-306	300.0
2.	Sodium bicarbonate	398.0
3.	Microcrystalline cellulose	45.0
4.	Sodium starch glycollate	30.0
5.	Magnesium stearate	9.0
15 6.	Talc	4.5
7.	Microcrystalline cellulose	4.5

Procedure:

- i) Sift and mix ingredients 1, 2, 3 & 4.
- ii) Slug the ingredients of step (i) to obtain slugs of desired hardness followed by
20 breaking of the slugs and passing of the slugs through #16 mesh to obtain granules.
- iii) Mix the granules of step (ii) with ingredients 5, 6 and 7.

D) Preparation of Capsule:

25 Fill the coated mini-tablets of step (B) (ii) and the granules of step (C) (iii) into a hard gelatin capsule.

Example-12: Tablet in tablet**A) Preparation of mini-tablets:**

S. No.	Ingredient	Quantity (mg/tablet)
30 1.	Amlodipine besylate	13.90
2.	Lactose	44.3
3.	Crospovidone	1.2
4.	Magnesium stearate	0.6

Procedure:

- i) Mix ingredients 1, 2, 3 & 4 and sift through mesh #30 sieve.
- ii) Compress the material of step (i) to obtain mini-tablets.

B) Preparation of tablet in tablet:

5	S. No. Ingredient	Quantity (mg/tablet)
	1. SLV-306	600.0
	2. Sodium carbonate	250.0
	3. Sodium lauryl sulfate	15.0
	4. Croscarmellose sodium	40.0
10	5. Microcrystalline cellulose	40.0
	6. Croscarmellose sodium	40.0
	7. Magnesium stearate	10.0
	8. Colloidal silicon dioxide	10.0

Procedure:

- 15 i) Sift and mix ingredients 1, 2, 3, 4 & 5.
- ii) Slug the ingredients of step (i) to obtain slugs of desired hardness followed by breaking of the slugs and passing of the slugs through #16 mesh to obtain granules.
- iii) Mix the granules of step (ii) with ingredients 6, 7 & 8.
- 20 iv) Compress the mini-tablets of step (A) (ii) with the granules of step (B) (iii) to obtain tablet in tablet.

Example-13: Beads

	S. No. Ingredient	Quantity (mg/capsule)
25	1. SLV-306	300.0
	2. Aspirin	75.0
	3. Sodium bicarbonate	125.0
	4. Croscarmellose sodium	10.0
	5. Povidone K-30	20.0
30	6. Gelatin	5.0
	7. Talc	5.0
	8. Microcrystalline cellulose	30.0
	9. Purified water	q.s.

10.	Sucrose	60.0
11.	Hydroxypropyl methylcellulose	5.0
12.	Polysorbate 80	5.0

Procedure:

- 5 i) Mix ingredients 1, 2, 3, 4, 7 & 8 and sift through mesh #40 sieve.
- ii) Dissolve ingredients 5, 6, 11 & 12 in 9 to form the binder solution.
- iii) Take mesh #40 sieve passed ingredient 10 as nucleus and sprinkle binder solution to sufficiently wet the sugar beads.
- iv) Dust the powder of step (i) over the sugar beads of step (iii). Repeat this process
- 10 until whole powder is converted into beads.
- v) Fill the beads of step (iv) into a suitable size hard gelatin capsule.

Example-14: Soft gelatin capsule, SMEDDS

S. No.	Ingredient	Quantity (mg/capsule)
15	1. SLV-306 calcium	150.0
	2. Clopidogrel	37.5
	3. Propylene glycol	150.0
	4. Polyglycerol oleic ester (Plurol Oleique® CC 497)	30.0
	5. Polyoxyl 40 hydrogenated castor oil	310.0

20 Procedure:

- i) Disperse ingredients 1 & 2 in ingredient 3 with continuous stirring to obtain a homogeneous dispersion.
- ii) Mix ingredients 4 & 5 together to obtain a homogeneous dispersion.
- iii) Add material of step (i) to the material of step (ii) with continuous stirring to obtain the
- 25 fill material.
- iv) Encapsulate the fill material into gelatin sheath to form soft gelatin capsule.

Example-15: Oral suspension

S. No.	Ingredient	Quantity (mg/100ml)
30	1. SLV-306	150.0
	2. Lamotrigine	500.0
	3. Selegiline hydrochloride	5.0
	4. Sodium carboxymethylcellulose	50.0
	5. Sorbitol solution (70% w/v)	80.0

6.	Citric acid monohydrate	1.5
7.	Sodium benzoate	1.0
8.	Purified water	q.s. to 100 ml

Procedure:

- 5 i) Mix ingredients 1, 2 & 3 together and sift through mesh #30 sieve.
- ii) Dissolve ingredients 5, 6 & 7 in ingredient 8 to obtain a homogeneous dispersion and disperse ingredient 4 in it.
- iii) Add the material of step (i) with continuous stirring to the material of step (ii) to obtain a homogeneous suspension.

10

Example-16: Oral liquid

S. No.	Ingredient	Quantity (mg/100ml)
1.	SLV-306	200.00
2.	Niacin	1000.00
15 3.	Folic acid	5.00
4.	Ethyl cellulose	60.00
5.	Ethyl alcohol	1.25
6.	Citric acid monohydrate	1.25
7.	Sodium citrate	0.50
20 8.	Glycerin	40.00
9.	Povidone K-30	3.00
10.	Propylene glycol	30.00
11.	Saccharine sodium	0.50
12.	Sodium chloride	0.50
25 13.	Purified water	q.s. to 100.00 ml

Procedure:

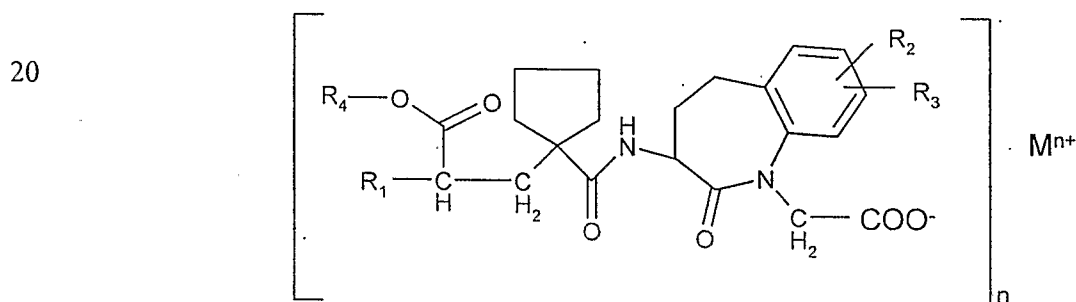
- i) Mix ingredients 1, 2 & 3 together and sift through mesh #30 sieve.
- ii) Dissolve 4 in 5 and disperse mixture of step (i) into it. Evaporate the solvent and pass the dried material through mesh #30 sieve.
- 30 iii) Dissolve ingredients 6, 7, 8, 9, 10, 11 & 12 in ingredient 13 to obtain a homogeneous dispersion.
- iv) Add the material of step (ii) with continuous stirring to the material of step (iii) to obtain a homogeneous dispersion.

Example-17: Injection

S. No.	Ingredient	Quantity/5ml
1.	Polyethylene glycol	1.50 ml
5 2.	Propylene glycol	1.25 ml
3.	Glycine Buffer pH 11.3	1.75 ml
4.	SLV-306	2.50 mg
5.	Phentolamine mesylate	5.00 mg
6.	Sodium hydroxide (NaOH) solution 4.0% w/v	0.50 ml
10	Procedure:	
	i)	Take specified quantity of Polyethylene glycol into a vessel.
	ii)	Add Propylene glycol to step (i) with continuous stirring using mechanical stirrer.
15	iii)	Add about half the quantity of the Glycine Buffer pH 11.3 to the material of step (ii) with continuous stirring to form a homogeneous mixture.
	iv)	Pass weighed amount of SLV-306 and Phentolamine mesylate through #60 sieve and add to the material of step (iii) with continuous stirring.
	v)	Add specified quantity of NaOH 4.0% solution to the material of step (iv) with continuous stirring to form a homogeneous solution.
20	vi)	Mix the solution of step (v) for about 30 minutes by continuous stirring.
	vii)	Add remaining quantity of Glycine Buffer pH 11.3 to the material of step (vi) to make up the volume.
	viii)	Mix the solution of step (vii) by continuous stirring.
25	ix)	Adjust the final pH to 10.0 by adding NaOH 4.0% w/v solution to the solution of step (viii).
	x)	Mix the solution of step (ix) by continuous stirring.

We claim:

1. A pharmaceutical composition comprising at least one endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor or its pharmaceutically acceptable salts, esters, hydrates, solvates, polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms, prodrugs or mixtures thereof as active agent in combination with at least one another active agent optionally with one or more pharmaceutically acceptable excipients.
2. A composition according to claim 1, wherein the endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor is selected from a group comprising CGS 26303, CGS 25462, phosphoramidon, candoxatril, sinorphan, omapatrilat, FR901533, TMC-66, SM-19712, SLV-306, KC-12615, KC-90095-1-AC, CGS-26303, CGS-30440, CGS-31447, CGS-26670, Sch-54470, or its pharmaceutically acceptable salts, esters, hydrates, solvates, polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms, prodrugs or mixtures thereof.
3. A pharmaceutical composition according to claim 1, wherein the endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor has the following general formula:

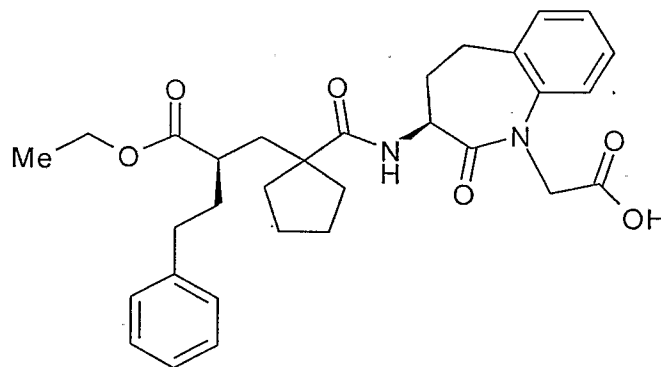


25

Wherein:

- R_1 is selected from the group consisting of (C_1-C_6) alkoxy (C_1-C_6) alkyl which may be substituted by a (C_1-C_6) alkoxy, phenyl- (C_1-C_6) -alkyl and phenyloxy- (C_1-C_6) -alkyl, wherein the phenyl group may be substituted with (C_1-C_6) alkyl, (C_1-C_6) alkoxy or halogen, and naphthyl- (C_1-C_6) -alkyl,
- R_2 and R_3 are both independently hydrogen or halogen,
- R_4 is a biolabile ester forming group,
- M is hydrogen or a metal ion, preferably a bivalent metal ion
- n is 1, 2 or 3;

- 4.. A composition according to claim 2, wherein the endothelin conversion enzyme (ECE) inhibitor and neutral endopeptidase (NEP) inhibitor is SLV-306 or its pharmaceutically acceptable salts, esters, hydrates, solvates, polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms, prodrugs or mixtures thereof, wherein the SLV-306 has the following formula:



5. A composition according to any of the claims 1-4, wherein the another active agent(s) is an antihypertensive selected from a group comprising calcium channel blockers, ACE Inhibitors, alpha-adrenergic receptor blockers, beta-adrenergic receptor blockers, diuretics, cerebral vasodilator, coronary vasodilator, peripheral vasodilator or mixtures thereof.
6. A composition according to claim 5, wherein the calcium channel blocker is selected from a group comprising amlodipine, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, perhexiline or mixtures thereof.
7. A composition according to claim 5, wherein the ACE Inhibitor is selected from a group comprising alacepril, benazepril, captopril, ceronapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moveltipril, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril or mixtures thereof.
8. A composition according to claim 5, wherein the alpha-adrenergic receptor

- blocker is selected from a group comprising amosulalol, arotinolol, dapiprazole, doxazosin, fenspiride, indoramin, labetalol, naftopidil, nicergoline, prazosin, tamsulosin, tolazoline, trimazosin, yohimbine or mixtures thereof.
9. A composition according to claim 5, wherein the beta-adrenergic receptor
5 blocker is selected from a group comprising acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butidine hydrochloride, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol,
10 metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol or mixtures thereof.
10. A composition according to claim 5, wherein the diuretic is selected from a
15 group comprising benzothiadiazine derivatives, diuretic organomercurials, diuretic purines, diuretic steroids, diuretic sulfonamide derivatives, diuretic uracils, amanozine, amiloride, arbutin, chlorazaniol, ethacrynic acid, etozolin, hydracarbazine, isosorbide, mannitol, metochalcone, muzolimine, perhexiline, ticrynafen, triamterene, theobromine, urea or mixtures thereof.
11. A composition according to claim 10, wherein the diuretic is a benzothiadiazine
20 derivative selected from a group comprising althiazide, bendroflumethiazide, benzthiazide, benzyhydrochlorothiazide, buthiazide, chlorothiazide, chlorthalidone, cyclopenthiazide, cyclothiazide, epithiazide, ethiazide, fenquizon, indapamide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, meticrane, metolazone, paraflutizide, polythiazide,
25 quinethazone, teclothiazide, trichlormethiazide or mixtures thereof.
12. A composition according to claim 10, wherein the diuretic is a sulfonamide
derivative selected from a group comprising acetazolamide, ambuside, azosemide, bumetanide, butazolamide, chloraminophenamide, clofenamide, clopamide, clorexolone, disulfamide, ethozolamide, furosemide, mefruside,
30 methazolamide, piretanide, torsemide, tripamide, xipamide or mixtures thereof.
13. A composition according to claim 5, wherein the cerebral vasodilator is selected
from a group comprising bencyclane, cinnarizine, citicoline, cyclandelate, ciclonicate, diisopropylamine dichloroacetate, eburnamonine, fasudil, fenoxedil,

flunarizine, ibudilast, ifenprodil, lomerizine, nafronyl, nicametate, nicergoline, nimodipine, papaverine, pentifylline, tinofedrine, vincamine, vinpocetine, viquidil or mixtures thereof.

14. A composition according to claim 5, wherein the coronary vasodilator is selected from a group comprising amotriphene, bendazol, benfurodil hemisuccinate, benziodarone, chloracizine, chromonar, clobenfural, clonitrate, cloricromen, dilazep, dipyridamole, droprenilamine, efloxate, erythrityl tetranitrate, fendiline, floredil, ganglefene, hexestrol bis(β -diethylaminoethyl)ether, hexobendine, itramin tosylate, khellin, lidoflazine, mannitol hexanitrate, medibazine, nitroglycerin, pentaerythritol tetranitrate, pentritinol, perhexiline, pimefylline, prenylamine, propatyl nitrate, trapidil, tricromyl, trimetazidine, trolnitrate phosphate, visnadine or mixtures thereof.
15. A composition according to claim 5, wherein the peripheral vasodilator is selected from a group comprising aluminium nicotinate, bamethan, bencyclane, betahistine, bradykinin, brovincamine, bufeniode, buflomedil, butalamine, cetiedil, ciclonicate, cinepazide, cinnarizine, cyclandelate, diisopropylamine dichloroacetate,eledoisin, fenoxedil, flunarizine, hepronicate, ifenprodil, iloprost, inositol niacinate, isoxsuprine, kallidin, kallikrein, moxisylyte, nafronyl, nicametate, nicergoline, nicofuranose, nyldrin, pentifylline, pentoxifylline, piribedil, prostaglandin E₁, suloctidil, tolazoline, xanthinol niacinate or mixtures thereof.
16. A composition according to any of the claims 1-4, wherein the another active agent(s) is an antidiabetic selected from a group comprising biguanides, thiazolidinediones, sulfonylureas, benzoic acid derivatives, glucosidase inhibitors or mixtures thereof.
17. A composition according to any of the claims 1-4, wherein the another active agent(s) is a platelet function altering agent.
18. A composition according to claim 17, wherein the platelet function altering agent is selected from a group comprising aspirin, ticlopidine, dipyridamole, clopidogrel, a glycoprotein IIb/IIIa receptor inhibitor, a non-steroidal anti-inflammatory drug, policosanol or mixtures thereof.
19. A composition according to any of the claims 1-4, wherein the another active agent(s) is a serum homocysteine lowering agent.

20. A composition according to claim 19, wherein the serum homocysteine lowering agent is selected from a group comprising folic acid, vitamin B6, vitamin B12 or mixtures thereof.
21. A composition according to any of the claims 1-4, wherein the another active agent is a lipid lowering agent.
22. A composition according to claim 21, wherein the lipid lowering agent is selected from a group comprising ezetimibe, niacin, or policosanol or its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms, or mixtures thereof.
23. A composition according to any of the claims 1-4, wherein the another active agent is a guanidine derivative selected from the group comprising bethanidine, debrisoquin, guanabenz, guanadrel, guanethidine, guanfacine, guanoxabenz, guanoxan or mixtures thereof.
24. A composition according to any of the claims 1-4, wherein the another active agent is a hydrazine or phthalazine selected from the group comprising dihydralazine, endralazine, hydralazine, pheniprazine, pildralazine or mixtures thereof.
25. A composition according to any of the claims 1-4, wherein the another active agent is an imidazole derivative selected from the group comprising clonidine, lofexidine, moxonidine, phentolamine, tiamenidine or mixtures thereof.
26. A composition according to claim 1, wherein the pharmaceutically acceptable excipients are selected from a group comprising diluents, disintegrants, binders, fillers, bulking agents, anti-adherents, anti-oxidants, buffering agents, colorants, flavoring agents, coating agents, plasticizers, organic solvents, stabilizers, preservatives, lubricants, glidants, chelating agents, either alone or in combination thereof.
27. A composition according to any of the claims 1-26 which is formulated to provide immediate delivery and/or controlled or prolonged delivery of the active agent(s).
28. A composition according to claim 1, wherein the composition comprises of at least two fractions wherein one fraction comprises the active agent(s) optionally with one or more pharmaceutically acceptable excipients in such quantities so as to provide an immediate release of the active agent(s) and the other fraction.

comprises the active agent(s) optionally with one or more pharmaceutically acceptable excipients in such quantities so as to provide a sustained release of the active agent(s).

29. A process for the preparation pharmaceutical composition according to claim 1,
5 comprising at least one endothelin conversion enzyme (ECE) inhibitor and/or neutral endopeptidase (NEP) inhibitor as active agent or its pharmaceutically acceptable salts, esters, hydrates, solvates, polymorphs, isomers, conjugate acids, enantiomers, tautomeric forms, prodrugs or mixtures thereof in combination with at least one another active agent; optionally with one or more pharmaceutically acceptable excipients, which comprises treating the combination of active agents
10 optionally with one or more other pharmaceutically acceptable excipients and formulating into a suitable dosage form.
30. A method of using the pharmaceutical composition according to claim 1 for the prophylaxis, treatment and/or amelioration of cardiovascular and other
15 associated disorders, which comprises administering to a subject in need thereof an effective amount of the composition.
31. A method according to claim 30, wherein the cardiovascular and other associated disorders are selected from but not limited to a group comprising chronic heart failure, coronary artery disease, congestive heart failure, angina, atherosclerosis,
20 hyperlipidemia, diabetes, myocardial infarction, cardiogenic shock, systemic and pulmonary hypertension, ischemia-reperfusion injury, coronary and systemic vasospastic disorders, cerebral vasospasm, and subarachnoid hemorrhage, hyperglycemia, hyperlipidemia, metabolic disorders, renal disorders, neurodegenerative disorders, or a combination of such disorders.
- 25 32. Use of the combination according to claim 1 comprising an ECE and/or NEP inhibitor with at least one another active agent for the manufacture of a medicament for the prevention treatment and/or amelioration of cardiovascular disease and/or for the reduction in the risk of cardiovascular disease and other associated disorders.
- 30 33. The pharmaceutical composition substantially as herein described and illustrated by the examples.
34. The process for the preparation of a pharmaceutical composition substantially as herein described and illustrated by the examples.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2006/000437

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/55 A61K31/155 A61K31/165 A61K31/397 A61K31/401
A61K31/4178 A61K31/4422 A61K31/4965 A61K31/549 A61K31/137
A61K31/415 A61K31/4365 A61K31/455 A61K31/53 A61K31/616

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)

A61K A61P

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, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/186083 A1 (MCMAHON ELLEN G [US] ET AL) 23 September 2004 (2004-09-23) cited in the application paragraphs [0029], [0035] - [0047], [0157], [0158], [0166], [0173] - [0197], [0202], [0240]; table 5 claims 1,4,5,18,19,22,29,43,46,49,50,53,57,58,61, 62	1-34
X	US 2004/063719 A1 (ADAMS MICHAEL A [CA] ET AL) 1 April 2004 (2004-04-01) cited in the application paragraphs [0015] - [0017], [0035], [0042] - [0048], [0050]; claims 1-4,6,8,16,42 ----- -/--	1-34

☒ Further documents are listed in the continuation of Box C.

☒ See patent family 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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

2 April 2007

Date of mailing of the international search report

13/04/2007

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2006/000437

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/24827 A (BASF AG [DE]; AMBERG WILHELM [DE]; KLING ANDREAS [DE]; HORNBERGER WILF) 12 April 2001 (2001-04-12) cited in the application page 4, line 29 - page 6, line 14 page 14, lines 7-27 -----	1-34
X	WO 96/35453 A (CHWALISZ KRISTOF [DE]; GARFIELD ROBERT E [US] CHWAKISZ KRISTOF [DE]; G) 14 November 1996 (1996-11-14) cited in the application page 8, lines 3-9 page 13, lines 12-31 page 15, lines 29-39 page 18, lines 7-15; claims 28,36,38,39; examples 1-5,10 -----	1-34
P,X	WO 2006/000564 A (SOLVAY PHARM GMBH [DE]; ZIEGLER DIETER [DE]; WITTE KLAUS [DE]; STRAUB) 5 January 2006 (2006-01-05) page 3, last paragraph - page 6, paragraph 1 page 9, last paragraph page 15, paragraph 2 - page 18, paragraph 1 page 20, paragraph 2 claims 3,15-19; example I; tables 1-3 -----	1-34
P,X	WO 2005/112939 A (SOLVAY PHARM GMBH [DE]; ZIEGLER DIETER [DE]; WITTE KLAUS [DE]; STRAUB) 1 December 2005 (2005-12-01) page 2, paragraph 5 - page 4, paragraph 2 page 7, paragraph 2-4 page 12, paragraph 2 -----	1-34
P,X	US 2005/267124 A1 (ZIEGLER DIETER [DE] ET AL) 1 December 2005 (2005-12-01) paragraphs [0013] - [0037], [0050], [0099]; claims 26-28 -----	1-34
P,X	WO 2006/064016 A (SOLVAY PHARM GMBH [DE]; WITTE KLAUS [DE]; ZIEGLER DIETER [DE]; STRAUB) 22 June 2006 (2006-06-22) page 4, line 25 - page 5, paragraph 30 page 16, line 16 - page 17, line 25 page 19, line 16 - page 20, line 13 claims 9,12,21,22,26; example I; tables 1-3 ----- -/--	1-34

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2006/000437

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2006/087371 A (SOLVAY PHARM GMBH [DE]; WITTE KLAUS [DE]; ZIEGLER DIETER [DE]; STRAUB) 24 August 2006 (2006-08-24) page 4, lines 1-24 page 10, lines 3-5 page 15, line 28 - page 17, line 23 page 20, line 29 - page 21, line 13 claims 9,12,17-21,27-29,35; example I; table 1 -----	1-34
A	DE 103 44 848 A1 (SOLVAY PHARM GMBH [DE]) 14 April 2005 (2005-04-14) the whole document -----	1-34
A	WO 03/059939 A (SOLVAY PHARM BV [NL]; VAN DER EERDEN JORIS A [NL]; DE JONG PAULUS P G) 24 July 2003 (2003-07-24) the whole document -----	1-34
A	WO 03/068266 A (SOLVAY PHARM BV [NL]; GORISSEN HENRICUS R M [NL]) 21 August 2003 (2003-08-21) the whole document -----	1-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2006/000437

Box II Observations where certain claims were found unsearchable (Continuation of item 2 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. ☒ Claims Nos.: 1 and 2; 30 and 31
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 30 and 31 are 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 compound/composition.
2. ☒ Claims Nos.: 1, 2, 5-34 (in part)
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 III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

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 II.1

Claims Nos.: 1 and 2; 30 and 31

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box II.2

Claims Nos.: 1, 2, 5-34 (in part)

The present claims 1, 2 and 5-34 relate to an extremely large number of possible combinations of compounds. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the combinations, namely for combinations with SLV-306 as ECE and NEP inhibitor (see the examples). The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1, 2 and 5-34 (PCT Guidelines 9.19 and 9.23).

The search of claims 1, 2 and 5-34 with respect to the ECE and/or NEP inhibitor component was restricted to the compound which appears to be supported, namely SLV-306, and to those representing a generalisation of its structural formula, namely to the compounds according to the formula as specified in dependent claim 3.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-15; and 26-34 (in part)

Pharmaceutical combinations comprising at least one ECE inhibitor and/or NEP inhibitor, and at least one active agent which is an antihypertensive.

2. claims: 16; and 26-34 (in part)

Pharmaceutical combinations comprising at least one ECE inhibitor and/or NEP inhibitor, and at least one active agent which is an antidiabetic.

3. claims: 17, 18; and 26-34 (in part)

Pharmaceutical combinations comprising at least one ECE inhibitor and/or NEP inhibitor, and at least one active agent which is a platelet function altering agent.

4. claims: 19, 20; and 26-34 (in part)

Pharmaceutical combinations comprising at least one ECE inhibitor and/or NEP inhibitor, and at least one active agent which is a serum homocysteine lowering agent.

5. claims: 21, 22; and 26-34 (in part)

Pharmaceutical combinations comprising at least one ECE inhibitor and/or NEP inhibitor, and at least one active agent which is a lipid lowering agent.

6. claims: 23; and 26-34 (in part)

Pharmaceutical combinations comprising at least one ECE inhibitor and/or NEP inhibitor, and at least one active agent which is a guanidine derivative.

7. claims: 24; and 26-34 (in part)

Pharmaceutical combinations comprising at least one ECE inhibitor and/or NEP inhibitor, and at least one active agent which is a hydrazine or phthalazine.

8. claims: 25; and 26-34 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Pharmaceutical combinations comprising at least one ECE inhibitor and/or NEP inhibitor, and at least one active agent which is a imidazole derivative.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2006/000437

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