	Docket Number	32219-US-DIV

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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

UTILITY PATENT APPLICATION TRANSMITTAL AND FEE SHEET

Transmitted herewith for filing under 37 CFR §1.53(b)(1) is a **divisional** of prior Application No. 10/341,868, filed January 14, 2003.

Applicant (or identifier): KSANDER ET AL.

Title: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Enclosed are:

1. ☒ Specification (Including Claims and Abstract) - 26 pages
2. ☐ Drawings - sheets
3. Declaration and Power of Attorney
   a. ☐ Newly executed (original or copy)
   b. ☒ Copy from a prior application (signed or with indication that original was signed)
      i. ☐ Deletion of Inventors
      Signed statement attached deleting inventor(s) named in the prior application
4. ☒ Incorporation By Reference
   The entire disclosure of the prior application, from which a copy of the Declaration and Power of Attorney is supplied under Box 3b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
5. ☐ Microfiche Computer Program (appendix)
6. Nucleotide and/or Amino Acid Sequence Submission
   ☐ Computer Readable Copy
   ☐ Paper Copy
   ☐ Statement Verifying Identity of Above Copies
7. ☒ Preliminary Amendment
8. ☐ Assignment Papers (Cover Sheet & Document(s))
9. ☐ English Translation of
10. ☒ Information Disclosure Statement
11. ☐ Certified Copy of Priority Document(s)
12. ☐ Return Receipt Postcard
13. ☒ Application Data Sheet
14. ☐ Other:

☒ The right to elect an invention or species that is different from that elected in parent Application No. 10/341,868 in the event of a restriction or election of species requirement that is identical or substantially similar to that made in said parent application is hereby reserved.

Filing fee calculation:

☒ Before calculating the filing fee, please enter the enclosed Preliminary Amendment.

☐ Before calculating the filing fee, please cancel claims .

Basic Filing Fee									$ 310
Search Fee									$ 510
Examination Fee									$ 210
Multiple Dependent Claim Fee ($ 370)									$
Foreign Language Surcharge ($ 130)									$
	For	Number Filed		Number Extra		Rate			
Extra Claims	Total Claims	11	-20	0	x	$ 50	=	$	
	Independent Claims	5	-3	2	x	$ 210	=	$	420
Application Size Fee									
Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof (rounded up to a whole number)		Rate			
26	- 100		/50	0	x	$ 260	=	$	
TOTAL FILING FEE								$	1,450

☒ Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $1,450. An additional copy of this paper is enclosed. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.16 and §1.17 which may be required in connection with this application, or credit any overpayment, to Deposit Account No. 19-0134 in the name of Novartis.

Please address all correspondence to the address associated with Customer No. 001095, which is currently:

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

Please direct all telephone calls to the undersigned at the number given below and all telefaxes to (973) 781-8064.

Respectfully submitted,

Date: 6/23/08

Gregory D. Ferraro
Attorney for Applicants
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Respectfully submitted,

Date: 6/23/08

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134
Tel. No. (862) 778-7831

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Citizenship Country:: United States of America

CORRESPONDENCE INFORMATION

Correspondence Customer Number:: 001095
Fax One:: 973-781-8064

APPLICATION INFORMATION

Title Line One:: METHODS OF TREATMENT AND PHARMACEUTICAL
Title Line Two:: COMPOSITION
Formal Drawings?:: No
Application Type:: Utility
Docket Number:: 32219-US-DIV
Secrecy Order in Parent Appl.?:: No

CONTINUITY INFORMATION

This application is a:: DIVISION OF
>Application One:: 10/341,868
Filing Date::01-14-2003

Which is a:: NON PROV. OF PROVISIONAL
>> Application Two:: 60/386,792
Filing Date::06-07-2002

And which is a:: NON PROV. OF PROVISIONAL
>> Application Three:: 60/349,660
Filing Date::01-17-2002

Source:: PrintEFS Version 2.0

CASE 32219-US-DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL.

APPLICATION NO:

Not yet Known

FILED:

Herewith

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

Prior to the examination of the above-referenced patent application, please enter the following preliminary amendment.

Amendment to the Specification begin on page 2 of this paper.

Amendment to the Specification:

Please insert the following as the first paragraph beneath the title on page 1:

--This application is a Divisional of Application No. 10/341,868 filed on January 14, 2003 and claims benefit of of U.S. Provisional Application No. 60/386,792, filed June 7, 2002 and U.S. Provisional Application No. 60/349,660, filed January 17, 2002, the entire disclosures of which are hereby incorporated by reference.--

REMARKS/ARGUMENTS

The foregoing amendment to the specification is to insert continutity information. No new matter has been added. Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

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Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134

Date: 6/23/08

METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Background of the Invention

The renin angiotensin system is a complex hormonal system comprised of a large molecular weight precursor, angiotensinogen, two processing enzymes, renin and angiotensin converting enzyme (ACE), and the vasoactive mediator angiotensin II (Ang II). See *J. Cardiovasc. Pharmacol.*, Vol. 15, Suppl. B, pp. S1-S5 (1990). The enzyme renin catalyzes the cleavage of angiotensinogen into the decapeptide angiotensin I, which has minimal biological activity on its own and is converted into the active octapeptide Ang II by ACE. Ang II has multiple biological actions on the cardiovascular system, including vasoconstriction, activation of the sympathetic nervous system, stimulation of aldosterone production, anti-natriuresis, stimulation of vascular growth and stimulation of cardiac growth. Ang II functions as a pressor hormone and is involved the pathophysiology of several forms of hypertension.

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 epinephrine and norepinephrine, as well as the increase of the activity of the sympathetic nervous system as a result of the formation of norepinephrine. Ang II also has an influence on electrolyte balance, produces, e.g., anti-natriuretic and anti-diuretic 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. Ang II is also involved in cell growth and migration and in extracellular matrix formation.

Ang II interacts with specific receptors on the surface of the target cell. It has been possible to identify receptor subtypes that 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 Ang II antagonists. Because of the inhibition of the AT 1-receptor such antagonists can be used, e.g., as anti-hypertensives or for the treatment of congestive heart failure, among other indications. Ang II antagonists are therefore understood to be those active ingredients which bind to the AT 1-receptor subtype.

Inhibitors of the renin angiotensin system are well-known drugs that lower blood pressure and exert beneficial actions in hypertension and in congestive heart failure as described. See, e.g, *N. Eng. J. Med.*, Vol. 316, No. 23, pp. 1429-1435 (1987). A large number of peptide and non-peptide inhibitors of the renin angiotensin system are known, the most widely studied being the ACE inhibitors, which includes the drugs captopril, enalapril, lisinopril, benazepril and spirapril. Although a major mode of action of ACE inhibitors involves prevention of formation of the vasoconstrictor peptide Ang II, it has been reported in *Hypertension*, Vol. 16, No. 4, pp. 363-370 (1990), that ACE cleaves a variety of peptide substrates, including the vasoactive peptides bradykinin and substance P. Prevention of the degradation of bradykinin by ACE inhibitors has been demonstrated, and the activity of the ACE inhibitors in some conditions has been reported in *Circ. Res.*, Vol. 66, No. 1, pp. 242-248 (1990), to be mediated by elevation of bradykinin levels rather than inhibition of Ang II formation. Consequently, it cannot be presumed that the effect of an ACE inhibitor is due solely to prevention of angiotensin formation and subsequent inhibition of the renin angiotensin system.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino terminal side of aromatic amino acids. See *Biochem. J.*, Vol. 241, pp. 237-247 (1987). Substrates for this enzyme include, but are not limited to, atrial natriuretic factors (ANFs), also known as ANPs, brain natriuretic peptide (BNP), met and leu enkephalin, bradykinin, neurokinin A and substance P.

ANPs are a family of vasodilator, diuretic and anti-hypertensive peptides which have been the subject of many recent reports in the literature. See, e.g., *Annu. Rev. Pharm. Tox.*, Vol. 29, pp. 23-54 (1989). One form, ANF 99-126, is a circulating peptide hormone which is released from the heart during conditions of cardiac distension. The function of ANF is to maintain salt and water homeostasis, as well as to regulate blood pressure. ANF is rapidly inactivated in the circulation by at least two processes: a receptor-mediated clearance reported in *Am. J. Physiol.*, Vol. 256, pp. R469-R475 (1989), and an enzymatic inactivation via NEP reported in *Biochem. J.*, Vol. 243, pp. 183-187 (1987). It has been previously demonstrated that inhibitors of NEP potentiate the hypotensive, diuretic, natriuretic and plasma ANF responses to pharmacological injection of ANF in experimental animals. The potentiation of ANF by two specific NEP inhibitors is reported by Sybertz et al., *J. Pharmacol. Exp. Ther.*, Vol. 250, No. 2, pp. 624-631 (1989), and in *Hypertension*, Vol.

15, No. 2, pp. 152-161 (1990), while the potentiation of ANF by NEP in general was disclosed in U.S. Patent No. 4,749,688. In U.S. Patent No. 4,740, 499, Olins disclosed the use of thiorphan and kelatorphan to potentiate atrial peptides. Moreover, NEP inhibitors lower blood pressure and exert ANF-like effects, such as diuresis and increased cyclic guanosine 3',5'-monophosphate (cGMP) excretion in some forms of experimental hypertension. The anti-hypertensive action of NEP inhibitors is mediated through ANF because antibodies to ANF will neutralize the reduction in blood pressure.

Darrow et al. in European Patent Application No. 498361 disclose treating hypertension or congestive heart failure with a combination of certain Ang II antagonists or certain renin inhibitors with certain NEP inhibitors.

Powell et al. in European Patent Application No. 726072 disclose treating hypertension or congestive heart failure with a combination of the Ang II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(*1H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]nonan-4-one with a NEP inhibitor or a dual acting vasopeptidase inhibitor (single molecular entity with both ACE and NEP inhibitory activities). Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of anti-hypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different mode of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for more efficacious combination therapy which has less deleterious side effects.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily

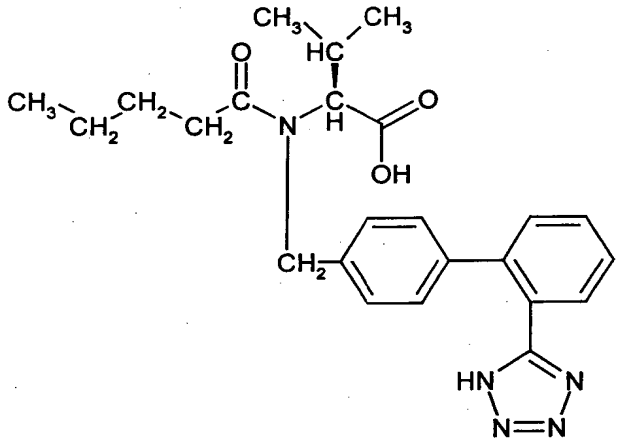
apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

Detailed Description of the Preferred Embodiments

In one aspect, the present invention relates to pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a NEP inhibitor or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.

In another embodiment, the present invention relates to methods of treating cardiac and renal related conditions by administration of the pharmaceutical composition comprising valsartan plus a NEP inhibitor.

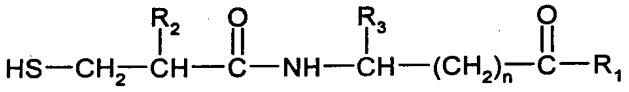
Valsartan is the AT 1-receptor antagonist (*S*)-*N*-(1-carboxy-2-methyl-prop-1-yl)-*N*-pentanoyl-*N*-[2;(*1H*-tetrazol-5-yl)biphenyl-4-yl-methyl]amine of formula (I)



(I)

and is disclosed in EP 0443983 A and U.S. Patent No. 5,399,578, the disclosures of which are incorporated herein in their entirety as if set forth herein.

A NEP inhibitor useful in said combination is a compound of the formula (II)



(II)

and pharmaceutically acceptable salts thereof,

wherein

R_2 is alkyl of 1 to 7 carbons, trifluoromethyl, phenyl, substituted phenyl, $-(CH_2)_{1\text{ to }4}$-phenyl, or $-(CH_2)_{1\text{ to }4}$-substituted phenyl;

R_3 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, $-(CH_2)_{1\text{ to }4}$-phenyl, or $-(CH_2)_{1\text{ to }4}$-substituted phenyl;

R_1 is hydroxy, alkoxy of 1 to 7 carbons, or NH_2;

n is an integer from 1 to 15; and

the term substituted phenyl refers to a substituent selected from lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, hydroxy, Cl, Br or F.

Preferred selective NEP inhibitors of formula (II) include compounds, wherein

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1 to 9; and

R_1 is hydroxy.

Even more preferred selective NEP inhibitors of formula (II) are reported in the literature as SQ 28,603 which is the compound of formula (II), wherein

R_2 is benzyl;

R_3 is hydrogen;

n is one; and

R_1 is hydroxy.

The preparation of the selective NEP inhibitors of formula (II), wherein R_2 is other than trifluoromethyl are disclosed by Delaney et al. in U.S. Patent No. 4,722,810. The preparation of the selective NEP inhibitors of formula (II), wherein R_2 is trifluoromethyl are disclosed by Delaney et al. in U.S. Patent No. 5,223,516.

NEP inhibitors within the scope of the present invention include compounds disclosed in U.S. Patent No. 4,610,816, herein incorporated by reference, including in particular *N*-[*N*-[1(*S*)-carboxyl-3-phenylproplyl]-(*S*)-phenylalanyl]-(*S*)-isoserine and *N*-[*N*-[((*1S*)-carboxy-2-phenyl)ethyl]-(*S*)-phenylalanyl]-β-alanine; compounds disclosed in U.S. Patent No. 4,929,641, in particular, *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)-

propionyl]methionine; SQ 28603 (*N*-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-β-alanine), disclosed in South African Patent Application No. 84/0670; UK 69578 (*cis*-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid) and its active enantiomer(s); thiorphan and its enantiomers; retro-thiorphan; phosphoramidon; and SQ 29072 (7-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]-heptanoic acid). Also suitable for use are any pro-drug forms of the above-listed NEP inhibitors, e.g., compounds in which one or more carboxylic acid groups are esterified.

NEP inhibitors within the scope of the present invention also include the compounds disclosed in U.S. Patent No. 5,217,996, particularly, *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester; the compounds disclosed in EP 00342850, particularly, (*S*)-*cis*-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; the compounds disclosed in GB 02218983, particularly, 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; the compounds disclosed in WO 92/14706, particularly, *N*-(1-(3-(*N*-*t*-butoxycarbonyl-(*S*)-prolylamino)-2(*S*)-*t*-butoxy-carbonylpropyl)cyclopentanecarbonyl)-*O*-benzyl-(*S*)-serine methyl ester; the compounds disclosed in EP 00343911; the compounds disclosed in JP 06234754; the compounds disclosed in EP 00361365, particularly, 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; the compounds disclosed in WO 90/09374, particularly, 3-[1-(*cis*-4-carboxycarbonyl-*cis*-3-butylcyclohexyl-*r*-1-carboamoyl)cyclopentyl]-*2S*-(2-methoxyethoxymethyl)propanoic acid; the compounds disclosed in JP 07157459, particularly, *N*-((*2S*)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; the compounds disclosed in WO 94/15908, particularly, *N*-(1-(*N*-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-*L*-phenylalanine; the compounds disclosed in U.S. Patent No. 5,273,990, particularly, (*S*)-(2-biphenyl-4-yl)-1-(*1H*-tetrazol-5-yl)ethylamino) methylphosphonic acid; the compounds disclosed in U.S. Patent No. 5,294,632, particularly, (*S*)-5-(*N*-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; the compounds disclosed in U.S. Patent No. 5,250,522, particularly, β-Alanine, 3-[1,1'-biphenyl]-4-yl-*N*-[diphenoxyphosphinyl)methyl]-*L*-alanyl; the compounds disclosed in EP 00636621, particularly, *N*-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; the compounds disclosed in WO 93/09101, particularly, 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; the compounds disclosed in EP 00590442, particularly, ((*L*)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-*L*-phenylalanyl)-β-alanine, *N*-

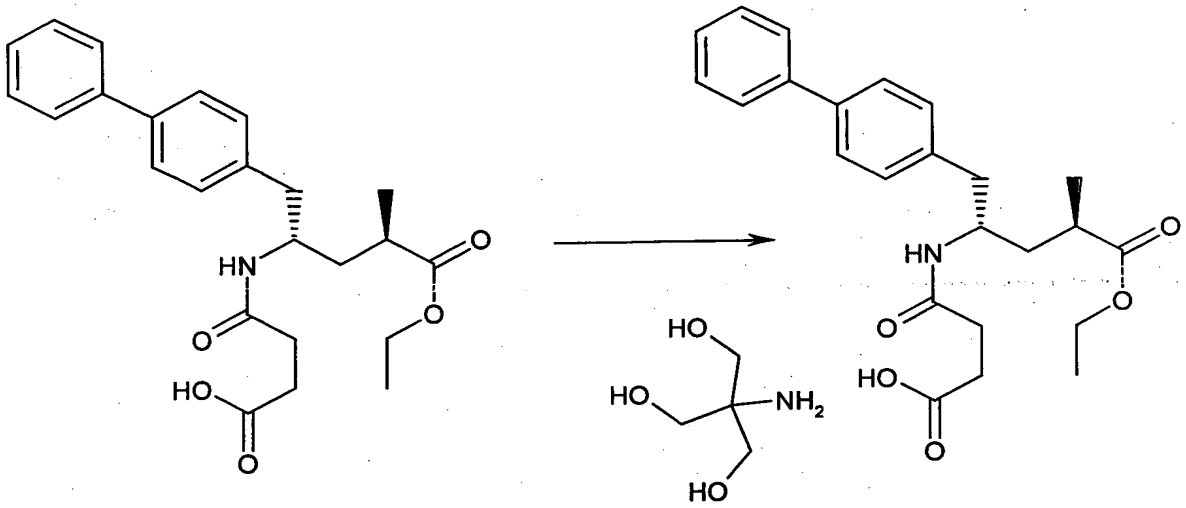
[*N*-[(*L*)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine, *N*-[*N*-[(*L*)-1-carboxy-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine, *N*-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, *N*-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(*S*)-isoserine, *N*-(*S*)-[3-mercapto-2-(2-methylphenyl)propionyl]-(*S*)-2-methoxy-(*R*)-alanine, *N*-[1-[[1(*S*)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(*S*)-isoserine, *N*-[1-[[1(*S*)-carbonyl-3-phenylpropy]amino]-cyclopentylcarbonyl]-(*S*)-isoserine, 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-*bis*-(*S*)-isoserine, 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-*bis*-(*S*)-methionine, *N*-(3-phenyl-2-(mercaptomethyl)-propionyl)-(*S*)-4-(methylmercapto)methionine, *N*-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, *N*-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, *N*-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(*S*)-isoserine, *N*-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(*S*)-methionine ethyl ester, 3(*S*)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; and the compounds disclosed in WO 93/10773, particularly, *N*-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group, for example, COOH, can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound comprises, e.g., both a carboxy and an amino group.

With respect to *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester, preferred salts include the sodium salt disclosed in U.S. Patent No. 5,217,996, the triethanolamine salt and the *tris*(hydroxymethyl)aminomethane salt. Preparation of the triethanolamine salt and the *tris*(hydroxymethyl)aminomethane salt may be carried out as follows:

Triethanolamine

To *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester (349 mg, 0.848 mmol) is added 5 mL of ethyl ether and 0.113 mL (0.848 mmol) of triethanolamine in 1 mL of ethyl acetate. The solid was collected and dried melting at 69-71°C.



Tris(hydroxymethyl) aminomethane

To *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester (3.2 g, 7.78 mmol) is added 32 mL of ethyl acetate and 940 mg (7.78 mmol) *tris*(hydroxymethyl)aminomethane. The suspension is diluted with 45 mL of ethyl acetate and refluxed overnight (~20 hours). The reaction is cooled to 0°C, filtered, solid washed with ethyl acetate and dried melting at 114-115°C.

It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days).

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects. The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof results in a significant response in a greater percentage of treated patients, that is, a greater responder rate results, regardless of the underlying etiology of the

condition. This is in accordance with the desires and requirements of the patients to be treated.

It can be shown that combination therapy with valsartan and a NEP inhibitor results in a more effective anti-hypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic or other secondary type of hypertension) through improved efficacy, as well as a greater responder rate. The combination is also useful in the treatment or prevention of heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling. It can further be shown that a valsartan and NEP inhibitor therapy proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A valsartan plus NEP inhibitor combination is also useful in treating atherosclerosis, angina (whether stable or unstable), and renal insufficiency (diabetic and non-diabetic). Furthermore, combination therapy using valsartan and a NEP inhibitor can improve endothelial dysfunction, thereby providing benefit in diseases in which normal endothelial function is disrupted, such as heart failure, angina pectoris and diabetes. Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's; glaucoma and stroke.

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

Representative studies are carried out with a combination of valsartan and *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester, e.g., applying the following methodology:

Drug efficacy is assessed in various animal models including the deoxycorticosterone acetate-salt (DOCA-salt) rat and the spontaneously hypertensive rat

(SHR), either maintained on a normal salt diet or with salt loading (4-8% salt in rat chow or 1% NaCl as drinking water).

The DOCA-salt test model utilizes either an acute or chronic study protocol. An acute study procedure involves assessment of the effects of various test substances over a six-hour experimental period using rats with indwelling femoral arterial and venous catheters. The acute study procedure evaluates test substances for their ability to reduce blood pressure during the established phase of DOCA-salt hypertension. In contrast, the chronic study procedure assesses the ability of test substances to prevent or delay the rise in blood pressure during the development phase of DOCA-salt hypertension. Therefore, blood pressure will be monitored in the chronic study procedure by means of a radiotransmitter. The radiotransmitter is surgically implanted into the abdominal aorta of rats, prior to the initiation of DOCA-salt treatment and thus, prior to the induction of hypertension. Blood pressure is chronically monitored for periods of up to six weeks (approximately one week prior to DOCA-salt administration and for five weeks thereafter).

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

Acute study procedure:

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

A 20 mm incision is made through the skin and underlying muscle to expose the left kidney. The kidney is freed of surrounding tissue, exteriorized and two ligatures (3-0 silk) are tied securely around the renal artery and vein proximal to their juncture with the aorta. The renal artery and vein are then severed and the kidney removed. The muscle and skin wounds are closed with 4-0 silk suture and stainless steel wound clips, respectively. At the same time, a 15 mm incision is made on the back of the neck and a three-week-release pellet (Innovative Research of America, Sarasota, FL) containing DOCA (100 mg/kg) is implanted subcutaneously (s.c.). The wound is then closed with stainless-steel clips and both wounds are treated with povidone/iodine; the rats are given a post-surgical intramuscular (i.m.) injection of procaine penicillin G (100,000 U) and buprenorphine (0.05-0.1 mg/kg) s.c. The

rats are immediately placed on 1% NaCl + 0.2% KCl drinking water; this treatment continues for at least 3 weeks at which time the animals have become hypertensive and available for experimentation.

Forty-eight hours prior to experimentation, animals are anesthetized with isoflurane and catheters are implanted in the femoral artery and vein for measuring arterial pressure, collection of blood and administration of test compounds. Rats are allowed to recover for 48 hours while tethered in a Plexiglas home cage, which also serves as the experimental chamber.

Chronic study procedure:

This procedure is the same as above except that rats are implanted with a radiotransmitter, 7-10 days prior to the unilateral nephrectomy and initiation of DOCA and salt. In addition, rats do not undergo surgery for placement of femoral arterial and venous catheters. Radiotransmitters are implanted as described in Bazil et al., "Telemetric Monitoring of Cardiovascular Parameters in Conscious Spontaneously Hypertensive Rats", *J. Cardiovasc. Pharmacol.*, Vol. 22, pp. 897-905 (1993).

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

Blood pressure, heart rate and activity are determined at various pre-selected time points before, during and after drug administration. All measurements are performed in unrestrained and undisturbed animals. The maximum study time, determined by battery life, could be as long as nine months. For studies of this duration, rats are dosed orally (1-3 mL/kg vehicle), no more than twice daily or drug is administered via the drinking water or mixed with food. For studies of a shorter duration, that is, up to eight weeks, drugs are given via s.c. implanted osmotic minipumps. Osmotic minipumps are selected based on drug delivery rate and time. Valsartan dosages range from 1-10 mg/kg/day and *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester range from 10-50 mg/kg/day.

Additionally, SHRs are utilized to study the effects of valsartan in combination with *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester. The hypertensive background of the SHR is modified either by chronic salt loading in an effort to suppress the renin angiotensin system (RAS) or chronic salt depletion to activate the RAS in the SHR. These manipulations will be carried out to more extensively evaluate the efficacy of the various test substances. Experiments performed in SHRs are supplied by Taconic Farms, Germantown, NY (Tac:N(SHR)fBR). A radiotelemetric device (Data Sciences International, Inc., St. Paul, MN) is implanted into the lower abdominal aorta of all test animals between the ages of 14-16 weeks of age. All SHRs are allowed to recover from the surgical implantation procedure for at least two weeks prior to the initiation of the experiments. Cardiovascular parameters are continuously monitored via the radiotransmitter and transmitted to a receiver where the digitized signal is then collected and stored using a computerized data acquisition system. Blood pressure (mean arterial, systolic and diastolic pressure) and heart rate are monitored in conscious, freely moving and undisturbed SHR in their home cages. The arterial blood pressure and heart rate are measured every 10 minutes for 10 seconds and recorded. Data reported for each rat represent the mean values averaged over a 24-hour period and are made up of the 144-10 minute samples collected each day. The baseline values for blood pressure and heart rate consist of the average of three consecutive 24-hour readings taken prior to initiating the drug treatments. All rats are individually housed in a temperature and humidity controlled room and are maintained on a 12-hour light dark cycle.

In addition to the cardiovascular parameters, weekly determinations of body weight also are recorded in all rats. Treatments are administered in the drinking water, via daily oral gavage or in osmotic minipumps as stated above. If given in drinking water, water consumption is measured five times per week. Valsartan and *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester doses for individual rats are then calculated based on water consumption for each rat, the concentration of drug substance in the drinking water and individual body weights. All drug solutions in the drinking water are made up fresh every three to four days. Typical dosages for valsartan in drinking water range from 3-30 mg/kg/day whereas the dosage of *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester is highly dependent upon the specific agent used. In most situations, a daily dose will not exceed 50 mg/kg/day when administered as the monotherapy. In combination, lower dosages of each agent are used and correspondingly, valsartan is given in the range of 1-30 mg/kg/day and

N-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester in dosages below 50 mg/kg/day. However, in cases wherein the responder rate is increased with combination treatment, the dosages are identical to those used as monotherapy.

When drugs are administered by oral gavage, the dose of valsartan ranges from 1-50 mg/kg/day and *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester does not exceed 100 mg/kg/day.

Upon completion of the chronic studies, SHR or DOCA-salt rats are anesthetized and the heart rapidly removed. After separation and removal of the atrial appendages, left ventricle and left plus right ventricle (total) are weighed and recorded. Left ventricular and total ventricular mass are then normalized to body weight and reported. All values reported for blood pressure and cardiac mass represent the group mean ± sem.

Vascular function and structure are evaluated after treatment to assess the beneficial effects of the combination. SHR are studied according to the methods described by Intengan et al., *Circulation*, Vol. 100, No. 22, pp. 2267-2275 (1999). Similarly, the methodology for assessing vascular function in DOCA-salt rats is described in Intengan et al., *Hypertension*, Vol. 34, No. 4, Part 2, pp. 907-913 (1999).

The available results indicate an unexpected therapeutic effect of a combination according to the invention.

In one aspect is the object of this invention to provide a pharmaceutical combination composition, e.g., for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease,

luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke which composition comprises:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In this composition, components (i) and (ii) can be obtained and administered together, one after the other or separately in one combined unit dose form or in two separate unit dose forms. The unit dose form may also be a fixed combination.

A further aspect of the present invention is a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

A therapeutically effective amount of each of the component of the combination of the present invention may be administered simultaneously or sequentially and in any order.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The pharmaceutical compositions according to the invention can be prepared in a manner known *per se* and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

The typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by sugars, such as lactose, sucrose, mannitol and sorbitol; starches, such as cornstarch, tapioca starch and potato starch; cellulose and derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates, such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates, such as magnesium stearate and calcium stearate; stearic acid; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; betacyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents and the like commonly used in pharmaceutical formulations.

The invention also relates to combining separate pharmaceutical compositions in kit form. That is a kit combining two separate units: a valsartan pharmaceutical composition and a NEP inhibitor pharmaceutical composition. The kit form is particularly advantageous when the separate components must be administered in different dosage forms, e.g., parenteral valsartan formulation and oral NEP formulation; or are administered at different dosage intervals.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1-90%, preferably of from about 1% to about 80%, of the active compounds. Pharmaceutical preparations for enteral or parenteral administration are, e.g., in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known *per se*, e.g., using conventional mixing,

granulation, coating, solubulizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

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

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

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

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

In case of NEP inhibitors, preferred dosage unit forms are, e.g., tablets or capsules comprising, e.g., from about 20 mg to about 800 mg, preferably from about 50 mg to about 700 mg, even more preferably from about 100 mg to about 600 mg and even more preferably from about 100 mg to about 300 mg, administered q.d.

The above doses encompass a therapeutically effective amount of the active ingredients of the present invention.

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

Formulation Example 1: Film-Coated Tablets

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan (= active ingredient)	80.00	
Microcrystalline cellulose/Avicel PH 102	34.00	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 screening mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compactor 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 tablets 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		
Valsartan (= active ingredient)	160.00	
Microcrystalline cellulose/Avicel PH 102	108.00	NF, Ph. Eur
Crospovidone	40.00	NF, Ph. Eur
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	1.50	Ph. Eur, NF
Magnesium stearate	5.00	NF, Ph. Eur
Blending		
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	1.50	Ph. Eur, NF
Magnesium stearate	4.00	NF, Ph. Eur
Coating		
Opadry® Light Brown 00F33172	10.00	
Total Tablet Mass	**330.00**	

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

Formulation Example 3.

Film-coated tablets

Components	Composition Per Unit (mg)	Standards
Core Internal Phase		
Valsartan [= active ingredient]	40.00	
Silica, colloidal anhydrous (colloidal silicon dioxide) [= glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= lubricant]	2.00	USP/NF
Crospovidone [= disintegrant]	20.00	Ph. Eur
Microcrystalline cellulose [= binding agent]	124.00	USP/NF
External Phase		
Silica, colloidal anhydrous (colloidal silicon dioxide) [= glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= lubricant]	2.00	USP/NF
Film Coating		
Opadry Brown 00F16711*	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)
Valsartan [= active ingredient]	80.00
Microcrystalline cellulose	25.10
Crospovidone	13.00
Povidone	12.50
Magnesium stearate	1.30
Sodium lauryl sulphate	0.60
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total Tablet Mass	**209.50**

The tablet is manufactured, e.g., as follows:

Granulation/Drying

Valsartan and microcrystallin cellulose are spray-granulated in a fluidized bed granulator with a granulating solution consisting of povidone and sodium lauryl sulphate dissolved in purified water. The granulate obtained is dried in a fluidized 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 de-dusted, visually inspected, weight-checked and quarantined until by Quality Assurance department.

Formulation Example 5:

Capsules

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

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

Formulation Example 6:

Hard Gelatine Capsule

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Sodium lauryl sulphate	0.60

Magnesium stearate	1.30
Povidone	12.50
Crospovidone	13.00
Microcystalline cellulose	21.10
Total Tablet Mass	**130.00**

Formulation Example 7:

A hard gelatin capsule, comprising as active ingredient, e.g., (*S*)-*N*-(1-carboxy-2-methylprop-1-yl)-*N*-pentanoyl-*N*-[2'(*1H*-tetrazol-5-yl)biphenyl-4-yl-methyl]amine, can be formulated, e.g., as follows:

Components	Composition Per Unit (mg)
(1) Valsartan	80.00
(2) Microcystalline cellulose	110.0
(3) Polyvidone K30	45.2
(4) Sodium lauryl sulfate	1.2
(5) Crospovidone	26.0
(6) Magnesium stearate	2.6

Components (1) and (2) are granulated with a solution of components (3) and (4) in water. The components (5) and (6) are added to the dry granulate and the mixture is filled into size 1 hard gelatin capsules.

All publications and patents mentioned herein are incorporate by reference in their entirety as if set forth in full herein.

What is claimed is:

1. A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of Claim 1, wherein the NEP inhibitor is selected from the group consisting of SQ 28,603, *N*-[*N*-[1(*S*)-carboxyl-3-phenylproplyl]-(*S*)-phenylalanyl]-(*S*)-isoserine, *N*-[*N*-[(*1S*)-carboxy-2-phenyl)ethyl]-(*S*)-phenylalanyl]-β-alanine, *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine, (*cis*-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid), thiorphan, retro-thiorphan, phosphoramidon, SQ 29072, *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester, (*S*)-*cis*-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid, 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid, *N*-(1-(3-(*N*-*t*-butoxycarbonyl-(*S*)-prolylamino)-2(*S*)-*t*-butoxy-carbonylpropyl)cyclopentanecarbonyl)-*O*-benzyl-(*S*)-serine methyl ester, 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid, 3-[1-(*cis*-4-carboxycarbonyl-*cis*-3-butylcyclohexyl-*r*-1-carboamoyl)cyclopentyl]-*2S*-(2-methoxyethoxymethyl)propanoic acid, *N*-((*2S*)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine, *N*-(1-(*N*-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-*L*-phenylalanine, (*S*)-(2-biphenyl-4-yl)-1-(*1H*-tetrazol-5-yl)ethylamino) methylphosphonic acid, (*S*)-5-(*N*-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole, β-alanine, 3-[1,1'-biphenyl]-4-yl-*N*-[diphenoxyphosphinyl)methyl]-*L*-alanyl, *N*-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide, 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid, (*L*)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-*L*-phenylalanyl)-β-alanine, *N*-[*N*-[(*L*)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine, *N*-[*N*-[(*L*)-1-carboxy-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine, *N*-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, *N*-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(*S*)-isoserine, *N*-(*S*)-[3-mercapto-2-(2-methylphenyl)propionyl]-(*S*)-2-methoxy-(*R*)-alanine,

N-[1-[[1(*S*)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(*S*)-isoserine, *N*-[1-[[1(*S*)-carbonyl-3-phenylpropy]amino]-cyclopentylcarbonyl]-(*S*)-isoserine, 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-*bis*-(*S*)-isoserine, 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-*bis*-(*S*)-methionine, *N*-(3-phenyl-2-(mercaptomethyl)-propionyl)-(*S*)-4-(methylmercapto)methionine, *N*-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, *N*-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, *N*-[1-(2-carboxy-4-phenylbutyl)-cyclcpentanecarbonyl]-(*S*)-isoserine, *N*-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam and *N*-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester, or in each case, a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of Claim 2, wherein *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester is a triethanolamine or *tris*(hydroxymethyl)aminomethane salt thereof.

4. A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising a NEP inhibitor and in a second container a pharmaceutical composition comprising valsartan.

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

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

6. A method as claimed in Claim 5, wherein the NEP inhibitor is selected from the group consisting of SQ 28,603, *N*-[*N*-[1(*S*)-carboxyl-3-phenylproplyl]-(*S*)-phenylalanyl]-(*S*)-isoserine, *N*-[*N*-[(*1S*)-carboxy-2-phenyl)etnyl]-(*S*)-phenylalanyl]-β-alanine, *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine, (*cis*-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid), thiorphan, retro-thiorphan, phosphoramidon, SQ 29072, *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester, (*S*)-*cis*-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid, 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid, *N*-(1-(3-(*N*-*t*-butoxycarbonyl-(*S*)-prolylamino)-2(*S*)-*t*-butoxy-carbonylpropyl)cyclopentanecarbonyl)-*O*-benzyl-(*S*)-serine methyl ester, 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid, 3-[1-(*cis*-4-carboxycarbonyl-*cis*-3-butylcyclohexyl-r-1-carboamoyl)cyclopentyl]-*2S*-(2-methoxyethoxymethyl)propanoic acid, *N*-((*2S*)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine, *N*-(1-(*N*-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-*L*-phenylalanine, (*S*)-(2-biphenyl-4-yl)-1-(*1H*-tetrazol-5-yl)ethylamino) methylphosphonic acid, (*S*)-5-(*N*-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole, β-alanine, 3-[1,1'-biphenyl]-4-yl-*N*-[diphenoxyphosphinyl)methyl]-*L*-alanyl, *N*-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide, 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid, (*L*)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-*L*-phenylalanyl)-β-alanine, *N*-[*N*-[(*L*)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine, *N*-[*N*-[(*L*)-1-carboxy-2-phenylethyl]-*L*-phenylalanyl]-(*R*)-alanine, *N*-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, *N*-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, *N*-[2(*S*)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(*S*)-isoserine, *N*-(*S*)-[3-mercapto-2-(2-methylphenyl)propionyl]-(*S*)-2-methoxy-(*R*)-alanine, *N*-[1-[[1(*S*)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine, *N*-[1-[[1(*S*)-carbonyl-3-phenylpropy]amino]-cyclopentylcarbonyl]-(*S*)-isoserine, 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-*bis*-(*S*)-isoserine, 1,1'-[dithiobis-[2(*S*)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-*bis*-(*S*)-methionine, *N*-(3-phenyl-2-(mercaptomethyl)-

propionyl)-(*S*)-4-(methylmercapto)methionine, *N*-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, *N*-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, *N*-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(*S*)-isoserine, *N*-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(*S*)-methionine ethyl ester, 3(*S*)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam and *N*-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester, and in each case, a pharmaceutically acceptable salt thereof.

7. The method of Claim 6, wherein *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester is a triethanolamine or tris(hydroxymethyl)aminomethane salt thereof.

8. A triethanolamine salt of *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester.

9. A *tris*(hydroxymethyl)aminomethane salt of *N*-(3-carboxy-1-oxopropyl)-(*4S*)-*p*-phenylphenylmethyl)-4-amino-*2R*-methylbutanoic acid ethyl ester.

10. A pharmaceutical composition comprising the salt of Claim 8.

11. A pharmaceutical composition comprising the salt of Claim 9.

Abstract of the Disclosure

The invention relates a pharmaceutical composition comprising a combination of:

(i) the AT 1- antagonist valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier and to a method for the treatment or prevention of a condition or disease

selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke, comprising administering a therapeutically effective amount of the pharmaceutical composition to a mammal in need thereof.

Case 4-32219A

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATIONS

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

the specification of which was filed on January 14, 2003 as U.S. Application No. **10/341,868.**

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims.

I acknowledge my duty to disclose all information which is known by me to be material to the patentability of this application as defined in 37 C.F.R. §1.56.

I hereby claim the benefit under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and under 35 U.S.C. §365(a) of any PCT international application(s) designating at least one country other than the United States listed below and have also listed below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application the priority of which is claimed for that subject matter:

None

I hereby claim the benefit under 35 USC §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date
60/386,792	June 7, 2002
60/349,660	January 17, 2002

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) listed below and under 35 U.S.C. §365(c) of any PCT international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose all information known by me to be material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date(s) of the prior application(s) and the national or PCT international filing date of this application:

None

I hereby appoint the attorneys and agents associated with Customer No. 001095, respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Please address all communications to the address associated with Customer No. 001095, which is currently Thomas Hoxie, Novartis Pharmaceuticals Corporation, Patent and Trademark Dept., One Health Plaza, East Hanover, NJ 07936-1080.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FIRST JOINT INVENTOR:

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Signature : _____

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SECOND JOINT INVENTOR:

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Date : 02/26/03 (MM/DD/YY)

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IMPORTANT: Before this declaration is signed, the patent application (the specification, the claims and this declaration) must be read and understood by each person signing it, and no changes may be made in the application after this declaration has been signed.

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL.

APPLICATION NO:

Not yet Known

FILED: Herewith

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed concurrently with the filing of the application. Therefore, no fees are required. If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

The listed references are of record in parent Application No. 10/341868 filed January 14, 2003, and copies are available therein. However, applicants are willing to send copies of any or all of these references at the Examiner's request.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

Respectfully submitted,

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-7831

Gregory D. Ferraro
Attorney for Applicants
Reg. No. 36,134

Date: 6/23/08

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO. 32219-US-DIV
APPLICATION NO. Not yet known
APPLICANT KSANDER ET AL.
FILING DATE Herewith
Group 1617

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA	4,610,816	09/09/86	Berger	549	452	06/15/84
	AB	4,722,810	02/02/88	Delaney et al.	260	402.5	08/13/86
	AC	4,740,499	04/26/88	Olins	514	13	07/28/86
	AD	4,749,688	06/07/88	Haslanger et al.	514	19	06/20/86
	AE	4,929,641	05/29/90	Haslanger et al.	514	506	05/11/88
	AF	5,217,996	06/08/93	Ksander	514	533	01/22/92
	AG	5,223,516	06/29/93	Delaney et al.	514	339	04/24/91
	AH	5,273,990	12/28/93	De Lombaert	514	381	09/03/92
	AI	5,294,632	03/15/94	Erion et al.	514	381	10/09/92
	AJ	5,399,578	03/21/95	Bühlmayer et al.	514	381	12/29/92
	AK	5,520,522	05/28/96	Rathore et al.	417	322	09/21/94
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM	0 342 850	11/23/89	EP			☐	☐
	AN	0 343 911	11/29/89	EP			☐	☐
	AO	0 361 365	04/04/90	EP			☐	☐
	AP	0 443 983	08/28/91	EP			☐	☐
	AQ	0636621B1	3/12/97	EP			☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AR	Almeida et al., "Clearance Function of Type C Receptors of Atrial Natriuretic Factor in Rats", *Am J Physiol*, Vol. 256, pp. R469-R475 (1989).
	AS	Bazil, Krulan and Webb, "Telemetric Monitoring of Cardiovascular Parameteres in Conscious Spontaneously Hypertensive Rats", *J Cardiovasc Pharmacol*, Vol. 22, pp. 897-905 (1993).
	AT	Consensus Trial Study Group, "Effects of Enalapril on Mortality in Severe Congestive Heart Failure", *N Eng J Med*, Vol. 316, No. 23, pp. 1429-1435 (1987).

EXAMINER | **DATE CONSIDERED**

*EXAMINER: Initial of reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO.
32219-US-DIV
APPLICATION NO.
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KSANDER ET AL.
FILING DATE
Herewith

Group
1617

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	CA	0 636 621	02/01/95	EP			☐	☐
	CB	2 218 983	11/29/89	GB			☐	☐
	CC	90/09374	08/23/90	WO			☐	☐
	CD	92/14706	09/03/92	WO			☐	☐
	CE	93/09101	05/13/93	WO			☐	☐
	CF	93/10773	06/10/93	WO			☐	☐
	CG	94/15908	07/1/94	WO (English Abstract)			☐	☐
	CH	03/066606	8/14/03	WO			☐	☐
	CI	01/74348	10/11/01	WO			☐	☐
	CJ	02/06253	1/24/02	WO			☐	☐
	CK	02/092622	11/21/02	WO			☐	☐
	CL	0 726 072	8/14/96	EP			☐	☐
	CM	0 498 361	8/12/92	EP			☐	☐
	CN						☐	☐
	CO						☐	☐
	CP						☐	☐
	CQ						☐	☐
	CR						☐	☐
	CS						☐	☐
	CT						☐	☐
	CU						☐	☐
	CV						☐	☐
	CW						☐	☐
	CX						☐	☐
	CY						☐	☐
	CZ						☐	☐

EXAMINER **DATE CONSIDERED**

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FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

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ATTY. DOCKET NO. 32219-US-DIV
APPLICATION NO. Not yet known
APPLICANT KSANDER ET AL.
FILING DATE Herewith
Group 1617

EXAMINER INITIAL		OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)
	DA	Stephenson et al., "The hydrolysis of a-human atrial natriuretic peptide by pig kindney microvillar membranes is initiated by endopeptidase-24.11 *Biochem J*, Vol. 243, pp. 183-187(1987).
	DB	Erdös, "Angiotensin I Converting Enzyme and the Changes in Our Concepts Through the Years" – Lewis K. Dahl Memorial Lecture, *Hypertension*, Vol. 16, No. 4, pp. 363-370 (1990).
	DC	Intengan, Park and Schiffrin, "Blood Pressure and Small Arteries in DOCA-Salt-Treated Genetically AVP-Deficient Rats", *Hypertension*, Vol. 34, No. 4, Part 2, pp. 907-913 (1999).
	DD	Intengan, Thibault, Li and Schiffrin, "Resistance Artery Mechanics, Structure, and Extracellular Components in Spontaneously Hypertensive Rats", *Circulation*, Vol. 100, No. 22, pp. 2267-2275 (1999).
	DE	Needleman et al., "The Biochemical Pharmacology of Atrial Peptides", *Annu Rev Pharm Tox*, Vol. 29, pp. 23-54 (1989).
	DF	Stephenson and Kenny, "Metabolism of Neuropeptides", *Biochem J*, Vol. 241, pp. 237-247 (1987).
	DG	Sybertz et al., "SCH 39370, a Neutral Metalloendopeptidase Inhibitor, Potentiates Biological Responses to Atrial Natriuretic Factor and Lowers Blood Pressure in Desoxycorticosterone Acetate-Sodium Hypertensive Rats", *J Pharmacol Exp Ther*, Vol. 250, No. 2, pp. 624-631 (1989).
	DH	Sybertz et al., "Atrial Natriuretic Factor-Potentiating and Antihypertensive Activity of SCH 34826", *Hypertension*, Vol. 15, No. 2, pp. 152-161 (1990).
	DI	Williford, Sharma, Korth and Sheu, "Spatial Heterogeneity of Intracellular Ca^{2+} Concentration in Nonbeating Guinea Pig Ventricular Myocytes", *Circ Res*, Vol. 66, No. 1, pp. 241-249 (1990).
	DJ	Zannad, "The Emerging Role of ACE Inhibitors in the Treatment of Cardiovascular Disease", *J Cardiovasc Pharmacol*, Vol. 15, Suppl. 2, pp. S1, S5 (1990).
	DK	CAPLUS Abstract AN 1986:573042`- Taub et al., f ZA8400670, 9/25//1985
	DL	CAPLUS Abstract AN 1995: 931230- Sugano et al., JP 07157459, 06/20/1995,
	DM	CAPLUS Abstract AN 1995:412660 – Yamada et al., JP 06234754, 8/23/1994
	DN	Matsumoto et al. "Blockade of renin-angiotensin system and enhancement of atrial natriuretic peptide with neutral endopedtidase inhibition cause natriuresis in congestive heart failure and renal dysfunction in conscious dogs". JASN, Hemodynamics and Vascular Regulation, pp. 517, (1993).

EXAMINER | **DATE CONSIDERED**

*EXAMINER: Initial of reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary M Ksander
Filer:	Gregory David Ferraro./Maureen McGee
Attorney Docket Number:	32219-US-DIV

Filed as Large Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	310	310
Utility Search Fee	1111	1	510	510
Utility Examination Fee	1311	1	210	210
Pages:				
Claims:				
Independent claims in excess of 3	1201	2	210	420
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1450**

Electronic Acknowledgement Receipt

EFS ID:	3528967
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary M Ksander
Customer Number:	01095
Filer:	Gregory David Ferraro./Maureen McGee
Filer Authorized By:	Gregory David Ferraro.
Attorney Docket Number:	32219-US-DIV
Receipt Date:	27-JUN-2008
Filing Date:	
Time Stamp:	10:02:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1450
RAM confirmation Number	5605
Deposit Account	190134
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219.pdf	1787072 b6ef57f8880e1e310c5bc4cf48b35b6e4bf7411b	yes	41

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal of New Application	1	2
Application Data Sheet	3	4
Preliminary Amendment	5	6
Applicant Arguments/Remarks Made in an Amendment	7	7
Specification	8	33
Oath or Declaration filed	34	36
Information Disclosure Statement Letter	37	38
Information Disclosure Statement (IDS) Filed	39	41

Warnings:

Information:

2	Fee Worksheet (PTO-06)	fee-info.pdf	8513 26142aa3a9210a88f5a84a627698007038a436b1	no	2

Warnings:

Information:

Total Files Size (in bytes):	1795585

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (12-04)

Filing Date: 06/27/08

Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 12/147,570

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	310
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	510
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	210
TOTAL CLAIMS (37 CFR 1.16(i))	11 minus 20 =	0	X$ 25		OR	X$50	0
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 minus 3 =	2	X$100			X$210	420
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			185			370	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	0		TOTAL	1450

APPLICATION AS AMENDED – PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/147,570	06/27/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT	06/27/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 11	Minus	** 20	= 0	X $ =		OR	X $50=	0
	Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 0	X $ =		OR	X $210=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/STEVEN WHIBLEY/

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/147,570	06/27/2008	1614	1450	32219-US-DIV	11	5

CONFIRMATION NO. 7174

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

FILING RECEIPT

OC00000030986372

Date Mailed: 07/17/2008

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Gary Michael Ksander, Amherst, NH;
Randy Lee Webb, Flemington, NJ;

Power of Attorney: The patent practitioners associated with Customer Number 001095

Domestic Priority data as claimed by applicant

This application is a DIV of 10/341,868 01/14/2003
which claims benefit of 60/386,792 06/07/2002
and claims benefit of 60/349,660 01/17/2002

Foreign Applications

If Required, Foreign Filing License Granted: 07/15/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/147,570**

Projected Publication Date: 10/23/2008

Non-Publication Request: No

Early Publication Request: No

Title

METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV

CONFIRMATION NO. 7174

1095
NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

PUBLICATION NOTICE

OC000000032749646

Title:METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Publication No.US-2008-0262059-A1
Publication Date:10/23/2008

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL.

APPLICATION NO: 12/147,570

FILED: JUNE 27, 2008

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is supplemental to the Information Disclosure Statement filed 6/27/08. Since Applicants believe this paper is being filed before the mailing date of a first Office Action on the merits, no fees are believed to be required under 37 C.F.R. §1.97(b)(3). If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

Copies of these references are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

Respectfully submitted,

Novartis
Pharma Intellectual Property
One Health Plaza, Building 101
East Hanover, NJ 07936-1080

Joseph T. Majka
Attorney for Applicants
Reg. No. 30,570
(862) 778-9499

Date: 24 Oct. 2008

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO. 32219-US-DIV
APPLICATION NO. 12/147,570
APPLICANT KSANDER ET AL.
FILING DATE JUNE 27, 2008
Group

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM						☐	☐
	AN						☐	☐
	AO						☐	☐
	AP						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AQ	Lajemi et al., "Genetics of the renin-angiotensin-aldosterone system and risk of arterial disease", ACE Inhibitors, Milestones in Drug Therapy, P. D'Orleans-Juste, G.E. Plante
	AR	Matsumoto et al., "Blockade of renin-angiotensin system and enhancement of atrial natriuretic peptide with neutral endopeptidase inhibition cause natriuresis in congestive heart failure and renal dysfunction in concious dogs", Hemodynamics and Vascular Regulation.
	AS T	Robi et al., "Neutral endopeptidase inhibitors and combined inhibitors of neutral endopeptidase and angiotensin converting enzyme" ACE inhibitors, Milestones in Drug therapy, P.D'Orleans-Juste, G.E. Plante.
		Wohlfart et al., "Crosstalk between ACE inhibitors, B2 kinin receptor and nitric oxide in endothelial cells", ACE inhibitors, Milestones in Drug therapy, P.D'Orleans-Juste, G.E. Plante.

EXAMINER **DATE CONSIDERED**

*EXAMINER: Initial of reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

Electronic Acknowledgement Receipt

EFS ID:	4171976
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	01095
Filer:	Joseph T. Majka/Monika Van Houten
Filer Authorized By:	Joseph T. Majka
Attorney Docket Number:	32219-US-DIV
Receipt Date:	24-OCT-2008
Filing Date:	27-JUN-2008
Time Stamp:	14:12:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219isupids102408.pdf	2702832 16fbc239595821e9878e549fc37fedcb228c8304	yes	17

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Information Disclosure Statement Letter	1	2
	Information Disclosure Statement (IDS) Filed (SB/08)	3	3
	NPL Documents	4	17
Warnings:			
Information:			
	Total Files Size (in bytes):	2702832	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

1095 7590 02/24/2009

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
02/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/147,570	KSANDER ET AL.	
	Examiner	Art Unit	
	JENNIFER MYONG M. KIM	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☐ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-11* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-4, 8-11 are drawn to a pharmaceutical composition comprising AT 1-antagonist valsartan and a NEP inhibitor, classified in class 514, subclass 222.8.

II. Claims 5-7, drawn to a method for the treatment or prevention of a condition or disease set forth in claim 5 administering a pharmaceutical composition comprising AT 1-antagonist valsartan and a NEP inhibitor, classified in class 514, subclass 222.8.

The inventions are distinct, each from the other because of the following reasons:

Inventions Group I and Group II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product since the product can be used to treat psychotic conditions.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above

and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicants are advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement

will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicants traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

If Applicants elect Group II, following election of species is required:

This application contains claims directed to the following patentably distinct species of the claimed invention: Various conditions or disease set forth in claim 5 (i.e. hypertension, heart failure, Alzheimer, glaucoma, diabetic nephrophay.. etc.).

Applicants are required under 35 U.S.C. 121 to elect a single ultimate disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, a condition or disease is generic.

Applicants are advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicants traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier.

Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JENNIFER M KIM/
Primary Examiner, Art Unit 1617

Jmk
February 17, 2009

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER MYONG M KIM	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/17/2009								
	1	÷								
	2	÷								
	3	÷								
	4	÷								
	5	÷								
	6	÷								
	7	÷								
	8	÷								
	9	÷								
	10	÷								
	11	÷								

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

KSANDER ET AL.

APPLICATION NO: 12/147,570

FILED: JUNE 27, 2008

FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

Sir:

In response to the Office Action dated February 24, 2009, please enter the following response.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

Amendments to the Claims

Claim 1 (original): A pharmaceutical composition comprising (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Claim 2 (original): The pharmaceutical composition of claim 1, wherein the NEP inhibitor is selected from the group consisting of SQ 28,603, N-[N-[1(S)-carboxyl-3-phenylproplyl]-(S)-phenylalanyl]-(S)-isoserine, N-[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine, (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid), thiorphan, retro-thiorphan, phosphoramidon, SQ 29072, N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid, 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid, N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester, 4-[[2-(Mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid, 3-[1-(Cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carboamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid, N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine, N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine, (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid, (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole, β-Alanine, 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl, N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide, 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid, (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine, N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, N-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine, N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine, N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine, N-[1-[[1(S)-carbonyl-3-phenylpropy]amino]-cyclopentylcarbonyl]-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine, N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine, N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine, N-[1-

(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam and N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester, or in each case, a pharmaceutically acceptable salt thereof.

Claim 3 (original): The pharmaceutical composition of claim 2 wherein N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is a triethanolamine or tris(hydroxymethyl)aminomethane salt thereof.

Claim 4 (original): A kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising a NEP inhibitor and in a second container a pharmaceutical composition comprising valsartan.

Claim 5 (original): A method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, comprising administering a therapeutically effective amount of combination of (i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

Claim 6 (original): A method as claimed in claim 5, wherein the NEP inhibitor is selected from the group consisting of SQ 28,603, N-[N-[1(S)-carboxyl-3-phenylproplyl]-(S)-phenylalanyl]-(S)-isoserine, N-[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine, (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid), thiorphan, retro-thiorphan, phosphoramidon, SQ 29072, N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid, 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-

carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid, N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester, 4-[[2-(Mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid, 3-[1-(Cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carboamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid, N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine, N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine, (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid, (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole, β-Alanine, 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl, N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide, 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid, (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine, N-[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, N-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine, N-(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine, N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine, N-[1-[[1(S)-carbonyl-3-phenylpropy]amino]-cyclopentylcarbonyl]-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine, N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine, N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine, N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam and N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester, and in each case, a pharmaceutically acceptable salt thereof.

Claim 7 (original): The method of claim 6, wherein N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is a triethanolamine or tris(hydroxymethyl)aminomethane salt thereof.

Claim 8 (original): A triethanolamine salt of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

Claim 9 (original): A tris(hydroxymethyl)aminomethane salt of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

Claim 10 (original): A pharmaceutical composition comprising the salt of claim 8.

Claim 11 (original): A pharmaceutical composition comprising the salt of claim 9.

Claim 12 (new): A pharmaceutical composition comprising:
valsartan or a pharmaceutically acceptable salt thereof; and
N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Claim 13 (new): The pharmaceutical composition of claim 12 wherein N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is a triethanolamine or tris(hydroxymethyl)aminomethane salt thereof.

REMARKS

The following is responsive to the restriction requirement dated February 24, 2009. Claims 1-11 were pending in the application and are subject to restriction and/or election requirement under 35 USC 121.

Applicants elect Group I directed to claims 1-4, 8-11 and newly added claims 12-13, without traverse. Claims 1-4, 8-11 and 12-13 encompass the elected invention.

Respectfully submitted

Novartis Pharmaceuticals Corp.
Patents Pharma
Reg. No. 53,283
One Health Plaza, Building 104
(862) 778-7831
Date: May 21, 2009

Lisa M. Matovcik
Reg. No. 53,283
for
Joseph T. Majka
Attorney for Applicants
Reg. No. 30,570
(862)778-9499

Re

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander, Gary Michael et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of February 24, 2009 has a shortened statutory time set to expire on March 24, 2009. A two-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $ 490 for payment of the extension fee. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9499

Lisa M. Matovcik
Reg. No. 53,283
for
Joseph Majka
Attorney for Applicant
Reg. No. 30,570

Date: May 21, 2009

Electronic Patent Application Fee Transmittal

Application Number:	12147570
Filing Date:	27-Jun-2008
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Joseph T. Majka/Monika Van Houten
Attorney Docket Number:	32219-US-DIV

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	1252	1	490	490

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**490**

Electronic Acknowledgement Receipt

EFS ID:	5375921
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	01095
Filer:	Joseph T. Majka/Monika Van Houten
Filer Authorized By:	Joseph T. Majka
Attorney Docket Number:	32219-US-DIV
Receipt Date:	21-MAY-2009
Filing Date:	27-JUN-2008
Time Stamp:	13:36:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$490
RAM confirmation Number	10841
Deposit Account	190134
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219-US-RRR052109.pdf	475171 45199e6fa7f16515e82f8ffc1da9a6ed5b5ac56a	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6
	Extension of Time	7	7

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	30726 bd1cb228c3d7e39c455ff29cc90e3565e706c515	no	2

Warnings:

Information:

Total Files Size (in bytes):	505897

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

1095 7590 08/07/2009

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
08/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/147,570	KSANDER ET AL.	
	Examiner	Art Unit	
	JENNIFER MYONG M. KIM	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/21/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *5-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/27/08; 10/24/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election **without traverse** of Group 1, claims 1-4 and 8-13, drawn to a pharmaceutical composition comprising AT-1 antagonist valsartan and a NEP inhibitors is acknowledged.

Accordingly, claims 5-7 are withdrawn from consideration since they are non-elected invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) of record.

Ksander teaches the compound, 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)antipode thereof (also known as N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) is a pharmacologically potent neutral endopeptidase enzyme inhibitor and it is useful for the treatment of cardiovascular disorders such as **hypertension**. (column 9, lines 5-15, column 12, lines 1-10, claims 1-22). Ksander teaches ammonium salts, mono-, di- or tri-lower **(alkyl or hydroxyalkyl)-ammonium salts** (e.g. **triethanolammonium**) are suitable pharmaceutically acceptable salts of the compound. (column 5, lines 35-45).

Ksander does not illustrate the specific salt form of the compound set forth in claims 8 and 9.

It would have been obvious to one of ordinary skill in the art to employ triethanolamine salt of the compound because Ksander teaches that triethanolamine salt is pharmaceutically acceptable salt of the compound. One would have been

motivated to employ the pharmaceutically acceptable salt of the compound e.g. **triethanolammonium** as taught by Ksander. Further, the specified salt (tris(hydroxymethyl)aminomethane salt) of the compound set forth in claim 9 is obvious because Ksander teaches the any ammonium salts, including tri-lower (**alkyl or hydroxyalkyl)-ammonium salt** is pharmaceutically acceptable and the antihypertensive utility is retained. Therefore, one of ordinary skill in the art would have been motivated to employ any one of ammonium salts, including tri-lower (**alkyl or hydroxyalkyl)-ammonium salt** including (tris(hydroxymethyl)aminomethane salt) in order to achieve an expected benefit of formulating the compound with its pharmaceutically acceptable salt useful for antihypertensive effect taught by Ksander. Accordingly, the instant claim is obvious therefrom.

Claims 1- 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) of record and Buhlmayer et al. (U.S.Patent No. 5,399,578) of record.

Ksander teaches a pharmaceutical composition comprising the compound, 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)antipode thereof (also known as N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) is a pharmacologically potent neutral endopeptidase enzyme (NEP) inhibitor and it is useful for the treatment of cardiovascular disorders such as **hypertension**. (column 9, lines 5-15, column 12, lines 1-10, claims 1-22). Ksander teaches ammonium salts, mono-, di- or tri-lower

(**alkyl or hydroxyalkyl)-ammonium salts** (e.g. **triethanolammonium**) are suitable pharmaceutically acceptable salts of the compound. (column 5, lines 35-45).

Buhlmayer et al. teach valsartan is useful for an anti-hypertensive treatment. (abstract, claims).

The claims differ from the cited references in claiming a pharmaceutical composition comprising combination of the specific NEP inhibitor and valsartan. To employ combinations of specific NEP inhibitor and valsartan would have been obvious because all the components are well known individually for treating hypertension. One of ordinary skill in the art would have been motivated to combine specific NEP inhibitor and valsartan in a single composition in order to achieve an expected benefit of antihypertensive effect of the combination. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JENNIFER M KIM/
Primary Examiner, Art Unit 1617

Jmk
July 28, 2009

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER MYONG M KIM	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/17/2009	07/28/2009							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
	5	÷	N							
	6	÷	N							
	7	÷	N							
	8	÷	✓							
	9	÷	✓							
	10	÷	✓							
	11	÷	✓							
	12		✓							
	13		✓							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER M KIM	1617

SEARCHED			
Class	Subclass	Date	Examiner
514	533, 381	7/29/2009	jmk

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search; STN; parent 10/341,868	7/29/2009	jmk

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO. 32219-US-DIV
APPLICATION NO. Not yet known
APPLICANT KSANDER ET AL.
FILING DATE Herewith
Group 1617

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA	4,610,816	09/09/86	Berger	549	452	06/15/84
	AB	4,722,810	02/02/88	Delaney et al.	260	402.5	08/13/86
	AC	4,740,499	04/26/88	Olins	514	13	07/28/86
	AD	4,749,688	06/07/88	Haslanger et al.	514	19	06/20/86
	AE	4,929,641	05/29/90	Haslanger et al.	514	506	05/11/88
	AF	5,217,996	06/08/93	Ksander	514	533	01/22/92
	AG	5,223,516	06/29/93	Delaney et al.	514	339	04/24/91
	AH	5,273,990	12/28/93	De Lombaert	514	381	09/03/92
	AI	5,294,632	03/15/94	Erion et al.	514	381	10/09/92
	AJ	5,399,578	03/21/95	Bühlmayer et al.	514	381	12/29/92
	AK	5,520,522	05/28/96	Rathore et al.	417	322	09/21/94
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM	0 342 850	11/23/89	EP			☐	☐
	AN	0 343 911	11/29/89	EP			☐	☐
	AO	0 361 365	04/04/90	EP			☐	☐
	AP	0 443 983	08/28/91	EP			☐	☐
	AQ	0636621B1	3/12/97	EP			☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AR	Almeida et al., "Clearance Function of Type C Receptors of Atrial Natriuretic Factor in Rats", *Am J Physiol*, Vol. 256, pp. R469-R475 (1989).
	AS	Bazil, Krulan and Webb, "Telemetric Monitoring of Cardiovascular Parameteres in Conscious Spontaneously Hypertensive Rats", *J Cardiovasc Pharmacol*, Vol. 22, pp. 897-905 (1993).
	AT	Consensus Trial Study Group, "Effects of Enalapril on Mortality in Severe Congestive Heart Failure", *N Eng J Med*, Vol. 316, No. 23, pp. 1429-1435 (1987).

EXAMINER | **DATE CONSIDERED**

*EXAMINER: Initial of reference considered, whether or not citation is in conformance with MPEP 609: Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /JK/

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

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Herewith

Group
1617

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	CA	0 636 621	02/01/95	EP			☐	☐
	CB	2 218 983	11/29/89	GB			☐	☐
	CC	90/09374	08/23/90	WO			☐	☐
	CD	92/14706	09/03/92	WO			☐	☐
	CE	93/09101	05/13/93	WO			☐	☐
	CF	93/10773	06/10/93	WO			☐	☐
	CG	94/15908	07/1/94	WO (English Abstract)			☐	☐
	CH	03/066606	8/14/03	WO			☐	☐
	CI	01/74348	10/11/01	WO			☐	☐
	CJ	02/06253	1/24/02	WO			☐	☐
	CK	02/092622	11/21/02	WO			☐	☐
	CL	0 726 072	8/14/96	EP			☐	☐
	CM	0 498 361	8/12/92	EP			☐	☐
	CN						☐	☐
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FILING DATE Herewith
Group 1617

EXAMINER INITIAL		OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)
	DA	Stephenson et al., "The hydrolysis of a-human atrial natriuretic peptide by pig kindney microvillar membranes is initiated by endopeptidase-24.11 *Biochem J*, Vol. 243, pp. 183-187(1987).
	DB	Erdös, "Angiotensin I Converting Enzyme and the Changes in Our Concepts Through the Years" – Lewis K. Dahl Memorial Lecture, *Hypertension*, Vol. 16, No. 4, pp. 363-370 (1990).
	DC	Intengan, Park and Schiffrin, "Blood Pressure and Small Arteries in DOCA-Salt-Treated Genetically AVP-Deficient Rats", *Hypertension*, Vol. 34, No. 4, Part 2, pp. 907-913 (1999).
	DD	Intengan, Thibault, Li and Schiffrin, "Resistance Artery Mechanics, Structure, and Extracellular Components in Spontaneously Hypertensive Rats", *Circulation*, Vol. 100, No. 22, pp. 2267-2275 (1999).
	DE	Needleman et al., "The Biochemical Pharmacology of Atrial Peptides", *Annu Rev Pharm Tox*, Vol. 29, pp. 23-54 (1989).
	DF	Stephenson and Kenny, "Metabolism of Neuropeptides", *Biochem J*, Vol. 241, pp. 237-247 (1987).
	DG	Sybertz et al., "SCH 39370, a Neutral Metalloendopeptidase Inhibitor, Potentiates Biological Responses to Atrial Natriuretic Factor and Lowers Blood Pressure in Desoxycorticosterone Acetate-Sodium Hypertensive Rats", *J Pharmacol Exp Ther*, Vol. 250, No. 2, pp. 624-631 (1989).
	DH	Sybertz et al., "Atrial Natriuretic Factor-Potentiating and Antihypertensive Activity of SCH 34826", *Hypertension*, Vol. 15, No. 2, pp. 152-161 (1990).
	DI	Williford, Sharma, Korth and Sheu, "Spatial Heterogeneity of Intracellular Ca^{2+} Concentration in Nonbeating Guinea Pig Ventricular Myocytes", *Circ Res*, Vol. 66, No. 1, pp. 241-249 (1990).
	DJ	Zannad, "The Emerging Role of ACE Inhibitors in the Treatment of Cardiovascular Disease", *J Cardiovasc Pharmacol*, Vol. 15, Suppl. 2, pp. S1, S5 (1990).
	DK	CAPLUS Abstract AN 1986:573042`- Taub et al., f ZA8400670, 9/25//1985
	DL	CAPLUS Abstract AN 1995: 931230- Sugano et al., JP 07157459, 06/20/1995,
	DM	CAPLUS Abstract AN 1995:412660 – Yamada et al., JP 06234754, 8/23/1994
	DN	Matsumoto et al. "Blockade of renin-angiotensin system and enhancement of atrial natriuretic peptide with neutral endopedtidase inhibition cause natriuresis in congestive heart failure and renal dysfunction in conscious dogs". JASN, Hemodynamics and Vascular Regulation, pp. 517, (1993).

EXAMINER /Jennifer Kim/ **DATE CONSIDERED** /Jennifer Kim/

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FORM PTO-1449 (REV. 7-85)
U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO.
32219-US-DIV
APPLICATION NO.
12/147,570
APPLICANT
KSANDER ET AL.
FILING DATE
JUNE 27, 2008
Group

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA						
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	AL						

FOREIGN PATENT DOCUMENTS

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	AM						☐	☐
	AN						☐	☐
	AO						☐	☐
	AP						☐	☐

NO DATE!!!

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AQ	Lajemi et al., "Genetics of the renin-angiotensin-aldosterone system and risk of arterial disease", ACE Inhibitors, Milestones in Drug Therapy, P. D'Orleans-Juste, G.E. Plante
	AR	Matsumoto et al., "Blockade of renin-angiotensin system and enhancement of atrial natriuretic peptide with neutral endopeptidase inhibition cause natriuresis in congestive heart failure and renal dysfunction in concious dogs", Hemodynamics and Vascular Regulation. /Jennifer Kim/
	AS T	Robi et al., "Neutral endopeptidase inhibitors and combined inhibitors of neutral endopeptidase and angiotensin converting enzyme" ACE inhibitors, Milestones in Drug therapy, P.D'Orleans-Juste, G.E. Plante.
		Wohlfart et al., "Crosstalk between ACE inhibitors, B2 kinin receptor and nitric oxide in endothelial cells" ACE inhibitors, Milestones in Drug therapy, P.D'Orleans-Juste, G.E. Plante.

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FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO. PAT032219-US-DIV

APPLICATION NO. 12/147570

APPLICANT
Ksander, Gary Michael et al.

FILING DATE
June 27, 2008

Group
1617

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA						
	AB						
	AC						
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	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM	0726072	02/07/96	EP			☐	☐
	AN	555175	01/13/93	EP			☐	☐
	AO						☐	☐
	AP						☐	☐
	AQ						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AR	LAJEMI et al., "Genetics of the renin-angiotensin-aldosterone system and risk of arterial disease"; ACE Inhibitors, Milestones in Drug Therapy, pages 11-27; P. D'Orleans-Juste, G.E. Plante (2001)
	AS	MATSUMOTO et al.; "Blockade of renin-angiotensin system and enhancement of atrial natriuretic peptide with neutral endopeptidase inhibition cause natriuresis in congestive heart failure and renal dysfunction in conscious dogs", ASN Program and Abstracts, Vol. 4, No. 3, page 517(September 1993)
	AT	ROBI et al., "Neutral endopeptidase inhibitors and combined inhibitors of neutral endopeptidase and angiotensin converting enzyme", Antihypersensitive Drugs,pages 113-212 , (1997)
	AU	WOHLFART, et al.; "Crosstalk between ACE Inhibitors, B2 kinin receptor and nitric oxide in endothelial cells", ACE Inhibitors, Milestones in Drug Therapy, P. D'Orleans-Juste, G.E. Plante (2001)

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 726 072 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
14.08.1996 Bulletin 1996/33

(51) Int. Cl.[6]: **A61K 31/415**, A61K 45/06

(21) Application number: **96101756.3**

(22) Date of filing: **07.02.1996**

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **08.02.1995 US 386366**

(71) Applicant: **BRISTOL-MYERS SQUIBB COMPANY**
Princeton, NJ 08543-4000 (US)

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- **Trippodo, Nick C.**
  Newtown, PA 18940 (US)

(74) Representative: **Josif, Albert, Dr.-Ing. et al**
Baaderstrasse 3
80469 München (DE)

(54) Composition for the treatment of hypertension and congestive heart failure, containing an angiotensin II antagonist and an endopeptidase inhibitor

(57) Hypertension and/or congestive heart failure are treated with the combination of the angiotensin II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]nonan-4-one and a selective neutral endopeptidase inhibitor or a dual acting neutral endopeptidase inhibitor.

EP 0 726 072 A2

Description

Darrow et al. in European Patent Application 498,361 disclose treating hypertension or congestive heart failure with a combination of an angiotensin II antagonist or a renin inhibitor with a neutral endopeptidase inhibitor.

Matsumoto et al., JASN, September 1993, disclose that the combined therapy of an angiotensin II blocker, DUP753, and a neutral endopeptidase inhibitor, candoxatril, may be useful in the treatment of congestive heart failure and renal failure.

Bernhart et al. in United States Patent 5,270,317 disclose a series of N-substituted heterocyclic derivatives which possess angiotensin II antagonist activity. Bernhart et al. disclose that such compounds can be used in the treatment of various cardiovascular complaints, especially hypertension, heart failure, and venous insufficiency, as well as in the treatment of glaucoma, diabetic retinopathy and various complaints of the central nervous system. It is also disclosed that such compound can be used in combination with other active agents such as tranquilizers, beta-blocking compounds, a calcium antagonist, or a diuretic.

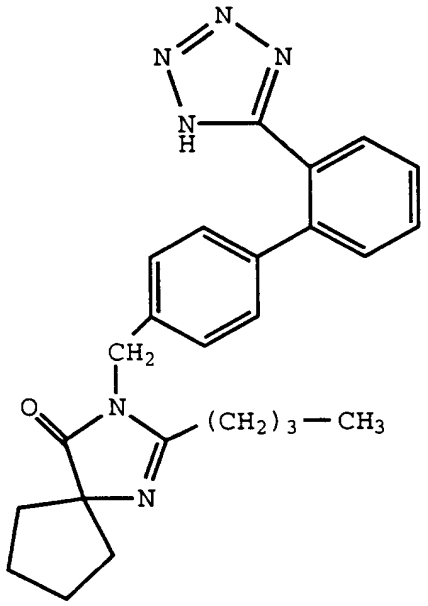
Selective neural endopeptidase inhibitors are taught by Delaney et al. in United States Patents 4,722,810 and 5,223,516 and the use of selective neutral endopeptidase inhibitors alone or in combination with angiotensin converting enzyme inhibitors to treat hypertension are disclosed by Delaney et al. U.K. Patent Application 2,207,351 and by Haslanger et al. in United States Patent 4,749,688. The treatment of congestive heart failure by administration of a combination of a selective neutral endopeptidase inhibitor and an angiotensin converting enzyme inhibitor is disclosed by Seymour in United States Patent 5,225,401.

Compounds possessing both neutral endopeptidase and angiotensin converting enzyme inhibition activity are disclosed by Flynn et al. in United States Patent 5,366,973, European Patent Application 481,522 and PCT Patent Applications WO 93/16103, and WO 94/10193, Warshawsky et al. European Patent Applications 534,363, 534,396 and 534,492, Fournie-Zaluski European Patent Application 524,553, Karanewsky et al. European Patent Application 599,444, Karanewsky European Patent Application 595,610, Robl et al., European Patent Application 629,627, Robl United States Patent 5,362,727 and European Patent Application 657,453.

This invention is directed to the discovery that the angiotensin II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4 -yl]methyl]-1,3-diazaspiro[4.4]nonan-4-one acts synergistically with a selective neutral endopeptidase inhibitor or a dual acting neutral endopeptidase inhibitor as defined below to reduce cardiac preload and afterload and enhance natriureses. The combination of this angiotensin II antagonist and the selective or dual acting neutral endopeptidase inhibitor produced significant reductions in left ventricular end diastolic pressure (LVEDP) and left ventricular systolic pressure (LVSP) that were greater than those produced by either treatment alone. Thus, the combination of this particular angiotensin II antagonist and the selective or dual acting neutral endopeptidase inhibitor is useful in treating hypertension and/or congestive heart failure.

The angiotensin II antagonist employed within this invention is the compound 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4 -yl]methyl]-1,3-diazaspiro[4.4]nonan-4-one having the structural formula

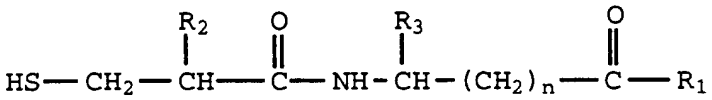
(I)



known in the literature as SR47436, BMS 186295, or irbesartan and pharmaceutically acceptable salts thereof such as the potassium and sodium salts. These angiotensin II antagonists and their method of preparation are disclosed by Bernhart et al. in United States Patent 5,270,317.

The selective neutral endopeptiadase inhibitor for use within this invention are those of the formula

(II)



and pharmaceutically acceptable salts thereof wherein:

R_2 is alkyl of 1 to 7 carbons, trifluoromethyl, phenyl, substituted phenyl, -$(CH_2)_{1\ to\ 4}$-phenyl, or -$(CH_2)_{1\ to\ 4}$-substituted phenyl;

R_3 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, -$(CH_2)_{1\ to\ 4}$-phenyl, or -$(CH_2)_{1\ to\ 4}$-substituted phenyl;

R_1 is hydroxy, alkoxy of 1 to 7 carbons, or NH_2;

n is an integer from 1 to 15; and

the term substituted phenyl refers to a substituent selected from lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, hydroxy, Cl, Br, or F.

Preferred are the selective neutral endopeptidase inhibitors of formula II wherein:

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1 to 9; and

R_1 is hydroxy.

Most preferred for use in this invention is the selective neutral endopeptidase inhibitor of formula II reported in the literature as SQ 28,603 which is the compound of formula II wherein:

R_2 is benzyl;

R_3 is hydrogen;

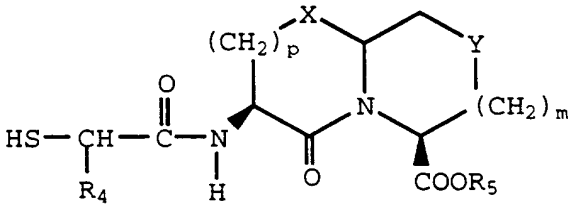
n is one; and

R_1 is hydroxy.

The preparation of the selective neutral endopeptidase inhibitors of formula II wherein R_2 is other than trifluoromethyl are disclosed by Delaney et al. in United States Patent 4,722,810. The preparation of the selective neutral endopeptidase inhibitors of formula II wherein R_2 is trifluoromethyl are disclosed by Delaney et al in United States Patent 5,223,516.

Dual acting neutral endopeptidase inhibitors suitable for use within this invention are compounds which possess both neutral endopeptidase inhibiting activity and angiotensin converting enzyme inhibiting activity. Particularly useful are the dual acting inhibitors of the formula

(III)



and pharmaceutically acceptable salts thereof wherein:

p is one or two;

X is O or S;

m is zero or one;

Y is CH_2, S or O provided that Y is S or O only when m is one;

R_4 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, -$(CH_2)_{1\ to\ 4}$-phenyl, -$(CH_2)_{1\ to\ 4}$-substituted phenyl, cycloalkyl of 3 to 7 carbons, -$(CH_2)_{1\ to\ 4}$-cycloalkyl of 3 to 7 carbons, heteroaryl, and -$(CH_2)_{1\ to\ 4}$-heteroaryl;

R_5 is hydrogen, alkyl of 1 to 7 carbons, -$(CH_2)_{1\ to\ 4}$-phenyl and -$(CH_2)_{1\ to\ 4}$-substituted phenyl;

the term substituted phenyl refers to a substituent selected from lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, hydroxy, Cl, Br, or F; and

the term heteroaryl refers to monocyclic rings of 5 or 6 atoms containing one or two O and S atoms and/or one to four N atoms provided that the total number of heteroatoms in the ring is 4 or less and bicyclic rings wherein the 5 or 6 membered heteroaryl ring as defined above is fused to a benzene or pyridyl ring.

Preferred are the dual acting neutral endopeptidase inhibitors of formula III wherein:

R_4 is benzyl, cyclopropylmethyl, or straight or branched chain alkyl of 3 to 5 carbons;
p is one or two;
X is O or S;
m is zero or one;
Y is CH_2, S, or O provided that Y is S or O when m is one; and
R_5 is hydrogen.

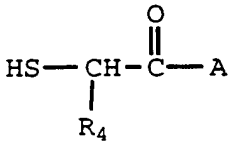
Most preferred for use in this invention is the dual acting neutral endopeptidase inhibitor of formula III wherein:

R_4 is benzyl;
p is two;
Y is S;
m is one;
Y is CH_2 ; and
R_5 is hydrogen.

The dual acting neutral endopeptidase inhibitors of formula III are disclosed in European Patent Application 629,627 of Robl et al.

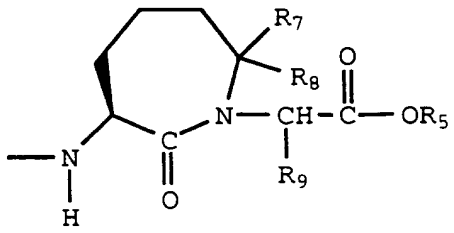
Also useful as neutral endopeptidase inhibitors for use within this invention are the dual acting inhibitors of the formula

(IV)



and pharmaceutically acceptable salts thereof wherein:

A is



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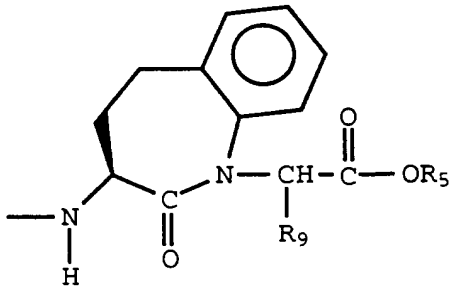

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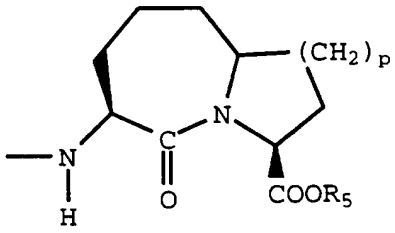
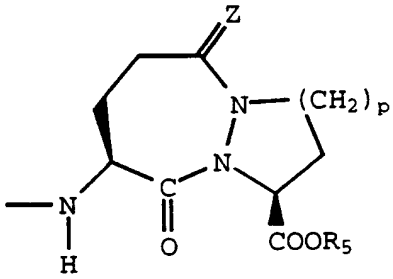


, or



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R_4, R_5, and p are as defined above;

R_7 and R_8 are both hydrogen, or both alkyl of 1 to 7 carbons, or R_7 is hydrogen and R_8 is alkyl of 1 to 7 carbons, phenyl, -$(CH_2)_{1\ to\ 4}$-phenyl and -$(CH_2)_{1\ to\ 4}$-substituted phenyl, or R_7 and R_8 taken together with the carbon to which they are attached complete a cycloalkyl of 3 to 5 carbons.

R_9 is hydrogen or alkyl of 1 to 7 carbons.

Z is oxo or two hydrogens.

Preferred are the dual acting neutral endopeptidase inhibitors of formula IV wherein:

R_4 is benzyl;

R_7 and R_8 are both methyl;

R_9 is hydrogen or methyl, especially hydrogen;

p is one or two; and
Z is oxo.

The compounds of formula IV and their method of preparation are disclosed in European Patent Application 599,444 and U.S. Patent Application Serial No. 160,540 filed December 1, 1993.

The angiotensin II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1,3-diazaspiro[4.4]nonan-4-one and the selective neutral endopeptidase inhibitor or dual acting neutral endopeptidase inhibitor may be administered from a single dosage form containing both types of compounds, may be administered in separate dosage forms taken at the same time, or may be administered separately on a carefully coordinated schedule. If administered separately, the two compounds can be administered from within several minutes of each other up to about 4 hours apart.

The selective or dual acting neutral endopeptidase inhibitor can be administered at a dosage range of from about 0.03 to about 1000 mg. per kg. of body weight per day with a dosage range of from about 0.3 to about 300 mg. per kg. of body weight per day being preferred. The angiotensin II antagonist can be administered at a dosage range of from about 0.001 to about 50 mg. per kg. of body weight with a dosage range of from about 0.1 to about 10 mg. per kg. of body weight being preferred.

Both compounds can be administered orally, parenterally, or one orally and the other parenterally. Each compound may be administered from one to about four times per day depending upon the duration of activity of the compounds and the severity of the congestive heart failure and/or hypertension being treated.

The compounds can be formulated, in the amounts described above, according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvents which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid of the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as stabilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

In the following examples, BMS 186295 refers to SR47436, i.e. the compound 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1,3-diazaspiro[4.4]nonan-4-one, and SQ 28603 refers to the compound (±)-N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-β-alanine.

Example 1

The studies described in this experiment were conducted in male hamsters of the BIO TO-2 strain when they were approximately 260 days of age and weighed on average 115 g. These animals develop a genetic form of cardiomyopathy that progresses uniformly among animals through different stages of heart failure. By 240 - 300 days of age the cardiomyopathic hamsters are characterized (as compared with control hamsters) by low mean arterial pressure, a 40% reduction in cardiac output and a decrease in renal blood flow. They display elevated cardiac filling pressure, depressed ventricular function, increased peripheral vascular resistance and have an 8-10-fold increase in plasma atrial natriuretic peptide concentration. Since most animals at this age do not have gross peripheral edema or elevated plasma renin activity, the cardiomyopathic hamsters were considered to be in compensated heart failure.

The experiments were conducted in conscious, unrestrained, cardiomyphathic hamsters three hours after placement of cardivascular catheters using brief anesthesia. The catheters allowed measurement of mean arterial pressure, left ventricular end diastolic pressure, left ventricular systolic pressure and heart rate, and provided a means for the administration of agents intravenously.

a) Inhibition of The Pressor Response To Angiotensin II

Preliminary experiments were conducted in conscious cardiomyopathic hamsters to determine a dose regimen of BMS 186295 that would nearly completely block the pressor response to angiotensin II for at least two hours. The pressor responses to two challenges of angiotensin II (100 ng/kg, i.v. dissolved in 0.9% sodium chloride, 1 ml/kg) were determined. This dose of angiotensin II produced over a 30% increase in mean arterial pressure. Based on the preliminary experiments, BMS 186295 was administered to 5 cardiomyopathic hamsters at 30 μmol/kg, i.v. followed by continuous i.v. infusion at 1 μmol/kg per min. Challenges of angiotensin II were then repeated at 10- to 30-minute intervals up to 150 minutes following the bolus injection of BMS 186295. The results are shown below.

Minutes	Change in mean arterial pressure, mm Hg
-20′	29±2
-10′	31±3
BMS-186295,	30 μmol/kg, i.v. followed by 1 μmol/kg/min, i.v.
10′	3±2
20′	2±1
30′	3±2
40′	2±1
50′	1±1
60′	4±1
70′	5±2
80′	4±1
90′′	3±1
120	3±1
150′	2±1

b) Cardiovascular Effects Of BMS 186295, SQ 28603, And the Combination Of These Agents

In this series of experiments baseline measurements of left ventricular end diastolic pressure, left ventricular systolic pressure and heart rate were determined in groups of conscious cardiomyopathic hamsters. Compounds or vehicle were administered intravenously, and measurements were repeated at 30-minute intervals up to 90 minutes after administration of the last agent. BMS 186295 was administered at 30 μmol/kg, i.v. (0.3 ml) followed by a continuous i.v. infusion at 1 μmol/kg per min (0.01 ml/min). BMS 186295 was prepared in 0.028 M potassium hydroxide and diluted to a final concentration of 0.17 M potassium hydroxide. Potassium hydroxide solution (0.17 M) was administered intravenously to the vehicle group at 0.3 ml followed by a continuous infusion at 0.01 ml/min. SQ 28603 was dissolved in 0.84% sodium bicarbonate and administered at 30 μmol/kg, i.v. This dose of SQ 28603 was previously shown to result in a doubling of plasma atrial natriuretic peptide concentration within 90 minutes in this model. One group of cardiomyopathic hamsters received the combination of BMS 186295 and SQ 28603. In this group BMS 186295 was administered according to the same dosage regimen described above; 30 minutes after the bolus injection of BMS 186295, SQ 28603 was administered at 30 μmol/kg, i.v.

Differences in age, body weight and baseline values among groups were evaluated by analysis of variance. Differences in changes from baseline among groups were evaluated by analysis of covariance with repeated measures and contrasts. The baseline value for each variable was used as the covariate. The level of significance was taken at $P < 0.05$. All data are expressed as mean ± standard error of the mean.

Left Ventricular End Diastolic Pressure (mm Hg)				
Minutes	Vehicle	SQ 28603	BMS 186295	BMS 186295 & SQ 28603
Baseline	19 ± 2	18 ± 3	17 ± 2	21 ± 2
BMS 186295 SQ 28603	18 ± 2	14 ± 3	18 ± 2	20 ± 2
30′	19 ± 1	14 ± 2	16 ± 2	12 ± 1
60′	18 ± 1	17 ± 3	16 ± 2	11 ± 2
90′	16 ± 2	16 ± 3	18 ± 3	10 ± 1

Change From Baseline (mm Hg)				
Minutes after last treatment	Vehicle	SQ 28603	BMS 186295	BMS 186296 & SQ 28603
30	1 ± 1	4 ± 1*	-1 ± 1	-10 ± 2*
60	-1 ± 1	-1 ± 2	-1 ± 1	-10 ± 3*†
90	-3 ± 1	-2 ± 1	1 ± 2	-11 ± 3*†

*P <0.05 vs Vehicle
†P <0.05 vs SQ 28603

Left Ventricular Systolic Pressure (mm Hg)				
Minutes	Vehicle	SQ 28603	BMS 186295	BMS 186295 & SQ 28603
Baseline	111 ± 3	117 ± 5	112 ± 2	107 ± 3
BMS 186295 SQ 28603	111 ± 3	108 ± 5	111 ± 1	104 ± 4
30′	111 ± 5	109 ± 5	114 ± 2	92 ± 2
60′	108 ± 3	105 ± 4	111 ± 2	88 ± 5
90′	105 ± 5	105 ± 5	112 ± 5	89 ± 4

Change From Baseline (mm Hg)				
Minutes After Last Treatment	Vehicle	SQ 28603	BMS 186295	BMS 186296 & SQ 28603
30	-1 ± 3	-8 ± 1*	2 ± 2	-16 ± 3*†
60	-3 ± 1	-12 ± 3*	-1 ± 2	-20 ± 4*†
90	-6 ± 4	-12 ± 2	1 ± 5	-18 ± 4*

*P <0.05 vs Vehicle
†P <0.05 vs SQ 28603

Heart Rate (beats/min)				
Minutes	Vehicle	SQ 28603	BMS 186295	BMS 186295 & SQ 28603
Baseline	350 ± 10	378 ± 12	338 ± 16	364 ± 6
BMS 186295 SQ 28603	365 ± 8	380 ± 7	364 ± 14	366 ± 12
30′	347 ± 15	381 ± 9	363 ± 20	366 ± 11
60′	345 ± 15	366 ± 9	367 ± 18	353 ± 10
90′	354 ± 13	378 ± 8	369 ± 28	351 ± 9

Change From Baseline (mm Hg)				
Minutes after last treatment	Vehicle	SQ 28603	BMS 186295	BMS 186296 & SQ 28603
30	-3 ± 15	3 ± 8	25 ± 9	1 ± 6
60	-5 ± 15	-13 ± 12*	29 ± 7*	-11 ± 9
90	7 ± 13	-1 ± 9	44 ± 11*	-14 ± 5

*P <0.05 vs Vehicle

Discussion of Results

Following the administration of BMS 186295, the pressor responses to angiotensin II were less than 17% of the response before the administration of the inhibitor. These results indicate that nearly complete inhibition of the pressor response to angiotensin II was achieved following the administered dosage regimen of BMS 186295, and suggests effective blockade of the angiotensin II receptors.

The combination of BMS 186295 and SQ 28603 produced cardiovascular effects that were greater than those with either treatment alone. Specifically, the combination caused significant decreases in left ventricular end diastolic pressure and left ventricular systolic pressure with no significant change in heart rate. SQ 28603 produced smaller decreases, whereas BMS 186295 had no significant effects on the measured cardiovascular pressures. Thus, the combination of BMS 186295 and SQ 28603 produced beneficial hemodynamic effects in cardiomyopathic hamsters with compensated heart failure.

Example 2

The studies described in this experiment were conducted in dogs that had been rendered hypertensive by prior unilateral nephrectomy and constriction of the remaining renal artery. This model is characterized by normal basal levels of plasma renin activity and is relatively resistant to the anti-hypertensive activity of angiotensin converting enzyme inhibitors and AT_1 receptor antagonists. Furthermore, the 1-kidney-1-clip (IKIC) hypertensive dogs have normal plasma concentrations of atrial natriutetic peptide and fail to develop depressor responses to neutral endopeptidase inhibitors.

The following experiments were conducted in fasted 1K1C hypertensive dogs lightly restrained in standard canine slings. An indwelling arterial catheter was accessed via a subcutaneous port for measurement of blood pressure via a Gould-Statham pressure transducer. Mean arterial pressure (MAP) was continuously recorded on a Gould chart writer and stored electronically using a Po-Ne-Mah data acquisition system. During each study, urine was collected at 20 minute intervals via a Foley bladder catheter for determination of urine volume. The concentrations of urinary sodium and potassium were measured using ion-selective electrodes and their rates of urinary excretion (μEq/min) were calculated. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by the renal clearances of exogenous creatinine and para-aminohippuric acid (PAH), respectively. The concentrations of creatinine and PAH in sequential samples of urine and plasma were determined by spectrophotometric assays and the clearances were calculated by the standard formula.

Arterial blood samples were drawn at the end of the control period and at 60 minute intervals thereafter for determination of the plasma concentrations of atrial natriuretic peptide (ANP), cyclic GMP and plasma renin activity (PRA) by separate radioimmunoassays. The plasma and urine samples were preserved and the assays were conducted according to standard radioimmunoassay procedures. Urinary excretion rates of cyclic GMP and ANP were calculated and expressed as pmol/min and fmol/min, respectively.

Four 1K1C hypertensive dogs were treated with the combination of 30 μmol/kg iv of BMS 186295 and 30 μmol/kg iv of SQ 28603. Vehicle (0.84% sodium bicarbonate), 30 μmol/kg iv of SQ 28603 and 30 μmol/kg iv of BMS 186295 were tested in 3 additional groups of 1K1C hypertensive dogs (n=4 to 5/treatment). In each study, baseline measurements were obtained during two 20 minute control periods. One of the treatments was then administered and sampling continued at 20 minute intervals for three hours.

To minimize inter-animal variability, each data point was expressed as the change from the average control value for that parameter. Significant differences among treatments were identified by analysis of variance for repeated measures. Contrasts were calculated to identify significant differences from the effects of vehicle and to compare the combination of SQ 28603 and BMS 186295 to the individual treatments. Results are given as mean ± SEM.

Results

Table 1

Mean Arterial Pressure (mm Hg)				
Time (min) after Treatment	Vehicle (n=5)	SQ 28603 (n=4)	BMS 186295 (n=4)	SQ 28603 + BMS 186295 (n=4)
Control	132±3	132±8	157±7	140±3
	Change from control			
20	3±1	6±1	-1±1	2±2
40	3±2	9±3 *	-10±1 *	2±1 †§
60	2±1	8±3 *	-8±2 *	0±2 †§
80	6±2	8±2	-5±2 *	-1±3 *
100	6±2	5±3	-4±1*	1±2 †
120	6±2	3±4	-1±2 *	2±2
140	7±2	4±2	-1±2 *	6±2 †
160	5±2	5±2	0±2	9±3 †
180	6±3	7±3	-1±3 *	6±4 †

* $p<0.05$ compared to vehicle
† $p<0.05$ compared to BMS 186295
§ $p<0.05$ compared to SQ 28603

BMS 186295 signigicantly reduced mean arterial pressure (MAP) (Table 1) in the conscious 1K1C hypertensive dogs whereas SQ 28603 initially increased MAP. The effects of the combination BMS 186295 and SQ 28603 were not consistently different from those of vehicle.

TABLE 2

Sodium Excretion (µEq/min)				
Time (min) after Treatment	Vehicle (n=5)	SQ 28603 (n=4)	BMS 186295 (n=4)	SQ 28603 + BMS 186295 (n=4)
Control	60±14	40±20	18±2	18±6
	Change from control			
20	-17±10	13±4	23±9	62±31 *†§
40	-16±12	21±16 *	41±13 *	83±34 *†§
60	-12±14	14±9 *	36±8 *	87±18 *†§
80	-11±14	25±13 *	27±6 *	70±16 *†§
100	-12±11	24±12 *	22±3 *	54±12 *†§
120	-16±13	35±19 *	30±4 *	60±21 *†§
140	-10±14	39±18 *	28±7 *	69±22 *†§
160	-4±15	44±19 *	30±7 *	68±16 *†
180	-3±13	44±18 *	30±2 *	74±19 *†§

* p<0.05 compared to vehicle
*† p<0.05 compared to *vehicle or †BMS186295
*†§ p<0.05 compared to *vehicle, †BMS186295 or SQ28603

TABLE 3

Urine Volume (ml/min)				
Time (min) after Treatment	Vehicle (n=5)	SQ 28603 (n=4)	BMS 186295 (n=4)	SQ 28603 + BMS 186295 (n=4)
Control	0.64±0.14	0.38±0.13	0.43±0.16	0.36±0.13
	Change from control			
20	-0.20±0.12	0.29±0.31 *	0.01±0.07	0.32±0.17 *
40	-0.27±0.14	0.15±0.13 *	0.09±0.14 *	0.51±0.22 *†§
60	-0.26±0.14	0.18±0.14 *	0.12±0.07 *	0.51±0.11 *†§
80	-0.26±0.15	0.21±0.15 *	0.05±0.06 *	0.34±0.08 *†
100	-0.23±0.14	0.07±0.08 *	-0.02±0.09 *	0.14±0.08 *
120	-0.30±0.13	0.12±0.13 *	-0.02±0.10 *	0.20±0.07 *
140	-0.25±0.14	0.20±0.10 *	-0.07±0.12 *	0.26±0.09 *†
160	-0.23±0.15	0.24±0.11 *	-0.07±0.16	0.16±0.03 *†
180	-0.22±0.14	0.17±0.06 *	-0.02±0.07 *	0.17±0.03 *

* p<0.05 compared to vehicle
*† p<0.05 compared to *vehicle or †BMS186295
*†§ p<0.05 compared to *vehicle, †BMS186295 or SQ28603

BMS 186295 and SQ 28603 each individually increased sodium excretion (TABLE 2) and urine volume (TABLE 3) in the conscious 1K1C hypertensive dogs. The natriuretic response to the combination of BMS 186295 and SQ 28603 was greater than the activity of either of the compounds administered singly. The increase in the amount of sodium excreted during the 3 hours after simultaneous injections of BMS 186295 and SQ 28603 (12.6±3.4 mEq/3 hr) approximated the sum of the natriuretic responses to BMS 186295 (5.4±1.0 mEq/3 hr) and to SQ 28603 (5.2±2.3 mEq/3 hr) given individually.

TABLE 4

Glomerular Filtration Rate (ml/min)				
Time (min) after Treatment	Vehicle (n=5)	SQ 28603 (n=4)	BMS 186295 (n=4)	SQ 28603 + BMS 186295 (n=4)
Control	50±4	39±5	45±10	46±4
	Change from control			
20	-2±2	6±11	-4±2	-8±7 §
40	0±4	3±2	-2±5	6±3 †
60	2±3	6±5	6±0	11±2 *
80	0±3	5±2	5±2	7±1 *
100	4±3	5±4	3±4	4±4
120	-1±2	5±1	4±3	12±2 *§
140	1±2	7±4	0±5	9±1 *
160	5±4	9±5	0±7	6±2
180	5±3	10±4	0±4	5±5

* $p<0.05$ compared to vehicle
§ $p<0.05$ compared to SQ 28603
† $p<0.05$ compared to BMS 186295
*§ $p<0.05$ compared to *vehicle or §SQ28603

TABLE 5

Effective Renal Plasma Flow (ml/min)				
Time (min) after Treatment	Vehicle (n=5)	SQ 28603 (n=4)	BMS 186295 (n=3)	SQ 28603 + BMS 186295 (n=4)
Control	144±18	123±15	127±41	142±30
	Change from control			
20	-25±10	6±38	-68±30 *	-84±19 *§
40	-27±17	-5±15	-54±35	-64±27 *§
60	-25±16	3±20	-35±24	-51±21 §
80	30±18	-20±6	-13±9	-45±21 †
100	-26±14	-25±10	-1±10	-41±23 †
120	-41±14	-15±6	-8±17 *	-15±8
140	-32±12	-11±12	8±3 *	-12±12
160	-21±13	-1±12	-14±12	-28±14
180	-21±15	-4±9	-12±11	-23±16

* $p<0.05$ compared to vehicle
*§ $p<0.05$ compared to *vehicle or §SQ28603
† $p<0.05$ compared to BMS 186295
§ $p<0.05$ compared to SQ 28603

The combination of BMS 186295 and SQ 28603 significantly increased GFR (TABLE 4) at several times during the 3 hour test when compared with the effects of vehicle even though effective renal plasma flow (TABLE 5) did not increase. The increase in GFR alone did not account for the full natriuretic response, as indicated by a significantly rise in fractional sodium excretion from 0.26±0.07% to 1.28±0.29%.

TABLE 6

ANP Excretion (fmol/min)				
Time (min) after Treatment	Vehicle (n=5)	SQ 28603 (n=4)	BMS 186295 (n=4)	SQ 28603 + BMS 186295 (n=4)
Control	1.2±0.1	1.9±0.2	1.5±0.6	1.5±0.4
	Change from control			
20	-0.1±0.1	20.8±4.9 *	-0.7±0.5	3.7±1.5
40	-0.1±0.1	24.0±4.6 *	-0.6±0.5	13.8±2.2
60	-0.1±0.1	45.2±24.2 *	-0.2±0.3	40.7±21.1 *†
80	-0.1±0.1	55.5±19.7 *	-0.4±0.3	30.3±8.1 *†§
100	-0.0±0.1	41.0±12.3 *	-0.6±0.4	27.0±10.9 *†
120	-0.2±0.1	48.3±21.5 *	-0.5±0.4	39.4±13.7 *†
140	-0.0±0.1	41.8±14.2 *	-0.6±0.4	37.2±14.9 *†
160	0.3±0.2	36.9±12.4 *	-0.5±0.4	30.1±12.4 *†
180	0.0±0.2	29.0±7.9 *	-0.6±0.4	33.2±10.0 *†§

* $p<0.05$ compared to vehicle

*† $p<0.05$ compared to *vehicle or †BMS186295

*†§ $p<0.05$ compared to *vehicle, †BMS186295 or SQ28603

TABLE 7

Cyclic GMP Excretion (pmol/min)				
Time (min) after Treatment	Vehicle (n=5)	SQ 28603 (n=4)	BMS 186295 (n=4)	SQ 28603 + BMS 186295 (n=4)
Control	1106±85	1017±180	1122±389	1030±170
	Change from control			
20	-177±172	106±295	-372±240	-202±144
40	-185±41	101±280	-277±255	164±94
60	-78±207	338±206	-150±203	432±174
80	-205±231	226±154	-309±199	313±144
100	-180±129	128±178	-266±193	106±97
120	-229±121	117±220	-283±236	139±66
140	-52±195	121±182	-449±206	194±156
160	-24±223	100±246	-391±199	229±62
180	76±246	343±170	-611±346	316±59

Urinary excretion of ANP (TABLE 6) increased significantly after administration of SQ 28603 alone and in combination with BMS 186295, indicating that the NEP inhibitor had prevented the degradation of ANP. Cyclic GMP (TABLE 7), the second messenger of the biological ANP receptor, tended to increase in the dogs receiving SQ 28603 alone (+32±28 nmol/3 hr) or the combination of BMS 186295 and SQ 28603 (+34±12 nmol/3 hr), but because of the variability

of the response, these changes did not achieve statistical significance compared to vehicle (-21±15 nmol/3 hr). These data suggested that the protection of renal ANP contributed to the natriuretic response. BMS 186295 given alone did not affect ANP excretion nor did it alter the ANP response to SQ 28603. Therefore, the enhanced response to the combination of BMS 186295 and SQ 28603 could not be attributed to an additional effect of the angiotensin II antagonist on the renal metabolism of ANP or the resultant accumulation of cyclic GMP.

TABLE 8

Plasma Renin Activity (pmol AI/ml/hr)				
Time (min) after Treatment	Vehicle (n=5)	SQ 28603 (n=4)	BMS 186295 (n=4)	SQ 28603 + BMS 186295 (n=4)
Control	0.45±0.10	0.16±0.02	0.55±0.07	-/90±0.09
	Change from control			
60	-0.09±0.07	-0.07±0.05	1.28±0.51 *	0.39±0.42 †
120	-0.04±0.11	-0.02±0.05	1.49±0.57 *	0.58±0.44 *†
180	-0.03±0.11	-0.01±0.7	1.24±0.62 *	0.36±0.16 †

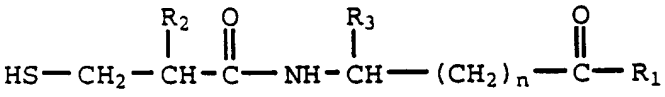
* $p<0.05$ compared to vehicle
† $p<0.05$ compared to BMS 186295
*† $p<0.05$ compared to *vehicle or †BMS186295

Finally, BMS 186295 significantly increased PRA (TABLE 8) indicating that the angiotensin receptor antagonist interrupted the negative feedback of angiotensin II on renin release. The smaller PRA response to BMS 186295 in the presence of SQ 28603 may be attributed to the inhibition of renin release by the increased ANP levels. Alternatively, BMS 186295 may have also activated the intrarenal baroreceptor by virtue of its depressor activity and thereby increased renin secretion.

Claims

1. Use of angiotensin II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]-nonan-4-one or a pharmaceutically acceptable salt thereof and a selective neutral endopeptidase inhibitor or a dual acting neutral endopeptidase inhibitor for manufacturing a medicament for treating hypertension and/or congestive heart failure in a mammalian specie in need of such treatment.

2. The use of Claim 1 wherein said endopeptidase inhibitor is a selective neutral endopeptidase inhibitor of the formula



or a pharmaceutically acceptable salt thereof wherein:

R_2 is alkyl of 1 to 7 carbons, trifluoromethyl, phenyl, substituted phenyl, $-(CH_2)_{1\text{ to }4}$-phenyl or $-(CH_2)_{1\text{ to }4}$-substituted phenyl;

R_3 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, $-(CH_2)_{1\text{ to }4}$-phenyl, or $-(CH_2)_{1\text{ to }4}$-substituted phenyl;

R_1 is hydroxy, alkoxy of 1 to 7 carbons, or NH_2; and

n is an integer from 1 to 15.

3. The method of Claim 2 wherein:

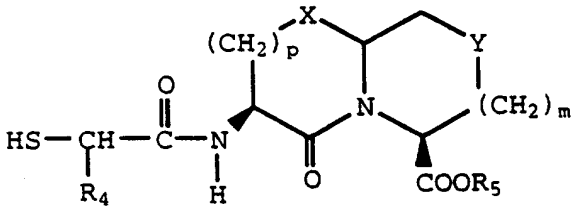
R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1 to 9; and
R_1 is hydroxy.

4. The use of Claim 2 wherein:
R_2 is benzyl;
R_3 is hydrogen;
n is one; and
R_1 is hydroxy.

5. The use of Claim 1 wherein said endopeptidase inhibitors is a dual acting inhibitor of the formula

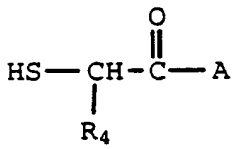


or a pharmaceutically acceptable salt thereof wherein:
p is one or two;
X is O or S;
m is zero or one;
Y is CH_2, S or O provided that Y is S or O only when m is one;
R_4 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, $-(CH_2)_{1\text{ to }4}$-phenyl, $-(CH_2)_{1\text{ to }4}$-substituted phenyl, cycloalkyl of 3 to 7 carbons, $-(CH_2)_{1\text{ to }4}$-cycloalkyl of 3 to 7 carbons, heteroaryl, and $-(CH_2)_{1\text{ to }4}$-heteroaryl; and
R_5 is hydrogen, alkyl of 1 to 7 carbons, $-(CH_2)_{1\text{ to }4}$-phenyl and $-(CH_2)_{1\text{ to }4}$-substituted phenyl.

6. The use of Claim 5 wherein:
R_4 is benzyl, cyclopropylmethyl, or straight or branched chain alkyl of 3 to 5 carbons;
p is one or two;
X is O or S;
m is zero or one;
Y is CH_2, S, or O provided that Y is S or O when m is one; and
R_5 is hydrogen.

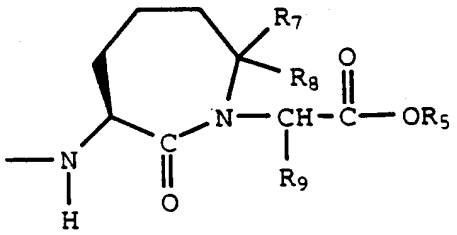
7. The use of Claim 5 wherein:
R_4 is benzyl;
p is two;
Y is S;
m is one;
Y is CH_2 ; and
R_5 is hydrogen.

8. The use of Claim 1 wherein said endopeptidase inhibitor is a dual acting inhibitor of the formula



or a pharmaceutically acceptable salt thereof wherein:

A is



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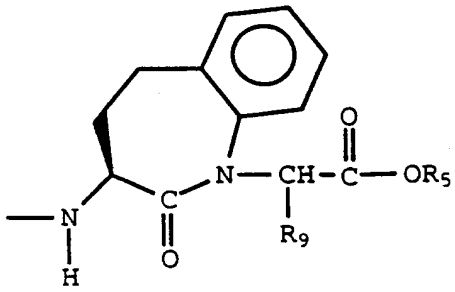

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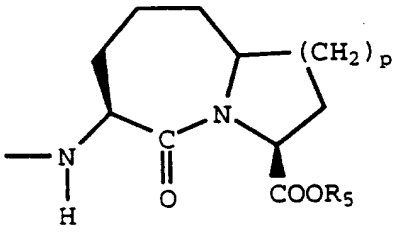
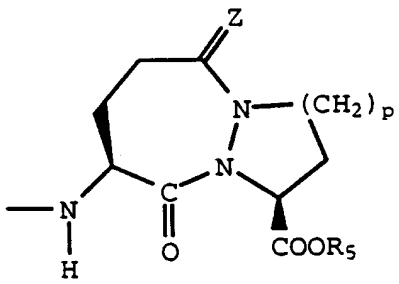


, or



;

p is one or two;

R_4 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, -$(CH_2)_{1\ to\ 4}$-phenyl, -$(CH_2)_{1\ to\ 4}$-substituted phenyl, cycloalkyl of 3 to 7 carbons, -$(CH_2)_{1\ to\ 4}$-cycloalkyl of 3 to 7 carbons, heteroaryl, and -$(CH_2)_{1\ to\ 4}$-heteroaryl;

R_5 is hydrogen, alkyl of 1 to 7 carbons, -$(CH_2)_{1\ to\ 4}$-phenyl and -$(CH_2)_{1\ to\ 4}$-substituted phenyl;

R_7 and R_8 are both hydrogen, or both alkyl of 1 to 7 carbons, or R_7 is hydrogen and R_8 is alkyl of 1 to 7 carbons, phenyl, -$(CH_2)_{1\ to\ 4}$-phenyl and -$(CH_2)_{1\ to\ 4}$-substituted phenyl, or R_7 and R_8 taken together with the carbon to which they are attached complete a cycloalkyl of 3 to 5 carbons;

R_9 is hydrogen or alkyl of 1 to 7 carbons; and

Z is oxo or two hydrogens.

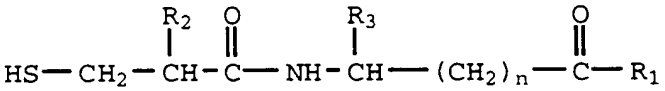
9. The use of Claim 8 wherein:
R_4 is benzyl;
R_7 and R_8 are both methyl;
R_9 is hydrogen or methyl, especially hydrogen;
p is one or two; and
Z is oxo.

10. The use of Claim 1 wherein said angiotensin II antagonist and said selective neutral endopeptidase inhibitor or said dual acting neutral endopeptidase inhibitor are administered from a single dosage form containing both types of compounds.

11. The use of Claim 1 wherein said angiotensin II antagonist and said selective neutral endopeptidase inhibitor or said dual acting neutral endopeptidase inhibitor are administered from separate dosage forms at about the same time.

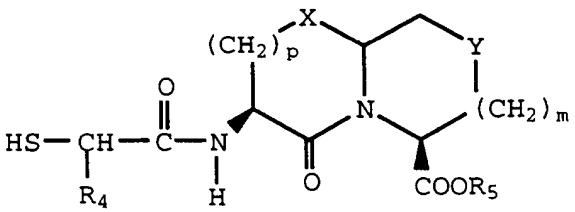
12. The use of Claim 1 wherein said angiotensin II antagonist and said selective neutral endopeptidase inhibitor or said dual acting neutral endopeptidase inhibitor are administered from separate dosage forms at from within several minutes of each other up to about 4 hours apart.

13. A composition useful for treating congestive heart failure and/or hypertension comprising a pharmaceutically acceptable carrier and an effective amount of the angiotensin II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]nonan-4-one or a pharmaceutically acceptable salt thereof and an effective amount of the selective neutral endopeptidase inhibitor of the formula



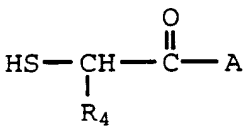
or a pharmaceutically acceptable salt thereof wherein R_1, R_2, R_3 and n are as defined in Claim 2.

14. A composition useful for treating congestive heart failure and/or hypertension comprising a pharmaceutically acceptable carrier and an effective amount of the angiotensin II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]nonan-4-one or a pharmaceutically acceptable salt thereof and an effective amount of the dual acting neutral endopeptidase inhibitor of the formula



or a pharmaceutically acceptable salt thereof wherein X,Y, m, p, R_4, and R_5 are as defined in Claim 5.

15. A composition useful for treating congestive heart failure and/or hypertension comprising a pharmaceutically acceptable carrier and an effective amount of the angiotensin II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[(2'-(1H-tetrazol-5-yl)-[1,1'biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]nonan-4-one or a pharmaceutically acceptable salt thereof and an effective amount of the dual acting neutral endopeptidase inhibitor of the formula



or a pharmaceutically acceptable salt thereof wherein A and R_4 are as defined in Claim 8.

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(54) Composition for the treatment of hypertension and congestive heart failure, containing an angiotensin II antagonist and an endopeptidase inhibitor

(57) Hypertension and/or congestive heart failure are treated with the combination of the angiotensin II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]nonan-4-one and a selective neutral endopeptidase inhibitor or a dual acting neutral endopeptidase inhibitor.

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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 96 10 1756

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP 0 629 408 A (MERCK SHARP & DOHME ;INST NAT SANTE RECH MED (FR)) 21 December 1994 * abstract * * page 2, line 13 - line 38; claims 1,6,9 * *	1,10-12	A61K31/415 A61K45/06
Y	* claims 1,6,9 *	2-9, 13-15	

D,X	EP 0 498 361 A (SCHERING CORP) 12 August 1992 * abstract; claims 1,4 *	1-4	
Y	* claims 1,4 *	5-15	

D,Y	US 5 270 317 A (BERNHART CLAUDE ET AL) 14 December 1993 * page 3, line 11 - line 33; claims 10-12 * * page 1, line 31 - line 33 *	1-15	

Y	EP 0 527 624 A (SQUIBB & SONS INC) 17 February 1993 * abstract; claims 1-4 *	1-15	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
D	& US 5 225 401 A	1-15	A61K

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INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	27 October 1997	Gonzalez Ramon, N

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 96 10 1756

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	WO 92 10097 A (SMITHKLINE BEECHAM CORP) 25 June 1992 * abstract; claim 1 * * page 2, line 28 - line 35 * * page 24, line 33 - line 36 * * page 16; example 8 *	1-15	
Y	EP 0 566 157 A (SCHERING CORP) * claims 1-3,7,8,16 *	1-15	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

EPO FORM 1503 03.82 (P04C10)

European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 96 10 1756

Claim(s) searched completely:
-

Claim(s) searched incompletely:
1-15

Reason for the limitation of the search:

In view of the large number of compounds, which are defined by the general definition in the independent claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application (see Guidelines, Part B, Chapter III, paragraph 3.6).

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(11) Publication number : **0 555 175 A1**

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(72) Inventor : **Ksander, Gary**
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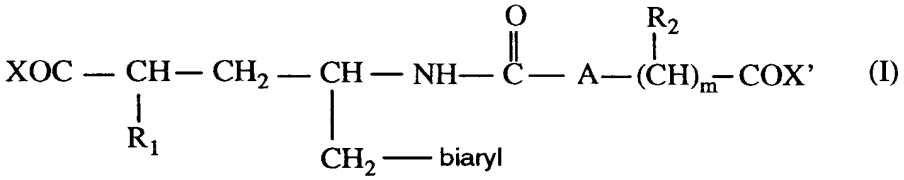
(54) Biaryl substituted 4-amino-butyric acid amides.

(57) The invention relates to biaryl substituted 4-amino-butyric acid derivatives of formula I



wherein COX and COX' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide ; R_1 represents hydrogen, lower alkyl, C_3-C_7-cycloalkyl-lower alkyl, aryl-lower alkyl, biaryl-lower alkyl, lower alkoxy, aryl-lower alkoxy, aryloxy, N-lower alkylamino, N,N-di-lower alkylamino, N-aryl-lower alkylamino, N,N-di-aryl-lower alkylamino, N-arylamino, N,N-diarylamino, lower alkanoylamino, aryl-lower alkanoylamino or aroylamino ; R_2 represents hydrogen, hydroxy, lower alkoxy, lower alkyl, aryl-lower alkyl, C_3-C_7-cycloalkyl-lower alkyl, amino-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkylthio-lower alkyl or aryl-lower alkoxy-lower alkyl ; biaryl represents phenyl substituted by carbocyclic or heterocyclic aryl ; A represents a direct bond, lower alkylene, phenylene or cyclohexylene ; m represents 1 or zero, provided that m represents 1 when A is a direct bond ; or pharmaceutically acceptable salts thereof ; pharmaceutical compositions comprising said compounds ; methods for the preparation of said compounds and for the preparation of intermediates ; and methods of treating disorders in mammals which are responsive to the inhibition of neutral endopeptidases by administration of said compounds to mammals in need of such treatment.

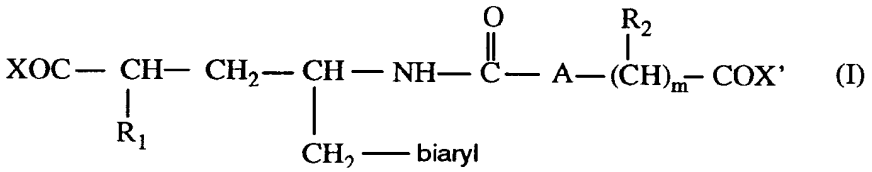
EP 0 555 175 A1

Summary of the Invention

Endogenous atrial natriuretic peptides (ANP), also called atrial natriuretic factors (ANF) have diuretic, natriuretic and vasorelaxant functions in mammals. The natural ANF peptides are metabolically inactivated, in particular by a degrading enzyme which has been recognized to correspond to the enzyme neutral endopeptidase (NEP) EC 3.4. 24.11, also responsible for e.g. the metabolic inactivation of enkephalins.

The aim of the present invention is to provide novel biaryl substituted 4-amino-butyric acid amide derivatives described below which are useful as neutral endopeptidase (NEP) inhibitors, e.g. as inhibitors of the ANF-degrading enzyme in mammals, so as to prolong and potentiate the diuretic, natriuretic and vasodilator properties of ANF in mammals, by inhibiting the degradation thereof to less active metabolites. The compounds of the invention are thus particularly useful for the treatment of conditions and disorders responsive to the inhibition of neutral endopeptidase EC 3.4. 24.11, particularly cardiovascular disorders, such as hypertension, renal insufficiency including edema and salt retention, pulmonary edema and congestive heart failure. By virtue of their inhibition of neutral endopeptidase, the compounds of the invention may also be useful for the treatment of pain, depression and certain psychotic conditions. Other potential indications include the treatment of angina, premenstrual syndrome, Meniere's disease, hyperaldosteronism, hypercalciuria, ascites, glaucoma, asthma, inflammations and gastrointestinal disorders such as diarrhea, irritable bowel syndrome and gastric hyperacidity.

The present invention relates to biaryl substituted 4-amino-butyric acid derivatives of formula I



(I)

wherein COX and COX' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; R_1 represents hydrogen, lower alkyl, C_3-C_7-cycloalkyl-lower alkyl, aryl-lower alkyl, biaryl-lower alkyl, lower alkoxy, aryl-lower alkoxy, aryloxy, N-lower alkylamino, N,N-di-lower alkylamino, N-aryl-lower alkylamino, N,N-di-aryl-lower alkylamino, N-arylamino, N,N-dialkylamino, lower alkanoylamino, aryl-lower alkanoylamino or aroylamino; R_2 represents hydrogen, hydroxy, lower alkoxy, lower alkyl, aryl-lower alkyl, C_3-C_7-cycloalkyl-lower alkyl, amino-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkylthio-lower alkyl or aryl-lower alkoxy-lower alkyl; biaryl represents phenyl substituted by carbocyclic or heterocyclic aryl; A represents a direct bond, lower alkylene, phenylene or cyclohexylene; m represents 1 or zero, provided that m represents 1 when A is a direct bond; or a pharmaceutically acceptable salt thereof.

Pharmaceutically acceptable ester and amide derivatives are preferably prodrug derivatives, such being convertible by solvolysis or under physiological conditions to the free carboxylic acids of formula I wherein COX and/or COX' represent carboxyl.

Compounds of formula I and derivatives thereof, depending on the nature of substituents, possess one or more asymmetric carbon atoms. The resulting diastereoisomers and optical antipodes are encompassed by the instant invention.

Detailed Description of the Invention

The definitions used herein, unless denoted otherwise, have the following meanings within the scope of the present invention.

The term biaryl represents phenyl substituted by carbocyclic aryl or heterocyclic aryl as defined herein, ortho, meta or para to the point of attachment of the phenyl ring, advantageously para; biaryl is also represented as the $-C_6H_4-R_3$ substituent in formulae herein.

Carbocyclic aryl preferably represents preferably monocyclic carbocyclic aryl or optionally substituted naphthyl.

Monocyclic carbocyclic aryl represents optionally substituted phenyl, being preferably phenyl or phenyl substituted by one to three substituents, such being advantageously lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, halogen, cyano, trifluoromethyl, lower alkanoylamino or lower alkoxycarbonyl. Monocyclic carbocyclic aryl particularly preferably represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, hydroxy, halogen, cyano or trifluoromethyl.

Optionally substituted naphthyl represents 1- or 2-naphthyl or 1- or 2-naphthyl preferably substituted by lower alkyl, lower alkoxy or halogen.

Heterocyclic aryl represents preferably monocyclic heterocyclic aryl such as optionally substituted thienyl, indolyl, imidazolyl, furanyl, pyridyl, pyrrolyl or N-lower alkylpyrrolyl.

Optionally substituted furanyl represents 2- or 3-furanyl or 2- or 3-furanyl preferably substituted by lower alkyl.

Optionally substituted pyridyl represents 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl preferably substituted by lower alkyl, halogen or cyano.

Optionally substituted thienyl represents 2- or 3-thienyl or 2- or 3-thienyl preferably substituted by lower alkyl.

Optionally substituted indolyl represents preferably 2- or 3-indolyl or 2- or 3-indolyl preferably substituted by lower alkyl, lower alkoxy or halogen.

Optionally substituted imidazolyl is preferably 1- or 2-imidazolyl or 1- or 2-imidazolyl preferably substituted by lower alkyl.

Optionally substituted pyrrolyl is preferably 2- or 3-pyrrolyl preferably substituted by lower alkyl.

Aryl e.g. as in aryl-lower alkyl, aryl-lower alkoxy, aryloxy, N-arylamino, N,N-diarylamino, N-aryl-lower alkylamino, N,N-di-lower alkylymino, aroylamino, aryl-lower alkylthio-lower alkyl, aryl-lower alkoxy-lower alkyl, aryl-lower alkoxycarbonyl or aryl-lower alkanoylamino is preferably phenyl or phenyl substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen, trifluoromethyl, cyano, lower alkanoylamino or lower alkoxycarbonyl.

The term "lower" referred to herein in connection with organic radicals or compounds respectively defines such with up to and including 7, preferably up and including 4 and advantageously one or two carbon atoms. Such may be straight chain or branched.

A lower alkyl group preferably contains 1-4 carbon atoms and represents e.g. ethyl, n- or iso-propyl, n-, iso-, sec.- or tert.-butyl or advantageously methyl.

A lower alkoxy group preferably contains 1-4 carbon atoms and represents for example methoxy, n-propoxy, isopropoxy, n-, iso-, sec.- or tert.-butoxy or advantageously ethoxy.

Aryl-lower alkyl is advantageously benzyl or phenethyl optionally substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen or trifluoromethyl.

Aryl-lower alkoxy represents advantageously e.g. benzyloxy, benzyloxy substituted by lower alkyl, lower alkoxy, lower alkanoyloxy, halogen or trifluoromethyl, or pyridylmethoxy.

Aryloxy preferably represents phenoxy or phenoxy substituted by lower alkyl, lower alkoxy, lower alkanoyloxy, halogen or trifluoromethyl.

N-arylamino and N,N-diarylamino represent advantageously N-phenylamino or N,N-diphenylamino optionally substituted in the phenyl moiety or phenyl moieties by lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen or trifluoromethyl.

N-Aryl-lower alkylamino preferably represents benzylamino or 1- or 2-phenylethylamino.

N,N-Di-aryl-lower alkylamino preferably represents di-benzylamino.

The term C_3-C_7-cycloalkyl represents a saturated cyclic hydrocarbon radical which contains 3 to 7 and preferably 5 to 7 ring carbons and is, most preferably, cyclopentyl or cyclohexyl.

The term cycloalkyl-lower alkyl represents preferably 1- or 2-(cyclopentyl or cyclohexyl)ethyl, 1-, 2- or 3-(cyclopentyl or cyclohexyl)propyl, or 1-, 2-, 3- or 4-(cyclopentyl or cyclohexyl)-butyl.

Amino-lower alkyl represents preferably amino-(ethyl, propyl or butyl), particularly omega-amino-(ethyl, propyl or butyl).

A N-lower alkylamino group preferably contains 1-4 carbon atoms in the lower alkyl portion and represents, for example, N-n-propyl-amino, N-iso-propylamino, N-n-butylamino, N-tert.-butylamino and advantageously N-methylamino or N-ethylamino.

A N,N-di-lower alkylamino group preferably contains 1-4 carbon atoms in each lower alkyl portion and represents, for example, N,N-dimethylamino, N-methyl-N-ethylamino and advantageously N,N-diethylamino.

Hydroxy-lower alkyl is for example 2-hydroxyethyl and preferably hydroxymethyl.

Lower alkylthio as in lower alkylthio-lower alkyl represents advantageously C_1-C_4-alkylthio and preferably methylthio or ethylthio.

Aryl-lower alkylthio represents advantageously phenyl-C_1-C_4-alkylthio and preferably benzylthio.

Lower alkoxy-lower alkyl represents advantageously C_1-C_4-alkoxy-C_1-C_4-alkyl and preferably (m)ethoxymethoxy, 2-(methoxy)-ethoxy or 2-ethoxy-ethoxy.

Aryl-lower alkoxy-lower alkyl represents advantageously phenyl-C_1-C_4-alkoxy-C_1-C_4-alkyl and preferably benzyloxy-methyl or 2-benzyloxy-ethoxy.

Lower alkylene represents branched or straight chain alkylene of 1 to 7 carbon atoms, advantageously

straight chain (or linear) alkylene, such as methylene, ethylene, propylene, butylene, pentylene or hexylene and most preferably straight chain C_1-C_4-alkylene.

Phenylene represents preferably 1,3 or 1,4-phenylene, advantageously 1,4-phenylene.

Cyclohexylene represents preferably 1,4-cyclohexylene.

Halogen (halo) preferably represents fluoro or chloro, but may also be bromo or iodo.

Lower alkanoyloxy advantageously contains 2 to 5 carbon atoms and is preferably acetoxy, pivaloyloxy or propionyloxy.

Lower alkanoylamino advantageously contains 2 to 5 carbon atoms and is preferably acetylamino or propionylamino.

A lower alkoxycarbonyl group preferably contains 1 to 4 carbon atoms in the alkoxy portion and represents, for example, methoxycarbonyl, n-propoxycarbonyl, iso-propoxycarbonyl or advantageously ethoxycarbonyl.

Aroylamino is preferably benzoylamino or benzoylamino substituted on the benzene ring by lower alkyl, lower alkoxy, halogen or trifluoromethyl.

Carboxyl esterified in form of a pharmaceutically acceptable ester, represents advantageously a prodrug ester that may be convertible by solvolysis or under physiological conditions to the free carboxylic acid, such being preferably C_1-C_{20}-alkoxycarbonyl, advantageously lower alkoxycarbonyl; (amino, acylamino, mono- or di-lower alkylamino)-lower alkoxycarbonyl; carboxy- lower alkoxycarbonyl, e.g. alpha-carboxy-lower alkoxycarbonyl; lower alkoxycarbonyl-lower alkoxycarbonyl, e.g. alpha-lower alkoxycarbonyl-lower alkoxycarbonyl; α-(di-lower alkylamino, amino, mono-lower alkylamino, morpholino, piperidino, pyrrolidino, 1-lower alkylpiperazino)-carbonyl-lower alkoxycarbonyl; aryl-lower alkoxycarbonyl, preferably optionally (halo, lower alkyl or lower alkoxy)-substituted benzyloxycarbonyl, or pyridylmethoxycarbonyl; 1-(hydroxy, lower alkanoyloxy or lower alkoxy)-lower alkoxycarbonyl, e.g. pivaloyloxymethoxycarbonyl; (hydroxy, lower alkanoyloxy or lower alkoxy)-lower alkoxymethoxycarbonyl; bicycloalkoxycarbonyl-lower alkoxycarbonyl, e.g. bicyclo-[2,2,1]-heptyloxycarbonyl-lower alkoxycarbonyl, especially bicyclo-[2,2,1]-heptyloxycarbonylmethoxycarbonyl such as bornyloxycarbonylmethoxycarbonyl; 1-(lower alkoxycarbonyloxy)-lower alkoxycarbonyl; 5-indanyloxycarbonyl; 3-phthalidoxycarbonyl and (lower alkyl, lower alkoxy or halo)-substituted 3-phthalidoxycarbonyl; polyhydroxy-lower alkoxycarbonyl or protected polyhydroxy-lower alkoxycarbonyl in which polyhydroxy-lower alkoxy and protected polyhydroxy-lower alkoxy represent preferably dihydroxypropyloxy or trihydroxybutyloxy wherein hydroxy groups are free or one or more, as appropriate, are protected in form of esters, e.g. a lower alkanoyl or a benzoyl ester, in form of ethers, e.g. a lower alkyl or benzyl ether, or, in case two vicinal hydroxy groups are involved, in the form of acetals or ketals, e.g. a lower alkylidene, a benzylidene or a 5- or 6-membered cycloalkylidene derivative.

Protected polyhydroxy-lower alkoxycarbonyl advantageously represents (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl.

Acyl as in acyloxy or acylamino represents preferably lower alkanoyl, carbocyclic aryl-lower alkanoyl, aroyl, lower alkoxycarbonyl or aryl-lower alkoxycarbonyl, advantageously lower alkanoyl. Lower alkoxycarbonyl for acyl is preferably t-butoxycarbonyl (abbreviated t-BOC). Aryl-lower alkoxycarbonyl for acyl is preferably benzyloxycarbonyl (abbreviated CBZ).

Carboxy-lower alkoxycarbonyl represents advantageously e.g. 1-carboxyethoxycarbonyl.

Lower alkoxycarbonyl-lower alkoxycarbonyl represents advantageously e.g. 1-(ethoxycarbonyl)ethoxycarbonyl.

Amino-lower alkoxycarbonyl, mono-lower alkylamino-lower alkoxycarbonyl, di-(lower)alkylamino-lower alkoxycarbonyl advantageously represent e.g. aminoethoxycarbonyl, ethylaminoethoxycarbonyl, diethylaminoethoxycarbonyl.

Lower alkylidene is preferably isopropylidene.

Cycloalkylidene is preferably cyclohexylidene.

Carboxyl esterified in form of a pharmaceutically acceptable prodrug ester represents most advantageously C_1-C_4-alkoxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, pivaloyloxymethoxycarbonyl, 1-(C_2-C_4-alkanoyloxy)-ethoxycarbonyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl, 5-indanyloxycarbonyl, 3-phthalidoxycarbonyl, bornyloxycarbonylmethoxycarbonyl, 1-(C_1-C_4-alkoxycarbonyloxy)-ethoxycarbonyl or 3-pyridylmethoxycarbonyl.

Carboxyl derivatized in the form of a pharmaceutically acceptable amide represents preferably carbamoyl or N-substituted carbamoyl, advantageously [lower alkylamino, arylamino, di-lower alkylamino, morpholino, N-lower alkylpiperazino, pyrrolidino, piperidino, perhydroazepino, (amino or acylamino)-lower alkylamino or aryl-lower alkylamino]-carbonyl.

Pharmaceutically acceptable salts are either pharmaceutically acceptable acid addition salts for any basic compounds of the invention or salts derived from pharmaceutically acceptable bases for any acidic compounds of the invention.

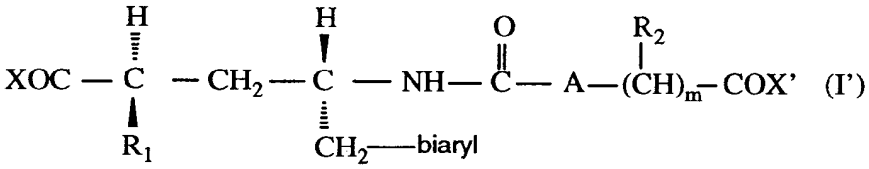
Pharmaceutically acceptable salts of basic compounds of the invention are acid addition salts, which are preferably such of therapeutically acceptable inorganic or organic acids, such as strong mineral acids, for example hydrohalic, e.g. hydrochloric or hydro-bromic acid, sulfuric, phosphoric or nitric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, gluconic, citric, maleic, fumaric, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, pamoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, 1,2-ethanedisulfonic acid, benzenesulfonic, p-toluenesulfonic, naphthalenesulfonic, sulfanilic, cyclohexylsulfamic acid, or ascorbic acid.

Pharmaceutically acceptable salts of the acidic compounds of the invention, e.g. those having a free carboxyl group are salts formed with pharmaceutically acceptable bases, e.g. alkali metal salts (e.g. sodium, potassium salts), alkaline earth metal salts (e.g. magnesium, calcium salts), ammonium salts, mono-, di- or tri-lower (alkyl or hydroxyalkyl)-ammonium salts (e.g. ethanolammonium, diethanolammonium, triethanolammonium, tromethamine salts).

The compounds of the invention, of formula I and derivatives thereof may contain several asymmetric carbon atoms, depending on the nature of the substituents. Thus the compounds of the invention exist in the form of geometric isomers, racemates, diastereoisomers, pure enantiomers or mixtures thereof, all of which are within the scope of the invention.

For example, the compounds of formula I exist in isomeric forms, e.g. wherein the asymmetric carbon atom on the butyryl chain bearing the R_1 and/or biarylmethyl groups may either exist in the S or R configuration. The compounds of the invention, e.g. those of formula I having said two asymmetric centers exist as two different racemic diastereoisomeric forms which may be called erythro and threo depending on the relative orientation of the R_1 and biarylmethyl substituents of the chain. Each of the two racemates consists of the optically active enantiomers (or antipodes) having (S,S), (R,R), (R,S) or (S,R) configurations, respectively.

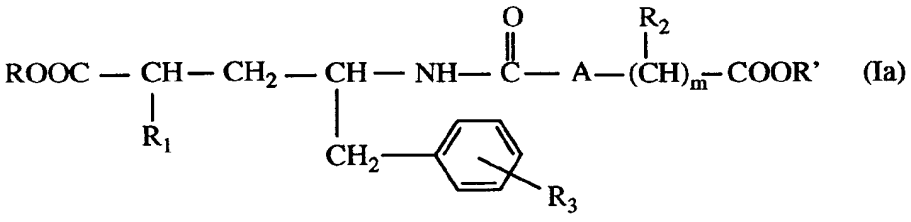
Preferred is the threo racemic form and particularly the enantiomeric form depicted in formula I'



wherein COX, COX' , R_1, R_2, A, biaryl and m have the meanings as defined herein above for compounds of formula I. The compounds of formulae Ia, Ib, Ic, Id, and Ie given below are present as well, preferably in the enantiomeric form depicted in formula I'.

Illustrative thereof, in the above compounds of formula I wherein R_1 is lower alkyl, the carbon atom carrying said substituent is assigned the (R)-configuration; and the carbon atom carrying the biarylmethyl substituent is assigned the (S)-configuration.

More particularly, the present invention is concerned with and has for its object the compounds of formula Ia



wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 represents hydrogen, lower alkyl, lower alkoxy, N-lower alkylamino, lower alkanoylamino, aryl-lower alkyl, aryl-lower alkoxy, aryloxy, N-arylamino or aroylamino wherein aryl in each case represents phenyl optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl, or aryl represents thienyl or furanyl optionally substituted by lower alkyl; R_2 represents hydrogen, hydroxy, lower alkyl or aryl-lower alkyl wherein aryl independently has the meaning given above under R_1; R_3 represents phenyl, or phenyl substituted by lower alkyl, lower alkoxy, halogen, cyano, acyloxy or trifluoromethyl; or R_3 represents thienyl or furanyl optionally substituted by lower alkyl; A represents a direct bond, lower

alkylene, 1,4-phenylene or 1,4-cyclohexylene; m represents 1 or zero provided that m represents 1 when A is a direct bond; or a pharmaceutically acceptable salt thereof.

Advantageously, R_3 is located in the para position.

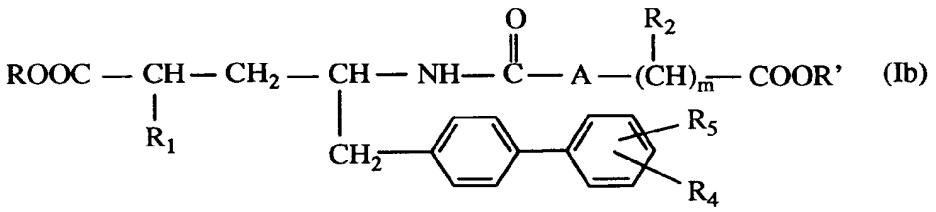
Particularly preferred embodiments of the invention as described above relate to:

a) compounds wherein R_3 is phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen, cyano, acyloxy or trifluoromethyl;

b) compounds wherein A is lower alkylene, m represents 1 or zero, and R_2 represents hydrogen, lower alkyl, hydroxy or lower alkoxy.

c) compounds wherein R_1 represents hydrogen, lower alkyl, lower alkoxy or aryl-lower alkyl wherein aryl represents phenyl optionally substituted by one or two of lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl; most preferably compounds wherein R_1 represents lower alkoxy or lower alkyl.

A particular embodiment of the invention relates to compounds of formula Ib



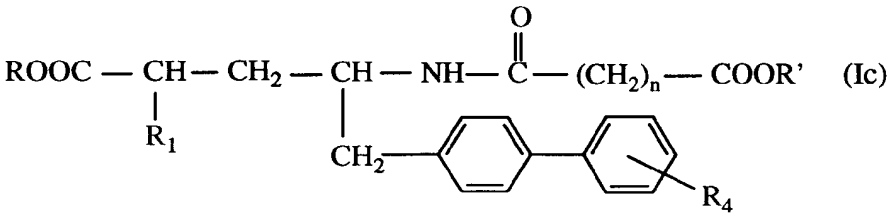
(Ib)

wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 is hydrogen, lower alkyl, lower alkoxy or aryl-lower alkyl wherein aryl represents phenyl optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl; R_2 represents hydrogen, hydroxy or lower alkoxy; R_4 and R_5 independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, halogen, cyano or trifluoromethyl; A represents lower alkylene; m represents 1 or zero; or a pharmaceutical acceptable salt thereof.

Particularly preferred are compounds of formula Ib wherein R and R' independently represent carboxyl, lower alkoxy-carbonyl or 5-indanyloxy-carbonyl; R_1 represents hydrogen, lower alkyl or lower alkoxy; A represents a direct bond or lower alkylene; R_2 represents hydrogen or hydroxy; R_4 and R_5 independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, halogen, cyano or trifluoromethyl; m represents 1 or zero, provided that m represents 1 when A is a direct bond; or a pharmaceutical acceptable salt thereof.

Particularly preferred are compounds of formula Ib wherein R and R' independently represent carboxyl or C_1-C_4-alkoxy-carbonyl; R_1 represents C_1-C_4-alkyl; R_2 represents hydroxy; A represents methylene; R_2 is hydroxy; R_4 and R_5 each are hydrogen; and m is 1; or a pharmaceutical acceptable salt thereof.

Particularly preferred are compounds of formula Ic



(Ic)

wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 is lower alkyl or lower alkoxy; R_4 represents hydrogen, lower alkyl, lower alkoxy, halogen, or trifluoromethyl; n represents an integer 1 through 6; or a pharmaceutical acceptable salt thereof.

Preferred are compounds of formula Ic wherein COOR and COOR' independently represent carboxyl, C_1-C_{20}-alkoxycarbonyl, (carbocyclic or heterocyclic aryl)-lower alkoxycarbonyl, (di-lower alkylamino, N-lower alkylpiperazino, morpholino, pyrrolidino, piperidino or perhydrazepino)-C_2 to C_4-alkoxycarbonyl, dihydroxypropyloxycarbonyl protected in form of a ketal, 5-indanyloxycarbonyl, 3-phthalidoxycarbonyl, bicycloalkoxycarbonyl-lower alkoxycarbonyl, α-(lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkoxycarbonyl, 1-lower alkoxycarbonyloxy)-lower alkoxycarbonyl or 1-(lower alkanoyloxy)-lower alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

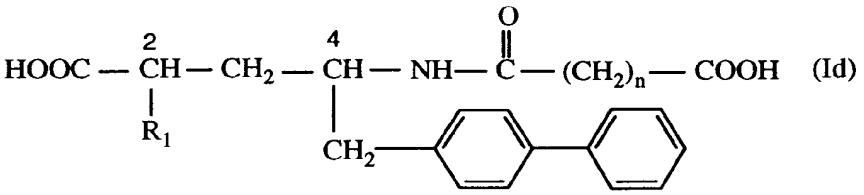
Particularly preferred are said compounds of formula Ic wherein COOR and COOR' independently represent carboxyl, C_1-C_4-alkoxycarbonyl, 3-pyridylmethoxycarbonyl, benzyloxycarbonyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, 5-indanyloxycarbonyl, 1-(C_2-C_5-alkanoyloxy)-ethoxycarbonyl, 3-phthalidoxycarbonyl, (2,2'-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl, bornyloxycarbonylmethoxycarbonyl, 1-(C_1-C_4-alkoxycarbonyloxy)-ethoxycarbonyl; or a pharmaceutically acceptable salt thereof.

Particularly preferred are compounds of formula Ic wherein R and R' independently represent caboxyl, lower alkoxy-carbonyl or 5-indanyloxy-carbonyl; R_1 is hydrogen, lower alkyl or lower alkoxy; R_4 represents hydrogen or lower alkyl; n represents an integer 1 through 4; or a pharmaceutical acceptable salt thereof.

Particularly preferred are compounds of formula Ic wherein R and R' independently represent caboxyl or C_1-C_4-alkoxy-carbonyl; R_1 is C_1-C_4-alkyl; R_4 is hydrogen; and n is 2; or a pharmaceutical acceptable salt thereof.

Especially preferred are compounds according to the present invention wherein COOR and COOR' independently represent carboxyl, C_1-C_4-alkoxycarbonyl or 5-indanyloxycarbonyl; or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the invention relates to compounds of formula Id

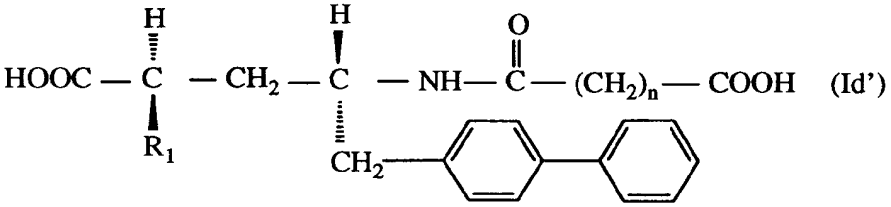


(Id)

wherein R_1 is lower alkyl; n is an integer 1 through 4; or a pharmaceutically acceptable mono- or di-ester derivative thereof in which one or two of the acidic hydroxy groups of the carboxyl functional groups are esterified in form of a mono- or di-pharmaceutically acceptable ester, or a pharmaceutically acceptable salt thereof; or an optical antipode thereof.

Preferred are said compounds of formula Id wherein R_1 is methyl and n is 2; and mono- or di-esters thereof.

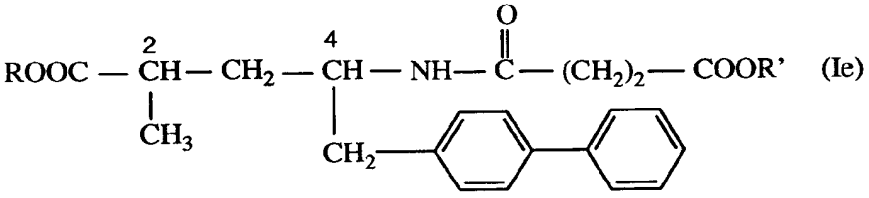
As discussed before, the butyric acid compounds of e.g. formula Id exist in two distinct diastereomeric forms which may be called erythro and threo. Preferred are e.g. the compounds of formula Id as the threo diastereomer (racemate), more particularly as the enantiomeric form having the R-configuration at C-atom 2 and the S-configuration at C-atom 4 and wherein the butyryl portion is as depicted in formula Id'



(Id')

wherein R_1 and n are as defined under formula Id; or a pharmaceutical acceptable mono- or diester derivative, especially a corresponding C_1-C_4-alkyl ester, thereof; or a pharmaceutical acceptable salt thereof.

Particularly preferred are compounds of formula Ie



(Ie)

wherein COOR and COOR' independently represent carboxyl or carboxyl esterified in form of a pharmaceutical acceptable prodrug ester, especially a corresponding C_1-C_4-alkyl ester, or a pharmaceutically acceptable salt

thereof.

Particularly preferred embodiments of the invention as described above relate to:

(a) compounds of the above formula Ie wherein R and R' independently represent hydrogen, C_1-C_4-alkyl, benzyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, pivaloyloxymethyl, 1-(C_2-C_4-alkanoyloxy)-ethyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methyl, 5-indanyl, 3-phthalidyl, bornyloxycarbonylmethyl, 1-(C_1-C_4-alkoxycarbonyloxy)-ethyl or 3-pyridylmethyl; or a pharmaceutically acceptable salt thereof;

(b) compounds of the above formula Ie wherein COOR' is carboxyl; and COOR represents carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester, especially a corresponding C_1-C_4-alkyl ester; or a pharmaceutically acceptable salt thereof;

(c) compounds of the above formula Ie having the R-configuration at C-atom 2 and the S-configuration at C-atom 4;

(d) the compound according to the above formula Ie wherein COOR is ethoxycarbonyl and COOR' is carboxyl, namely being 4-[N-(3-carboxy-1-oxopropyl)-amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R, 4S)-antipode thereof or a pharmaceutical acceptable salt thereof.

Preferred are said compounds of formula Ie wherein R is C_1-C_4-alkyl and R' is hydrogen; or a pharmaceutically acceptable salt thereof.

The novel compounds of the invention are pharmacologically potent neutral endopeptidase enzyme inhibitors which inhibit e.g. the degradation of atrial natriuretic factors (ANF) in mammals. They thus potentiate the diuretic and natriuretic effect of exogenous or endogenous ANF in mammals.

The compounds of the invention are thus particularly useful in mammals as diuretic, natriuretic (saluretic) and antihypertensive agents for the treatment of e.g. hypertension, congestive heart failure and edema.

As neutral endopeptidase inhibitors, the compounds are also e.g. enkephalinase inhibitors so as to inhibit the degradation of endogenous enkephalins and may thus also be useful for the treatment of pain in mammals.

The above-cited properties are demonstrable in vitro and in vivo tests, using advantageously mammals, e.g. mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterally, parenterally, advantageously intravenously, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10^{-4} molar and 10^{-9} molar concentrations. The dosage in vivo may range depending on the route of administration, between about 0.01 and 50 mg/kg, advantageously between about 1.0 and 25 mg/kg.

The analgesic activity can be determined by measuring the potentiation of the analgesic effects of enkephalin and derivatives thereof, and by classical analgesic tests, such as the phenyl-p-benzoquinone induced writing test [J. Pharmacol. Exp. Therap. 125, 237 (1959)] and the hot plate test in the mouse [J. Pharmacol. Exp. Therap. 107, 385 (1953).

The antihypertensive activity can be determined in the spontaneously hypertensive rat, Goldblatt rat or Goldblatt dog by direct measurement of blood pressure. Advantageously, the effect is measured in the DOCA-salt hypertensive rat and/or renal hypertensive rat or dog model.

The diuretic (saluretic) activity can be determined in standard diuretic screens, e.g. as described in "New Antihypertensive Drugs", Spectrum Publications, 1976, pages 307-321, or by measuring the potentiation of atrial natriuretic factor-induced natriuresis and diuresis in the rat.

The potentiation of ANF can also be determined by measuring the increase in ANF plasma level achieved.

The in vitro inhibition of neutral endopeptidase (NEP) 3.4.24.11 can be determined as follows: Neutral endopeptidase 3.4.24.11 activity is determined by the hydrolysis of the substrate glutaryl-Ala-Ala-Phe-2-naphthylamide (GAAP) using a modified procedure of Orlowski and Wilk (1981). The incubation mixture (total volume 125 µl) contains 4.2 µg of protein (rat kidney cortex membranes prepared by method of Maeda et al, 1983), 50 mM tris buffer, pH 7.4 at 25°C, 500 µM substrate (final concentration), and leucine aminopeptidase M (2.5 µg). The mixture is incubated for 10 minutes at 25°C and 100 µl of fast garnet (250 µg fast garnet/ml of 10% Tween 20 in 1 M sodium acetate, pH 4.2) is added. Enzyme activity is measured spectrophotometrically at 540 nm. One unit of NEP 24.11 activity is defined as 1 nmol of 2-naphthylamine released per minute at 25°C at pH 7.4. IC_{50} values are determined, i.e. the concentration of test compound required for 50% inhibition of the release of 2-naphthylamine.

Neutral endopeptidase activity is also determined using ANF as a substrate. Atrial natriuretic factor degrading activity is determined by measuring the disappearance of rat-ANF (r-ANF) using a 3 minute reverse phase-HPLC separation. An aliquot of the enzyme in 50 mM Tris HCl buffer, pH 7.4, is preincubated at 37°C for 2 minutes and the reaction is initiated by the addition of 4 nmol of r-ANF in a total volume of 50 µl. The reaction is terminated after 4 minutes with the addition of 30 µl of 0.27% trifluoroacetic acid (TFA). Forty microliters of the mixture is injected into a reverse phase-HPLC and analyzed using a C_4 cardridge in a 3 minute,

isocratic separation. Twenty-three percent of buffer B (0.1 % TFA in 80% acetonitrile) is used. Buffer A is 0.1 % TFA in water. One unit of activity is defined as the hydrolysis of 1 nmol of r-ANF per minute at 37°C at pH 7.4. IC_{50} values are determined, i.e. the concentration of test compound required for 50% inhibition of the hydrolysis of ANF.

The test compound is dissolved in dimethyl sulfoxide or 0.25 M sodium bicarbonate solution, and the solution is diluted with pH 7.4 buffer to the desired concentration.

In vitro testing is most appropriate for the free carboxylic acids of the invention

The effect of the compounds of the invention on rat plasma ANF concentration can be determined as follows:

Male Sprague-Dawley rats (275-390 g) are anesthetized with ketamine (150 mg/kg)/acepromazine (10%) and instrumented with catheters in the femoral artery and vein to obtain blood samples and infuse ANF, respectively. The rats are tethered with a swivel system and are allowed to recover for 24 hours before being studied in the conscious, unrestrained state.

In this assay, plasma ANF levels are determined in the presence and absence of NEP inhibition. On the day of study, all rats are infused continuously with ANF at 450 ng/kg/min. i.v. for the entire 5 hours of the experiment. Sixty minutes after beginning the infusion, blood samples for baseline ANF measurements are obtained (time 0) and the rats are then randomly divided into groups treated with the test compound or vehicle. Additional blood samples are taken 30, 60, 120, 180 and 240 minutes after administration of the test compound.

Plasma concentrations are determined by a specific radioimmunoassay. The plasma is diluted (X 12.5, X 25 and X 50) in buffer containing: 50 mM Tris (pH 6.8), 154 mM NaCl, 0.3% bovine serum albumin, 0.01 % EDTA. One hundred microliters of standards [rANF (99-126)] or samples are added to 100 µl of rabbit anti-rANF serum and incubated at 4°C for 16 hours. Ten thousand cpm of [^{125}I]rANF are then added to the reaction mixture which is incubated at 4°C for an additional 24 hours. Goat anti-rabbit IgG serum coupled to paramagnetic particles is added to the reaction mixture and bound [^{125}I]rANF is pelleted by exposing the mixture to an attracting magnetic rack. The supernatant is decanted and the pellets counted in a gamma counter. All determinations are performed in duplicate. Plasma ANF levels are expressed as a percent of those measured in vehicle-treated animals which received ANF alone (450 ng/kg/min i.v.).

Illustrative of the invention, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester at doses of about 1-30 mg/kg p.o., administered in 10% ethanol/polyethylene glycol (PEG) 400, produces significant increases in plasma ANF levels.

The antihypertensive effect can be determined in desoxycorticosterone acetate (DOCA)-salt hypertensive rats.

DOCA-salt hypertensive rats (280-380 g) are prepared by the standard method. Rats underwent a unilateral nephrectomy and one week later are implanted with silastic pellets containing 100 mg/kg of DOCA. The rats are maintained on 1% NaCl/0.2% KCl drinking water for three to five weeks until sustained hypertension is established. The antihypertensive activity is evaluated at this time.

Two days before an experiment, the rats are anesthetized with methoxyflurane and instrumented with catheters in the femoral artery to measure arterial blood pressure. Forty-eight hours later, baseline arterial pressure and heart rate are recorded during a 1 hour period. The test compound (30 mg/kg p.o.) or vehicle is then administered and the same cardiovascular parameters are monitored for an additional 5 hours.

Illustrative of the invention, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester at a dose of 30 mg/kg p.o., administered in PEG 400, produces a significant reduction in blood pressure in the DOCA-salt hypertensive rat model.

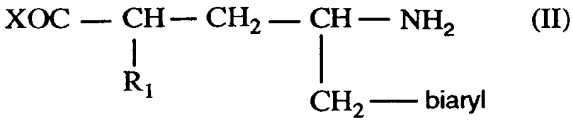
The potentiation of the natriuretic effect of ANF can be determined as follows:

Male Sprague-Dawley rats (280-360 g) are anesthetized with Inactin (100 mg/kg i.p.) and instrumented with catheters in the femoral artery, femoral vein and urinary bladder to measur arterial pressure, administer ANF and collect urine, respectively. A continuous infusion of normal saline (33 µl/min) is maintained throughout the experiment to promote diuresis and sodium excretion. The experimental protocol consists of an initial 15 minute collection period (designated as pre-control) followed by three additional collection periods. Immediately after completion of the pre-control period, test compound or vehicle is administered; nothing is done for the next 45 minutes. Then, blood pressure and renal measurements are obtained during a second collection period (designated control; 15 min). At the conclusion of this period, ANF is administered (1 µg/kg i.v. bolus) to all animals and arterial pressure and renal parameters are determined during two consecutive 15 minutes collection periods.

Mean arterial pressure, urine flow and urinary sodium excretion are determined for all collection periods. Blood pressure is measured with a Gould p50 pressure transducer, urine flow is determined gravimetrically, sodium concentration is measured by flame photometry, and urinary sodium excretion is calculated as the product of wine flow and urine sodium concentration.

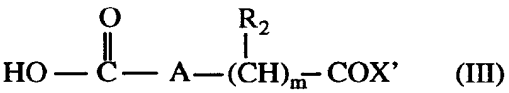
The compounds of the invention are thus particularly useful as inhibitors of neutral endopeptidase, enhancing the potency and duration of action of atrial natriuretic peptide(s). The compounds are therefore particularly useful for the treatment of cardiovascular disorders such as hypertension, edema and salt retention, and cardiac conditions such as congestive heart failure. The invention furthermore relates to the use of the compounds according to the invention for the preparation of medicaments, in particular of medicaments useful as inhibitors of neutral endopeptidase, enhancing the potency and duration of action of atrial natriuretic peptide(s) and for therapeutic and prophylactic treatment. Also included therein is the industrial preparation of the active substances in form of a commercial package.

The compounds of the invention of formula I may be prepared using the following process which comprises: condensing a compound of formula II



(II)

wherein COX, R_1 and biaryl have the meaning as defined above, in temporarily protected form if required; with a compound of formula III



(III)

or a reactive functional derivative or a salt thereof, wherein A, R_2, m and COX' have the meaning as defined above, in temporarily protected form if required; and, if temporarily protecting any interfering reactive group(s), removing said protecting group(s), and then isolating the resulting inventive compound; and, if desired, converting any resulting compound into another compound of the invention, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into the free compound or into another salt, and/or, if desired, separating a mixture of isomers or racemates obtained into the single isomers or racemates, and/or, id desired, resolving a racemate obtained into the optical antipodes.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as carboxyl, amino and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected carboxyl, amino and hydroxy groups are those that can be converted under mild conditions into free carboxyl, amino and hydroxy groups without other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components and under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (carboxyl group, amino group etc.), the structure and stability of the molecule of which the substituent is a part, and the reaction conditions.

Well-known protecting groups that meet these conditions and their introduction and removal are described, for example, in J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York 1973, T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1984, and also in "The Peptides", Vol. I, Schroeder and Luebke, Academic Press, London, New York, 1965.

The preparation of compounds of the invention according to the above process, i.e. the condensation of an amine of formula II with the acid of formula III, or a functional reactive derivative thereof, is carried out by methodology well-known for peptide synthesis.

Reactive functional derivatives of compounds of formula III are preferably halides, anhydrides such as succinic anhydride, glutaric anhydride, or mixed anhydrides such as the pivaloyl, alkoxycarbonyl or cyanoacetyl anhydride.

The condensation of an amine of formula II with a free carboxylic acid of formula III is carried out advantageously in the presence of a condensing agent such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide and hydroxybenzotriazole in an inert polar solvent such as dimethylformamide or methylene chloride, preferably at room temperature.

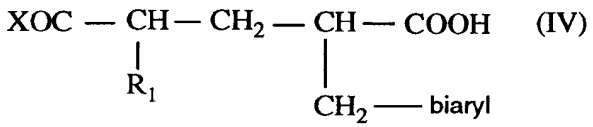
The condensation of an amine of formula II with a reactive functional derivative of an acid of formula III in the form of an acid halide, advantageously an acid chloride, anhydride or mixed anhydride, is carried out in

an inert solvent such as toluene or methylene chloride, advantageously in the presence of a base, e.g. an inorganic base such as potassium carbonate or an organic base such as triethylamine or pyridine, preferably at room temperature.

The starting materials of formula III are acids or functional derivatives thereof known in the art or which may be prepared by conventional methods known in the art.

The starting materials of formula II are known or, if new, may be prepared according to conventional methods, e.g., those illustrated by the examples herein.

For example, the compounds of formula II may be prepared by converting a compound of formula IV

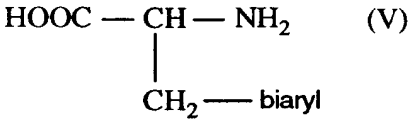


(IV)

wherein COX, R_1 and biaryl have the meaning mentioned above, in temporarily protected form if required, into a suitable carboxylic acid amide or carboxylic acid azide and then subjecting this compound to a Hofmann reaction or to a Curtius rearrangement in a manner well known in the art. The compounds of formula IV are known, for example, from US patent No. 5,021,430 or may be prepared analogous to the methods described therein.

In a preferred alternative route, the starting materials of formula II may be prepared by

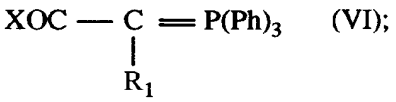
(a) reducing the carboxylic group of a biarylalanine of formula V



(V)

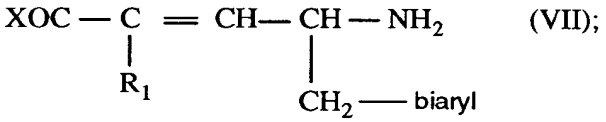
in temporarily protected form if required, to yield the respective aldehyde;

(b) subsequently reacting said aldehyde with a triphenylphosphonium compound of formula VI



(VI);

(c) hydrogenating the resulting compound of formula VII



(VII);

and, if temporarily protecting any interfering reactive group(s), removing said protective group(s) and then isolating the resulting product. In the above formulae V, VI and VII, the variables COX, R_1 and biaryl have the meaning as defined under formula I. The above reaction steps (a), (b) and (c) are carried out by methodology well-known in the art.

For example, in step (a) the compound of formula V, advantageously an amino protected compound of formula V, is reacted first of all with a hydroxylamine or a salt thereof, e.g. with N,O-dimethylhydroxylamine hydrochloride; the resulting hydroxylamine amide is then reduced to the aldehyde in a conventionel manner, e.g. with lithium aluminum hydride.

Reaction step (b) represents a conventional Wittig reaction which may be performed in a manner known in the art.

Reaction step (c) as well represents a commonly known hydrogenation reaction which may be performed e.g. with molecular hydrogen in the presence of a suitable catalyst such as palladium/charcoal.

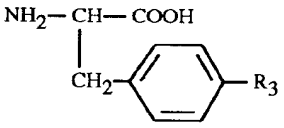
Biarylalanines of formula V are either known in the art or can be prepared according to methods reported

in the art.

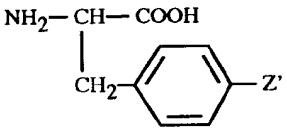
As to the preparation of the biarylalanines of formula V as starting materials in optically active form, such can be prepared e.g. by resolution or by one of the following methods:

(a) Adapting a method described in Tetrahedron Letters 1988, 6075, a biarylmethanol, e.g. 4-biphenylylmethanol, is converted to a reactive derivative, e.g. the bromide, which is then condensed with an N-acyl derivative of 2,3-diphenyl-6-oxomorpholine, e.g. the N-carbobenzyloxy-(2R,3S)-isomer, in the presence of a strong base such as sodium bis-trimethylsilylamide, to yield e.g. N-carbobenzyloxy-2(R), 3(S), 5(S)-6-oxo-2,3-diphenyl-5-(4-biphenylylmethyl)morpholine. Catalytic hydrogenolysis, e.g. using hydrogen and palladium on charcoal as catalyst, yields the optically active (S)-(+)-4-biphenylalanine.

(b) Alternatively, using the Pd (0)-catalyzed cross-coupling reaction described in Tetrahedron Letters 31, 1665 (1990), J. Organic Chemistry 55, 906 (1990) and Tetrahedron 45, 6670 (1989) as developed by W. Shieh et al, the substantially optically pure chiral biarylalanines, of the formula



or the N-acyl and/or carboxy ester derivatives thereof wherein R_3 has meaning as defined hereinabove, can be prepared by: condensing a reactive esterified optically active tyrosine derivative of the formula



wherein the amino and carboxy groups are in protected form (as N-acyl and esterified carboxy ester derivatives), and Z' represents reactive esterified hydroxy (advantageously trifluoromethylsulfonyloxy) with an aryl boronic acid in which aryl corresponds to R_3 as defined above, in the presence of a palladium (0) catalyst, in particular tetrakis(triphenylphosphine)palladium (0), and in the presence of an anhydrous base (such as an alkali metal carbonate), in an inert solvent (such as xylene or toluene) at an elevated temperature ranging from about 50 to 150°C, and removing any protecting groups as required.

For example, N-t-butoxycarbonyl-tyrosine methyl ester is first converted to N-t-butoxycarbonyl-4-trifluoromethylsulfonyloxy-phenylalanine methyl ester (N-t-butoxycarbonyltyrosine triflate methyl ester). This compound is then condensed with an arylboronic acid (e.g. phenylboronic acid) in the presence of anhydrous potassium carbonate, and tetrakis (triphenylphosphine) palladium (0) complex as catalyst, in toluene preferably at an elevated temperature, advantageously at about 100° to obtain N-t-butoxycarbonyl-4-biphenylalanine methyl ester. After N-deacylation, substantially optically pure 4-biphenylalanine methyl ester is obtained with a configuration corresponding to that of the tyrosine derivative used as starting material.

The arylboronic acids are either commercial or can be prepared as described in the literature, e.g. J. Org. Chem. 49, 5237 (1984).

The triphenylphosphonium compounds of formula VI are either known in the art or can be prepared according to methods reported in the art.

Compounds of the invention wherein COX or COX' represent carboxyl derivatized in form of a pharmaceutically acceptable amide can also be prepared according to the above methods using corresponding starting materials wherein COX or COX' represent carbamoyl or N-substituted carbamoyl.

The compounds of the invention so obtained, can be converted into each other according to conventional methods. Thus, for example, resulting amides or esters may be hydrolyzed with aqueous alkalies, such as alkali metal carbonates or hydroxides. Resulting free acids may be esterified with e.g. said unsubstituted or substituted alkanols or reactive esterified derivatives thereof such as alkyl halides, or diazoalkanes. Free acids are also converted into said metal, ammonium or acid addition salts in conventional manner.

Thus, any resulting free acid or base can be converted into a corresponding metal, ammonium or acid addition salt respectively, by reacting it with an equivalent amount of the corresponding base, basic salt, acid or ion exchange preparation, e.g. said free acids with alkali or ammonium hydroxides or carbonates, or e.g. free amines with said inorganic or organic acids respectively. Any resulting salt may also be converted into the free compound, by liberating the latter with stronger acids or bases, respectively. In view of the close relationship

between the free compounds and the salts thereof, whenever a compound of the invention, or intermediate, is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, may also be obtained in the form of their hydrates, or include other solvents used for the crystallization. Furthermore, the functional derivatives of the free acids of formula I, wherein the carboxy groups are esterified by identical or different radicals may be prepared by condensing a free acid of formula I or a mono- or di-ester derivative thereof with an esterifying agent of the formula VIII

$$R_6\text{-}Z \qquad \text{(VIII)}$$

wherein Z represents hydroxy or a reactive esterified hydroxyl group; and R_6 represents an esterifying radical as defined herein for the carboxylic esters (encompassed e.g. by COX or COX' representing esterified carboxy), in particular said non-aromatic radicals.

A reactive esterified hydroxyl group, such as Z in a compound of the formula VIII, is a hydroxyl group esterified by a strong inorganic or organic acid. Corresponding Z groups are in particular halo, for example chloro, bromo or preferably iodo, also sulfonyloxy groups, such as lower alkyl- or arylsulfonyloxy groups, for example (methane-, ethane-, benzene- or toluene-) sulfonyloxy groups, also the trifluoromethylsulfonyloxy group.

The esterification of the carboxyl groups, optionally in salt form, with a compound of formula VIII wherein Z represents a reactive esterified hydroxyl group, is performed in a manner known per se, in the presence of for example an organic base, such as an organic amine, for example a tertiary amine, such as tri-lower alkylamine, for example trimethylamine, triethylamine or ethyl-di-isopropylamine, an N,N-di-lower-alkyl-aniline, for example N,N-di-methylaniline, a cyclic tertiary amine, such as an N-lower-alkylated morpholine, for example N-methyl-morpholine, a base of the pyridine type, for example pyridine, an inorganic base, for example hydroxides, carbonates, or hydrogen carbonates of alkali metals or alkaline-earth metals, for example sodium, potassium or calcium hydroxide, carbonate or hydrogen carbonate, or a quaternary ammonium base, such as a tetraalkylammonium hydroxide, carbonate or hydrogen carbonate, for example in which alkyl is e.g. methyl, ethyl, propyl, isopropyl, butyl, or the like, or an alkali metal salt of bis-trialkylsilylamide (e.g. trimethyl) optionally in the presence of a crown ether such as 18-crown-6 in a suitable inert solvent or solvent mixture, e.g. acetonitrile, toluene, and the like.

A trifunctional free acid, e.g. of the formula I, or a monoester or diester thereof, is preferably first converted into a salt of one of the stated organic or inorganic bases, especially into the sodium or potassium salt, and is then reacted with a compound of the formula VIII. The compounds of formula VIII are known or can be prepared by methods well-known to the art.

A compound of the formula or VIII wherein Z is a reactive esterified hydroxyl group can be prepared in situ. For example, a compound of the formula VIII wherein Z is chloro can be converted by treatment with sodium iodide in a solvent, for example in acetone or acetonitrile, into a compound of the formula VIII wherein Z is iodo; or esterification can be carried out with a chloro compound of the formula VIII in the presence of sodium iodide.

Esterification of a compound with a free carboxyl group using in excess an alcohol of formula VIII (wherein Z represents hydroxy) is carried out in a manner known per se, e.g. in the presence of an acid catalyst e.g. sulfuric acid or boron trifluoride etherate, preferably at an elevated temperature, advantageously ranging from about 40°C to 100°C. Alternately, the esterification of a compound with a free carboxyl group can be carried out with at least an equimolar amount of the alcohol in the presence of a condensing agent such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide in a polar solvent such as methylene chloride, in the presence of a base if required, e.g. such as 4-(dimethylamino)pyridine.

Conversely, carboxylic acid esters can be converted to compounds of the invention with a free carboxy group using methods and conditions generally known in the art and illustrated herein. Depending on type of ester involved, useful reagents include aqueous acids or bases; also anhydrous reagents such as trialkylsilyl halides, hydrobromic acid in glacial acetic acid; also hydrogen and a hydrogenolysis catalyst. For instance, trialkyl esters can be converted to the free trifunctional acids by treatment with hydrobromic acid in glacial acetic acid, e.g. at room temperature or elevated temperature. Also trialkyl esters can be converted to the mono esters wherein carboxy only remains esterified, by treatment with e.g. trimethylsilyl bromide at room temperature.

Any benzyl esters can be selectively hydrogenolyzed with e.g. hydrogen in the presence of a catalyst such as palladium on charcoal.

In the case mixtures of stereoisomers or optical isomers of the above compounds are obtained, these can be separated into the single isomers by methods in themselves known, e.g., by fractional distillation, crystallization and/or chromatography. Racemic products can be resolved into the optical antipodes, for example, by separation of diastereomeric salts thereof, e.g., for basic compounds by the fractional crystallization of d- or 1-(tartrate, mandelate or camphorsulfonate) salts, or for acidic compounds by fractional crystallization of d- or 1-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine,

brucine or strychnine)-salts.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, alkaline or acidic condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, preferably near the boiling point of the solvents used, at atmospheric or superatmospheric pressure.

The invention further includes any variant of said processes, in which an intermediate product obtainable at any stage of the process is used as a starting material and any remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes. Mainly those starting materials should be used in said reactions, that lead to the formation of those compounds indicated above as being preferred.

The present invention additionally relates to the use in mammals of the compounds of the invention and their pharmaceutically acceptable, non-toxic acid addition salts, or pharmaceutical compositions thereof, as medicaments, e.g. as neutral endopeptidase inhibitors, e.g. for the treatment of cardiovascular disorders such as hypertension, edema, salt retention and congestive heart failure.

The present invention also relates to the use of the compounds of the invention for the preparation of pharmaceutical compositions especially pharmaceutical compositions having neutral endopeptidase inhibiting activity, and e.g. antihypertensive or saluretic activity.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, for the treatment of cardiovascular disorders, such as hypertension, comprising an effective amount of a pharmacologically active compound of the invention or a pharmaceutically acceptable salt thereof, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salts and/or polyethyleneglycol; for tablets also c) binders, e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired, d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, the compositions may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound, optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

A unit dosage for a mammal of about 50 to 70 kg may contain between about 10 and 100 mg of the active ingredient. The dosage of active compound is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration.

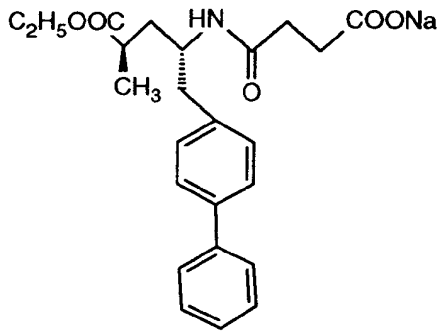
The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mm Hg. Optical rotations are measured at room temperature at 589 nm (D line of sodium), 365 nm or other wavelengths as specified in the examples.

The prefixes R and S are used to indicate the absolute configuration at each asymmetric center.

Example 1

To a solution of N-(3-carbo(t)butoxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbuta-

noic acid ethyl ester (0.80 g) in 15 ml of CH_2Cl_2 at room temperature are added 3 ml of trifluoroacetic acid. The mixture is stirred overnight and concentrated. The residue is dissolved in tetrahydrofuran (THF), and 6.5 ml of 1N NaOH is added. The mixture is concentrated and triturated with ether. The solid can be recrystallized from methylene chloride-hexane to give sodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methyl butanoic acid ethyl ester melting at 159-160°C; $[\alpha]_D^{20}$ = - 11.4° (methanol).



The starting material is prepared as follows:

A solution of α-t-BOC-(R)-tyrosine methyl ester (5.9 g, 20 mmol) and pyridine (8 mL, 100 mmol) in methylene chloride (30 mL) is cooled to 0-5°C. Trifluoromethanesulfonic anhydride (4 mL, 23 mmol) is added at 0-5°C, and the resulting mixture is held for another 30 minutes. The reaction mixture is diluted with water (60 mL) and methylene chloride (100 mL), and washed sequentially with 0.5 N sodium hydroxide solution (1 x 50 mL), water (1 x 60 mL), 10% citric acid solution (2 x 75 mL) and water (1 x 60 mL). The organic phase is dried over $MgSO_4$ and concentrated to an oil. The oil is purified by column chromatography (silica gel, hexane/ethyl acetate, 2:1 to give methyl(R)-2-(t-butoxycarbonylamino)-3-[4-(trifluoromethylsulfonyloxy)phenyl]-propionate which crystallizes on standing; m.p. 46-48°C; $[\alpha]^{20}_D$-36.01° (c=1, $CHCl_3$).

Nitrogen is passed through a suspension of (R)-2-(t-butoxycarbonylamino)-3-[4-(trifluoromethylsulfonyloxy)-phenyl]-propionate (1.75mmol), phenylboronic acid (3.5 mmol), anhydrous potassium carbonate (2.63 mmol) and toluene (17 mL) for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) is added, and the mixture is heated at 85-90° for 3 hours. The reaction mixture is cooled to 25°C, diluted with ethyl acetate (17 mL) and washed sequentially with saturated sodium bicarbonate (1 x 20 mL), water (1 x 20 mL), 10% citric acid (1 x 20 mL), water (1 x 20 mL) and saturated sodium chloride solution (1 x 20 mL). The organic phase is concentrated, and the residue is purified by column chromatography (silica gel, hexane/ethyl acetate 2:1) to yield methyl (R)-2-(t-butoxycarbonylamino)-3-(p-phenylphenyl)-propionate which can also be called N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine methyl ester.

To a solution of N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine methyl ester (6.8 g) in 60 ml of THF and 20 ml of methanol are added 20 ml of aqueous 1 N sodium hydroxide solution. The mixture is stirred for 1 h at room temperature and then acidified with 21 ml of 1 N hydrochloric acid. The aqueous solution is extracted 3x with ethyl acetate. The combined organic extracts are dried ($MgSO_4$), filtered and concentrated to give N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine, m.p. 98-99°C; $[\alpha]^{20}_D$ -18.59° (c=1, methanol).

To a solution of N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine (4.8 g) in 70 ml of methylene chloride (CH_2Cl_2) at 0°C with 1.65 g of N,O-dimethylhydroxylamine HCl, 1.7 g of triethylamine and 2.85 g of hydroxybenzotriazole are added 5.37 g of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. The mixture is stirred 17 h at room temperature. The mixture is concentrated taken up in ethyl acetate (EtOAc) and washed with saturated sodium bicarbonate, 1N HCl and brine, then dried ($MgSO_4$), filtered and concentrated to give N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine N,O-dimethyl hydroxylamine amide.

To a 0°C solution of N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine N,O-dimethyl hydroxylamine amide (5.2 g) in 250 ml of diethyl ether are added 0.64 g of lithium aluminum hydride. The reaction is stirred for 30 min. and quenched with aqueous potassium hydrogen sulfate. The mixture is stirred for additional 5 min., poured onto 1N HCl, extracted (3x) with EtOAc, dried ($MgSO_4$), filtered, and concentrated to give N-(R)-4-t-butoxycarbonyl-(p-phenylphenyl)-alanine carboxaldehyde as a colorless oil.

To a 0°C solution of N-(R)-t-butoxycarbonyl-(p-phenylphenyl)-alanine carboxaldehyde (4.4 g) in 200 ml of CH_2Cl_2 are added 10 g of carboethoxyethylidene phenyl phosphorane. The mixture is warmed to room temperature, stirred for 1 h, washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue is chromatographed on silica gel eluting with (1:2) ether:hexane to give N-t-butoxycarbonyl-(4R)-(p-phenylphenylmethyl)-4-amino-2-methyl-2-butenoic acid ethyl ester.

A solution of N-t-butoxycarbonyl-(4R)-(p-phenylphenylmethyl)-4-amino-2-methyl-2-butenoic acid ethyl ester (4.2 g) in 400 ml of ethanol is suspended with 2.0 g of 5% palladium on charcoal and then is hydrogenated at 50 psi for 6h. The catalyst is removed by filtration and the filtrate is concentrated to give N-t-butoxycarbonyl(4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester as a 80:20 mixture of diastereomers.

To the N-t-butoxycarbonyl(4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester (4.2 g) in 40 ml of CH_2Cl_2 at 0°C is bubbled dry hydrogen chloride gas for 15 min. The mixture is stirred 2 h and concentrated to give (4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester hydrochloride as a 80:20 mixture of diastereomers.

To a room temperature solution of the above amine salt (3.12 g) in 15 ml of CH_2Cl_2 and 15 ml of pyridine are added 13.5 g of succinic anhydride. The mixture is stirred for 17 h, concentrated, dissolved in ethyl acetate, washed with 1N HCl and brine, and dried ($MgSO_4$) to give N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester as a 80:20 mixture of diastereomers.

The above N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester diastereomeric mixture (3.9 g) and N,N-dimethylformamide-di-t-butyl acetal (8.8 ml) are heated at 80°C in 40 ml of toluene for 2 h. The mixture is poured onto ice- 1N HCl, extracted with ether, chromatographed on silica gel eluting with (2:1) toluene:ethyl acetate to give N-(3-carbo(t)butoxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester as the more polar material and the corresponding (S,S) diastereomer as the less polar material.

Example 2

To a solution of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester (0.33 g) in 20 ml of (1:1) ethanol:tetrahydrofuran (THF) at room temperature are added 5 ml of 1N sodium hydroxide solution (NaOH) and stirred for 17 h. The mixture is concentrated, dissolved in water and washed with ether. The aqueous layer is acidified with 1N hydrochloric acid (HCl), extracted 3x with ethyl acetate (EtOAc), dried over magnesium sulfate ($MgSO_4$), filtered and concentrated. The residue is triturated with ether to yield N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid melting at 158-164°C, $[\alpha]_D^{20}$ = -23.5° (methanol).

Example 3

Following the procedures described in Examples 1 or 2, the following compounds are prepared:

(a) N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2S-methylbutanoic acid melting at 165-167°C;

(b) N-(3-carboxy-1-oxopropyl)-(4S)-[p-(4-methylphenyl)phenylmethyl]-4-amino-2R-methyl butanoic acid melting at 165-170°C, $[\alpha]_D^{20}$= -18.4° (c=1, methanol);

(c) N-(3-carboxy-1-oxopropyl)-(4R)-(p-phenylphenylmethyl)-4-amino-2S-methylbutanoic acid, melting at 145-149°C;

(d) N-(3-carboxy-1-oxopropyl)-(4R)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid, melting at 162-165°C;

(e) N-(3-carboxy-1-oxopropyl)-4(S,R)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methyl butanoic acid, melting at 165-167°C;

(f) Sodium N-(3-carboxy-1-oxopropyl)-4(S,R)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methylbutanoic acid ethyl ester, melting at 165-167°C;

(g) Sodium N-(3-carboxy-1-oxopropyl)-(4R)-(p-phenylphenylmethyl)-4-amino-2S-methylbutanoic acid ethyl ester, melting at 117-120°C;

(h) N-(3-ethoxycarbonyl-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid, melting at 178-190°C;

(i) N-(2-carboxy-1-oxoethyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methylbutanoic acid, melting at 160-161°C;

j) N-(5-carboxy-1-oxopentyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid, melting at 124-127°C;

(k) Sodium N-(3-carboxy-1-oxopropyl)-4(S,R)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methoxybutanoic acid, melting at 180-185°C;

(l) Sodium N-(3-carboxy-1-oxopropyl)-4(S,R)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methoxybutanoic acid indanyl ester, melting at 134-136°C;

(m) N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-butanoic acid, melting at 163-

166°C;
(n) N-(3-carboxy-3-hydroxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid, melting at 156-170°C.

Example 4

Following the procedures described in example 1 except substituting glutaric anhydride for succinic anhydride, the following compounds are prepared:
(a) N-(4-carboxy-1-oxobutyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid, melting at 152-155°C.
(b) Sodium N-(4-carboxy-1-oxobutyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, melting at 68-72°C.

Example 5

Following the procedures described in example 1 except substituting carbobutoxyethylidene phenyl phosphorane for carboethoxyethylidene phenyl phosphorane, the following compound is prepared:
Sodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid n-butyl ester, melting at 155-165°C.

Example 6

To a room temperature solution of N-t-butoxycarbonyl-(4R)-(p-phenylphenylmethyl)-4-amino-2-methyl-2-butenoic acid ethyl ester (0.50 g) in 2 ml ethanol and 4 ml THF are added 2.0 ml of 1N NaOH. The reaction is stirred until the disappearance of starting material monitored by thin layer chromatography. The mixture is concentrated, dissolved in sodium bicarbonate and washed with ether. The aqueous layer is acidified with 3N HCl and extracted (3x) with ethyl acetate. The organic extracts are washed with brine, dried ($MgSO_4$), filtered and concentrated to give N-t-butoxycarbonyl-(4R)-(p-phenylphenylmethyl)-4-amino-2-methyl-2-butenoic acid.
To a room temperature solution of N-t-butoxycarbonyl-(4R)-(p-phenylphenylmethyl)-4-amino-2-methyl-2-butenoic acid (0.30 g) in 10 ml of CH_2Cl_2 are added 0.123 g of dimethyl aminopyridine, 0.203 g of 5-indanol and 0.387 g of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. The mixture is stirred overnight, and then is concentrated and taken up in ethyl acetate. The organics are washed with saturated sodium bicarbonate (2x), 1N HCl (2x) and brine (2x), dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel eluting with (1:4) ethyl acetate:hexane to give N-t-butoxycarbonyl(4R)-(p-phenylphenylmethyl)-4-amino-2-methyl-2-butenoic acid indanyl ester. This material is converted to sodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid indanyl ester melting at 60-65°C according to the procedures described in example 1.

Example 7

To a solution of (4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester hydrochloride (0.84 g) in 10 ml of methylene chloride are added 0.58 g of adipic acid mono methyl ester, 0.293 g of triethylamine, 0.49 g of hydroxybenzotriazole and 0.928 g of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. The reaction is stirred at room temperature overnight. The mixture is concentrated and the residue is taken up in ethyl acetate. The organics are washed with sodium bicarbonate, 1N HCl, brine, dried ($MgSO_4$), filtered and evaporated. The residue is chromatographed on silica gel eluting with (1:2) ethyl acetate:hexane to give the more polar diastereomer N-(5-carbomethoxy-1-oxopentyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester. The less polar (S,S) diastereomer is also isolated.
To a solution of N-(5-carbomethoxy-1-oxopentyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (0.58 g) in 10 ml of THF and 10 ml of ethanol are added 4.0 ml of 1N NaOH. The reaction is stirred overnight. The mixture is concentrated taken up in water and washed with ether (2x). The aqueous layer is acidified with 2N HCl and extracted with ethyl acetate (2x). The organics are dried ($MgSO_4$), filtered, concentrated and recrystallized from methylene chloride-ether to give N-(5-carboxy-1-oxopentyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid, melting at 124-127°C.

Example 8

Preparation of 1,000 capsules each containing 50 mg of the active ingredient, as follows:

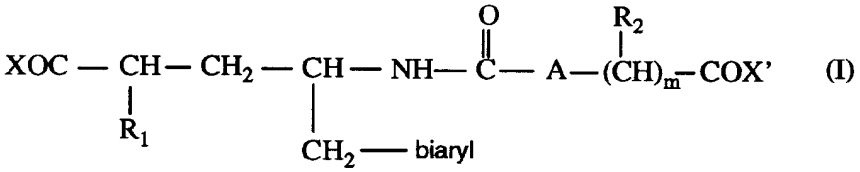
N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester sodium salt	50.00 g
Lactose	187.00 g
Modified starch	80.00 g
Magnesium stearate	3.00 g

Procedure: All the powders are passed through a screen with openings of 0.6 mm. The drug substance is placed in a suitable mixer and mixed first with the magnesium stearate, then with the lactose and starch until homogenous. No. 2 hard gelatin capsules are filled with 300 mg of said mixture each, using a capsule filling machine.

Analogously capsules are prepared, containing about 10-100 mg of the other compounds disclosed and exemplified herein, e.g. the compounds of examples 1-7.

Claims

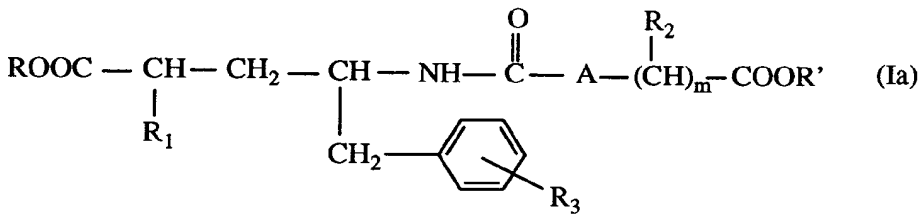
1. A compound of formula I



(I)

wherein COX and COX' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; R_1 represents hydrogen, lower alkyl, C_3-C_7-cycloalkyl-lower alkyl, aryl-lower alkyl, biaryl-lower alkyl, lower alkoxy, aryl-lower alkoxy, aryloxy, N-lower alkylamino, N,N-di-lower alkylamino, N-aryl-lower alkylamino, N,N-di-aryl-lower alkylamino, N-arylamino, N,N-diarylamino, lower alkanoylamino, aryl-lower alkanoylamino or aroylamino; R_2 represents hydrogen, hydroxy, lower alkoxy, lower alkyl, aryl-lower alkyl, C_3-C_7-cycloalkyl-lower alkyl, amino-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkylthio-lower alkyl or aryl-lower alkoxy-lower alkyl; biaryl represents phenyl substituted by carbocyclic or heterocyclic aryl; A represents a direct bond, lower alkylene, phenylene or cyclohexylene; m represents 1 or zero, provided that m represents 1 when A is a direct bond; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 of formula Ia



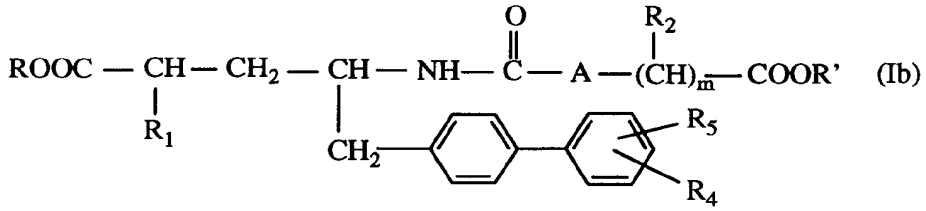
(Ia)

wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 represents hydrogen, lower alkyl, lower alkoxy, N-lower alkylamino, lower alkanoylamino, aryl-lower alkyl, aryl-lower alkoxy, aryloxy, N-arylamino or aroylamino wherein aryl in each case represents phenyl optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl; or aryl represents thienyl or furanyl optionally substituted by lower alkyl; R_2 represents hydrogen, hydroxy, lower alkyl or aryl-lower alkyl wherein aryl has the meaning given above, R_3 represents phenyl, or phenyl substituted by lower alkyl, lower alkoxy, halogen, cyano, acyloxy or trifluor-

omethyl; or R_3 represents thienyl or furanyl optionally substituted by lower alkyl; A represents a direct bond, lower alkylene, 1,4-phenylene or 1,4-cyclohexylene; m represents 1 or zero provided that m represents 1 when A is a direct bond; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 wherein R_3 is located in the para position.

4. A compound according to claim 1 of formula Ib



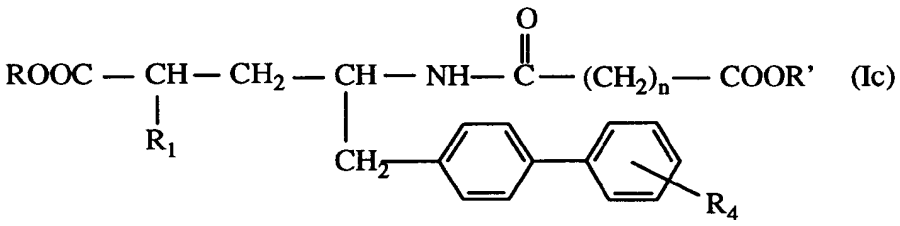
(Ib)

wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 is hydrogen, lower alkyl, lower alkoxy or aryl-lower alkyl wherein aryl represents phenyl optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl; R_2 represents hydrogen, hydroxy or lower alkoxy; R_4 and R_5 independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, halogen, cyano or trifluoromethyl; A represents lower alkylene; m represents 1 or zero; or a pharmaceutical acceptable salt thereof.

5. A compound according to claim 4 of formula Ib wherein R and R' independently represent carboxyl, lower alkoxy-carbonyl or 5-indanyloxy-carbonyl; R_1 represents hydrogen, lower alkyl or lower alkoxy; A represents a direct bond or lower alkylene; R_2 represents hydrogen or hydroxy; R_4 and R_5 independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, halogen, cyano or trifluoromethyl; m represents 1 or zero, provided that m represents 1 when A is a direct bond; or a pharmaceutical acceptable salt thereof.

6. A compound according to claim 4 wherein R and R' independently represent carboxyl or C_1-C_4-alkoxy-carbonyl; R_1 represents C_1-C_4-alkyl; R_2 represents hydroxy; A represents methylene; R_2 is hydroxy; R_4 and R_5 each are hydrogen; and m is 1; or a pharmaceutical acceptable salt thereof.

7. A compound according to claim 4 of formula Ic



(Ic)

wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 is lower alkyl or lower alkoxy; R_4 represents hydrogen, lower alkyl, lower alkoxy, halogen, or fluoromethyl; n represents an integer 1 through 6; or a pharmaceutical acceptable salt thereof.

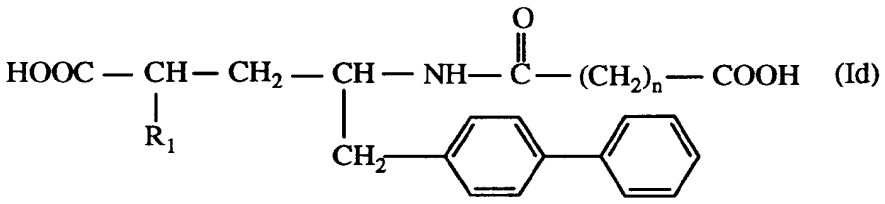
8. A compound according to claim 7 of formula Ic wherein R and R' independently represent caboxyl, lower alkoxy-carbonyl or 5-indanyloxy-carbonyl; R_1 is hydrogen, lower alkyl or lower alkoxy; R_4 represents hydrogen or lower alkyl; n represents an integer 1 through 4; or a pharmaceutical acceptable salt thereof.

9. A compound according to claim 7 of formula Ic wherein R and R' independently represent caboxyl or C_1-C_4-alkoxy-carbonyl; R_1 is C_1-C_4-alkyl; R_4 is hydrogen; and n is 2; or a pharmaceutical acceptable salt thereof.

10. A compound according to claim 7 of formula Ic wherein COOR and COOR' independently represent car-

boxyl, C_1-C_{20}-alkoxycarbonyl, (carbocyclic or heterocyclic aryl)-lower alkoxycarbonyl, (di-lower alkylamino, N-lower alkylpiperazino, morpholino, pyrrolidino, piperidino or perhydrazepino)-C_2 to C_4-alkoxycarbonyl, dihydroxypropyloxycarbonyl protected in form of a ketal, 5-indanyloxycarbonyl, 3-phthalidoxycarbonyl, bicycloalkoxycarbonyl-lower alkoxycarbonyl, α-(lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkoxycarbonyl, 1-(lower alkoxycarbonyloxy)-lower alkoxycarbonyl or 1-(lower alkanoyloxy)-lower alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

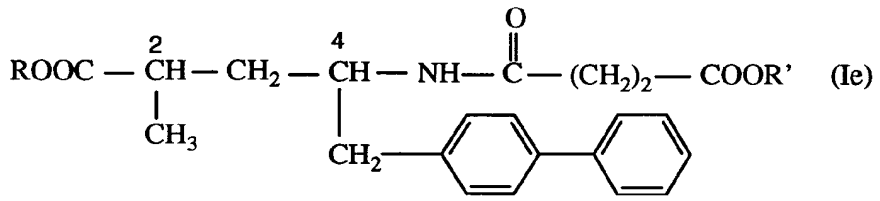
11. A compound according to claim 1 of formula Id



wherein R_1 is lower alkyl; n is an integer 1 through 4; or a pharmaceutically acceptable mono- or di-ester derivative thereof in which one or two of the acidic hydroxy groups of the carboxyl functional groups are esterified in form of a mono- or di-pharmaceutically acceptable ester, or a pharmaceutically acceptable salt thereof; or an optical antipode thereof.

12. A compound according to claim 11 of formula Id wherein R_1 is methyl and n is 2.

13. A compound according to claim 11 of formula Ie



wherein COOR and COOR' independently represent carboxyl or carboxyl esterified in form of a pharmaceutical acceptable prodrug ester, or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 13 wherein R and R' independently represent hydrogen, C_1-C_4-alkyl, benzyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, pivaloyloxymethyl, 1-(C_2-C_4-alkanoyloxy)-ethyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methyl, 5-indanyl, 3-phthalidyl, bornyloxycarbonylmethyl, 1-(C_1-C_4-alkoxycarbonyloxy)-ethyl or 3-pyridylmethyl; or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 13 wherein COOR' is carboxyl; and COOR represents carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester, or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 15 wherein COOR represents carboxyl or C_1-C_4-alkoxy-carbonyl; or a pharmaceutically acceptable salt thereof.

17. A compound according to claim 13 having the R-configuration at C-atom 2 and the S-configuration at C-atom 4.

18. A compound according to claim 17 being 4-[N-(3-carboxy-1-oxopropyl)-amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R, 4S)-antipode thereof or a pharmaceutical acceptable salt thereof.

19. A compound according to claim 1 selected from the group consisting of:
N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester;
N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid;

N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2S-methylbutanoic acid;
N-(3-carboxy-1-oxopropyl)-(4S)-[p-(4-methylphenyl)phenylmethyl]-4-amino-2R-methyl butanoic acid;
N-(3-carboxy-1-oxopropyl)-(4R)-(p-phenylphenylmethyl)-4-amino-2 S-methylbutanoic acid;
N-(3-carboxy-1-oxopropyl)-(4R)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid;
N-(3-carboxy-1-oxopropyl)-4(S,R)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methyl butanoic acid;
N-(3-carboxy-1-oxopropyl)-4(S,R)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methylbutanoic acid ethyl ester;N-(3-carboxy-1-oxopropyl)-(4R)-(p-phenylphenylmethyl)-4-amino-2S-methylbutanoic acid ethyl ester;
N-(3-ethoxycarbonyl-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid;
N-(2-carboxy-1-oxoethyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methylbutanoic acid;
N-(5-carboxy-1-oxopentyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid;
N-(3-carboxy-1-oxopropyl)-4(S,R)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methoxybutanoic acid;
N-(3-carboxy-1-oxopropyl)-4(S,R)-(p-phenylphenylmethyl)-4-amino-2(S,R)-methoxybutanoic acid indanyl ester;
N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-butanoic acid;
N-(3-carboxy-3-hydroxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid;
N-(4-carboxy-1-oxobutyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid;
N-(4-carboxy-1-oxobutyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester; and
N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid n-butyl ester;
or a salt thereof.

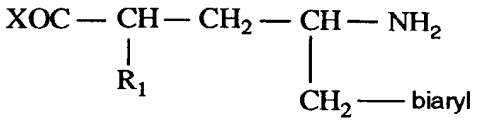
20. A compound according to any one of claims 1 to 18 for use in the prophylactic or therapeutic treatment of the human or animal body.

21. A pharmaceutical composition comprising an effective neutral endopeptidase inhibiting amount of a compound of claim 1 in combination with one or more pharmaceutically acceptable carriers.

22. A neutral endopeptidase inhibiting pharmaceutical composition according to claim 20 comprising an effective neutral endopeptidase inhibiting amount of 4-[N-(3-carboxy-1-oxopropyl)-amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R, 4S)-antipode thereof or a pharmaceutical acceptable salt thereof.

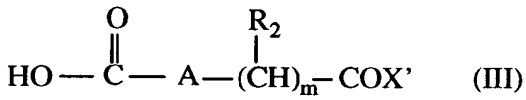
23. Use of a compound according to any one of claims 1 to 20 or a pharmaceutically acceptable prodrug ester of any above said compound with a free carboxyl group; or a pharmaceutically acceptable salt of any said compound with a free acid or basic salt forming group; for the manufacture of a neutral endopeptidase inhibiting pharmaceutical composition.

24. A process for the preparation of a compound of claim 1 which comprises condensing a compound of formula II



(II)

wherein COX, R_1 and biaryl have the meaning as defined in claim 1, in temporarily protected form if required; with a compound of formula III



(III)

or a reactive functional derivative or a salt thereof, wherein A, R_2, m and COX' have the meaning as defined in claim 1, in temporarily protected form if required; and, if temporarily protecting any interfering reactive group(s), removing said protecting group(s), and then isolating the resulting compound of said claim; and, if desired, converting any resulting compound into another compound of said claim.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number EP 93810016.1

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	CHEMICAL ABSTRACTS, vol. 112, no. 1, January 01, 1990 Columbus, Ohio, USA G.M. KSANDER et al. "Enkephalinase inhibitors.1; 2,4-Dibenzylglutaric acid derivatives", page 777, abstract-no. 7 912p & J. Med. Chem. 1989, 32(12), 2519-26 + Chemical Abstracts, Twelfth Collective Index, Formulas, page 12745F, column 1, lines 108-111 + --	1,20, 21,23	C 07 C 233/47 C 07 C 235/12 A 61 K 31/195 A 61 K 31/215
A	EP - A - 0 225 292 (CIBA-GEIGY) * Claims 1,8; page 8, line 23 - page 10, line 3 * --	1,20, 21,23, 24	
D,A	US - A - 5 021 430 (KSANDER) * Claims, column 11, line 15 - column 13, line 19 * --	1,20, 21,23, 24	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C 07 C 233/00 C 07 C 235/00
A	WO - A - 91/05 555 (THE SALK INSTITUTE BIO-TECHNOLOGY) * Tables 1,2,3; abstract * --	1,20, 21,23	
A	DD - A - 250 531 (AKADEMIE DER WISSENSCHAFTEN DER DDR) * Totality * ----	1,20, 21,23, 24	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	15-04-1993	KÖRBER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

Electronic Patent Application Fee Transmittal

Application Number:	12147570
Filing Date:	27-Jun-2008
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Joseph T. Majka
Attorney Docket Number:	32219-US-DIV

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	6190256
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	01095
Filer:	Joseph T. Majka
Filer Authorized By:	
Attorney Docket Number:	32219-US-DIV
Receipt Date:	02-OCT-2009
Filing Date:	27-JUN-2008
Time Stamp:	08:24:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	6122
Deposit Account	190134
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Supp_docs_100109.pdf	384221 04e9cc086de1ee611d554328bcf6ec44dbfb5c85	yes	4
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	2	
	Miscellaneous Incoming Letter		3	3	
	Information Disclosure Statement (IDS) Filed (SB/08)		4	4	
Warnings:					
Information:					
2	Foreign Reference	EP726072.pdf	749716 5c812bbc00990aa769035f17f9558169b118cc20	no	23
Warnings:					
Information:					
3	Foreign Reference	EP555175.pdf	1504602 183ef2a7b4193f89e91af2dd7c0b187863a5348e	no	22
Warnings:					
Information:					
4	NPL Documents	LAJEMI_et_al.pdf	1459686 ebc74b73a426c6003c6cb8e2685a4fcbf4593fb8	no	19
Warnings:					
Information:					
5	NPL Documents	MATSUMOTO_et_al.pdf	390046 27bc15fc856a066b563640c67b8e1549b44ab0e7	no	2
Warnings:					
Information:					
6	NPL Documents	ROBI_et_al.pdf	5084353 3491102fd623e6eb1c8c4acc3afe75db0ee19de6	no	101
Warnings:					
Information:					
7	Transmittal Letter	WOHLFART_et_al.pdf	739958 95f11d46c2cb0fd2c3440b20dd872440735b6438	no	9

Warnings:					
Information:					
8	Fee Worksheet (PTO-875)	fee-info.pdf	30610 ad5f0115945d54a5bfa8738884cce0845c5a6987	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	10343192	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander, Gary Michael et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed:

☒ supplemental to the Information Disclosure Statements filed June 27, 2008, October 24, 2008 and August 7, 2009

If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134 in the name of Novartis.

☒ This Information Disclosure Statement is being filed in accordance with 37 C.F.R. §1.97(c) or 37 C.F.R. §1.97(d).

☒ A letter for payment of fee set forth in 37 C.F.R. §1.17(p) is enclosed.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

☒ Copies of the references are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

Respectfully submitted,

Joseph Majka
Attorney for Applicant
Reg. No. 30,570

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9499

Date: 04/1, 2019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander, Gary Michael et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

FEE LETTER FOR INFORMATION DISCLOSURE STATEMENT

Sir:

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $180 for payment of the fee pursuant to 37 CFR §1.17(p) for the submission of an Information Disclosure Statement under 37 CFR §1.97(c).

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9499
Date: Oct. 1, 2009

Joseph Majka
Attorney for Applicant
Reg. No. 30,570

DRAFT

APPLICATION SERIAL NO:12/147,570
CASE 32219-US-DIV

DO NOT ENTER INTO FILE
FOR DISCUSSION PURPOSES ONLY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander, Gary. M. et al.
APPLICATION NO: 12/147,570
FILED: June 27, 2008
FOR: Method of Treatment and Pharmaceutical Composition

Art Unit: 1617
Examiner: Kim, Jennifer M.

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CLAIM PROPOSALS

Amendments to the Claims:

Please cancel claims 1-13.

Please add new claims 14-17.

Listing of Claims:

Claims 1-13 (cancelled)

Claim 14 (new): A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof;

(ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable carrier;

wherein said (i) AT 1-antagonist valsartan or pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof, are administered in combination in a 1:1 ratio.

Claim 15 (new): The pharmaceutical composition of claim 14, wherein said (i) AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof are administered in amounts effective to treat hypertension or heart failure.

Claim 16 (new): The pharmaceutical composition of claim 14 wherein (ii) said NEP inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

Claim 17 (new): The pharmaceutical composition of claim 16 in the form of a capsule or tablet.

Remarks

Support for the 1:1 ratio can be found in Applicants' specification on page 16, paragraphs three and four from the bottom, i.e. 20 mg. Thus, no new matter is added.

Novartis Pharmaceuticals Corporation
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Joseph Majka
Attorney for Applicants
Reg. No. 30,570

Metabolic & Cardiovascular Disease

Novartis
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Patents Pharma

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Fax (973) 781-8064
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NOVARTIS

Fax

PLEASE DO NOT ENTER INTO THE FILE. THE CLAIM PROPOSALS ARE FOR DISCUSSION PURPOSES ONLY.

Attention Examiner Kim

Fax no. 571-273-8300

Number of pages including cover page: 4

Date November 24, 2009

Concerning **Application Serial No. 12/147,570, Case No. 32219-US-DIV**

Dear Examiner Kim,

Please find attached a Draft Claim Proposal for the above case for our telephone interview scheduled Wednesday, November 25, 2009 at 2:00pm.

I will call you at 2:00 pm.

With kind regards,

Joseph Majka

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

1095 7590 12/01/2009

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1628	

MAIL DATE	DELIVERY MODE
12/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Interview Summary	Application No.	Applicant(s)	
	12/147,570	KSANDER ET AL.	
	Examiner	Art Unit	
	JENNIFER M. KIM	1628	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JENNIFER M. KIM*. (3)_____.

(2) *Mr. Majka*. (4)_____.

Date of Interview: *25 November 2009*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *Pending claims*.

Identification of prior art discussed: *Ksander et al. (U.S.Patent Nos. 7,468,390B2 and 5,217,996)*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The general nature of the invention and the 35 U.S.C. 103 rejection made in the previous Office Action was discussed. Mr.Majka will file the response to the last Office Action*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/JENNIFER M KIM/ Primary Examiner, Art Unit 1628	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

———

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander, Gary Michael et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

This Reply is submitted in response to the Office Action mailed August 7, 2009 and the Communication dated December 1, 2009. A two -month extension of time petition is included herewith. Reconsideration of the present rejections and withdrawal of the present rejections are respectfully requested.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Remarks/Arguments

Applicants' representative would like to thank the Examiner for the courteous interview on 25 November 2009, in which U.S. Patents 7,468,390 B2 and 5,217,996 were discussed, as summarized in the Interview Summary dated 1 December 2009 and in the remarks below.

Claims 1-13 have been cancelled and substituted with new claims 14-17. Support for new claims 14-17 having the specified AT 1-antagonist and the specified NEP inhibitor in about a 1:1 ratio can be found in Applicants' specification on page 9; page 14, and page 16 paragraphs two, three and four from the bottom, i.e. 20 mg. Thus, no new matter is added.

Former claims 8-13 were rejected under 35 USC 103(a) as obvious over US Patent 5,217,996 to Ksander. The rejection, as applied to new claims 14-17, is respectfully traversed. Ksander teaches, in Example 8, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester sodium salt. However, Ksander fails to teach or suggest a pharmaceutical composition comprising, *inter alia*:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof.

Ksander also fails to teach or suggest a pharmaceutical composition wherein the (i) AT 1-antagonist valsartan or pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof, are administered in combination in about a 1:1 ratio. For the reasons set forth hereinabove, withdrawal of this ground of rejection under 35 USC 103 is respectfully requested.

Former claims 1-4 were rejected under 35 USC 103(a) as obvious over US Patent 5,217,996 to Ksander and US Patent 5,399,578 to Buhlmayer et al. The rejection as applied to new claims 14-17 is respectfully traversed. Ksander teaches, in Example 8, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester sodium salt and Buhlmayer et al. teach valsartan. The Examiner maintains that the employment of the specific NEP inhibitor and valsartan would have been obvious because all the components are well known for treating

hypertension and one of ordinary skill in the art would have been motivated to combine said specific components to treat hypertension. This rejection cannot stand, however, because Applicants have already overcome the *prima facie* case for obviousness, as demonstrated by the issuance of U.S. Patent 7,468,390 ('390 patent) to Ksander et al. During the prosecution of the '390 patent, Applicants presented experimental data showing that the combination of valsartan and the specific NEP inhibitor (AHU377) had a synergistic, unexpected and surprising antihypertensive effect which was not taught or obvious from the cited prior art of US Patent 5,217,996 to Ksander and US Patent 5,399,578 to Buhlmayer et al. See Reasons for Allowance in the '309 patent. For the reasons set forth hereinabove, Applicants respectfully maintain that their claimed pharmaceutical composition is novel and non-obvious over Ksander and Buhlmayer et al., and withdrawal of this ground of rejection under 35 USC 103, is respectfully requested.

In view of the foregoing remarks and amendments, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9499

Joseph Majka
Attorney for Applicant
Reg. No. 30,570

Date: December 23, 2009

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander, Gary Michael et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1617
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of August 7, 2009 has a shortened statutory time set to expire on November 7, 2009. A two-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $490 for payment of the extension fee. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9499

Joseph Majka
Attorney for Applicant
Reg. No. 30,570

Date: December 23, 2009

Electronic Patent Application Fee Transmittal

Application Number:	12147570
Filing Date:	27-Jun-2008
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Joseph T. Majka/Monika Van Houten
Attorney Docket Number:	32219-US-DIV

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	1252	1	490	490

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**490**

Electronic Acknowledgement Receipt

EFS ID:	6703395
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	01095
Filer:	Joseph T. Majka/Monika Van Houten
Filer Authorized By:	Joseph T. Majka
Attorney Docket Number:	32219-US-DIV
Receipt Date:	23-DEC-2009
Filing Date:	27-JUN-2008
Time Stamp:	16:43:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$490
RAM confirmation Number	3798
Deposit Account	190134
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219-ROA.pdf	812180 c7ba3a9ecee66fab2aee44be327cfcda6abf758e	yes	6

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	3
Applicant Arguments/Remarks Made in an Amendment	4	5
Extension of Time	6	6

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	30726 2802d90dadc142a5c5448e9549972f3d056afcf5	no	2

Warnings:

Information:

Total Files Size (in bytes):	842906

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-13 (cancelled)

Claim 14 (new): A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof;

(ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable carrier;

wherein said (i) AT 1-antagonist valsartan or pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof, are administered in combination in about a 1:1 ratio.

Claim 15 (new): The pharmaceutical composition of claim 14, wherein said (i) AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof are administered in amounts effective to treat hypertension or heart failure.

Claim 16 (new): The pharmaceutical composition of claim 14 wherein (ii) said NEP inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

Claim 17 (new): The pharmaceutical composition of claim 16 in the form of a capsule or tablet.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/147,570	06/27/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 12/23/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 4	Minus	** 20	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 1	Minus	***5	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GYZELL P. JOHNSON/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

1095 7590 02/24/2010

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
02/24/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/147,570	KSANDER ET AL.	
	Examiner	Art Unit	
	JENNIFER M. KIM	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/2/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed December 23, 2009 have been received and entered into the application.

Response to Arguments

Applicants' arguments filed December 23, 2010 have been fully considered but they are not persuasive. Applicants argue that the new claims 14-17 are amended to drawn to "a 1:1 ratio is supported by Applicants' specification of page 9, page 14 and page 16, i.e. 20mg. This is not persuasive because such limitation of "1:1 ratio" lack literal support in the specification as originally filed. The specification of pages 9,14 and 16 have been carefully reviewed. However, it only discloses specific amounts of each of the active agents, i.e 20mg instead of the broad range of 1:1 ratio.

Applicants argue that Ksander fails to teach the combination as well as the combination having the 1:1 ratio. This is not persuasive because to employ combinations of specific NEP inhibitor and valsartan would have been obvious because all the components are well known individually for treating hypertension. One of ordinary skill in the art would have been motivated to combine specific NEP inhibitor and valsartan in a single composition in order to achieve an expected benefit of

antihypertensive effect of the combination. Further, such ratio is obvious because Ksander (U.S.Patent 5,217,996 column 18, lines 59-65) of record teaches the effective amount of claimed NEP inhibitor between about 10mg and 100mg while Buhlmayer et al. teaches the effective dosage of valsartan as 10mg to about 250mg (column 27, lines 40-45). Therefore the claimed 1:1 ratio is obviously achieved upon the administration of the claimed combination in the individually known effective amounts for the treatment of hypertension in order to achieve at least an additive effect. Applicants argue that during the prosecution of the '390 patent, Applicants presented experimental data showing that the combination of valsartan and the specific NEP inhibitor (AHU377) has a synergistic, unexpected and surprising antihypertensive effect which was not taught or obvious from the cited prior art. This is not persuasive because the '390 patent has been granted based on the previously presented experimental data. Applicants have not presented any evidence to support a surprising and unexpected result of the claimed broad ratio of "1:1". Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Instant specification supports the specific amount “20mg” of valsartan and “20mg” of the NEP inhibitor, however, the limitation of broad ratio of “1:1" is not supported in the specification as originally filed.

This is a new Matter rejection.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) of record and Buhlmayer et al. (U.S.Patent No. 5,399,578) of record.

Ksander teaches a pharmaceutical composition comprising the compound, 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)antipode thereof (also known as N-(3-caroxy-1-oxopropyl)-(4S)-p-

phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) is a pharmacologically potent neutral endopeptidase enzyme (NEP) inhibitor and it is useful for the treatment of cardiovascular disorders such as **hypertension**. (column 9, lines 5-15, column 12, lines 1-10, claims 1-22). Ksander teaches ammonium salts, mono-, di- or tri-lower (**alkyl or hydroxyalkyl)-ammonium salts** (e.g. **triethanolammonium**) are suitable pharmaceutically acceptable salts of the compound. (column 5, lines 35-45). Ksander teaches the effective amount of claimed NEP inhibitor between about 10mg and 100mg. Ksander teaches that the composition can be prepared as a tablet or a capsule formulation (example 8, column 18, lines 18-35).

Buhlmayer et al. teach valsartan is useful for an anti-hypertensive treatment. (abstract, claims). Buhlmayer et al. teach the effective dosage of valsartan as 10mg to about 250mg (column 27, lines 40-45). Buhlmayer et al. teach that valsartan can be formulated as capsules or tablets (column 26, lines 30-40).

The claims differ from the cited references in claiming a pharmaceutical composition comprising combination of the specific NEP inhibitor and valsartan. To employ combinations of specific NEP inhibitor and valsartan would have been obvious because all the components are well known individually for treating hypertension. One of ordinary skill in the art would have been motivated to combine specific NEP inhibitor and valsartan in a single composition in order to achieve an expected benefit of antihypertensive effect of the combination. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). Further, the claimed ratio of 1:1 is obvious because

Ksander (U.S.Patent 5,217,996 column 18, lines 59-65) of record teaches the effective amount of claimed NEP inhibitor between about 10mg and 100mg while Buhlmayer et al. teaches the effective dosage of valsartan as 10mg to about 250mg (column 27, lines 40-45). Therefore the claimed 1:1 ratio is obviously achieved upon the administration of the claimed combination in the individually known effective amounts for the treatment of hypertension in order to achieve at least an additive effect.

Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER M KIM/
Primary Examiner, Art Unit 1628

Jmk
February 22, 2010

FORM PTO-1449 (REV. 7-85) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO. PAT032219-US-DIV

APPLICATION NO. 12/147570

APPLICANT
Ksander, Gary Michael et al.

FILING DATE
June 27, 2008

Group
1617

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						
	AL						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AM	0726072	02/07/96	EP			☐	☐
	AN	555175	01/13/93	EP			☐	☐
	AO						☐	☐
	AP						☐	☐
	AQ						☐	☐

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent pages, Etc.)

	AR	LAJEMI et al., "Genetics of the renin-angiotensin-aldosterone system and risk of arterial disease"; ACE Inhibitors, Milestones in Drug Therapy, pages 11-27; P. D'Orleans-Juste, G.E. Plante (2001)
	AS	MATSUMOTO et al.; "Blockade of renin-angiotensin system and enhancement of atrial natriuretic peptide with neutral endopeptidase inhibition cause natriuresis in congestive heart failure and renal dysfunction in conscious dogs", ASN Program and Abstracts, Vol. 4, No. 3, page 517(September 1993)
	AT	ROBI et al., "Neutral endopeptidase inhibitors and combined inhibitors of neutral endopeptidase and angiotensin converting enzyme", Antihypersensitive Drugs,pages 113-212 , (1997)
	AU	WOHLFART, et al.; "Crosstalk between ACE Inhibitors, B2 kinin receptor and nitric oxide in endothelial cells", ACE Inhibitors, Milestones in Drug Therapy, P. D'Orleans-Juste, G.E. Plante (2001)

EXAMINER	/Jennifer Kim/	DATE CONSIDERED	02/16/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include a copy of this form with the next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /JK/

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER M KIM	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/17/2009	07/28/2009	02/22/2010						
	1	÷	✓	-						
	2	÷	✓	-						
	3	÷	✓	-						
	4	÷	✓	-						
	5	÷	N	-						
	6	÷	N	-						
	7	÷	N	-						
	8	÷	✓	-						
	9	÷	✓	-						
	10	÷	✓	-						
	11	÷	✓	-						
	12		✓	-						
	13		✓	-						
	14			✓						
	15			✓						
	16			✓						
	17			✓						

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER M KIM	1617

SEARCHED			
Class	Subclass	Date	Examiner
514	533, 381	7/29/2009	jmk
	Updated	2/22/2010	jmk

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search; STN; parent 10/341,868	7/29/2009	jmk
Updated	2/22/2010	jmk

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Webb, Randy Lee et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1628
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

NOTICE OF APPEAL

Sir:

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the Office Action dated February 24, 2010 finally rejecting claims 14-17.

☒ Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $540 for payment of the appeal fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

☐ The appeal fee was paid in a previous appeal herein. The examiner re-opened prosecution prior to any decision by the Board of Patent Appeals and Interferences. No fee is now due.

☒ Enclosed is a Petition for Extension of Time.

Respectfully submitted,

Joseph Majka
Attorney for Applicant
Reg. No. 30,570

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9499

Date: June 30, 2010

Electronic Patent Application Fee Transmittal

Application Number:	12147570
Filing Date:	27-Jun-2008
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Joseph T. Majka/Linda Adams
Attorney Docket Number:	32219-US-DIV

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Notice of appeal	1401	1	540	540
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	1252	1	490	490
Miscellaneous:				
			Total in USD ($)	**1030**

Electronic Acknowledgement Receipt

EFS ID:	7923181
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	01095
Filer:	Joseph T. Majka/Linda Adams
Filer Authorized By:	Joseph T. Majka
Attorney Docket Number:	32219-US-DIV
Receipt Date:	30-JUN-2010
Filing Date:	27-JUN-2008
Time Stamp:	11:20:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1030
RAM confirmation Number	21169
Deposit Account	190134
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		32219_Appeal.pdf	239499 8416b5b9d499289851205dcbe351c42e9c5675d9	yes	2

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Extension of Time	1	1
Notice of Appeal Filed	2	2

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	32270 2793a2ba8c34f8c6c4428b6da7a093ceb7c465eb	no	2

Warnings:

Information:

Total Files Size (in bytes):	271769

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Webb, Randy Lee et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1628
Examiner: Kim, Jennifer M

MS: After Final
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

NOTICE OF APPEAL
PETITION FOR EXTENSION OF TIME

Sir:

The period for filing a Notice of Appeal has a shortened statutory time set to expire on May 24, 2010. A two-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $490 for payment of the extension fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Joseph Majka
Attorney for Applicant
Reg. No. 30,570

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9499

Date: June 30, 2010

PTO/SB/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	12/147570
Filing Date	June 27, 2008
First Named Inventor	Ksander, Gary Michael et al.
Art unit	1628
Examiner Name	Kim, Jennifer M
Attorney Docket Number	PAT032219-US-DIV

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant must request non-entry of such amendment(s).
   - a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. ☐ Other _____
   - b. ☒ Enclosed
     - i. ☐ Amendment/Reply
     - ii. ☐ Affidavit(s)/Declaration(s)
     - iii. ☒ Information Disclosure Statement (IDS)
     - iv. ☐ Other _____
2. Miscellaneous
   - a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. ☐ Other _____
3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   - a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 19-0134 in the name of Novartis.
     - i. ☒ RCE fee required under 37 CFR 1.17(e)
     - ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. ☐ Other _____
   - b. ☐ Check in the amount of $_____ enclosed
   - c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit Card information should not be included on this form. Provide credit card information and authorization on PTO-2038

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	Cozette McAvoy	Date	21st July 2010
Name (Print/Type)	Cozette M. McAvoy	Registration No.	60,457

Case PAT032219-US-DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KSANDER, GARY MICHAEL ET AL.
APPLICATION NO: 12/147570
FILED: JUNE 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

ART UNIT: 1628
EXAMINER: KIM, JENNIFER M

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed:

☒ supplemental to the Information Disclosure Statement filed October 2, 2009.

If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134 in the name of Novartis.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

☒ Copies of the references are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

Respectfully submitted,

Cozette M. McAvoy
Attorney for Applicant
Reg. No. 60,457

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9499

Date: 21st July 2010

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	12/147570
Filing Date	June 27, 2008
First Named Inventor	Ksander, Gary Michael et al.
Art unit	1628
Examiner Name	Kim, Jennifer M
Attorney Docket Number	PAT032219-US-DIV

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		TRIPPODO et al., "Repression of Angiotensin II and Potentiation of Bradykinin Contribute to the Synergistic Effects of Dual Metalloprotease Inhibition in Heart Failure:, J. Pharmacol. Exp. Ther., Vol. 272, pp. 619-627, (1995).	☐
		HOWES et al., "Angiotensin receptor antagonists and ACE inhibitors", Australian Family Physician, Vol. 27, pp. 914-921, (1998).	☐
		CRISCIONE et al., "Pharmacological profile of valsartan: a potent, orally active, nonpeptide antagonists of the angiotensin II AT-receptor sybtype", Br. J. Pharmacol., Vol. 110, pp. 761-771, (1993).	☐
		Abstract of J. Pharmacol. Exp., Ther., Vol. 265, pp. 1339-1347, (1993).	☐
		Search dated May 29, 2008 (26 pages) cited by opponent Mundipharma GMBH on June 26, 2008, submitted in corresponding EP application 03704413.8	☐
		Search dated May 29, 2008 (3 pages) cited by opponent Mundipharma GMBH on June 26, 2008, submitted in corresponding EP application 03704413.8	☐
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			☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant.
[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.
This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Patent Application Fee Transmittal

Application Number:	12147570
Filing Date:	27-Jun-2008
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Cozette Marie McAvoy/Cindy Klepacky
Attorney Docket Number:	32219-US-DIV

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**810**

Electronic Acknowledgement Receipt

EFS ID:	8057748
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	01095
Filer:	Cozette Marie McAvoy/Cindy Klepacky
Filer Authorized By:	Cozette Marie McAvoy
Attorney Docket Number:	32219-US-DIV
Receipt Date:	21-JUL-2010
Filing Date:	27-JUN-2008
Time Stamp:	10:54:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$810
RAM confirmation Number	6986
Deposit Account	190134
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219_RCE_IDS.pdf	167382 db45ffd6d341b027a794dfd9bc001ef8b220519c	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Request for Continued Examination (RCE)		1	1	
	Transmittal Letter		2	2	
	Information Disclosure Statement (IDS) Filed (SB/08)		3	3	
Warnings:					
Information:					
2	NPL Documents	10_Tripoddo.pdf	909864 44d6f18a6c7c562de01b7f4bbacb7714552f7c9d	no	9
Warnings:					
Information:					
3	NPL Documents	11_Howes.pdf	544740 2b4c44e4fbba157c67d6810b2aac36a044695cf2	no	6
Warnings:					
Information:					
4	NPL Documents	12_Criscione.pdf	1052043 1d1f566ff1b41674d93095226a78a2bbf87ac31b	no	12
Warnings:					
Information:					
5	NPL Documents	14_Abstract_J_Pharmacol.pdf	78928 eb474abe708798bfde22a17a8103b1d1dd87f327	no	1
Warnings:					
Information:					
6	NPL Documents	Search_1.pdf	1652414 7081a819c5211fd1453fa8efab4600491164bafe	no	25
Warnings:					
Information:					
7	NPL Documents	Search_2.pdf	168865 ab553fc83d69b14fc57fb34ff5d4a7dedfae90b4	no	3

Warnings:					
Information:					
8	Fee Worksheet (PTO-875)	fee-info.pdf	30627 a4757c004da5e14fe7e9256b9d57a2b73cd765da	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4604863	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

1095 7590 10/04/2010

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1628	

MAIL DATE	DELIVERY MODE
10/04/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/147,570	KSANDER ET AL.	
	Examiner	Art Unit	
	JENNIFER M. KIM	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/21/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/21/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 21, 2010 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Instant specification supports the specific amount “20mg” of valsartan and “20mg” of the NEP inhibitor,

however, the limitation of broad ratio of "1:1" is not supported in the specification as originally filed.

This is a new Matter rejection.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ksander (U.S.Patent No. 5,217,996) of record and Buhlmayer et al. (U.S.Patent No. 5,399,578) of record.

Ksander teaches a pharmaceutical composition comprising the compound, 4-[N-(3-carboxy-1-oxo-propyl)amino]-4-(p-phenylphenylmethyl)-2-methylbutanoic acid ethyl ester, the (2R,4S)antipode thereof (also known as N-(3-caroxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino2R-methylbutanoic acid ethyl ester) is a pharmacologically potent neutral endopeptidase enzyme (NEP) inhibitor and it is useful for the treatment of cardiovascular disorders such as **hypertension**. (column 9, lines 5-15, column 12, lines 1-10, claims 1-22). Ksander teaches ammonium salts, mono-, di- or tri-lower (**alkyl or hydroxyalkyl)-ammonium salts** (e.g. **triethanolammonium**) are suitable pharmaceutically acceptable salts of the compound. (column 5, lines 35-45). Ksander teaches the effective amount of claimed NEP inhibitor between about 10mg and 100mg.

Ksander teaches that the composition can be prepared as a tablet or a capsule formulation (example 8, column 18, lines 18-35).

Buhlmayer et al. teach valsartan is useful for an anti-hypertensive treatment. (abstract, claims). Buhlmayer et al. teach the effective dosage of valsartan as 10mg to about 250mg (column 27, lines 40-45). Buhlmayer et al. teach that valsartan can be formulated as capsules or tablets (column 26, lines 30-40).

The claims differ from the cited references in claiming a pharmaceutical composition comprising combination of the specific NEP inhibitor and valsartan. To employ combinations of specific NEP inhibitor and valsartan would have been obvious because all the components are well known individually for treating hypertension. One of ordinary skill in the art would have been motivated to combine specific NEP inhibitor and valsartan in a single composition in order to achieve an expected benefit of antihypertensive effect of the combination. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). Further, the claimed ratio of 1:1 is obvious because Ksander (U.S.Patent 5,217,996 column 18, lines 59-65) of record teaches the effective amount of claimed NEP inhibitor between about 10mg and 100mg while Buhlmayer et al. teaches the effective dosage of valsartan as 10mg to about 250mg (column 27, lines 40-45). Therefore the claimed 1:1 ratio is obviously achieved upon the administration of the claimed combination in the individually known effective amounts for the treatment of hypertension in order to achieve at least an additive effect.

Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Response to Arguments

Applicants' arguments filed December 23, 2010 have been fully considered but they are not persuasive. Applicants argue that the new claims 14-17 are amended to drawn to "a 1:1 ratio is supported by Applicants' specification of page 9, page 14 and page 16, i.e. 20mg. This is not persuasive because such limitation of "1:1 ratio" lack literal support in the specification as originally filed. The specification of pages 9,14 and 16 have been carefully reviewed. However, it only discloses specific amounts of each of the active agents, i.e 20mg instead of the broad range of 1:1 ratio.

Applicants argue that Ksander fails to teach the combination as well as the combination having the 1:1 ratio. This is not persuasive because to employ combinations of specific NEP inhibitor and valsartan would have been obvious because all the components are well known individually for treating hypertension. One of ordinary skill in the art would have been motivated to combine specific NEP inhibitor and valsartan in a single composition in order to achieve an expected benefit of antihypertensive effect of the combination. Further, such ratio is obvious because Ksander (U.S.Patent 5,217,996 column 18, lines 59-65) of record teaches the effective

amount of claimed NEP inhibitor between about 10mg and 100mg while Buhlmayer et al. teaches the effective dosage of valsartan as 10mg to about 250mg (column 27, lines 40-45). Therefore the claimed 1:1 ratio is obviously achieved upon the administration of the claimed combination in the individually known effective amounts for the treatment of hypertension in order to achieve at least an additive effect. Applicants argue that during the prosecution of the '390 patent, Applicants presented experimental data showing that the combination of valsartan and the specific NEP inhibitor (AHU377) has a synergistic, unexpected and surprising antihypertensive effect which was not taught or obvious from the cited prior art. This is not persuasive because the '390 patent has been granted based on the previously presented experimental data. Applicants have not presented any evidence to support a surprising and unexpected result of the claimed broad ratio of "1:1". Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER M KIM/
Primary Examiner, Art Unit 1628

Jmk
September 30, 2010

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	12/147570
Filing Date	June 27, 2008
First Named Inventor	Ksander, Gary Michael et al.
Art unit	1628
Examiner Name	Kim, Jennifer M
Attorney Docket Number	PAT032219-US-DIV

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		TRIPPODO et al., "Repression of Angiotensin II and Potentiation of Bradykinin Contribute to the Synergistic Effects of Dual Metalloprotease Inhibition in Heart Failure:, J. Pharmacol. Exp. Ther., Vol. 272, pp. 619-627, (1995).	☐
		HOWES et al., "Angiotensin receptor antagonists and ACE inhibitors", Australian Family Physician, Vol. 27, pp. 914-921, (1998).	☐
		CRISCIONE et al., "Pharmacological profile of valsartan: a potent, orally active, nonpeptide antagonists of the angiotensin II AT-receptor sybtype", Br. J. Pharmacol., Vol. 110, pp. 761-771, (1993).	☐
		Abstract of J. Pharmacol. Exp., Ther., Vol. 265, pp. 1339-1347, (1993).	☐
		Search dated May 29, 2008 (26 pages) cited by opponent Mundipharma GMBH on June 26, 2008, submitted in corresponding EP application 03704413.8	☐
		Search dated May 29, 2008 (3 pages) cited by opponent Mundipharma GMBH on June 26, 2008, submitted in corresponding EP application 03704413.8	☐
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Examiner Signature	/Jennifer Kim/	Date Considered	09/30/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw a line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant.
[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.
This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.K./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER M KIM	1617

SEARCHED			
Class	Subclass	Date	Examiner
514	533, 381	7/29/2009	jmk
	Updated	2/22/2010	jmk
	Updated	9/30/2010	jmk

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search; STN; parent 10/341,868	7/29/2009	jmk
Updated	2/22/2010	jmk
Updated	9/30/2010	jmk

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER M KIM	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/17/2009	07/28/2009	02/22/2010	09/30/2010					
	1	÷	✓	-	-					
	2	÷	✓	-	-					
	3	÷	✓	-	-					
	4	÷	✓	-	-					
	5	÷	N	-	-					
	6	÷	N	-	-					
	7	÷	N	-	-					
	8	÷	✓	-	-					
	9	÷	✓	-	-					
	10	÷	✓	-	-					
	11	÷	✓	-	-					
	12		✓	-	-					
	13		✓	-	-					
	14			✓	✓					
	15			✓	✓					
	16			✓	✓					
	17			✓	✓					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Ksander, Gary. M. et al.
APPLICATION NO: 12/147,570
FILED: June 27, 2008
FOR: Method of Treatment and Pharmaceutical Composition

Art Unit: 1617
Examiner: Kim, Jennifer M.

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply is submitted in response to the Non-Final Office Action mailed October 4, 2010. Reconsideration of the present rejections and withdrawal of the present rejections are respectfully requested.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

Listing of Claims:

Claims 1-13 (cancelled)

14. (Previously presented): A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof;

(ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable carrier;

wherein said (i) AT 1-antagonist valsartan or pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof, are administered in combination in about a 1:1 ratio.

15. (Previously presented): The pharmaceutical composition of claim 14, wherein said (i) AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof are administered in amounts effective to treat hypertension or heart failure.

16. (Previously presented): The pharmaceutical composition of claim 14 wherein (ii) said NEP inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

17. (Previously presented): The pharmaceutical composition of claim 16 in the form of a capsule or tablet.

Remarks/Arguments

Reconsideration of this application, is respectfully requested. Claims 14-17 were pending in the present application. Accordingly, claims 14-17 remain pending in the application. A petition for a three-month extension of time is enclosed herewith.

Rejection under 35 U.S.C. § 112, 1st paragraph

Claims 14-17 were rejected under 35 U.S.C. § 112, first paragraph as not complying with the written description requirement. Applicants disagree. Applicants again point out that support for claims 14-17 having the specified AT 1-antagonist and the specified NEP inhibitor in about a 1:1 ratio can be found in Applicants' specification on page 9; page 14, and page 16 paragraphs two, three and four from the bottom, i.e. 20 mg. Applicants claimed ratio of 1:1 is an exemplary embodiment, which is fully supported (**MPEP § 2100**, emphasis added) and allows Applicants the full scope to which they are entitled under Section 112. Further, Applicants point out that no new matter was added.

Rejections under 35 U.S.C. § 103(a)

Claims 14-17 stand rejected as unpatentable under 35 U.S.C. 103(a) over U.S. Patent No. 5,217,996 (Ksander reference) in view of U.S. Patent No. 5,399,578 (Buhlmayer et al., reference) of record. Applicants disagree. The Office concedes that claimed invention differs from the cited references in claiming a pharmaceutical composition comprising a combination of the specific NEP inhibitor and valsartan. The Office has not met its burden under Section 103 to specifically point out how Applicants specific NEP inhibitor and its combination with valsartan is obvious over the prior art of record. Applicants again point out that Ksander teaches, in Example 8, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester sodium salt and Buhlmayer et al. teach valsartan. First, Ksander however fails to teach or suggest a pharmaceutical composition comprising, *inter alia*:

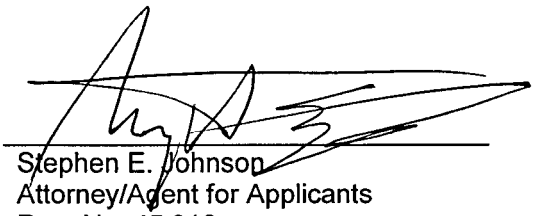
(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof.

Ksander also fails to teach or suggest a pharmaceutical composition wherein the (i) AT 1-antagonist valsartan or pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof, are administered in combination in about a 1:1 ratio. The Examiner maintains that the employment of the specific NEP inhibitor and valsartan would

have been obvious because all the components are well known for treating hypertension and one of ordinary skill in the art would have been motivated to combine said specific components to treat hypertension. This rejection cannot stand, however, because Applicants have already overcome the *prima facie* case for obviousness, as demonstrated by the issuance of U.S. Patent 7,468,390 ('390 patent) to Ksander et al. During the prosecution of the '390 patent, Applicants presented experimental data showing that the combination of valsartan and the specific NEP inhibitor (AHU377) had a synergistic, unexpected and surprising antihypertensive effect which was not taught or obvious from the cited prior art of US Patent 5,217,996 to Ksander and US Patent 5,399,578 to Buhlmayer et al. See Reasons for Allowance in the '309 patent. For the reasons set forth hereinabove, Applicants respectfully maintain that their claimed pharmaceutical composition is novel and non-obvious over Ksander and Buhlmayer et al., and withdrawal of this ground of rejection under 35 USC 103 is again respectfully requested.

In view of the foregoing remarks and amendments, it is firmly believed that claims 14-17 of the present application are in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
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Stephen E. Johnson
Attorney/Agent for Applicants
Reg. No. 45,916

Date: April 4, 2011

Electronic Patent Application Fee Transmittal

Application Number:	12147570
Filing Date:	27-Jun-2008
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Stephen E. Johnson
Attorney Docket Number:	32219-US-DIV

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1110**

Electronic Acknowledgement Receipt

EFS ID:	9801425
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	01095
Filer:	Stephen E. Johnson
Filer Authorized By:	
Attorney Docket Number:	32219-US-DIV
Receipt Date:	04-APR-2011
Filing Date:	27-JUN-2008
Time Stamp:	14:30:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1110
RAM confirmation Number	732
Deposit Account	190134
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219-US-DIV.pdf	169754 181accefa5e08d5892f576cb67f77b5a417c3d8d	yes	5

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Extension of Time	1	1
Amendment/Req. Reconsideration-After Non-Final Reject	2	2
Claims	3	3
Applicant Arguments/Remarks Made in an Amendment	4	5

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	30376 0b328184ebc4c1da7b01add8c891e41cce467d47	no	2

Warnings:

Information:

Total Files Size (in bytes):	200130

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CASE PAT032219-US-DIV

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Webb, Randy Lee et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1628
Examiner: Kim, Jennifer M

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Sir:

The Office Action of October 4, 2010 has a shortened statutory time set to expire on January 4, 2011. A three-month extension is hereby requested pursuant to 37 CFR §1.136(a).

Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $1110 for payment of the extension fee. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-1422

Stephen E. Johnson
Attorney/Agent for Applicant
Reg. No. 45,916

Date: April 4, 2011

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/147,570	06/27/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 04/04/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 4	Minus	** 20	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 1	Minus	***5	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/PARTHENIA MERRILL/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

1095 7590 06/09/2011

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1628	

MAIL DATE	DELIVERY MODE
06/09/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	12/147,570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER M. KIM	1628

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER M KIM	1617

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/17/2009	07/28/2009	02/22/2010	09/30/2010	06/07/2011				
	1	÷	✓	-	-	-				
	2	÷	✓	-	-	-				
	3	÷	✓	-	-	-				
	4	÷	✓	-	-	-				
	5	÷	N	-	-	-				
	6	÷	N	-	-	-				
	7	÷	N	-	-	-				
	8	÷	✓	-	-	-				
	9	÷	✓	-	-	-				
	10	÷	✓	-	-	-				
	11	÷	✓	-	-	-				
	12		✓	-	-	-				
	13		✓	-	-	-				
	14			✓	✓	✓				
	15			✓	✓	✓				
	16			✓	✓	✓				
	17			✓	✓	✓				

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER M KIM	1617

SEARCHED			
Class	Subclass	Date	Examiner
514	533, 381	7/29/2009	jmk
	Updated	2/22/2010	jmk
	Updated	9/30/2010	jmk

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search; STN; parent 10/341,868	7/29/2009	jmk
Updated	2/22/2010	jmk
Updated	9/30/2010	jmk

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

DETAILED ACTION

The amendment filed on April 4, 2011 have been received and entered into the application.

Response to Arguments

Applicant's arguments with respect to claims 14-17 have been considered and are persuasive. Upon further consideration, the new ground(s) of rejection is made in this Office Action. A telephone call was made to an attorney of record, Mr. Johnson to accelerate the prosecution of instant Application. However, it did not result in a decision. Accordingly, this Office Action is made non-final.

Priority

This application discloses and claims only subject matter disclosed in prior Application No. 10/341,868, filed January 14, 2003, now U.S.Patent No. 7,468,390 and names an inventor or inventors named in the prior application. Accordingly, this application may constitute **a continuation** or division. Applicants' amendment to the specification on June 27, 2008 indicates as a division. However, in this case, it would be proper for Applicants to file as **a continuation** because this application is not distinct or independent from the earlier or parent application of 10/341,868.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 7,468,390 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass a same subject matter comprising a pharmaceutical composition comprising the same active agents.

As such, the claims of the instant Application and the patented claims would have been obvious variations of the other to one of ordinary skill in the art.

None of the claims are allowed.

Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER M KIM/
Primary Examiner, Art Unit 1628

Jmk
June 7, 2011

CASE PAT032219-US-DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Webb, Randy Lee et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1628
Examiner: Kim, Jennifer M
Conf. No.:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

TERMINAL DISCLAIMER

Sir:

Novartis AG, a corporation having a place of business at Novartis AG, Lichtstrasse 35, 4056 Basel, SWITZERLAND, represents that it is the assignee and owner of the entire interest in the above-identified application by virtue of an assignment which was recorded in the United States Patent and Trademark Office on .

Novartis AG hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the above-identified application which would extend beyond the expiration date of the full statutory term defined in 35 USC §154 and §173, as presently shortened by any terminal disclaimer, of prior **Patent No. 7,468,390** issued December 23, 2008. Said Patent No. 7,468,390 is also assigned to Novartis AG by virtue of the same assignment.

Novartis AG hereby agrees that any patent granted on the above-identified application shall be enforceable only for and during such period that it and prior Patent No. 7,468,390 are commonly owned. This agreement runs with any patent granted on the above-identified application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, Novartis AG does not disclaim the terminal part of any patent granted on the above-identified application that would extend to the expiration date of the full statutory term as defined in 35 USC §154 and §173 of prior Patent No. 7,468,390, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent

jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR §1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

A terminal disclaimer fee under 37 CFR §1.20(d) is included.

Signed this 9th day of September, by the undersigned attorney of record.

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-1422

Stephen Johnson
for Applicant
Reg. No. 45,916

Electronic Patent Application Fee Transmittal

Application Number:	12147570
Filing Date:	27-Jun-2008
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Stephen E. Johnson/Monika van Houten
Attorney Docket Number:	32219-US-DIV

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Statutory or terminal disclaimer	1814	1	140	140
		Total in USD ($)		**140**

Electronic Acknowledgement Receipt

EFS ID:	10915040
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	01095
Filer:	Stephen E. Johnson/Monika van Houten
Filer Authorized By:	Stephen E. Johnson
Attorney Docket Number:	32219-US-DIV
Receipt Date:	09-SEP-2011
Filing Date:	27-JUN-2008
Time Stamp:	15:07:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$140
RAM confirmation Number	1689
Deposit Account	190134
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		32219-US-CNT.pdf	214886 106e6d28f4e3995f6297614b26f027b4de39dbf4	yes	8

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Specification	2	2
Claims	3	3
Applicant Arguments/Remarks Made in an Amendment	4	4
Application Data Sheet	5	6
Terminal Disclaimer Filed	7	8

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30286 a55e0e0eae02e1930c938e1ef1adae7307d6ced8	no	2

Warnings:

Information:

Total Files Size (in bytes):	245172

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Webb, Randy Lee et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1628
Examiner: Kim, Jennifer M
Conf. No.:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

This Amendment is submitted in response to the Office Action mailed June 9, 2011. Reconsideration of the present rejections and withdrawal of the present rejections are respectfully requested.

Amendments to the specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of the claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the specification:

Please replace the priority paragraph beneath the title on page 1 with the following paragraph:

This application is a continuation application of U.S. Pat. Appl. No. 10/341,868 filed on January 14, 2003 and claims benefit of U.S. Provisional Pat. Appl. No. 60/386,792, filed June 7, 2002 and U.S. Provisional Pat. Appl. No. 60/349,660, filed January 17, 2002, the entire disclosures of which are hereby incorporated by reference.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1.-13. Cancelled

14. (Previously presented) A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof;

(ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable carrier;

wherein said (i) AT 1-antagonist valsartan or pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof, are administered in combination in about a 1:1 ratio.

15. (Previously presented) The pharmaceutical composition of claim 14, wherein said (i) AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N -(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof are administered in amounts effective to treat hypertension or heart failure.

16. (Previously presented) The pharmaceutical composition of claim 14 wherein (ii) said NEP inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

17. (Previously presented) The pharmaceutical composition of claim 16 in the form of a capsule or tablet.

Remarks/Arguments

Reconsideration of this application, as amended, is respectfully requested. Claims 14-17 were pending in the present application. Applicants gratefully acknowledge allowance of claims 14-17 by the Office and the reasons set forth at page 2 of the Office Action prior to a non-statutory obviousness-type double patenting rejection. Accordingly, claims 14-17 remain pending. Applicants have corrected the pending application to a continuation application and have amended the priority statement in the specification at page 1 and submit with this Amendment a supplemental application disclosure statement.

Non-Statutory Obviousness-Type Double Patenting

Claims 14-17 were rejected as unpatentable over claims 1-3 of U.S. Pat. No. 7,468,390. Applicants traverse the rejection and submit a Terminal Disclaimer pursuant to 37 C.F.R. § 1.321, thereby obviating the Non-Statutory Obviousness-Type Double Patenting rejection. Applicants respectfully request the Office to withdraw the Non-Statutory Obviousness-Type Double Patenting rejection for claims 14-17.

CONCLUSIONS

Consideration and entry of these amendments and remarks are respectfully requested. Claims 14-17 are now in condition for allowance and Applicants respectfully request that a Notice of Allowance be issued as soon as possible. Should the Examiner have any questions, please contact the undersigned.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-1422

Stephen Johnson
for Applicant
Reg. No. 45,916

Date: September 9, 2011

INVENTOR INFORMATION

Supplemental ADS

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State or Province of Residence:: New Hampshire
Country of Residence:: United States of America
Citizenship Country:: United States of America
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Country of Residence:: United States of America
Citizenship Country:: United States of America

CORRESPONDENCE INFORMATION

Correspondence Customer Number:: 001095
Fax One:: 973-781-8064

APPLICATION INFORMATION

Title Line One:: METHODS OF TREATMENT AND PHARMACEUTICAL
Title Line Two:: COMPOSITION
Formal Drawings?:: No
Application Type:: Utility
Docket Number:: 32219-US-DIV
Secrecy Order in Parent Appl.?:: No

CONTINUITY INFORMATION

This application is a::CONTINUATION OF
> Application One:: 10/341,868
Filing Date:: 01-14-2003

Which is a:: NON PROV. OF PROVISIONAL
>> Application Two:: 60/386,792
Filing Date:: 06-07-2002

And which is a:: NON PROV. OF PROVISIONAL
>> Application Three:: 60/349,660
Filing Date:: 01-17-2002

Source:: PrintEFS Version 2.0

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/147,570	06/27/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 09/09/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 4	Minus	** 20	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 1	Minus	***5	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/JOY j. DOBBS/

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/147,570	KSANDER ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 09 SEPT 2011	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

JAB

U.S. Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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NOTICE OF ALLOWANCE AND FEE(S) DUE

1095 7590 09/23/2011

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER
KIM, JENNIFER M

ART UNIT	PAPER NUMBER
1628	

DATE MAILED: 09/23/2011

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

TITLE OF INVENTION: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	12/23/2011

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 09/23/2011

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ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

TITLE OF INVENTION: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	12/23/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
KIM, JENNIFER M	1628	514-533000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

1095 7590 09/23/2011

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1628	

DATE MAILED: 09/23/2011

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	12/147,570	KSANDER ET AL.	
	Examiner	Art Unit	
	JENNIFER M. KIM	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *9/9/2011*.
2. ☒ The allowed claim(s) is/are *14-17*.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/JENNIFER M KIM/
Primary Examiner, Art Unit 1628

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

The terminal disclaimer filed on September 9, 2011 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent No. 7,468,390 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Applicants presented the experimental data showing that the combination of valsartan and the specific NEP inhibitor (AH377) has a synergistic, unexpected and surprising antihypertensive effect in the parent Application 10/341,868 which is not taught or obvious from the cited prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is

(571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1628

Jmk
September 19, 2011

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12147570	KSANDER ET AL.
	Examiner	Art Unit
	JENNIFER M KIM	1617

SEARCHED			
Class	Subclass	Date	Examiner
514	533, 381	7/29/2009	jmk
	Updated	2/22/2010	jmk
	Updated	9/30/2010	jmk
514	563 updated	9/20/2011	jmk

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search; STN; parent 10/341,868	7/29/2009	jmk
Updated	2/22/2010	jmk
Updated	9/30/2010	jmk
Updated	9/20/2011	jmk

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
514	381, 561, 563	9/20/2011	jmk

Freeform Search

Database: US Pre-Grant Publication Full-Text Database
US Patents Full-Text Database
Unpublished Applications Full-Text Database

Search Type: Prior Art Interference

Term: (514/533.ccls. or 514/381.ccls. or 514/563.ccls.) and (valsartan).clm. and(nep).clm.

Recall Text

Display: 10 **Documents in Display Format:** - **Starting with Number** 1

Generate: Hit List Hit Count Side by Side Image

Search Clear Interrupt

Search History

DATE: Tuesday, September 20, 2011 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
Interference Searches				
DB=PGPB,USPT,UPAD; PLUR=YES; OP=OR				
L3	(514/533.ccls. or 514/381.ccls. or 514/563.ccls.) and (valsartan).clm. and(nep).clm.	15	L3	L3
L2	(514/533.ccls. or 514/381.ccls. or 514/563.ccls.) and (valsartan).clm.	195	L2	L2
L1	(514/533.ccls. or 514/381.ccls. or 514/563.ccls.) and (valsartan and (carboxy and oxyopropyl and methylbutanoic and pentanoic)).clm.	0	L1	L1

END OF SEARCH HISTORY

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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BIB DATA SHEET

CONFIRMATION NO. 7174

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/147,570	06/27/2008	514	1628	32219-US-DIV

APPLICANTS

Gary Michael Ksander, Amherst, NH;
Randy Lee Webb, Flemington, NJ;

**** CONTINUING DATA ****************************

This application is a DIV of 10/341,868 01/14/2003 PAT 7,468,390
which claims benefit of 60/386,792 06/07/2002
and claims benefit of 60/349,660 01/17/2002

**** FOREIGN APPLICATIONS ****************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

07/15/2008

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /JENNIFER M KIM/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NH	0	11	5

ADDRESS

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080
UNITED STATES

TITLE

METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

FILING FEE RECEIVED		
1450	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
12147570	KSANDER ET AL.
Examiner	**Art Unit**
JENNIFER M KIM	1628

ORIGINAL		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
514	533	A 6 1 K 31 / 235 (2006.01.01)	
		A 6 1 K 31 / 41 (2006.01.01)	
CROSS REFERENCE(S)		A 6 1 K 31 / 195 (2006.01.01)	

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	381	561	563		

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	14														
2	15														
3	16														
4	17														

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	4	
/JENNIFER M KIM/ Primary Examiner.Art Unit 1628	9/20/11	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 09/23/2011

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EAST HANOVER, NJ 07936-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	06/27/2008	Gary Michael Ksander	32219-US-DIV	7174

TITLE OF INVENTION: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	12/23/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
KIM, JENNIFER M	1628	514-533000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 **Stephen E. Johnson**

2

3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: **Novartis AG**

(B) RESIDENCE: (CITY and STATE OR COUNTRY): **Basel, Switzerland – Assignment recorded on 11/8/2011 Reel 027189, Frame 0457**

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☒ Issue Fee

☒ Publication Fee (No small entity discount permitted)

☒ Advance Order - # of Copies 10

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 190134 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date Dec. 9, 2011

Typed or printed name **Stephen E. Johnson** Registration No. **45,916**

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	12147570
Filing Date:	27-Jun-2008
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Filer:	Stephen E. Johnson/Monika Van Houten
Attorney Docket Number:	32219-US-DIV

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1740	1740
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Printed copy of patent - no color	8001	10	3	30
		Total in USD ($)		**2070**

Electronic Acknowledgement Receipt

EFS ID:	11641749
Application Number:	12147570
International Application Number:	
Confirmation Number:	7174
Title of Invention:	METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION
First Named Inventor/Applicant Name:	Gary Michael Ksander
Customer Number:	1095
Filer:	Stephen E. Johnson/Monika Van Houten
Filer Authorized By:	Stephen E. Johnson
Attorney Docket Number:	32219-US-DIV
Receipt Date:	16-DEC-2011
Filing Date:	27-JUN-2008
Time Stamp:	16:02:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2070
RAM confirmation Number	2985
Deposit Account	190134
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	32219-US-IssueFee.pdf	144570 7d1de0ba08c91d47781a4d38b5f25cd0aca6b1ba	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	33601 037447b290f7f7feae9adda031f4dade39490c29	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	178171		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/147,570	01/24/2012	8101659	32219-US-DIV	7174

1095 7590 01/04/2012

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Gary Michael Ksander, Amherst, NH;
Randy Lee Webb, Flemington, NJ;

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10	
EV724612488US Express Mail Label Number	1 September 2015 Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 8,101,659
ISSUED: January 24, 2012
INVENTORS: Gary Michael Ksander and Randy Lee Webb
FOR: Methods of Treatment and Pharmaceutical Composition

MS Hatch-Waxman PTE
Director for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C. § 156

Sir:

Pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.710 *et seq.*, Novartis Pharmaceuticals Corporation ("Applicant"), a Corporation organized under the laws of United States, hereby requests an extension, due to regulatory review, of the patent term of U.S. Patent No. 8,101,659, which was granted on January 24, 2012.

Applicant asserts that it is the owner of the entire right, title and interest in U.S. Patent No. 8,101,659 by virtue of an assignment from the inventors, Gary Michael Ksander and Randy Lee Webb, to Novartis AG and subsequent assignment from Novartis AG to Novartis Pharmaceuticals Corporation. The assignment from the inventors to Novartis AG is recorded in the U.S. Patent and Trademark Office (USPTO) at Reel 27189 Frame 457 on November 8, 2011 and the assignment from Novartis AG to Novartis Pharmaceuticals Corporation is recorded in the U.S. Patent and Trademark Office (USPTO) at Reel 26002 Frame 790 on March 23, 2011. Copies of the assignments and recordation information are attached hereto as **Appendix A.**

In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Applicant provides the following information in support of its request for a patent term extension. The following sections are numbered analogously to 37 C.F.R. § 1.740.

1. Identification of the Approved Product

The approved product is ENTRESTO™ (sacubitril and valsartan), which is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, in the form of a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively. ENTRESTO™ is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

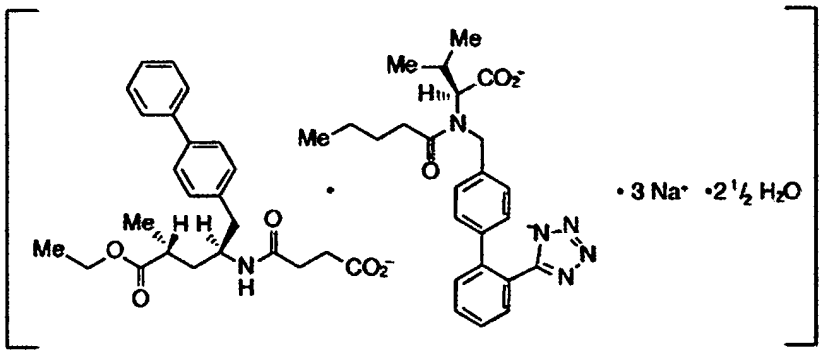
Chemical Name

The complex is chemically described as Octadecasodiumhexakis(4-{[(1S,3R)-1-([1,1′-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4oxobutanoate)hexakis(N-pentanoyl-N-{[2′-(1H-tetrazol-1-id-5-yl)[1,1′-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15).

Molecular Formula

Its empirical formula (hemipentahydrate) is $C_{48}H_{55}N_6O_8Na_3$ 2.5 H_2O. Its molecular mass is 957.99.

Structural Formula



Physical Form

ENTRESTO™ is provided as film-coated tablets for oral administration, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan.

2. Identification of the Federal Statute under which Regulatory Review Occurred

The approved product was subject to regulatory review under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355).

3. The Date of Permission for Commercial Marketing

The approved product received permission for commercial marketing under section 505 of the Federal Food, Drug and Cosmetic Act on July 7, 2015. A copy of the Food and Drug Administration (FDA) approval letter is attached hereto as **Appendix B.**

4. Active Ingredient Statement

The active ingredients in ENTRESTO™ are sacubitril and valsartan. Sacubitril, either alone or in combination with another active ingredient, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act prior to the approval of NDA No. 207620 by the United States Food and Drug Administration on July 7, 2015.

Valsartan was approved for commercial marketing both alone and in combination with other active ingredients. Valsartan capsules were approved under the trade name DIOVAN® on December 23, 1996, and valsartan tablets were approved on July 8, 2001, under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) for treatment of hypertension. On August 14, 2002, both valsartan capsules and tablets were approved for treatment of heart failure (NYHA class II-IV) in patients who are intolerant to an ACE (angiotensin converting enzyme) inhibitor. On August 3, 2005, the use of valsartan 40, 80, 160, and 320 mg tablets (DIOVAN®) was approved in the treatment of patients with post-myocardial infarction: In clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, valsartan is indicated to reduce cardiovascular mortality.

Valsartan and hydrochlorothiazide was approved under the trade name DIOVAN HCT® on March 6, 1998 under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) for treatment of hypertension.

Valsartan and amlodipine besylate tablets were approved under the trade name EXFORGE® on June 20, 2007, under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) for the treatment of hypertension.

Valsartan, amlodipine besylate and hydrochlorothiazide tablets were approved under the trade name EXFORGE HCT® on April 30, 2009, under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) for the treatment of hypertension.

5. Statement of Timely Filing

The last day on which this application could be submitted is September 4, 2015, which is 60 days beginning on the date of approval of NDA No. 207620 (July 7, 2015). This application is timely filed, because it is being submitted on or prior to September 4, 2015.

6. Identification of Patent for which Extension is Sought

This application seeks to extend the term of U.S. Patent No. 8,101,659, which issued January 24, 2012 to inventors Gary Michael Ksander and Randy Lee Webb. The term of U.S. Patent No. 8,101,659, as calculated under 35 U.S.C. § 154, would otherwise expire on January 14, 2023.

7. Patent Copy

A complete copy of U.S. Patent No. 8,101,659, identified in **section 6** above, is attached as **Appendix C.**

8. Copy of Any Disclaimer, Certificate of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate Issued in the Patent

No Reexamination certificate, no certificate of correction, and no Reissue has been issued, filed or requested with respect to U.S. Patent No. 8,101,659. A copy of a disclaimer (terminal disclaimer over U.S. Patent No. 7,468,390) is provided herewith in **Appendix D**. A copy of a receipt of the only maintenance fee payment required to date is provided herewith in **Appendix E**.

9. Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product

U.S. Patent No. 8,101,659 claims the approved product, ENTRESTO™. Claims 1-4 of U.S. Patent No. 8,101,659 read on the approved product (they recite compositions that include the approved product).

Claim 1 reads as follows:

1. A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof;

(ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable carrier;

wherein said (i) AT 1-antagonist valsartan or pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof, are administered in combination in about a 1:1 ratio.

Claim 1 reads on the approved product as follows:

As mentioned above, the approved product, ENTRESTO™, is a combination of sacubitril and valsartan. In claim 1, valsartan is explicitly recited in (i) and sacubitril is recited as N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester in (ii).

10. Statement of the Relevant Dates to Determine the Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(A) IND 77318 became effective on April 8, 2007 and IND 104628 became effective on October 31, 2009. IND 77318 was the first IND for the administration of sacubitril/valsartan for hypertension.

IND 104628 was for the administration of sacubitril/valsartan for heart failure and makes a cross reference to certain IND 77318 data such as pharmacology and toxicity information.

(B) A New Drug Application (NDA) for ENTRESTO™ was initially submitted to the FDA on December 17, 2014 with NDA No. 207620.

(C) NDA No. 207620 was approved on July 7, 2015.

11. Brief Description of Activities Undertaken During the Regulatory Review Period

As brief description of the significant activities undertaken during the applicable regulatory review period and the significant dates applicable to such activities is, attached hereto as chronologies for INDs 77318 and 104628 (**Appendix F**), and NDA 207620 (**Appendix G**).

12. Opinion of Eligibility for Extension and Statement of Length of Extension Claimed

Applicant is of the opinion that U.S. Patent No. 8,101,659 is eligible for extension under 35 U.S.C. § 156 and 37 C.F.R. § 1.720 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. § 156(a) and 37 C.F.R. § 1.720(a)

U.S. Patent No. 8,101,659 claims a product as defined in 37 C.F.R. § 1.710(b)(1).

(b) 35 U.S.C. § 156(a)(1) and 37 C.F.R. § 1.720(g)

The term of U.S. Patent No. 8,101,659 (expiring January 14, 2023) has not expired before the submission of this application.

(c) 35 U.S.C. § 156(a)(2) and 37 C.F.R. § 1.720(b)

The term of U.S. Patent No. 8,101,659 has never been extended.

(d) 35 U.S.C. § 156(a)(3) and 37 C.F.R. § 1.720(c)

The application for extension of the term of U.S. Patent No. 8,101,659 is submitted by the authorized attorney of the owner of record thereof in accordance with the requirements of 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.

(e) 35 U.S.C. § 156(a)(4) and 37 C.F.R. § 1.720(d)

The approved product, ENTRESTO™, has been subjected to a regulatory review period under 35 U.S.C. § 156(g) before its commercial marketing or use.

(f) 37 C.F.R. § 1.720(h)

No other patent term has been extended for the same regulatory review period for the approved product, ENTRESTO™.

(g) 35 U.S.C. § 156(a)(5)(A) and 37 C.F.R. § 1.720(e)(1)

The permission for the commercial marketing or use of the approved product, ENTRESTO™, is the first received permission for commercial marketing or use of

ENTRESTO™ under section 505, the provision of law under which the applicable regulatory review occurred.

12.1 Calculation of length of extension claimed under 37 C.F.R. § 1.740(a)(12)

The length of extension of the patent term of U.S. Patent No. 8,101,659 requested by Applicant is 732 days, which length was calculated in accordance with 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began April 8, 2007 (the effective date of IND No. 77318) and ended on July 7, 2015 (the date NDA No. 207620 was issued), amounting to a total of 3014 days, which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period," began on April 8, 2007 and ended on December 17, 2014, which is 2811 days;

(ii) The period for review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Application Period," began on December 17, 2014 and ended on July 7, 2015, which is 203 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in subparagraph (12.1)(a) above (3014 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (January 24, 2012), i.e., 1753 days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e., zero days, and

(iii) One-half of the number of days remaining in the period in subparagraph (12.1)(a)(i) after subtracting the number of days in subparagraphs (12.1)(b)(i) and (12.1)(b)(ii), which is one-half of (2811 - [1753 + 0]) = 529 days;

which results in a period of 3014 - [1753 + 0 + 529 days] = 732 days.

(c) The number of days as determined in subparagraph (12.1)(b) (732 days), when added to the original term (January 14, 2023), would result in the date of January 15, 2025.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (July 7, 2015) would result in the date of July 7, 2029.

(e) The earlier date as determined by subparagraphs (12.1)(c) and (12.1)(d) is January 15, 2025.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. 8,101,659 (January 14, 2023), results in the date January 14, 2028.

(g) The earlier date as determined in subparagraphs (12.1)(e) and (12.1)(f) is January 15, 2025.

13. Duty of Disclosure Acknowledgement Under 37 C.F.R. § 1.740(a)(13)

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought. Applicant hereby informs the Director that Patent Term Extension applications for United States Patent Numbers 7,468,390; 8,404,744; 8,796,331; and 8,877,938 are being concurrently filed for ENTRESTO™.

14. Fee Charge

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 19-0134 as authorized in the attached transmittal letter, submitted in triplicate.

15. Correspondence Address Required by 37 C.F.R. § 1.740(a)(15)

All correspondence relating to this application for patent term extension should be addressed to:

David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080
(862) 778-5806

Certification Under 37 C.F.R. § 1.740(b)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted as one original and two copies thereof (for a total of three copies) in accordance with 37 C.F.R. § 1.740(b).

Respectfully submitted,

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 101
East Hanover, NJ 07936-1080

David Kurlandsky
Attorney for Applicant
Reg. No. 41,505
(862) 778-5806

Date: September 1, 2015

Attachments: Appendix A-G

APPENDIX A

Assignment / Assignment Recordation

Patent Assignment Abstract of Title

Total Assignments: 2

Application #: 12147570 **Filing Dt:** 06/27/2008 **Patent #:** 8101659 **Issue Dt:** 01/24/2012

PCT #: NONE **Intl Reg #:** **Publication #:** US20080262059 **Pub Dt:** 10/23/2008

Inventors: Gary Michael Ksander, Randy Lee Webb

Title: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Assignment: 1

Reel/Frame: 027189 / 0457 **Received:** 11/08/2011 **Recorded:** 11/08/2011 **Mailed:** 11/08/2011 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: KSANDER, GARY MICHAEL **Exec Dt:** 02/20/2003

WEBB, RANDY LEE **Exec Dt:** 02/26/2003

Assignee: NOVARTIS AG
LICHTSTRASSE 35
BASEL, SWITZERLAND 4056

Correspondent: NOVARTIS PHARMACEUTICALS CORPORATION
ONE HEALTH PLAZA
BLDG. 101
EAST HANOVER, NJ 07936-1080

Assignment: 2

Reel/Frame: 026002 / 0790 **Received:** 03/23/2011 **Recorded:** 03/23/2011 **Mailed:** 03/28/2011 **Pages:** 7

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: NOVARTIS AG **Exec Dt:** 03/17/2011

Assignee: NOVARTIS PHARMACEUTICALS CORPORATION
ONE HEALTH PLAZA
EAST HANOVER, NEW JERSEY 07936

Correspondent: LINDA ADAMS
NOVARTIS PHARMACEUTICALS CORP.
ONE HEALTH PLAZA
EAST HANOVER, NJ 07936

Search Results as of: 08/13/2015 14:22:40 PM

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ASSIGNMENT

We,

Gary Michael Ksander	residing at	37 The Flume Amherst, New Hampshire 03031
Randy Lee Webb	residing at	17 Honeyman Drive Flemington, New Jersey 08822,

for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Novartis AG**, a company organized under the laws of the Swiss Confederation, having a place of business at Lichtstrasse 35, Basel, Switzerland 4056, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for the United States and its territories and possessions in and to the invention entitled:

METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

invented by us and described in the application for United States Letters Patent

Application No. 10/341,868, filed January 14, 2002,

including (1) said application for United States Letters Patent and all continuations and divisions thereof (including further continuations and divisions such as, but not limited to, continuations of continuations and divisions of continuations), (2) all United States Letters Patent which may be issued and/or granted on all such applications, (3) all applications for reissues and extensions of and reexamination certificates for all such United States Letters Patent and (4) all reissues and extensions and reexamination certificates issued for all such United States Letters Patent, the said interest being the entire ownership of said invention and all of said applications, United States Letters Patent (including reissue Letters Patent), extensions and reexamination certificates to be held and enjoyed by the said Novartis AG and its successors and assigns to the full end of the terms to which said United States Letters Patent (including reissue Letters Patent), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of said applications for United States Letters Patent (including reissue Letters Patent), extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, United States Letters Patent (including reissue Letters Patent), extensions and reexamination certificates in said assignee.

Signed this 26th day of February, 2003 by _____
Gary Michael Ksander

Signed this 26th day of February, 2003 by _____
Randy Lee Webb

ASSIGNMENT

WHEREAS, **Novartis AG**, a company organized under the laws of the Swiss Confederations, of Lichtstrasse 35, 4056 Basel, Switzerland, its successors, assigns and legal representatives (hereinafter "Assignor") is the owner of all the right, title and interest in and to the United States Patent applications listed on attached Schedule A;

WHEREAS, **Novartis Pharmaceuticals Corporation**, corporation organized under the laws of the State of Delaware, with corporate offices at One Health Plaza, East Hanover, New Jersey 07936 (hereinafter "ASSIGNEE") desires to acquire said interest of Assignor in said inventions and patent application and **Novartis AG** is willing to assign its interest therein to **Novartis Pharmaceuticals Corporation;**

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, Assignor, acting through its legal representatives, all right, title and interest in said inventions and patent application and any divisions, reissues, continuations, continuations-in-part, and extensions thereof, for the United States and its territorial possessions, the same to be held and enjoyed by the Assignee for its use and enjoyment, and for the use and enjoyment of its successors, assigns or other legal representatives, as fully and entirely as the same would have been held and enjoyed by the Assignor, if this assignment and sale had not be made.

IN WITNESS WHEREOF, Assignor has caused this Assignment to be duly executed this 17 th day of March, 2011.

NOVARTIS AG

_____ L.S.
Name: Peter J. Waibel
Title: Head, U.S. Patent Litigation
Duly Authorized Signatory

_____ L.S.
Name: Joseph T. Majka
Title: Duly Authorized Signatory
Patent Attorney

Schedule A
DIOVAN / EXFORGE
Novartis AG

Patent No.	Date of Issuance	Docket No.
6,071,931	06/06/2000	PAT020595-US-PCT
6174910	02/18/1997	PAT020753-US-PCT
6485745	11/26/2002	PAT020921-US-CNT
6858228	02/22/2005	PAT020921-US-CNT02
6294197	09/25/2001	PAT020921-US-PCT
6395728	05/28/2002	PAT030560-US-DIV
6204281	03/20/2001	PAT030560-US-NP02
6465502	10/15/2002	PAT030755-US-NP
6211217	03/16/1999	PAT030863-US-NP
7687528	03/30/2010	PAT031559-US-CNT
7,468,390	12/23/2008	PAT032219-US-NP
6869970	03/22/2005	PAT032345-US-NP
7700784	04/20/2010	PAT033615-US-PCT
7728024	06/01/2010	PAT034353-US-PCT

Application No.	Date of Filing	Docket No.
11/208131	08/19/2005	PAT020921-US-REI
12/237439	09/25/2008	PAT030755-US-CNT
10/072516	02/06/2002	PAT030755-US-DIV
12/828751	07/01/2010	PAT031488-US-CNT02
12/186172	08/05/2008	PAT031525-US-CNT02
12/705655	02/15/2010	PAT031559-US-PCTD02

Schedule A
DIOVAN / EXFORGE
Novartis AG

12/147570	06/27/2008	PAT032219-US-DIV
11/013111	12/15/2004	PAT032345-US-DIV
12/363926	02/02/2009	PAT032492-US-CNT
12/188604	08/08/2008	PAT032494-US-CNT
12/338066	12/18/2008	PAT032495-US-CNT
12/815704	06/15/10	PAT032676-US-CNT02
12/341669	12/22/2008	PAT033204-US-CNT
10/564337	07/15/2004	PAT033277-US-PCT
12/764571	04/21/2010	PAT033421-US-CNT
12/715477	03/02/2010	PAT033615-US-PCTD
11/416260	05/02/2006	PAT034254-US-NP
12/852542	08/09/2010	PAT034458-US-CNT
11/722360	11/08/2006	PAT034579-US-PCT
12/159742	12/28/2006	PAT034758-US-PCT
11/915096	11/20/2007	PAT050004-US-PCT
12/438798	09/11/2007	PAT050353-US-PCT
12/377949	08/29/2007	PAT050383-US-PCT
12/522767	01/10/2008	PAT050481-US-PCT
12/517105	12/03/2007	PAT050535-US-PCT
12/919165	02/27/2009	PAT052275-US-PCT

12/681657	10/07/2008	PAT052278-US-PCT
12/741251	11/04/2008	PAT052325-US-PCT
12/863213	01/16/2009	PAT052466-US-PCT

APPENDIX B

FDA Approval Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207620

NDA APPROVAL

Novartis Pharmaceuticals Corp.
Attention: Masha Berkhin, PharmD
Global Program Regulatory Director
One Health Plaza
Building 100
East Hanover, NJ 07936

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) dated December 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ENTRESTO (sacubitril/valsartan) Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg.

We acknowledge receipt of your amendments dated January 15, 16 (two), 20, 22, 28 (two), 30, February 2, 5, 11, 18, 20, 24, 26, March 3, 10, 12, 13, 17, April 2, 3, 8, 15 (two), 16, 20, 21, 24, 29, May 1, 4, 6, 7, 13, 15 (two), 22, 26, June 2, 3, 4, 11, 12, 15, 19, 25, 26, and July 1, 2, and 6, 2015.

This new drug application provides for the use of ENTRESTO (sacubitril/valsartan) Tablets, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an angiotensin converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

In addition, the revised comparability protocols for 1) drug product manufacturing site, control, batch size, and process and 2) (b)(4) intermediate manufacturing site, control, batch size, and process as included in Submission 0000 dated September 30, 2014 are approved. Regulatory notification of changes to the approved protocols must be made via a prior approval supplement.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content

of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 11, 2015, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for ENTRESTO was not referred to an FDA advisory committee because:

- The safety profile is acceptable for ENTRESTO to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

  ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.
- The application did not raise significant safety or efficacy issues that were unexpected for a drug of these classes
- The application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease
- Outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. The causes and mechanisms of heart failure are different in children compared to adults. Heart failure in children is most commonly caused by congenital heart malformations and cardiomyopathy whereas the primary etiology of adult heart failure is ischemic heart disease due to atherosclerotic coronary artery disease. The form of heart failure seen in adults is rare in children; hence conducting a trial is highly impractical.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of angioedema in Black patients or to identify an unexpected serious risk of cognitive dysfunction with the use of Entresto (sacubitril/valsartan).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess or identify these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2924-1 Conduct an epidemiologic study using claims or electronic health records data to evaluate the incidence of angioedema in Black patients treated with Entresto compared to a control drug. A target sample size, supported by sample size calculation, should be included in the protocol.

The timetable you submitted on June 19, 2015, states that you will conduct this study according to the following schedule:

Draft Protocol Submission	December 2015
Final Protocol submission	July 2016
Interim Report #1	July 2017
Interim Report #2	July 2018
Final Report Submission:	July 2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the unexpected serious risks of cognitive dysfunction with the use of Entresto (sacubitril/valsartan).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2924-2 A multicenter, randomized, double-blind, active-controlled trial to evaluate the effects of Entresto compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and PET imaging in patients with chronic heart failure with preserved ejection fraction.

The timetable you submitted on July 6, 2015, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission	November 2015
Final Protocol submission	April 2016
Trial Completion	October 2021
Final Report Submission:	March 2022

Submit the protocols to your IND 104628, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2924-3 Development of a new dissolution method for all the strengths with demonstrated discriminating ability, [(b)(4)], and setting of the final dissolution acceptance criterion for Entresto™ (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg using the new dissolution method and data from the overall multipoint dissolution profile from a minimum of 12 commercial batches per strength, manufactured under the same conditions as those used for the manufacture of the batches used in pivotal clinical trials. The FDA will be open to providing feedback during the method's development process as needed.

The timetable you submitted on June 25, 2015, states that you will conduct this study according to the following schedule:

Dissolution Method Development Report Submission:	February 2016
Final Report Submission:	July 2016

Submit clinical protocols to your IND 104628 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol,**" "**Postmarketing Commitment Final Report,**" or "**Postmarketing Commitment Correspondence.**"

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, please call:

Alexis Childers, RAC
Senior Regulatory Project Manager
(301) 796-0442

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
07/07/2015

APPENDIX C

Copy of 8101659 Patent

US008101659B2

(12) **United States Patent**
Ksander et al.

(10) **Patent No.: US 8,101,659 B2**
(45) **Date of Patent: Jan. 24, 2012**

(54) **METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Gary M Ksander**, Amherst, NH (US); **Randy L Webb**, Flemington, NJ (US)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/147,570**

(22) Filed: **Jun. 27, 2008**

(65) **Prior Publication Data**

US 2008/0262059 A1 Oct. 23, 2008

Related U.S. Application Data

(62) Division of application No. 10/341,868, filed on Jan. 14, 2003, now Pat. No. 7,468,390.

(60) Provisional application No. 60/386,792, filed on Jun. 7, 2002, provisional application No. 60/349,660, filed on Jan. 17, 2002.

(51) **Int. Cl.**
A61K 31/235 (2006.01)
A61K 31/41 (2006.01)
A61K 31/195 (2006.01)

(52) **U.S. Cl.** **514/533**; 514/381; 514/561; 514/563

(58) **Field of Classification Search** 514/533, 514/381, 563

See application file for complete search history.

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Primary Examiner — Jennifer M Kim

(74) *Attorney, Agent, or Firm* - Stephen E. Johnson

(57) **ABSTRACT**

The invention relates a pharmaceutical composition comprising a combination of:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier and to a method for the treatment or prevention of a condition or disease

selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke, comprising administering a therapeutically effective amount of the pharmaceutical composition to a mammal in need thereof.

4 Claims, No Drawings

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Search dated May 29, 2008 (3 pages) cited by opponent Mundipharma GMBH on Jun. 26, 2008, submitted in corresponding EP application 03704413.8.

METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

This application is a continuation application of U.S. patent application Ser. No. 10/341,868 filed on Jan. 14, 2003 and claims benefit of U.S. Provisional Pat. Appl. No. 60/386,792, filed Jun. 7, 2002 and U.S. Provisional Pat. Appl. No. 60/349,660, filed Jan. 17, 2002, the entire disclosures of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

The renin angiotensin system is a complex hormonal system comprised of a large molecular weight precursor, angiotensinogen, two processing enzymes, renin and angiotensin converting enzyme (ACE), and the vasoactive mediator angiotensin II (Ang II). See *J. Cardiovasc. Pharmacol.*, Vol. 15, Suppl. B, pp. S1-S5 (1990). The enzyme renin catalyzes the cleavage of angiotensinogen into the decapeptide angiotensin I, which has minimal biological activity on its own and is converted into the active octapeptide Ang II by ACE. Ang II has multiple biological actions on the cardiovascular system, including vasoconstriction, activation of the sympathetic nervous system, stimulation of aldosterone production, antinatriuresis, stimulation of vascular growth and stimulation of cardiac growth. Ang II functions as a pressor hormone and is involved the pathophysiology of several forms of hypertension.

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 epinephrine and norepinephrine, as well as the increase of the activity of the sympathetic nervous system as a result of the formation of norepinephrine. Ang II also has an influence on electrolyte balance, produces, e.g., anti-natriuretic and anti-diuretic 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. Ang II is also involved in cell growth and migration and in extracellular matrix formation.

Ang II interacts with specific receptors on the surface of the target cell. It has been possible to identify receptor subtypes that 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 Ang II antagonists. Because of the inhibition of the AT 1-receptor such antagonists can be used, e.g., as anti-hypertensive's or for the treatment of congestive heart failure, among other indications. Ang II antagonists are therefore understood to be those active ingredients which bind to the AT 1-receptor subtype.

Inhibitors of the renin angiotensin system are well-known drugs that lower blood pressure and exert beneficial actions in hypertension and in congestive heart failure as described. See, e.g, *N. Eng. J. Med., Vol.* 316, No. 23, pp. 1429-1435 (1987). A large number of peptide and non-peptide inhibitors of the renin angiotensin system are known, the most widely studied being the ACE inhibitors, which includes the drugs captopril, enalapril, lisinopril, benazepril and spirapril. Although a major mode of action of ACE inhibitors involves prevention of formation of the vasoconstrictor peptide Ang II, it has been reported in *Hypertension*, Vol. 16, No. 4, pp. 363-370 (1990), that ACE cleaves a variety of peptide substrates, including the vasoactive peptides bradykinin and substance P. Prevention of the degradation of bradykinin by ACE inhibitors has been demonstrated, and the activity of the ACE inhibitors in some conditions has been reported in *Circ. Res.*, Vol. 66, No. 1, pp. 242-248 (1990), to be mediated by elevation of bradykinin levels rather than inhibition of Ang II formation. Consequently, it cannot be presumed that the effect of an ACE inhibitor is due solely to prevention of angiotensin formation and subsequent inhibition of the renin angiotensin system.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino terminal side of aromatic amino acids. See *Biochem. J.*, Vol. 241, pp. 237-247 (1987). Substrates for this enzyme include, but are not limited to, atrial natriuretic factors (ANFs), also known as ANPs, brain natriuretic peptide (BNP), met and leu enkephalin, bradykinin, neurokinin A and substance P.

ANPs are a family of vasodilator, diuretic and anti-hypertensive peptides which have been the subject of many recent reports in the literature. See, e.g., *Annu. Rev. Pharm. Tox.*, Vol. 29, pp. 23-54 (1989). One form, ANF 99-126, is a circulating peptide hormone which is released from the heart during conditions of cardiac distension. The function of ANF is to maintain salt and water homeostasis, as well as to regulate blood pressure. ANF is rapidly inactivated in the circulation by at least two processes: a receptor-mediated clearance reported in *Am. J. Physiol.*, Vol. 256, pp. R469-R475 (1989), and an enzymatic inactivation via NEP reported in *Biochem. J.*, Vol. 243, pp. 183-187 (1987). It has been previously demonstrated that inhibitors of NEP potentiate the hypotensive, diuretic, natriuretic and plasma ANF responses to pharmacological injection of ANF in experimental animals. The potentiation of ANF by two specific NEP inhibitors is reported by Sybertz et al., *J. Pharmacol. Exp. Ther.*, Vol. 250, No. 2, pp. 624-631 (1989), and in *Hypertension*, Vol. 15, No. 2, pp. 152-161 (1990), while the potentiation of ANF by NEP in general was disclosed in U.S. Pat. No. 4,749,688. In U.S. Pat. No. 4,740,499, Olins disclosed the use of thiorphan and kelatorphan to potentiate atrial peptides. Moreover, NEP inhibitors lower blood pressure and exert ANF-like effects, such as diuresis and increased cyclic guanosine 3',5'-monophosphate (cGMP) excretion in some forms of experimental hypertension. The anti-hypertensive action of NEP inhibitors is mediated through ANF because antibodies to ANF will neutralize the reduction in blood pressure.

Darrow et al. in European Patent Application No. 498361 disclose treating hypertension or congestive heart failure with a combination of certain Ang II antagonists or certain renin inhibitors with certain NEP inhibitors.

Powell et al. in European Patent Application No. 726072 disclose treating hypertension or congestive heart failure with a combination of the Ang II antagonist 2-butyl-6,7,8,9-tetrahydro-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]nonan-4-one with a NEP inhibitor or a dual acting vasopeptidase inhibitor (single molecular entity with both ACE and NEP inhibitory activities). Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of anti-hypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just

considering any combination of drugs having different mode of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for more efficacious combination therapy which has less deleterious side effects.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

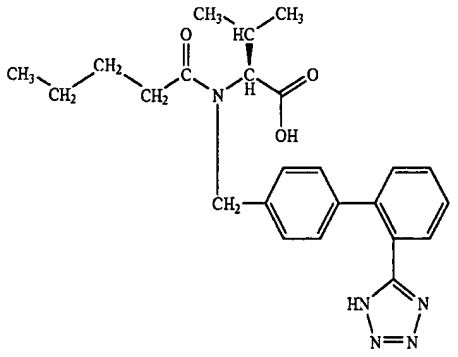
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one aspect, the present invention relates to pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a NEP inhibitor or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.

In another embodiment, the present invention relates to methods of treating cardiac and renal related conditions by administration of the pharmaceutical composition comprising valsartan plus a NEP inhibitor.

Valsartan is the AT 1-receptor antagonist (S)—N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2; (1H tetrazol 5-yl)biphenyl-4-yl-methyl]amine of formula (I)

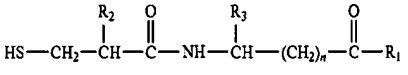
(I)



and is disclosed in EP 0443983 Å and U.S. Pat. No. 5,399,578, the disclosures of which are incorporated herein in their entirety as if set forth herein.

A NEP inhibitor useful in said combination is a compound of the formula (II)

(II)



and pharmaceutically acceptable salts thereof,
wherein

R_2 is alkyl of 1 to 7 carbons, trifluoromethyl, phenyl, substituted phenyl, —$(CH_2)_{1\ to\ 4}$-phenyl, or —$(CH_2)_{1\ to\ 4}$-substituted phenyl;

R_3 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, —$(CH_2)_{1\ to\ 4}$-phenyl, or —$(CH_2)_{1\ to\ 4}$-substituted phenyl;

R_1 is hydroxy, alkoxy of 1 to 7 carbons, or NH_2;

n is an integer from 1 to 15; and

the term substituted phenyl refers to a substituent selected from lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, hydroxy, Cl, Br or F.

Preferred selective NEP inhibitors of formula (II) include compounds, wherein

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1 to 9; and

R_1 is hydroxy.

Even more preferred selective NEP inhibitors of formula (II) are reported in the literature as SQ 28,603 which is the compound of formula (II),
wherein

R_2 is benzyl;

R_3 is hydrogen;

n is one; and

R_1 is hydroxy.

The preparation of the selective NEP inhibitors of formula (II), wherein R_2 is other than trifluoromethyl are disclosed by Delaney et al. in U.S. Pat. No. 4,722,810. The preparation of the selective NEP inhibitors of formula (II), wherein R_2 is trifluoromethyl are disclosed by Delaney et al. in U.S. Pat. No. 5,223,516.

NEP inhibitors within the scope of the present invention include compounds disclosed in U.S. Pat. No. 4,610,816, herein incorporated by reference, including in particular N—[N-[1(S)-carboxyl-3-phenylproplyl]-(S)-phenylalanyl]-(S)-isoserine and N—[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine; compounds disclosed in U.S. Pat. No. 4,929,641, in particular, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; SQ 28603 (N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]-β-alanine), disclosed in South African Patent Application No. 84/0670; UK 69578 (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid) and its active enantiomer(s); thiorphan and its enantiomers; retro-thiorphan; phosphoramidon; and SQ 29072 (7-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]-heptanoic acid). Also suitable for use are any pro-drug forms of the above-listed NEP inhibitors, e.g., compounds in which one or more carboxylic acid groups are esterified.

NEP inhibitors within the scope of the present invention also include the compounds disclosed in U.S. Pat. No. 5,217,996, particularly, N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester; the compounds disclosed in EP 00342850, particularly, (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxy-ethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; the compounds disclosed in GB 02218983, particularly, 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; the compounds disclosed in WO 92/14706, particularly, N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; the compounds disclosed in EP 00343911; the compounds disclosed in JP 06234754; the compounds disclosed in EP 00361365, particularly, 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; the compounds disclosed in WO 90/09374, particularly, 3-[(1-(cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carboamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)pro-

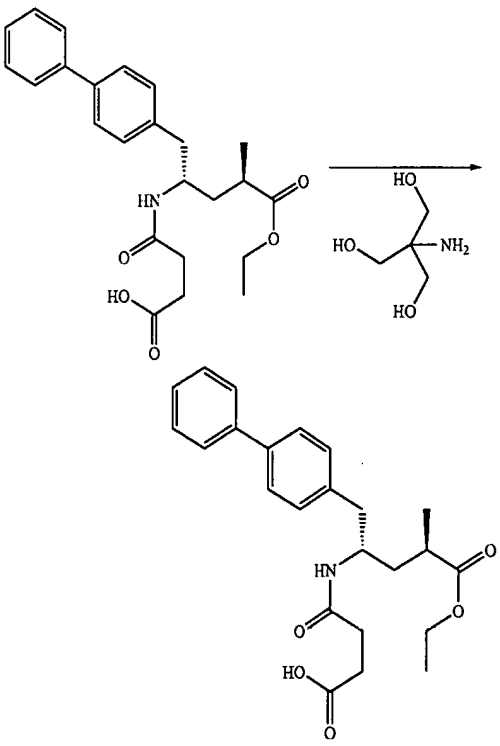
panoic acid; the compounds disclosed in JP 07157459, particularly, N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; the compounds disclosed in WO 94/15908, particularly, N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; the compounds disclosed in U.S. Pat. No. 5,273,990, particularly, (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid; the compounds disclosed in U.S. Pat. No. 5,294,632, particularly, (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; the compounds disclosed in U.S. Pat. No. 5,250,522, particularly, β-Alanine, 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; the compounds disclosed in EP 00636621, particularly, N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; the compounds disclosed in WO 93/09101, particularly, 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; the compounds disclosed in EP 00590442, particularly, ((L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine, N—[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N—[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine, N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester, N-[2-mercaptomethyl-3-(2-methylphenyl)propioyl]-methionine, N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine, N—(S)-[3-mercapto-2-(2-methylphenyl) propionyl]-(S)-2-methoxy-(R)-alanine, N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino] cyclopentylcarbonyl](S)-isoserine, N-[1-[[1(S)-carbonyl-3-phenylpropy]amino]-cyclopentylcarbonyl]-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine, 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine, N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine, N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid, N-[1-(2-carboxy-4-phenylbutyl)-cyclopentanecarbonyl]-(S)-isoserine, N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester, 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl] amino-ε-caprolactam; and the compounds disclosed in WO 93/10773, particularly, N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group, for example, COOH, can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound comprises, e.g., both a carboxy and an amino group.

With respect to N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, preferred salts include the sodium salt disclosed in U.S. Pat. No. 5,217,996, the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt. Preparation of the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt may be carried out as follows:

Triethanolamine

To N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (349 mg, 0.848 mmol) is added 5 mL of ethyl ether and 0.113 mL (0.848 mmol) of triethanolamine in 1 mL of ethyl acetate. The solid was collected and dried melting at 69-71° C.



Tris(hydroxymethyl)aminomethane

To N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (3.2 g, 7.78 mmol) is added 32 mL of ethyl acetate and 940 mg (7.78 mmol) tris(hydroxymethyl)aminomethane. The suspension is diluted with 45 mL of ethyl acetate and refluxed overnight (~20 hours). The reaction is cooled to 0° C., filtered, solid washed with ethyl acetate and dried melting at 114-115° C.

It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days).

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects. The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof results in a significant response in a greater percentage of treated patients, that is, a greater responder rate results, regardless of the underlying etiology of the condition. This is in accordance with the desires and requirements of the patients to be treated.

It can be shown that combination therapy with valsartan and a NEP inhibitor results in a more effective anti-hypertensive therapy (whether for malignant, essential, reno-vascular,

diabetic, isolated systolic or other secondary type of hypertension) through improved efficacy, as well as a greater responder rate. The combination is also useful in the treatment or prevention of heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling. It can further be shown that a valsartan and NEP inhibitor therapy proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A valsartan plus NEP inhibitor combination is also useful in treating atherosclerosis, angina (whether stable or unstable), and renal insufficiency (diabetic and non-diabetic). Furthermore, combination therapy using valsartan and a NEP inhibitor can improve endothelial dysfunction, thereby providing benefit in diseases in which normal endothelial function is disrupted, such as heart failure, angina pectoris and diabetes. Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's; glaucoma and stroke.

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

Representative studies are carried out with a combination of valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester, e.g., applying the following methodology:

Drug efficacy is assessed in various animal models including the deoxycorticosterone acetate-salt (DOCA-salt) rat and the spontaneously hypertensive rat (SHR), either maintained on a normal salt diet or with salt loading (4-8% salt in rat chow or 1% NaCl as drinking water).

The DOCA-salt test model utilizes either an acute or chronic study protocol. An acute study procedure involves assessment of the effects of various test substances over a six-hour experimental period using rats with indwelling femoral arterial and venous catheters. The acute study procedure evaluates test substances for their ability to reduce blood pressure during the established phase of DOCA-salt hypertension. In contrast, the chronic study procedure assesses the ability of test substances to prevent or delay the rise in blood pressure during the development phase of DOCA-salt hypertension. Therefore, blood pressure will be monitored in the chronic study procedure by means of a radiotransmitter. The radiotransmitter is surgically implanted into the abdominal aorta of rats, prior to the initiation of DOCA-salt treatment and thus, prior to the induction of hypertension. Blood pressure is chronically monitored for periods of up to six weeks (approximately one week prior to DOCA-salt administration and for five weeks thereafter).

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

Acute Study Procedure:

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

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

Forty-eight hours prior to experimentation, animals are anesthetized with isoflurane and catheters are implanted in the femoral artery and vein for measuring arterial pressure, collection of blood and administration of test compounds. Rats are allowed to recover for 48 hours while tethered in a Plexiglas home cage, which also serves as the experimental chamber.

Chronic Study Procedure:

This procedure is the same as above except that rats are implanted with a radiotransmitter, 7-10 days prior to the unilateral nephrectomy and initiation of DOCA and salt. In addition, rats do not undergo surgery for placement of femoral arterial and venous catheters. Radiotransmitters are implanted as described in Bazil et al., "Telemetric Monitoring of Cardiovascular Parameters in Conscious Spontaneously Hypertensive Rats", *J. Cardiovasc. Pharmacol.*, Vol. 22, pp. 897-905 (1993).

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

Blood pressure, heart rate and activity are determined at various pre-selected time points before, during and after drug administration. All measurements are performed in unrestrained and undisturbed animals. The maximum study time, determined by battery life, could be as long as nine months. For studies of this duration, rats are dosed orally (1-3 mL/kg vehicle), no more than twice daily or drug is administered via the drinking water or mixed with food. For studies of a shorter duration, that is, up to eight weeks, drugs are given via s.c. implanted osmotic minipumps. Osmotic minipumps are selected based on drug delivery rate and time. Valsartan dosages range from 1-10 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester range from 10-50 mg/kg/day.

Additionally, SHRs are utilized to study the effects of valsartan in combination with N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester. The hypertensive background of the SHR is modified either by chronic salt loading in an effort to suppress the renin angiotensin system (RAS) or chronic salt depletion to activate the RAS in the SHR. These manipulations will be carried out to more extensively evaluate the efficacy of the

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

In addition to the cardiovascular parameters, weekly determinations of body weight also are recorded in all rats. Treatments are administered in the drinking water, via daily oral gavage or in osmotic minipumps as stated above. If given in drinking water, water consumption is measured five times per week. Valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester doses for individual rats are then calculated based on water consumption for each rat, the concentration of drug substance in the drinking water and individual body weights. All drug solutions in the drinking water are made up fresh every three to four days. Typical dosages for valsartan in drinking water range from 3-30 mg/kg/day whereas the dosage of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is highly dependent upon the specific agent used. In most situations, a daily dose will not exceed 50 mg/kg/day when administered as the monotherapy. In combination, lower dosages of each agent are used and correspondingly, valsartan is given in the range of 1-30 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester in dosages below 50 mg/kg/day. However, in cases wherein the responder rate is increased with combination treatment, the dosages are identical to those used as monotherapy.

When drugs are administered by oral gavage, the dose of valsartan ranges from 1-50 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R methylbutanoic acid ethyl ester does not exceed 100 mg/kg/day.

Upon completion of the chronic studies, SHR or DOCA-salt rats are anesthetized and the heart rapidly removed. After separation and removal of the atrial appendages, left ventricle and left plus right ventricle (total) are weighed and recorded. Left ventricular and total ventricular mass are then normalized to body weight and reported. All values reported for blood pressure and cardiac mass represent the group mean±sem.

Vascular function and structure are evaluated after treatment to assess the beneficial effects of the combination. SHR are studied according to the methods described by Intengan et al., *Circulation*, Vol. 100, No. 22, pp. 2267-2275 (1999). Similarly, the methodology for assessing vascular function in DOCA-salt rats is described in Intengan et al., *Hypertension, Vol.* 34, No. 4, Part 2, pp. 907-913 (1999).

The available results indicate an unexpected therapeutic effect of a combination according to the invention.

In one aspect is the object of this invention to provide a pharmaceutical combination composition, e.g., for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke which composition comprises:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In this composition, components (i) and (ii) can be obtained and administered together, one after the other or separately in one combined unit dose form or in two separate unit dose forms. The unit dose form may also be a fixed combination.

A further aspect of the present invention is a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure, such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, such as Alzheimer's, glaucoma and stroke, comprising administering a therapeutically effective amount of combination of:

(i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof; and

(ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

A therapeutically effective amount of each of the component of the combination of the present invention may be administered simultaneously or sequentially and in any order.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the

pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

The typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by sugars, such as lactose, sucrose, mannitol and sorbitol; starches, such as cornstarch, tapioca starch and potato starch; cellulose and derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates, such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates, such as magnesium stearate and calcium stearate; stearic acid; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; betacyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents and the like commonly used in pharmaceutical formulations.

The invention also relates to combining separate pharmaceutical compositions in kit form. That is a kit combining two separate units: a valsartan pharmaceutical composition and a NEP inhibitor pharmaceutical composition. The kit form is particularly advantageous when the separate components must be administered in different dosage forms, e.g., parenteral valsartan formulation and oral NEP formulation; or are administered at different dosage intervals.

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

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

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

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

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

In case of NEP inhibitors, preferred dosage unit forms are, e.g., tablets or capsules comprising, e.g., from about 20 mg to about 800 mg, preferably from about 50 mg to about 700 mg, even more preferably from about 100 mg to about 600 mg and even more preferably from about 100 mg to about 300 mg, administered q.d.

The above doses encompass a therapeutically effective amount of the active ingredients of the present invention.

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

Formulation Example 1

Film-Coated Tablets

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan (=active ingredient)	80.00	
Microcrystalline cellulose/Avicel PH 102	54.00	NF, Ph. Eur
Crospovidone	20.00	NF, Ph. Eur
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	0.75	Ph. Eur, NF
Magnesium stearate	2.5	NF, Ph. Eur
Blending		
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	0.75	Ph. Eur, NF
Magnesium stearate	2.00	NF, Ph. Eur
Coating		
Purified water*	—	
DIOLACK Pale Red 00F34899	7.00	
Total Tablet Mass	167.00	

*Removed during processing.

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

A mixture of valsartan, microcrystalline cellulose, crospovidone, part of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200, silicon dioxide and magnesium stearate is premixed in a diffusion mixer and then sieve through a screening mill. The resulting mixture is again premixed in a diffusion mixer, compacted in a roller compactor 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 tablets 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		
Valsartan (=active ingredient)	160.00	
Microcrystalline cellulose/Avicel PH 102	108.00	NF, Ph. Eur
Crospovidone	40.00	NF, Ph. Eur
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	1.50	Ph. Eur, NF
Magnesium stearate	5.00	NF, Ph. Eur
Blending		
Colloidal anhydrous silica/colloidal silicon dioxide/Aerosil 200	1.50	Ph. Eur, NF
Magnesium stearate	4.00	NF, Ph. Eur
Coating		
Opadry ® Light Brown 00F33172	10.00	
Total Tablet Mass	330.00	

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

Formulation Example 3

Film-coated tablets		
Components	Composition Per Unit (mg)	Standards
Core Internal Phase		
Valsartan [=active ingredient]	40.00	
Silica, colloidal anhydrous (colloidal silicon dioxide) [=glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [=lubricant]	2.00	USP/NF
Crospovidone [=disintegrant]	20.00	Ph. Eur
Microcrystalline cellulose [=binding agent]	124.00	USP/NF
External Phase		
Silica, colloidal anhydrous (colloidal silicon dioxide) [=glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [=lubricant]	2.00	USP/NF
Film Coating		
Opadry Brown 00F16711*	9.40	
Purified water**	—	
Total Tablet Mass	199.44	

*The composition of the Opadry brown 00F16711 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)
Valsartan [=active ingredient]	80.00
Microcrystalline cellulose	25.10
Crospovidone	13.00
Povidone	12.50
Magnesium stearate	1.30
Sodium lauryl sulphate	0.60
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540
Gelatin	74.969
Total Tablet Mass	209.50

The tablet is manufactured, e.g., as follows:

Granulation/Drying

Valsartan and microcrystallin cellulose are spray-granulated in a fluidized bed granulator with a granulating solution consisting of povidone and sodium lauryl sulphate dissolved in purified water. The granulate obtained is dried in a fluidized 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 de-dusted, visually inspected, weight-checked and quarantined until by Quality Assurance department.

Formulation Example 5

Capsules	
Components	Composition Per Unit (mg)
Valsartan [=active ingredient]	160.00
Microcrystalline cellulose	50.20
Crospovidone	26.00
Povidone	25.00
Magnesium stearate	2.60
Sodium lauryl sulphate	1.20

-continued

Capsules	
Components	Composition Per Unit (mg)
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)
Valsartan [=active ingredient]	80.00
Sodium lauryl sulphate	0.60
Magnesium stearate	1.30
Povidone	12.50
Crospovidone	13.00
Microcystalline cellulose	21.10
Total Tablet Mass	130.00

Formulation Example 7

A hard gelatin capsule, comprising as active ingredient, e.g., (S)—N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine, can be formulated, e.g., as follows:

Components	Composition Per Unit (mg)
(1) Valsartan	80.00
(2) Microcystalline cellulose	110.0
(3) Polyvidone K30	45.2
(4) Sodium lauryl sulfate	1.2

-continued

Components	Composition Per Unit (mg)
(5) Crospovidone	26.0
(6) Magnesium stearate	2.6

Components (1) and (2) are granulated with a solution of components (3) and (4) in water. The components (5) and (6) are added to the dry granulate and the mixture is filled into size 1 hard gelatin capsules.

All publications and patents mentioned herein are incorporate by reference in their entirety as if set forth in full herein.

What is claimed is:

1. A pharmaceutical composition comprising:

(i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof;

(ii) the NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable carrier;

wherein said (i) AT 1-antagonist valsartan or pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof, are administered in combination in about a 1:1 ratio.

2. The pharmaceutical composition of claim 1, wherein said (i) AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and said (ii) NEP inhibitor N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or (2R,4S)-5-biphenyl-4-yl-4(3-carboxy-propionyl amino)-2-methyl-pentanoic acid or pharmaceutically acceptable salt thereof are administered in amounts effective to treat hypertension or heart failure.

3. The pharmaceutical composition of claim 1 wherein (ii) said NEP inhibitor is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

4. The pharmaceutical composition of claim 3 in the form of a capsule or tablet.

* * * * *

APPENDIX D

Terminal Disclaimer

CASE PAT032219-US-DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Webb, Randy Lee et al.
APPLICATION NO: 12/147570
FILED: June 27, 2008
FOR: METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION

Art Unit: 1628
Examiner: Kim, Jennifer M
Conf. No.:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

TERMINAL DISCLAIMER

Sir:

Novartis AG, a corporation having a place of business at Novartis AG, Lichtstrasse 35, 4056 Basel, SWITZERLAND, represents that it is the assignee and owner of the entire interest in the above-identified application by virtue of an assignment which was recorded in the United States Patent and Trademark Office on .

Novartis AG hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the above-identified application which would extend beyond the expiration date of the full statutory term defined in 35 USC §154 and §173, as presently shortened by any terminal disclaimer, of prior **Patent No. 7,468,390** issued December 23, 2008. Said Patent No. 7,468,390 is also assigned to Novartis AG by virtue of the same assignment.

Novartis AG hereby agrees that any patent granted on the above-identified application shall be enforceable only for and during such period that it and prior Patent No. 7,468,390 are commonly owned. This agreement runs with any patent granted on the above-identified application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, Novartis AG does not disclaim the terminal part of any patent granted on the above-identified application that would extend to the expiration date of the full statutory term as defined in 35 USC §154 and §173 of prior Patent No. 7,468,390, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent

jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR §1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

A terminal disclaimer fee under 37 CFR §1.20(d) is included.

Signed this 9th day of September, by the undersigned attorney of record.

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-1422

Stephen Johnson
for Applicant
Reg. No. 45,916

APPENDIX E

Maintenance Fee Receipt

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER NJ 07936-1080

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	ENTITY STATUS	ATTY DKT NUMBER
8101659	**$1,600.00**	**$0.00**	**07/08/15**	**12147570**	**01/24/12**	**06/27/08**	**04**	**LARGE**	**32219-US-DIV**

PTOL-439 (Rev. 09/2006)

APPENDIX F

IND Chronology

FDA Interaction Date	Content Summary
3/8/2007	Original IND for LCZ696 in the treatment of hypertension. The purpose of this IND is to support a phase 1 clinical study in healthy volunteers to generate pharmacokinetic information on LCZ696. Please note that this IND was originally submitted under IND 75,612, but FDA issued a new IND number after receiving the submission. (PS)
3/16/2007	FDA LETTER Acknowledging receipt of the original IND submitted on March 8, 2007.
3/27/2007	Email from FDA asking for clarification on the original IND.
4/3/2007	Email response to FDA CMC questions (ES)
4/13/2007	At this time, Novartis is submitting a CMC information amendment in response to the FDA request on April 2, 2007. The FDA requested the following: A detailed description of the container closure system for the LCZ696 drug substance, and a certificate of analysis (C of A) for the clinical batch of the LCZ696 300 mg drug product (PS)
4/25/2007	FDA LETTER Comments and requests for information on the clinical and chemistry sections of the IND.
4/27/2007	HA meeting minutes of the March 29, 2007, FDA/Novartis Pre-IND meeting to discuss Novartis' proposed Phase 2 development plan under IND 77,318.
4/30/2007	Request for Type B meeting to seek the Division's input and comments on Novartis' proposed development program for LCZ696 which would establish it as a safe and effective first-line antihypertensive (PS)
5/3/2007	Response to FDA comments and request for information made in the FDA letter dated April 25, 2007 (PS)
5/24/2007	Novartis is hereby notifying the FDA that they plan to submit on June 26, 2007 for the Agency's review and assessment the following carcinogenicity study protocols 104 week oral (gavage) carcinogenicity study in rats; and 104 week oral (gavage) carcinogenicity study in mice (PS)
6/5/2007	15 day IND safety report, reporting a new unexpected finding of hydrocephaly in an embryo fetal development study in rabbits (PS)
6/28/2007	This Amendment provides updated information 'concerning the LCZ696 drug substance synthesis and controls as well as CMC information for new LCZ696 film-coated tablets: 100 mg (KN 6002384.002), 200 mg (KN 6002385.002) and 400 mg (KN 6002386.002). In addition, CMC information for a 100 mg AHU377 comparator product (KN 6002372.001), and VAL489 80 mg (KN 3748175,010) and 160 mg (KN 3748183.010) comparator products is provided. Placebo documentation to .match the three LCZ696 film-coated tablets (KNs 6002387.001, 6002387,002 and 60023S7.003), AHU377 comparator product (KN 6002373.001) and the two VAL489 comparator products (KN 3755667.030) is also included. (PS)
6/28/2007	Request for special protocol assessment for Protocol 104 week oral (gavage) carcinogenicity study in mice (Appendix 1); and 104 week oral (gavage) carcinogenicity study in rats (Appendix 2) (PS)

FDA Interaction Date	Content Summary
7/6/2007	FDA LETTER Acknowledging receipt of serial number 005 submitted on June 29, 2007, for a special carcinogenicity protocol assessment.
7/9/2007	New protocol CLCZ696A2103 new protocol entitled: An open-label
7/9/2007	FDA FAX Responding the Carcinogenicity Special Protocol Assessment Request.
7/11/2007	Briefing book for Pre-IND meeting scheduled for August 15, 2007 to discuss the intended development of this product (PS)
8/13/2007	Email from FDA containing the 2nd Pre-IND meeting FDA preliminary responses.
8/15/2007	Novartis meeting minutes (not submitted) of the August 15, 2007 Pre-IND meeting to discuss issues associated with the development of LCZ-696, a molecule containing the active moieties of valsartan and AHU, a neutral endopeptidase inhibitor (NEPI) in a 1:1 ratio. The product is being developed for the treatment of hypertension.
8/16/2007	FDA LETTER Pre-IND meeting confirmation for the August 15, 2007 Type B meeting.
9/5/2007	New protocol Study CLCZ696A2201 entitled: A multi-center
9/18/2007	New investigators to Study CLCZ696A2201 (PS)
9/18/2007	FDA meeting minutes of the Type B meeting between Novartis and the FDA held on August 15, 2007 to discuss issues associated with the development of LCZ-696, a molecule containing the active moieties of valsartan and AHU, a neutral endopeptidase inhibitor (NEPI) in a 1:1 ratio. The product is being developed for the treatment of hypertension.
9/18/2007	TELECON with FDA to discuss Novartis' inquiry regarding confirming LCZ eligible for 3 years of marketing exclusivity, not 5 years as it contains valsartan.
9/19/2007	Email regarding the FDA meeting minutes of the August 15, 2007 Type B meeting.
10/3/2007	New investigators to study CLCZ696A2201. (PS)
10/16/2007	New investigators to Study CLCZ696A2201. (PS)
11/28/2007	New investigators to Study CLCZ696A2201. (PS)
1/9/2008	New investigator to study CLCZ696A2201. (PS)
2/21/2008	New investigator to study CLCZ696A2201. (PS)
8/11/2008	Annual report covering the period April 8, 2007 to April 7, 2008 (eCTD-seq0017)
2/5/2009	Request for Type B meeting on April 6, 2009 to seek the Agency's feedback on Novartis' proposed clinical development program for LCZ696 in the treatment of chronic heart failure (PS)
2/11/2009	Record of Contact of telecon between Ed Lee of Novartis and Quynh Nguyen at the Cardio-Renal Division of FDA regarding the Type B meeting request submitted to IND 77,318 on February 5, 2009 (ES)
2/11/2009	Email correspondence providing the Agency with the re-submission of the Type B meeting request that was previously submitted to IND 77,318 on February 5, 2009 as Ser. No. 018 (PS)

FDA Interaction Date	Content Summary
2/23/2009	General Correspondence requesting withdrawal of Type B Meeting request, submitted to the FDA on February 5, 2009 in Sequence No. 0018 (eCTD-seq-0019)
3/20/2009	Submission of an Information Amendment to provide updated Chemistry, Manufacturing and Controls information regarding LCZ696 drug substance, drug product, and placebo (eCTD-seq0020)
5/6/2009	Submission of New Protocol for study CLCZ696B2214, entitled 'A twelve-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the efficacy, safety and tolerability of LCZ696 compared to valsartan in patients with chronic heart failure and preserved left-ventricular ejection fraction' (eCTD-seq0021)
6/5/2009	Annual Report covering the period from April 07, 2008 to April 07, 2009 (eCTD-seq0022)
10/22/2009	Submission of New Protocol, CLCZ696B2105, entitled 'An open-label, single dose study to investigate the absorption, distribution, metabolism, and elimination of 200 mg [14C]LCZ696 and its metabolites in healthy male subjects.' (eCTD-seq0023)
11/18/2009	Submission of New Investigators to studies LCZ696B2105, LCZ696B2214 (eCTD-seq0024)
12/10/2009	Submission of New Investigators to study CLCZ696B2214 (eCTD-seq0025)
12/17/2009	Submission of New Investigators to study LCZ696B2214 (eCTD-seq0026)
1/8/2010	Submission of Information Amendment to provide updated Chemistry, Manufacturing and Controls Information regarding LCZ696 drug substance, drug product, and placebo (eCTD-seq0027)
1/13/2010	Submission of New Investigators for study LCZ696B2214 (eCTD-seq0028)
2/24/2010	Submission of Change in Protocol: Amendment 1 to study CLCZ696B2214 (eCTD-seq0029)
4/21/2010	Submission of New Investigators to study CLCZ696A2201 (eCTD-seq0030)
4/29/2010	Submission of Change in Protocol; Amendment # 2 to study CLCZ696B2214 (eCTD-seq0032)
4/30/2010	Submission of New Investigator to study LCZ696B2214 (eCTD-seq0031)
6/3/2010	Submission of Annual Report covering the period from April 7, 2009 to April 7, 2010 (eCTD-seq0033)
6/9/2010	Submission of Changes in Protocol to studies CLCZ696A2102, CLCZ696A2103, CLCZ696A2201 and Transfer of Obligations to studies CLCZ696A2102 CLCZ696A2103, CLCZ696A2201, CLCZ696B2105, CLCZ696B2214 (eCTD-seq0034)
6/15/2010	Submission of Amendment # 1 to study CLCZ696A2201 and New Investigator to study CLCZ696B2214 (eCTD-seq0035)
8/9/2010	Submission of Amendment 3 to protocol CLCZ69662214
8/30/2010	Safety Report PHHO2010TW11790 (eCTD-seq0038)
9/1/2010	Submission of New Investigators to study LCZ696B2214 (eCTD-seq0037)

FDA Interaction Date	Content Summary
9/23/2010	New Investigator for protocol CLCZ696B2214 (eCTD-seq0039).
9/27/2010	Transfer of obligation for study CLCZ976B2214 (eCTD-seq0040)
10/20/2010	Safety Report PHHO2010GB13984 (eCTD-seq0041)
10/26/2010	CMC amendment to provide for changes to the analytical methods, drug product specifications, and packaging information (eCTD-seq0042).
11/17/2010	CMC Amendment to provide updated information for the drug substance and drug product (eCTD-seq0043).
12/3/2010	This Correspondence provides information about immediate change in contact at Novartis for this application.
12/6/2010	Correspondence sent to the FDA to notify them of the intent to export LCZ696 tablets for investigational use (PS).
12/9/2010	Telecon held on December 9, 2010 to confirm the receipt of the export notice for LCZ696.
12/17/2010	New Protocol CLCZ696A2223, a multi-center, randomized, double-blind, placebo and active controlled, parallel group study to evaluate the dose response of AHU377 in combination with valsartan 320 mg after 8 week treatment in patients with mild-to-moderate systolic hypertension (eCTD-seq0045).
12/17/2010	Transfer of Obligation for protocol CLCZ696B2214 (eCTD-seq0046)
12/22/2010	New Investigators for protocol LCZ696A2223 (eCTD-seq-0047)
1/7/2011	Safety Report PHHO2010TW19816 7-day Safety Report (PS).
1/10/2011	Safety Report PHHO2010TW19816 (eCTD-seq0049)
1/13/2011	New Investigator(s) for protocol(s) CLCZ696A2223 and CLCZ696B2214 (eCTD-seq0048).
1/18/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0050)
2/4/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0051)
2/11/2011	Submission of an Information Amendment to provide updated Chemistry, Manufacturing and Controls Information regarding LCZ696 drug substance (eCTD-seq0052)
2/22/2011	Safety Report PHHO2010TW19816;follow-up(eCTD-seq0053)
2/28/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0055)
3/4/2011	Transfer of Obligations for protocol CLCZ696A2223 (eCTD-seq0054).
4/6/2011	New investigator for protocol CLCZ696A2223(eCTD-seq0056)
4/8/2011	Submission of Change in Protocol; Amendment # 1 to study CLCZ696B2223 (eCTD-seq0057)
4/21/2011	New Investigator for CLCZ696A2223 (eCTD-seq0058).
5/23/2011	Annual Report covering the period from 07-April-2010 to 07-April-2011 (eCTD-seq0059).
6/8/2011	Novartis is submitting an Information Amendment to provide updated CMC Information regarding the clinical trial material. (eCTD-seq0060)

FDA Interaction Date	Content Summary
6/23/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0061)
6/30/2011	Amendment 2 to Protocol CLCZ696A2223 (eCTD-seq0062)
7/12/2011	Safety Report PHHO2010TW19998 7-Day safety report (PS).
7/18/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0063)
7/18/2011	Safety Report PHHO2010TW19998 (eCTD-seq0064)
9/9/2011	New investigators for protocols LCZ696B2214 & LCZ696A2223 (eCTD-seq0065)
9/14/2011	Safety Report PHHO2010TW19998; follow-up (eCTD-seq0067)
9/14/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0066)
10/21/2011	CMC information amendment to provide updated Chemistry, Manufacturing and Controls Information regarding LCZ696 drug substance and clinical trial material. (eCTD-seq0068)
10/25/2011	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0070)
10/25/2011	Safety Report PHHO2010TW19998; follow-up (eCTD-seq0069)
11/18/2011	New Investigator for protocol LCZ696A2223 (eCTD-seq0071).
1/12/2012	New Investigator(s) for protocol(s) LCZ696A2223 (eCTD-seq0072).
3/22/2012	Change in regulatory contact from Simon Ducher to Leigh Strachan (eCTD-seq0073)
5/18/2012	Transfer of obligations for study LCZ696B2214 (eCTD-seq0075)
6/4/2012	Annual Report covering the period from 07April2011 to 07April2012 (eCTD-seq0074)
7/24/2012	Information Amendment to provide updated Chemistry, Manufacturing and Controls Information for a new formulation of LCZ696 50 mg Film-coated tablets (FMI, Final Marketing Image). Reference is made to 6002752_AMEN_CP_840_2 for a complete summary of the changes (eCTD-seq0076).
8/8/2012	New Protocol CLCZ696A2222, entitled 'A randomized, double-blind, crossover study to assess the effects of LCZ696 and valsartan in Asian patients with salt-sensitive hypertension (eCTD-seq0077)"
9/12/2012	New Investigator for protocol LCZ696A2222 (eCTD-seq0078)
9/21/2012	New Protocol CLCZ696A2216 entitled A randomized
10/25/2012	Novartis is submitting an Information Amendment to provide updated Chemistry, Manufacturing and Controls information for a new comparator and placebo to match the comparator. In addition, minor updates to control of LCZ696 drug product as well as an updated packaging sites list are included. Reference is made to 6002752_AMEN_CP_840_3 for a complete summary of the changes. (eCTD-seq0079)
11/2/2012	Safety Report PHHO2012JP015393 (eCTD-seq0081)
11/19/2012	FDA advice-information request regarding protocol CLCZ696A2216.
11/19/2012	Safety Report PHHO2012JP015393; follow-up (eCTD-seq0082)
12/10/2012	New Investigators for protocol lcz696a2216 (eCTD-seq0083).

FDA Interaction Date	Content Summary
12/12/2012	Response to FDA request dated November 19, 2012 regarding new protocol CLCZ696A2216. (eCTD-seq0084)
12/17/2012	Safety Report PHHO2012JP015393; follow-up (eCTD-seq 0085)
12/24/2012	Submission of Transfer of Obligations for Study No. CLCZ696A2222. (eCTD-seq0086)
12/27/2012	Safety Report PHHO2012JP018459 7-Day safety report (PS)
1/4/2013	Safety Report PHHO2012JP018459 (eCTD-seq 0087)
1/7/2013	Safety Report PHHO2012JP018459 follow-up (eCTD-seq0088)
1/18/2013	Amendment 1 to Protocol CLCZ696A2222 (eCTD-Seq0090)
1/18/2013	New Investigators for Study CLCZ696A2216. (eCTD-seq0089)
1/21/2013	Safety Report PHHO2012JP018459; follow-up (eCTD-seq0091)
1/24/2013	Safety Report PHHO2013JP000956 (eCTD-seq0092)
1/25/2013	Safety Report PHHO2013JP000998 (eCTD-seq0093)
1/31/2013	Safety Report PHHO2012JP018459; follow-up (eCTD-seq0094)
2/1/2013	Safety Report PHHO2013ZA001555 (eCTD-seq0096)
2/1/2013	Safety Report PHHO2013JP001480 (eCTD-seq0095)
2/5/2013	Safety Report PHHO2013JP000956; follow-up (eCTD-Seq0097)
2/6/2013	P Safety Report HHO2013JP000998; follow-up (eCTD-seq0098)
2/7/2013	Safety Report PHHO2013JP000956; follow-up (eCTD-seq0099)
2/12/2013	Safety Report PHHO2011BR17514 7-Day safety report (PS).
2/14/2013	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0100)
2/19/2013	Safety Report PHHO2013JP000998; follow-up (eCTD-seq0101)
2/20/2013	Safety Report PHHO2012DE013453; follow-up (eCTD-seq0102)
2/20/2013	Safety Report PHH02011BR17514 Follow-up (eCTD-seq0103)
2/23/2013	Safety Report PHHO2013JP000956; follow-up (eCTD-seq0105)
2/25/2013	New Investigators for protocols CLCZ696A2222, CLCZ696A2216 (eCTD-seq0104)
2/27/2013	Safety Report PHHO2013JP001480; follow-up (eCTD-seq0106)
2/27/2013	Safety Report PHHO2013DE002628 (eCTD-seq0107)
3/11/2013	Novartis is submitting an information Amendment to provide updated Chemistry, Manufacturing and Control information for a comparator (Olmesartan Medoxomil). (eCTD-seq0108)
3/14/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0109) The receipts are not available for this submission.
3/15/2013	Safety Report PHHO2013DE002628 Follow-up (eCTD-seq0110) The receipts are not available for this submission.
3/22/2013	Safety Report PHHO2013JP000998 Follow-up (eCTD-seq0111)
3/22/2013	Safety Report PHHO2010IL18897 Follow-up (eCTD-seq0112)
3/26/2013	Safety Report PHHO2013JP004048 (eCTD-seq0114)
3/28/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0115)

FDA Interaction Date	Content Summary
4/5/2013	Novartis is submitting an Information Amendment to provide updated CMC information for a placebo matching a valsartan comparator. This amendment supports a batch specific extension for this placebo in the on-going trial CLCZ696A2222 (new shelf life: 63 months). (eCTD-seq0117)
4/5/2013	Clinical Information Amendment is submitted to provide final Clinical Study Report for LCZ696B2214 (eCTD-Seq0113)
4/5/2013	Safety Report PHHO2012JP018459; follow-up (eCTD-seq0116)
4/11/2013	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0118)
4/16/2013	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0119)
4/16/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0120)
4/16/2013	Safety Report PHHO2012BR018051 7-day report (PS)
4/17/2013	Safety Report PHHO2013JP004048; follow-up (eCTD-seq0121)
4/18/2013	Safety Report PHHO2012BR018051 (eCTD-seq0123)
4/24/2013	This submission is to provide the recently updated Investigator's Brochure (edition 12) for LCZ696 which can be found in Section 1.14.4.1 (eCTD-seq0122)
4/30/2013	Amendment 2 for Protocol CLCZ696A2222 (eCTD-Seq0124)
5/1/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0126)
5/1/2013	Safety Report PHHO2012BR018051 Follow-up (eCTD-seq0125)
5/6/2013	Safety Report PHHO2013BR005937 7-day report (PS)
5/8/2013	Safety Report PHHO2013JP005683 (eCTD-seq0128)
5/13/2013	Safety Report PHHO2013JP000998 Follow-up (eCTD-seq0129)
5/14/2013	Safety Report PHHO2013BR005937 (eCTD-seq0130)
5/15/2013	Safety Report PHHO2010TW11790 Follow-up (eCTD-seq0131)
5/21/2013	Safety Report PHH02011TW09929; follow-up (eCTD-seq0132)
5/21/2013	Safety Report PHHO2011SI18084 Follow-up (eCTD-seq0133)
5/29/2013	Safety Report PHHO2013JP005683 Follow-up (eCTD-seq0134)
5/30/2013	Safety Report PHHO2013US006665 (eCTD-seq0135)
6/4/2013	Annual Report covering the period from April 08, 2012 through April 07, 2013 (eCTD-seq0127)
6/4/2013	PHHO2011BR17560 Follow-up (eCTD-seq0136)
6/6/2013	PHHO2011BR09808 Follow-up (eCTD-seq0140) The Receipts are not available for this submission.
6/6/2013	Safety Report PHHO2012FR018676 Follow-up (eCTD-seq0139)
6/7/2013	Safety Report PHHO2013JP000956 Follow-Up (eCTD-seq0141)
6/12/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0143)
6/13/2013	Safety Report PHH02013JP000956 Follow-up (eCTD-seq0144)
6/14/2013	Safety Report PHHO2013JP005683; follow-up (eCTD-seq0142).
6/18/2013	In accordance with 21 CFR §312.31, Novartis is providing the Clinical Study Reports for CLCZ696A2201 entitled A multi-center

FDA Interaction Date	Content Summary
6/19/2013	The purpose of this submission is to complete the record by submitting the actual reports to the application (eCTD-seq0138)
6/21/2013	Safety Report PHH02013JP000956 Follow-up (eCTD-seq0146)
6/26/2013	Information Amendment-CMC - Novartis is submitting an information Amendment to provide updated Chemistry, Manufacturing and Control information for a comparator (amlodipine besylate tablets) and placebo matching this comparator in addition to other minor CMC updates.
6/27/2013	Safety Report PHHO2013JP000956 follow-up (eCTD-seq0149)
7/1/2013	Safety Report PHH02011TW09929 Follow-up (eCTD-seq0150)
7/3/2013	New Protocol CLCZ696A2320
7/3/2013	Email response to FDA as to whether or not the new Phase 3 protocols are to be considered pivotal studies.
7/4/2013	New Protocol for CLCZ696A2318 entitled 'A randomized, 8-week, double-blind, parallel-group, active controlled, multicenter study to evaluate the efficacy and safety of LCZ696 200 mg in comparison with olmesartan 20 mg in patients with essential hypertension not adequately responsive to olmesartan 20 mg treatment' and TOO (eCTD-Seq0148)
7/5/2013	Safety Report PHHO2013US006665 follow-up (eCTD-seq0151)
7/12/2013	Safety Report PHHO2013US006665 Follow-up (eCTD-seq0153)
7/13/2013	Safety Report PHHO2012GB017225 follow-up (eCTD-seq0152)
7/18/2013	Safety Report PHHO2013JP000956 Follow-Up (eCTD-seq0154)
7/31/2013	Safety Report PHHO2013PH009418 7-Day (PS)
8/1/2013	Information Amendment to provide updated Chemistry, Manufacturing and Control information for LCZ696 film-coated tablets 50 mg, 100 mg, 200 mg and 400 mg and to introduce a new placebo (matching 50 mg FMI formulation. Reference is made to 6002572 AMEN_CP_840_6 for detailed information (eCTD-seq0155)
8/1/2013	Cross reference to the Clinical Study Report for CLCZ696A2124 (eCTD-seq0156).
8/2/2013	Safety Report PHHO2012ZA008690 7-Day safety report (PS).
8/2/2013	Safety Report PHH02013ZA008690 (eCTD-seq0158)
8/2/2013	Safety Report PHHO2013JP000956 Follow-Up (eCTD-seq0159)
8/6/2013	Safety Report PHHO2012FR018676 Follow-Up (eCTD-seq0160)
8/8/2013	Safety Report PHHO2013JP000956 follow-up (eCTD-seq0163)
8/8/2013	Safety Report PHHO2012BR018051follow-up (eCTD-seq0161)
8/8/2013	Safety Report PHHO2013DE002628 follow-up (eCTD-seq0162)
8/8/2013	Safety Report PHHO2013PH009418 (eCTD-seq0164)
8/9/2013	Safety Report PHHO2012NL008767 Follow-Up (eCTD-seq0165)
8/12/2013	New Protocol for clcz696a2126 entitled A randomized
8/14/2013	Submission of updated Transfer of Sponsor Obligations for study CLCZ696A2320. (eCTD-seq0166)

FDA Interaction Date	Content Summary
8/15/2013	Email exchange with FDA will let us conduct study CLCZ696A2126 under the existing HTN IND. However, any further studies regarding the effect of LCZ696 on amyloid-' concentrations in cerebrospinal fluid would need to be to a new IND to the Division of Neurology Products (DNP).
8/19/2013	CMC Information Amendment (Pubs 74563) (eCTD-seq0167)
8/22/2013	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0170)
8/22/2013	Safety Report PHHO2012BR018051 Follow-up (eCTD-seq0169)
8/22/2013	Safety Report PHHO2010TW19998 Follow-up (eCTD-seq0168)
8/30/2013	FDA LETTER providing statistical comments and recommendations for LCZ696A2318 and LCZ696A2320.
9/9/2013	Safety Report PHHO2013TW011210 7-Day safety report (PS)
9/10/2013	Safety Report PHHO2013TW011210 (eCTD-seq0172)
9/12/2013	New Investigator for protocol LCZ696A2216 (eCTD-seq0171)
9/13/2013	New Investigators for protocols CLCZ696A2318, A2320 (eCTD-seq0173)
9/24/2013	Amendment 1 to Study CLCZ696A2126. (eCTD-seq0176)
9/30/2013	New Investigator Batch for protocols CLCZ696A2318, A2320, A2126 (eCTD-seq0175)
10/1/2013	Safety Report PHHO2012JP017363 (eCTD-seq0178).
10/4/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0179)
10/9/2013	Clinical Information Amendment eCTD-seq0180)
10/10/2013	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0182)
10/11/2013	New Investigator A2318,A2320 (eCTD-seq0181)
10/21/2013	Submission provides updated Transfer of Sponsor Obligations for study LCZ696A2126. (eCTD-seq0183)
10/21/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0184)
10/24/2013	Safety Report PHHO2013PH009418; follow-up (eCTD-seq0177)
11/1/2013	Safety Report PHHO2013JP005683, followup (eCTD-seq0186)
11/6/2013	New Investigator(s) for protocol(s) LCZ696A2318, LCZ696A2320 (eCTD-seq0185)
11/12/2013	Novartis is providing 15 day IND safety report to report a new, unexpected, and potentially adverse finding of increased levels of amyloid beta (A') in the cerebrospinal fluid (CSF), in the absence of changes of levels in the brain, which was observed during a 2-week oral investigative study in cynomolgus monkeys treated with LCZ696. (eCTD-seq0187)
11/26/2013	NEW INVESTIGATORS/Change in Form FDA 1572;(eCTD-seq0188)
11/27/2013	Safety Report PHHO2012AR010257 Follow-up (eCTD-seq0190)
11/29/2013	Information Amendment (Clinical)
12/5/2013	Safety Report PHHO2010TW11790 Follow-up (eCTD-seq0191)
12/12/2013	Information Amendment-Clinical: Submitting an Erratum to the recently updated Investigator Brochure (Edition 13) (eCTD-Seq0192)
12/19/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0193)

FDA Interaction Date	Content Summary
1/15/2014	Amendment 01 to Protocol CLCZ696A2320, CLCZ696A2320E1 (eCTD-seq0194)
1/16/2014	Safety Report PHHO2013TW011210; follow up (eCTD-seq0196)
1/21/2014	Safety Report Protocol Amendment (New investigator) LCZ696A2318; eCTDseq0195
2/5/2014	PHHO2013TW011210; follow-up (eCTD-seq0197)
2/27/2014	CMC Information amendment is submitted to provide information on Comparator, Olmesartan medoxomil 10mg, 20mg and 40mg Hard non-gelatin capsule tablet content regarding the extension of Shelf-life from 18 months to 24 months and extension of In-use period from 1 month to 1.5 months based on available additional stability data. (eCTD-Seq0198)
2/27/2014	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0199)
3/4/2014	Safety Report PHHO2011IS18084; follow-up (eCTD-seq0200)
3/18/2014	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0201)
3/27/2014	Safety Report PHHO2011IN12674; follow-up (eCTD-seq0205)
3/28/2014	Information Amendment-Clinical: Update IB Edition-14 is being submitted (eCTD-Seq0203)
3/28/2014	Request to submit the DSUR in lieu of the annual report using the existing reporting period July 31, 2013 - July 30, 2014. (eCTD-seq0202)
3/29/2014	Safety Report PHHO2013TW011210; Follow-up (eCTD-seq0204)
4/7/2014	Safety Report PHHO2012FR018676; follow-up (eCTD-seq0206)
4/17/2014	Email to FDA to inform project manager that data from A2126, which was run under this IND, has been submitted to IND 104,628 and a cross reference statement is pending.
4/18/2014	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0209)
4/22/2014	The purpose of this submission is to provide a cross reference in [Module 1.4.4] to preliminary information submitted to IND 104,628 about LCZ696A2126, which is being run under this IND. (eCTD-seq0208)
4/25/2014	FDA Letter requesting follow up information regarding the statistical considerations for Protocol LCZ696A2318.
4/25/2014	FDA Letter providing agreement to Novartis' proposal (submitted March 28, 2014) for switching to the DSUR after the IND Annual Report due June 5th is submitted.
4/25/2014	FDA Letter requesting changes to Section 6 of the Investigator's Brochure.
5/7/2014	Submission provides response to FDA request dated April 25, 2014 regarding study CLCZ696A2318 along with an update on recruitment for CLCZ696A2318 and change in contact from Leigh Strachan to Masha Berkhin. (eCTD-seq0211)
5/9/2014	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0212)
5/12/2014	Safety Report PHHO2012GB001045, follow-up (eCTDseq 0213)
5/20/2014	New Investigator for Protocol CLCL696A2216 and 1572 Changes (eCTD-seq0214)
5/28/2014	Safety Report PHHO2014IT007104 (eCTD-seq0215)

FDA Interaction Date	Content Summary
5/28/2014	Safety Report PHHO2011IN12674; follow-up (eCTD-seq0216)
5/29/2014	Safety Report PHHO2012ZA008690; follow-up (eCTD-seq0217)
5/30/2014	Annual Report covering the period from 08 April 2013 through 07 April 2014 (eCTD-seq0210)
6/10/2014	Safety Report PHHO2014IT007104; follow-up (eCTD-seq0218)
6/16/2014	Novartis is submitting updated version of the Investigator's Brochure Edition 15 (eCTD-seq0219)
6/18/2014	Amendment 1 to protocol CLCZ696A2216 (eCTD-seq0220)
6/27/2014	CMC Information Amendment Pubs 85228 (eCTD-seq0221)
7/6/2014	Safety Report PHHO2014US008920 (eCTD-seq0223)
7/10/2014	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0224)
7/14/2014	Novartis is providing the Clinical Study Report for CLCZ696A2222. (eCTD-seq0222)
7/14/2014	Safety Report PHHO2010GB15448; follow-up (eCTD-seq0225)
7/15/2014	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0228)
7/15/2014	Safety Report PHHO2010IL18897; follow-up (eCTD-seq0226)
7/16/2014	Safety Report PHHO2014US008920 Follow-up (eCTD-seq0229)
7/19/2014	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0230)
7/21/2014	Safety Report PHHO2011FI06062 Follow-up (eCTD-seq0231)
7/31/2014	Novartis is submitting an information Amendment to include the current information on LCZ696 drug substance and LCZ696 50mg, 100mg, 200mg and 400mg and placebo Film-coated tablet. (eCTD-seq0233)
8/5/2014	Safety Report PHHO2013SK004806 7-day (eCTD-seq0234)
8/6/2014	Novartis is submitting clinical study report for study CLCZ696A2126 (eCTD-seq0232)
8/11/2014	Safety Report PHHO2012RU017982 7-day safety report (eCTD-seq0237)
8/12/2014	Safety Report PHHO2010HU17146 Follow-up (eCTD-seq0238)
8/14/2014	Safety Report PHHO2013SK004806 (eCTD-seq0239)
8/15/2014	Safety Report PHHO2011IN11799; follow-up (eCTD-seq0247)
8/15/2014	Safety Report PHHO2012AR010257; follow-up (eCTD-seq0246)
8/15/2014	Safety Report PHHO2012GB017225; follow-up (eCTD-seq0245)
8/15/2014	Safety Report PHHO2014US008920 Follow-up (eCTD-seq0244)
8/18/2014	FDA advice information request letter regarding Investigator's Brochure Edition 15, dated June 4, 2014.
8/18/2014	Safety Report PHHO2014RU006393; 7-Day safety report (eCTD-seq0248)
8/20/2014	Safety Report PHHO2012RU017982 (eCTD-seq0249)
8/21/2014	Safety Report PHHO2012PH006218 (eCTD-seq0251)
8/25/2014	Safety Report PHHO2013IN010949 (eCTD-seq0252)
8/25/2014	Safety Report PHHO2014RU006393 (eCTD-seq0253)

FDA Interaction Date	Content Summary
8/25/2014	Safety Report PHHO2012ZA008690; follow-up (eCTD-seq0254)
9/1/2014	Safety Report PHHO2012US009119 7-Day safety report (eCTD-seq0255)
9/5/2014	Safety Report PHHO2014US008920; follow-up (eCTD-seq0256)
9/8/2014	Safety Report PHHO2012US009119 (eCTD-seq0257)
9/26/2014	Safety Report PHHO2013PH009418; follow-up (eCTD-seq0258)
9/30/2014	DSUR Annual report covering the period from 31July 2013 through 30June 2014 (eCTD-seq0250)
10/7/2014	Novartis is amending the base DSUR 104,628 by providing Regional Appendix 2 (List of subjects who died during the reporting period) and Appendix 3 (List of subjects who dropped out of studies during the reporting period). (eCTD-seq0259)
10/14/2014	Safety Report PHHO2011FI06062; Follow-up (eCTD-seq0261)
10/15/2014	Safety Report PHHO2013CN003844 7-Day safety report (eCTD-seq0262)
10/17/2014	New Investigator CLCZ696A2216 (eCTD-seq0260)
10/24/2014	Safety Report PHHO2012GB006694; follow-up (eCTD-seq0264)
1/23/2015	Novartis is submitting an information Amendment to inform the agency regarding the changes to specifications (eCTD-seq0268).
1/26/2015	Amendment 2 to CSR CLCZ696B2214. (eCTD-seq0267)
2/10/2015	Safety Report PHHO2013CN003844 (eCTD-seq0263)
2/26/2015	CMC Information Amendment to inform the agency regarding a typographical error in the description of Valsartan 80mg film-coated tablet that were used as a comparator in LCZ696 clinical study D2301 (eCTD-Seq0273).
2/27/2015	Clinical Information amendment to provide the Clinical Study Report for CLCZ696A2201 and CLCZ696A2223 (eCTD-Seq0269)
3/23/2015	Novartis is submitting Amendment 1 for CSRs CLCZ696A2201 and CLCZ696A2223. (eCTD-seq0270)
4/9/2015	Submission provides CSR's CLCZ696A2315 and CLCZ696A2318. (eCTD-seq0272)
4/16/2015	Clinical Information Amendment Updated IB Ed 16 (eCTD-seq0274)
4/17/2015	Amendment 1 to protocol CLCZ696A2216 (eCTD-seq0275).
6/10/2015	Submission provides CSRs CLCZ696A2219, CLCZ696A2219E1, LCZ696A1306, LCZ696A2316, LCZ696A2319, LCZ696A1304 and LCZ696A1305. (eCTD-seq0271)
6/26/2015	Information Amendment - CMC: To inform the agency regarding the addition of Singapore Pharmaceutical Manufacturing Pte .Ltd. as additional manufacturing and quality control site for LCZ696 50mg, 100mg, 200mg (eCTD-Seq0277)

FDA Interaction Date	Content Summary
2/20/2009	Request for Type B meeting to obtain feedback on proposed clinical development program for treatment of chronic heart failure. Meeting is requested to be held on April 13, 2009 (PS)
3/5/2009	FDA letter providing meeting confirmation for Pre-IND meeting, scheduled for April 22, 2009
3/20/2009	Submission of Briefing Book in support of Type B meeting to discuss the proposed clinical development program for the use of LCZ696 in the treatment of chronic heart failure has been scheduled for Wednesday, April 22, 2009 (PS)
6/2/2009	FDA meeting minutes for Pre-IND Meeting of April 22, 2009
6/9/2009	Briefing Book for Special Protocol Assessment for Study CLCZ696B2314
6/30/2009	Email providing the Agency with the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is referenced in Novartis' SPA
7/1/2009	Email correspondence providing the Agency with reference for Green, Porter, et al. 2000
7/16/2009	FDA LETTER stating that FDA does not agree with the special protocol assessment request dated June 9, 2009.
7/23/2009	Email regarding April 22, 2009 meeting and FDA comments regarding special protocol assessment received on July 16, 2009.
7/24/2009	Request for FDA Type A Pre-IND meeting to discuss the Agency's response to Special Protocol Assessment for Study CLCZ696B2314 dated July 16, 2009 (PS).
7/30/2009	FDA Letter granting Type A meeting as per Novartis' request on July 24, 2009, to discuss the Agency's response the Special Protocol Assessment for Study CLCZ696B2314
8/5/2009	Briefing book for the Type A meeting scheduled for August 20, 2009 to discuss the Agency's response to your Special Protocol Assessment for Study CLCZ696B2314. (ES) Note: This BB was submitted to Archives without cover letter of form.
8/18/2009	FDA Fax Providing SPA Follow-up Meeting Preliminary Responses
8/19/2009	Email correspondence regarding preliminary response to Type A meeting
8/20/2009	Novartis recap of meeting with the FDA to reach agreement on key elements of the proposed outcomes trial protocol CLCZ696B2314, which was previously submitted to the Agency under a Special Protocol Assessment (SPA)
8/27/2009	FDA minutes of the August 20, 2009 Type A SPA Follow-up teleconference with Novartis.
10/1/2009	Submission of Original IND for the indication of chronic heart failure (eCTD-seq0005)
10/15/2009	FDA Letter acknowledging receipt of Original IND
11/3/2009	Amendment providing updated drug substance stability data (up to 24 months) which support an extension in the re-test period from 24 months to 36 months (eCTD-seq0007)
11/6/2009	FDA Letter providing comments and requesting information regarding the development of LCZ696 for chronic heart failure and reduced ejection fraction.

FDA Interaction Date	Content Summary
11/10/2009	General Correspondence providing the Agency with notification of intent to submit Carcinogenicity study for protocol assessment within 30 days (eCTD-seq0008)
11/11/2009	Request for Type C meeting to discuss the proposed strategy for utilizing a Patient Reported Outcomes (PRO) instrument in the Phase 3 outcomes study (CLCZ696B2314) in chronic heart failure being conducted under this IND (eCTD-seq0009)
11/16/2009	FDA letter granting Type C meeting on January 21, 2010, to discuss proposed strategy for utilizing a Patient Reported Outcomes (PRO) instrument in your Phase 3 outcomes study (CLCZ696B2314) in chronic heart failure.
12/1/2009	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0010)
12/15/2009	Request for Special Protocol Assessment of the proposed Carcinogenicity Study Protocols in the mouse and rat, which will be included as part of the toxicology package to support the chronic heart failure indication under this IND. Included in the SPA package are the (eCTD-seq0012)
12/16/2009	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0011)
12/17/2009	Briefing Book for the Type C meeting to be held on January 21, 2010 to discuss the Patient Reported Outcomes instrument for Study CLCZ696B2314 (eCTD-seq0013).
1/6/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0014)
1/7/2010	Request for Carcinogenicity Study Protocol Assessment for rat study 0870373 (eCTD-seq0015)
1/19/2010	FDA fax providing Novartis with the Agency's preliminary responses in preparation for the Type C meeting scheduled for January 21, 2010 (PS)
1/22/2010	Submission of New Investigator to study CLCZ696B2314 (eCTD-seq0016)
2/8/2010	Submission of New Investigator to study CLCZ696B2314 (eCTD-seq0017)
2/10/2010	Submission of Information Amendment to provide updated Chemistry, Manufacturing and Controls Information regarding LCZ696 drug substance, drug product, and (eCTD-seq0018)
2/12/2010	Type C meeting minutes from January 21, 2010 meeting
3/5/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0019)
3/24/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0020)
4/22/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0021)
5/6/2010	Submission of New Investigators to studies CLCZ696B2314 (eCTD-seq0022)
5/27/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0023)
6/8/2010	Submission of Transfer of Obligations to study CLCZ696B2314 (eCTD-seq0024)
6/18/2010	Submission of New Investigators to study LCZ696B2314 (eCTD-seq0025)
7/7/2010	Study CLCZ696B2314 new investigator (eCTD-seq0026)
7/28/2010	Safety Report PHHO2010DE10636 (eCTD-seq0028)
7/30/2010	Submission of New Investigator to study CLCZ696B2314 (eCTD-seq0027)
8/3/2010	Safety Report PHHO2010DE10636; follow-up (eCTD-seq0029)
8/9/2010	Safety Report PHHO2010DE10636; follow-up (eCTD-seq0030)
8/24/2010	Safety Report PHHO2010DE10636; follow-up (eCTD-seq0032)

FDA Interaction Date	Content Summary
8/25/2010	Submission of New Investigators to study CLCZ696B2314 (eCTD-seq0031)
9/17/2010	New Investigators for protocol CLCZ696B2314 (eCTD-seq0033)
10/22/2010	Safety Report PHHO2010GB15448 7-day safety report. (PS)
10/22/2010	New Investigators for Protocol CLCZ696B2314 (eCTD-seq0034)
10/22/2010	Safety Report PHHO2010GB15448; (eCTD-seq0035)
10/27/2010	Safety Report PHHO2010GB13984; (eCTD-seq0037)
11/3/2010	7 Day Safety Report PHHO2010HU16306 (PS).
11/4/2010	New Investigator(s) for protocol(s) LCZ696B2314 (eCTD-seq0036)
11/11/2010	Safety Report PHHO2010HU16306; (eCTD-seq0038)
11/19/2010	New Investigators for protocols CLCZ696B2314 (eCTD-seq0039)"
11/22/2010	Safety Report PHHO2010GB16454 (eCTD-seq0040)
11/24/2010	Safety Report PHHO2010HU17146 (eCTD-seq0043)
11/24/2010	Safety Report PHHO2010HU16306; follow-up (eCTD-seq0044)
11/29/2010	Safety Report PHHO2010TW17370 (eCTD-seq0046)
11/29/2010	7 Day safety report PHHO2010GB16454 (PS).
11/30/2010	Safety Report PHHO2010HU17146; follow-up (eCTD-seq0047)
12/1/2010	Amendment to provide for an extension of shelf life for a comparator for use in clinical studies (eCTD-seq0045).
12/6/2010	Change in responsibility to Simon Ducher (eCTD-seq0042).
12/7/2010	Safety Report PHHO2010GB13984;follow-up (eCTD-seq0050)
12/7/2010	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0049)
12/7/2010	Safety Report PHHO2010TW17370 (eCTD-seq0051)
12/8/2010	7 Day Safety report PHHO2010DE18191 (PS).
12/8/2010	Safety Report PHHO2010HU17146; follow-up (eCTD-seq0052)
12/9/2010	New Investigator for protocol CLCZ696B2314 (eCTD-seq0048)
12/13/2010	Safety Report PHHO2010DE18191 (eCTD-seq0054)
12/17/2010	Amendment 1 to protocol CLCZ696B2314 (eCTD-seq0053).
12/20/2010	Annual Report covering the period from 01-Nov-2009 to 31-Oct-2010 (eCTD-seq0041)
12/20/2010	7 Day safety report PHHO2010US18903 (PS).
12/21/2010	Request for Type C meeting to discuss the proposed strategy for utilizing a Patient Reported Outcomes instrument in patients with preserved chronic heart failure (eCTD-seq0055).
12/22/2010	Safety Report PHHO2010TW11790 (eCTD-seq0057)
12/22/2010	Safety Report PHHO2010IL18897 (eCTD-seq0056)
12/28/2010	Safety Report PHHO2010TW11790; follow-up (eCTD-seq0060)
1/3/2011	FDA LETTER confirming the Type C meeting to be held on March 1, 2011 to discuss the proposed strategy for using a Patient Reported Outcomes instrument.
1/3/2011	Safety Report PHHO2010US18903; follow-up (eCTD-seq0061)
1/5/2011	Safety Report PHHO2010IL18897; follow-up (eCTD-seq0062)
1/13/2011	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0063)

FDA Interaction Date	Content Summary
1/21/2011	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0065)
1/22/2011	Safety Report PHHO2010US18903 (eCTD-seq0058)
1/25/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0064).
1/28/2011	Safety Report PHHO2010DE18191; follow-up (eCTD-seq0059)
1/31/2011	Briefing Book for the Type C meeting to be held on March 1, 2011 to discuss the strategy for utilizing a Patient Reported Outcomes instrument (eCTD-seq0066).
2/2/2011	Email from the FDA cancelling the meeting to be held on March 1, 2011 because the review of the briefing document will be completed in mid-April.
2/18/2011	New Investigators for protocol CLCZ696B2314 (eCTD-seq0067)
2/18/2011	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0068)
2/18/2011	Safety Report PHHO2010IL18897; follow-up (eCTD-seq0069)
3/15/2011	Safety Report PHHO2011IL04325 7-Day safety report (PS).
3/22/2011	Safety Report PHHO2011IL04325 (eCTD-seq0071)
3/31/2011	Safety Report PHHO2010GB13984; follow-up (eCTD-seq0072)
4/6/2011	New Investigators for protocol CLCZ696B2314 (eCTD-seq0070)
4/7/2011	Safety Report PHHO2010HU18329 (eCTD-seq0073)
4/12/2011	Safety Report PHHO2011FI06062 7-Day safety report (PS).
4/13/2011	Safety Report PHHO2011FI06062 (eCTD-seq0074)
4/18/2011	Safety Report PHHO2011FI06062; follow-up (eCTD-seq0075)
4/20/2011	FDA comments on submission dated January 31, 2011 regarding PRO SYMPL-HF.
4/26/2011	Safety Report PHHO2011FI06062; follow-up (eCTD-seq0077)
5/3/2011	New Investigators for protocol CLCZ696B2314 (eCTD-seq0076).
5/3/2011	Safety Report PHHO2011PL07181 (eCTD-seq0078)
5/14/2011	Safety Report PHHO2011HU06255 (eCTD-seq0080)
5/16/2011	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0081)
5/20/2011	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0082)
5/24/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0079)
5/25/2011	Safety Report PHHO2011PL07181; follow-up (eCTD-seq0083)
6/10/2011	Safety Report PHHO2011BR09808 7-Day safety report (PS).
6/15/2011	Response to FDA advice letter dated April 20, 2011 regarding PRO SYMPL-HF. (eCTD-seq0084)
6/17/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0085)
6/17/2011	Safety Report PHHO2011BR09808 (eCTD-seq0087)
6/21/2011	Safety Report PHHO2011TW09929 (eCTD-seq0088)
6/22/2011	Amendment # 2 to protocol CLCZ696B2314 (eCTD-seq0086).
6/22/2011	Telecon regarding request for teleconference with FDA to discuss a new PRO instrument (SYMPL-HF).
6/23/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0089)
6/27/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0091)
7/1/2011	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0092)
7/6/2011	New Investigator for protocol CLCZ696B2314 (eCTDseq0090)
7/6/2011	Safety Report PHHO2011HU06255; follow-up (eCTD-seq0093)

FDA Interaction Date	Content Summary
7/12/2011	FDA response to Novartis request for clarification regarding FDA advice letter dated April 20, 2011.
7/12/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0094)
7/15/2011	Safety Report PHHO2011HU06255; follow-up (eCTD-seq0095)
7/18/2011	Safety Report PHHO2011IN11799 7-Day safety report (PS).
7/22/2011	Safety Report PHHO2011IN11799 (eCTD-seq0096)
7/26/2011	FDA minutes of the July 19, 2011 teleconference with Novartis to discuss advice letter dated July 12, 2011.
8/1/2011	Safety Report PHHO2011GB12663 7-Day safety report (PS).
8/1/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0097)
8/5/2011	Email notification to FDA regarding enalapril comparator used in CLCZ696B2314 trial.
8/8/2011	Safety Report PHHO2011GB12663 (eCTD-seq0098)
8/12/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0099)
8/18/2011	Safety Report PHHO2011PH11140 7-Day safety report (PS)
8/22/2011	Change in Transfer of Obligations for Protocol CLCZ696B2314 (new CRO). (eCTD-seq0100)
8/24/2011	Safety Report PHHO2011GB12663; follow-up (eCTD-seq0101)
8/25/2011	Safety Report PHHO2011PH11140 (eCTD-seq0103)
8/26/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0104)
8/30/2011	New Investigator for protocol CLCZ696B2314 (eCTD-seq0102)
9/2/2011	Submission of notifications to the FDA about supply issue of enalapril in CLCZ696B2314. (eCTD-seq0105)
9/9/2011	Transfer of Obligations for Protocol CLCZ696B2314. (eCTD-seq0106)
9/14/2011	Safety Report PHHO2011FR14817 (eCTD-seq0107)
9/22/2011	Safety Report PHHO2011FI06062; follow-up (eCTD-seq0108)
9/23/2011	Safety Report PHHO2011PH15876 7-Day Safety Report (PS)
9/26/2011	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0109)
9/29/2011	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0112)
9/29/2011	Safety Report PHHO2011PH15876 (eCTD-seq0111)
10/3/2011	Safety Report PHHO2010HU17146; follow-up (eCTD-seq0113)
10/7/2011	New Investigators for Protocol CLCZ696B2314 (eCTD-seq0110)
10/7/2011	Safety Report PHHO2011TW16144 (eCTD-seq0114)
10/20/2011	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0116)
10/20/2011	Safety Report PHHO2011BR17560 (eCTD-seq0115)
11/1/2011	New Investigator's for Protocol CLCZ696B2314 (eCTD-seq0117)
11/2/2011	Safety Report PHHO2011IS18084 7-Day safety report (PS)
11/3/2011	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0119)
11/8/2011	Safety Report PHHO2011IS18084 (eCTD-seq0120)
11/29/2011	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0121)
12/9/2011	Annual Report covering the period from 31-Oct-2010 to 31-Oct-2011 (eCTD-seq0118)
12/21/2011	New Investigator for protocol CLCZ696B2314 (eCTD-Seq0122).

FDA Interaction Date	Content Summary
12/22/2011	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0123)
1/4/2012	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0124)
1/11/2012	Email from FDA agreeing to request an EOP2 meeting for HF-PEF indication under IND 104,628.
1/18/2012	Safety Report PHHO2012BE001036 7-Day safety report (PS)
1/18/2012	Safety Report PHHO2012GB001045 7-Day safety report (PS)
1/24/2012	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0125)
1/24/2012	Safety Report PHHO2012BE001036; (eCTD-seq0126)
1/25/2012	Safety Report PHHO2012GB001045 (eCTD-seq0127)
2/1/2012	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0128)
2/3/2012	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0130)
2/3/2012	Safety Report PHHO2012ZA001868 7-Day safety report (PS)
2/9/2012	New Investigators for protocol CLCZ696B2314 (eCTD-seq0131).
2/9/2012	Safety Report PHHO2012ZA001868; (eCTD-seq0132)
2/15/2012	Safety Report PHHO2012BR002454 (eCTD-seq0133).
2/28/2012	Safety Report PHHO2012BR002454; follow-up (eCTD-seq0135)
3/2/2012	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0129)
3/2/2012	New Protocol for Study CLCZ696B2107 (eCTD-seq0134)
3/7/2012	Safety Report PHHO2012PL003313 (eCTD-seq0136)
3/13/2012	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0137).
3/20/2012	Safety Report PHHO2012BR003913 (eCTD-seq0138)
3/26/2012	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0140).
3/27/2012	New Investigator for Protocol CLCZ696B2107 and CLCZ696B2314 (eCTD-seq0139)
3/29/2012	Submission contains Investigator Brochure Edition 11, dated March 13, 2012 replacing Edition 10, dated February 21, 2011. (eCTD-seq0141)
4/5/2012	Safety Report PHHO2012BR003913; follow-up(eCTD-seq0142)
4/9/2012	Safety Report PHHO2012TW003618 (eCTD-seq0144)
4/9/2012	Safety Report PHHO2012PL003313 (eCTD-seq0145)
4/13/2012	Novartis is requesting a Type B EOP2 meeting to seek feedback from the Agency on the proposed clinical development program for LCZ696 for the treatment of heart failure in patients with preserved ejection fraction. (eCTD-seq0143)
4/16/2012	Safety Report PHHO2012TW003618; follow-up (eCTD-seq0148)
4/17/2012	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0146)
4/20/2012	Change in transfer of obligations for protocol CLCZ696B2314 (new CRO). (eCTD-seq0147)
4/20/2012	New Protocol for Study LCZ696A2120 (eCTD-seq0149)
5/1/2012	FDA letter advising Type B EOP2 meeting granted for June 18, 2012.
5/8/2012	New investigator for protocol LCZ696A2120,CLCZ696B2314 (eCTD-seq0150)
5/9/2012	Safety Report PHHO2012GB006694 (eCTD-seq0152)
5/14/2012	New Investigator for Protocol CLCZ696B2314 (eCTD-seq0153).
5/14/2012	Briefing Book for the June 18, 2012 Type B EOP2 meeting (eCTD-seq0151). (BLINDED)

FDA Interaction Date	Content Summary
5/29/2012	Safety Report PHHO2012BR005720 (eCTD-seq0154)
6/1/2012	Safety Report PHHO2012HK007713 (eCTD-seq0155)
6/8/2012	Safety Report PHHO2011IN12674 7-Day Safety report (PS).
6/12/2012	New Protocol CLCZ696A2119, entitled 'An open label, three-period, single sequence study to evaluate the pharmacokinetic drug-drug interaction between LCZ696 and amlodipine in healthy volunteers' (eCTD-seq0156)
6/13/2012	FDA preliminary response to meeting questions for meeting scheduled for June 18, 2012.
6/18/2012	Safety Report PHHO2011IN12674 (eCTD-seq0157)
6/20/2012	Safety Report PHHO2010HU18329 (eCTD-seq0158)
6/20/2012	Safety Report PHHO2012BR008797 (eCTD-seq0159)
6/21/2012	Safety Report PHHO2012NL008767 (eCTD-seq0160)
6/25/2012	Email to FDA containing Novartis meeting minutes from the EOP2 meeting held on June 18, 2012 for the HF-PEF indication.
6/26/2012	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0163)
6/26/2012	Safety Report PHHO2011BR17560; follow-up (eCTD-seq0162)
7/3/2012	New Investigators for protocol CLCZ696A2119, B2314 (eCTD-seq0161)
7/5/2012	Safety Report PHHO2012BR008797; follow-up (eCTD-seq0165)
7/9/2012	Safety Report PHHO2011BR09808; follow-up (eCTD-seq0166)
7/9/2012	Safety Report PHHO2011BR17560; follow-up (eCTD-seq0167)
7/10/2012	New Protocol CLCZ696B2122, entitled 'An open-label, three-period, single-sequence study to evaluate the pharmacokinetic drug-drug interaction between LCZ696 and metformin in healthy volunteers of Japanese descent' (eCTD-seq0164)
7/12/2012	Safety Report PHHO2012AR010257 7-Day safety report (PS)
7/17/2012	FDA meeting minutes from EOP2 meeting held on June 18, 2012.
7/18/2012	Safety Report PHHO2012BR008797; follow-up (eCTD-seq0172)
7/20/2012	Request for Type C CMC meeting to gain agreement on the proposed drug substance staring materials. Submission includes briefing book. (eCTD-seq0170)
7/23/2012	New Investigators for protocols LCZ696B2122,B2314 (eCTD-seq0171)
7/24/2012	Safety Report PHHO2012BR003913; follow-up (eCTD-seq0174)
7/24/2012	Safety Report PHHO2012AR010257 (eCTD-seq0173)
7/25/2012	Safety Report PHHO2011BR17514 (eCTD-seq0175)
7/25/2012	Email regarding objection to proposed EOP2 meeting minutes changes.
8/2/2012	Change in regulatory contact from Simon Ducher to Alison Mickle (eCTD-seq0177)
8/9/2012	Study CLCZ696B2114 new protocol, includes transfer of obligations. (eCTD-seq0168)
8/9/2012	Study CLCZ696B2125 new protocol, includes transfer of obligations (eCTD-seq0169)
8/10/2012	Safety Report PHHO2012EC005568 (eCTD-seq0178)
8/17/2012	Safety Report PHHO2012US011818 7-Day safety report (PS)

FDA Interaction Date	Content Summary
8/22/2012	New Investigators for protocols CLCZ696B2114, CLCZ696B2125 and CLCZ696B2314 (eCTD-seq0179)
8/22/2012	Safety Report PHHO2012NL008767; follow-up (eCTD-seq0180)
8/23/2012	Safety Report PHHO2012GB011913 (eCTD-seq0181)
8/23/2012	Safety Report PHHO2012US011818 (eCTD-seq0182)
8/31/2012	Safety Report PHHO2012US011818; follow-up (eCTD-seq0184)
8/31/2012	Safety Report PHHO2012IS012355 (eCTD-seq0185)
9/11/2012	New Investigator for protocol CLCZ696B2314 (eCTD-seq0183)
9/11/2012	Safety Report PHHO2012GB011913; follow-up (eCTD-seq0187)
9/13/2012	New Investigator(s) for protocol(s) CLCZ696B2314 (eCTD-seq0186).
9/18/2012	Novartis' request on July 23, 2012 to propose two changes to the meeting minutes related to the reflection of the role of AHU in the indication statement and role of valsartan in the treatment of HF-PEF. On July 25, 2012 Novartis was informed by the FDA Project Manager that the minutes were deemed to accurately reflect the discussion and therefore the minutes will not be modified as per Novartis proposed changes. (eCTD-seq0188)
9/20/2012	Safety Report PHHO2012PE012764 7-Day safety report (PS)
9/21/2012	New Protocol CLCZ696B2113, entitled An open-label
9/21/2012	Safety Report PHHO2010HU18329; follow-up(eCTD-seq0191)
9/21/2012	Safety Report PHHO2012PE012764 7-Day safety report (PS)
9/25/2012	Safety Report PHHO2012DE013453 7-Day safety report (PS)
9/26/2012	Submission provides a drug supply issue notification for study CLCZ696B2314 whereby the allocated study medication for two patients was switched. (eCTD-seq0192)
9/27/2012	New Investigator(s) for Protocol CLCZ696B2314 (eCTD-seq0190)
9/27/2012	Safety Report PHHO2012TR013235 (eCTD-seq0193)
9/28/2012	Safety Report PHHO2012IN013259 (eCTD-seq0195)
9/29/2012	Safety Report PHHO2012PE012764 (eCTD-seq0194)
10/3/2012	Safety Report PHHO2012ES007783 (eCTD-seq0199)
10/3/2012	Safety Report PHHO2012DE013453 (eCTD-seq0198)
10/3/2012	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0197)
10/5/2012	Novartis telephone report regarding the objection to the HF-PEF end of phase 2 meeting minutes (S-0188).
10/9/2012	Safety Report PHHO2012PE012764; follow-up (eCTD-seq0201)
10/9/2012	Safety Report PHHO2012BR013598 (eCTD-seq0202)
10/11/2012	Novartis is requesting for FDA feedback for LCZ696B2314 (PARADIGM) ' Statistical Analysis Plan. (eCTD-seq0196)
10/12/2012	Safety Report PHHO2012TR013235; follow-up (eCTD-seq0204)
10/18/2012	Safety Report PHHO2012IS012355; follow-up (eCTD-seq0206)
10/19/2012	New Investigator for protocol CLCZ696B2314 (eCTD-seq0200)
10/22/2012	Safety Report PHHO2012DE014709 (eCTD-seq0207)
10/23/2012	New Investigator for Protocol CLCZ696B2113 (eCTD-Seq0203)

FDA Interaction Date	Content Summary
10/24/2012	Information amendment - Pharmacology/toxicology for Reports DMPK R0900652, 0970613, 0870734 (eCTD-seq0205)
10/31/2012	Safety Report PHHO2012ZA015482 7-Day safety report (PS)
10/31/2012	Safety Report PHHO2012IL015128 (eCTD-seq0208)
11/1/2012	Safety Report PHHO2012EC015122 (eCTD-seq0209)
11/6/2012	Safety Report PHHO2012ZA015482 (eCTD-seq0210)
11/9/2012	FDA advice/information request regarding question in briefing package.
11/15/2012	Safety Report PHHO2012IL015128; follow up (eCTD-seq0212)
11/19/2012	New investigator for protocol CLCZ696B2122 (eCTD-seq0211)
11/21/2012	Safety Report PHHO2012ZA015482; follow-up (eCTD-seq0213)
11/21/2012	Safety Report PHHO2012BR016272 (eCTD-seq0214)
12/3/2012	Safety Report PHHO2012IL015128; follow-up (eCTD-seq0216)
12/3/2012	Safety Report PHHO2012IT005964 (eCTD-Seq0217)
12/11/2012	Safety Report PHHO2012ES004570 (eCTD-Seq0218)
12/12/2012	Annual Report covering the period from 01-November-2011 to 31-October-2012 (eCTD-seq0215)
12/13/2012	Safety Report PHHO2012ZA017679 7-Day Safety Report (PS)
12/17/2012	Pharm/Tox reports for Study 1170562, DMPK R1200239. (eCTD-seq0219)
12/18/2012	New protocol CLCZ696A2124 entitled, An open-label
12/19/2012	Safety Report PHHO2012DE014709; follow-up (eCTD-seq0222)
12/19/2012	Safety Report PHHO2012BR013598; follow-up (eCTD-seq0221)
12/20/2012	Safety Report PHHO2012ZA017679 (eCTD-seq0223)
12/24/2012	Safety Report PHHO2012ZA017679; follow-up (eCTD-seq0224)
1/3/2013	Safety Report PHHO2012FR018676 7-Day safety report (PS)
1/3/2013	Safety Report PHHO2012DE018401 (eCTD-seq 0226)
1/3/2013	Safety Report PHHO2012BR016272; follow-up (eCTD-seq 0225)
1/8/2013	Request to submit the DSUR in lieu of the annual report using the existing reporting period July 31, 2012 to July 30 2013.(eCTD-seq0227)
1/9/2013	Submission provides for a revised Transfer of Sponsor Obligation for Study CLCZ696B2314 to capture the addition of Cognizant Technology Solutions India Pvt. Ltd., as noted on the Transfer of Obligation in Module 1.3.1.4. (eCTD-seq0228)
1/9/2013	Safety Report PHHO2012FR018676 (eCTD-Seq0229)
1/10/2013	Safety Report PHHO2012DE018401; follow-up (eCTD-seq0230)
1/15/2013	Safety Report PHHO2012FR018676; follow-up (eCTD-seq0231)
1/18/2013	New Investigator for Study CLCZ696B2314. (eCTD-seq0232)
1/25/2013	Safety Report PHHO2013IN000955 (eCTD-seq0235)
1/25/2013	Safety Report PHHO2013IN000955 7-Day safety report (PS)
1/30/2013	Email correspondence from FDA regarding the SAP and Patient Narrative Proposal.
2/1/2013	Safety Report PHHO2013ZA001555 (eCTD-seq0238)
2/1/2013	Safety Report PHHO2012ES007783; follow-up (eCTD-seq0237)
2/4/2013	Safety Report PHHO2012ES007783; follow-up (eCTD-seq0239).

FDA Interaction Date	Content Summary
2/4/2013	Safety Report PHHO2012ES007783 Follow-Up (eCTD-seq0239)
2/5/2013	New Investigator for Study No. CLCZ696B2122. (eCTD-seq0236)
2/6/2013	Email from FDA regarding the pediatric plan timeline.
2/6/2013	Safety Report PHHO2013JP000998; follow-up (eCTD-seq0240)
2/7/2013	Safety Report PHHO2012IL015128; follow-up (eCTD-seq0242)
2/8/2013	Response to FDA email request dated January 30, 2013 regarding Statistical Analysis Plan. (eCTD-seq0241)
2/12/2013	PHHO2011BR17514 7-Day safety report (PS).
2/13/2013	New Investigator for protocol CLCZ696A2124 and TOO for CLCZ696B2122 (eCTD-seq0234).
2/14/2013	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0243)
2/19/2013	Safety Report PHHO2013JP000998; follow-up (eCTD-seq0244)
2/20/2013	Safety Report PHHO2012DE013453; follow-up (eCTD-seq0245)
2/20/2013	Safety Report PHH02011BR17514 Follow-up (eCTD-seq0246)
2/27/2013	FDA letter granting harmonized DSUR for IND 104,628.
2/27/2013	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0248)
3/6/2013	FDA letter is an agreement for the PARADIGM-HF statistical analysis plan (SAP).
3/12/2013	Amendment 3 to protocol CLCZ696B2314 (eCTD-Seq0247)
3/14/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0249) The receipts are not available for this submission.
3/15/2013	Safety Report PHHO2013DE002628 Follow-up (eCTD-seq0250) The receipts are not available for this submission.
3/22/2013	Safety Report PHHO2013JP000998 Follow-up (eCTD-seq0251)
3/22/2013	Safety Report PHHO2010IL18897 Follow-up (eCTD-seq0252)
3/28/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0253)
4/1/2013	Novartis is providing a final summary of the case regarding a drug supply issue for study CLCZ696B2314. (eCTD-seq0254)
4/5/2013	Information Amendment: Clinical Study Report for CLCZ696B2214, PARAMOUNT - providing notification that the study report for CLCZ696B2214 (PARAMOUNT) has been submitted to IND 77318 (eCTD-Seq0255)
4/10/2013	Safety Report PHHO2013DE002628; folow-up (eCTD-seq0256)
4/16/2013	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0257)
4/16/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0258)
4/16/2013	Safety Report PHHO2012BR018051 7-day report (PS)
4/18/2013	Safety Report PHHO2012BR018051 Follow-Up (eCTD-seq0260)
4/19/2013	Clinical Information Amendment submitted to provide an updated version of the Investigator's Brochure Edition 12 (eCTD-Seq0259)
5/1/2013	Safety Report PHHO2011TW09929 Follow-up (eCTD-seq0263)
5/1/2013	Safety Report PHHO2012BR018051 Follow-up (eCTD-seq0262)
5/1/2013	Safety Report PHH02012EC015122 Follow-up (eCTD-seq0264)
5/3/2013	Submission of Transfer of Sponsor Obligation for Study CLCZ696A2124. (eCTD-seq0261)
5/3/2013	Safety Report PHHO2013BR001096 (eCTD-seq0265)

FDA Interaction Date	Content Summary
5/6/2013	Safety Report PHHO2013BR005937 7-day report (PS).
5/8/2013	Safety Report PHHO2013JP005683 (eCTD-seq0266)
5/9/2013	Safety Report PHHO2013BR001096 (eCTD-seq0267)
5/13/2013	Safety Report PHHO2013JP000998 Follow-up (eCTD-seq0268)
5/14/2013	Safety Report PHHO2013BR005937 (eCTD-seq0270)
5/15/2013	Safety Report PHHO2010TW11790 Follow-up (eCTD-seq0271)
5/17/2013	Clinical Study Report for CLCZ696B2107. (eCTD-seq0269)
5/17/2013	Safety Report PHHO2013CO006094 (eCTD-seq0272)
5/21/2013	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0273)
5/21/2013	Safety Report PHHO2011IS18084 Follow-up (eCTD-seq0274)
5/24/2013	New Investigator for Study CLCZ696B2314. (eCTD-seq0275)
5/29/2013	Safety Report PHHO2013JP005683 Follow-up (eCTD-seq0276)
5/30/2013	Safety Report PHHO2013US006665 (eCTD-seq0277)
5/31/2013	Safety Report PHH02010HU18329 Follow-up (eCTD-seq0278)
6/4/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0279)
6/6/2013	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0282)
6/6/2013	Safety Report PHHO2012FR018676 Follow-up (eCTD-seq0281)
6/12/2013	Clinical Information Amendment is submitted to provide the CSR for CLCZ696A2120. (eCTD-seq0280)
6/12/2013	Safety Report PHHO2011BR17560 Follow-up (eCTD-seq0285)
6/12/2013	Safety Report PHH02013BR001096 Follow-up (eCTD-seq0284)
6/13/2013	Safety Report PHH02012EC015122 Follow-up (eCTD-seq0286)
6/14/2013	Safety Report PHHO2013JP005683; follow-up (eCTD-seq0283)
6/24/2013	Safety Report PHHO2013IL007648 Follow-Up (eCTD-seq0287)
6/27/2013	Safety Report PHHO2012EC015122 Follow-Up (eCTD-seq0288)
7/1/2013	Submission provides change in regulatory contact from Alison Mickle to Kanan Solanki. (eCTD-seq0290)
7/3/2013	Submission of revised Transfers of Sponsor Obligation for Studies CLCZ696A2119, CLCZ696A2120, CLCZ696B2107, CLCZ696B2114, CLCZ696B2122 and CLCZ696B2125. (eCTD-seq0289)
7/5/2013	Safety Report PHHO2013US006665 follow-up (eCTD-seq0293)
7/9/2013	Safety Report PHHO2013BR001096 Follow-Up (eCTD-seq0294)
7/11/2013	New Investigator for Study CLCZ696B2314. (eCTD-seq0295)
7/12/2013	Safety Report PHHO2013US006665 Follow-up (eCTD-seq0298)
7/13/2013	Safety Report PHHO2012GB017225 follow-up (eCTD-seq0296)
7/16/2013	New Protocol CLCZ696B2228, entitled A multicenter
7/17/2013	Safety Report PHHO2013IL007648 follow-up (eCTD-seq0299)
7/26/2013	Information amendment to protocol CLCZ696A2124 (eCTD-seq0300)
7/31/2013	Safety Report PHHO2013PH009418 7-Day (PS)
8/2/2013	Safety Report PHHO2012ZA008690 7-Day safety report (PS).
8/2/2013	Safety Report PHH02013ZA008690 (eCTD-seq0301)
8/6/2013	Safety Report PHHO2012FR018676 Follow-Up (eCTD-seq0303)

FDA Interaction Date	Content Summary
8/8/2013	Safety Report PHHO2012BR018051 follow-up (eCTD-seq0304)
8/8/2013	Safety Report PHHO2013DE002628 follow-up (eCTD-seq0305)
8/8/2013	Safety Report PHHO2013PH009418 (eCTD-seq0306)
8/9/2013	Safety Report PHHO2012NL008767 Follow-Up (eCTD-seq0308)
8/12/2013	Safety Report PHHO2012TL015128 Follow-Up (eCTD-req0310)
8/12/2013	Safety Report PHHO2012IT005094 Follow-Up (eCTD-seq0309)
8/14/2013	Email regarding Study D2301 Submission Timeline agreement from FDA.
8/14/2013	Clinical Information Amendment providing CSRs to studies CLCZ696B2122, CLCZ696B2114, CLCZ696B2125 and CLCZ696B2113. In addition Amendment 1 to Clinical Study Report CLCZ696B2107 is provided (eCTD-Seq0307).
8/16/2013	Submission of New Protocol CLCZ696D2301. (eCTD-seq0302)
8/19/2013	Safety Report PHHO2013CO006094 Follow-Up (eCTD-seq0311)
8/20/2013	Safety Report PHHO2012ES004570 follow-up (eCTD-seq0312)
8/20/2013	Safety Report PHHO2012IL015128 follow-up (eCTD-seq0313)
8/22/2013	Safety Report PHHO2010TW19816; follow-up (eCTD-seq0316)
8/22/2013	Safety Report PHHO2012BR018051 Follow-up (eCTD-seq0315)
8/22/2013	Safety Report PHHO2010TW19998 Follow-up (eCTD-seq0314)
8/23/2013	Safety Report PHHO2012BR005720 Follow-up (eCTD-seq0317)
9/5/2013	Safety Report PHHO2012IL015128 follow-up (eCTD-seq0319)
9/6/2013	Safety Report PHHO2012BR005720 follow-up (eCTD-seq0321)
9/9/2013	Safety Report PHHO2013TW011210 7-Day safety report PS.
9/10/2013	Response to FDA request dated June 18, 2012 regarding study CLCZ696D2301. (eCTD-seq0320)
9/10/2013	Safety Report PHHO2013TW011210 (eCTD-seq0322)
9/17/2013	Safety Report PHHO2013TW011210 follow up (eCTD-seq0323)
9/18/2013	Safety Report PHHO2012ES004570; follow-up (eCTD-seq0325)
9/19/2013	New Investigator for Study CLCZ696B2314 (eCTD-seq0324).
9/24/2013	Safety Report PHHO2012BR008797 follow-up (eCTD-seq0326)
9/25/2013	DSUR Annual report covering Period from 31 July 2012 through 30 July 2013 (eCTD-seq0318)
9/26/2013	New Protocol for CLCZ696B2116 entitled 'An open-label, two-period, single-sequence study to evaluate the pharmacokinetic and pharmacodynamic drug-drug interaction between orally administered LCZ696 and furosemide in healthy subjects' and TOO (eCTD-Seq0328)
10/4/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0329)
10/7/2013	Safety Report PHHO2013ES004570 follow-up (eCTD-seq0331)
10/9/2013	Clinical Information Amendment is submitted to provide notification that Amendment 1 of the Clinical Study Report for CLCZ696B2214 (PARAMOUNT) has been submitted to IND 77,318 (eCTD-seq0330).
10/10/2013	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0332)
10/17/2013	New Investigator for Study CLCZ696D2301. (eCTD-seq0333)
10/21/2013	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0336)

FDA Interaction Date	Content Summary
10/22/2013	Submission of change in regulatory contact from Dr. Kanan Solanki to Dr. Masha Berkhin. (eCTD-seq0335)
10/23/2013	New Investigators for Study LCZ696B2216 and Study LCZ696B2228. (eCTD-seq0334)
10/24/2013	New Investigator for Study CLCZ696B2314. (eCTD-seq0337)
10/24/2013	Safety Report PHHO2013PH009418; follow-up (eCTD-seq0327)
10/25/2013	The purpose of this submission is to notify the Agency that following portfolio review Novartis has decided to postpone recruitment of study CLCZ696D2301; PARAGONHF (HFpEF). (eCTD-seq0339)
10/28/2013	New Investigators for Protocol LCZ696D2301 (eCTD-Seq0338)
10/30/2013	Safety Report PHHO2012HK007713 Follow-up (eCTD-seq0340)
10/31/2013	Safety Report PHHO2013BR001096 follow-up (eCTD-seq0341)
11/1/2013	Safety Report PHHO2013JP005683,followup (eCTD-seq0342)
11/8/2013	New Investigator for Study CLCZ696B2228. (eCTD-seq0344)
11/12/2013	New Investigator for Study CLCZ696D2301. (eCTD-seq0345)
11/12/2013	Novartis is providing a preclinical 15 day IND safety report to notify the Agency of a new, unexpected, and potentially adverse finding of increased levels of amyloid beta (A') in the cerebrospinal fluid (CSF), in the absence of changes of levels in the brain, which was observed during a 2-week oral investigative study in cynomolgus monkeys treated with LCZ696; the human translatability and potential consequences of these changes are currently unknown. (eCTD-seq0343)
11/20/2013	Submission is to provide the agency with the Statistical Analysis Plan (SAP) for study CLCZ696D2301 (PARAGON). (eCTD-seq0346)
11/25/2013	New Investigators for protocol LCZ696D2301 (eCTD-seq0060)
11/27/2013	Safety Report PHHO2012AR010257 Follow-up (eCTD-seq0348)
12/2/2013	Submission provides IB Edition 13 and updated ICFs. (eCTD-seq0349)
12/4/2013	Safety Report PHHO2010TW11790 Follow-up (eCTD-seq0350)
12/10/2013	New Investigator(s) for protocol(s) CLCZ696B2228 and CLCZ696D2301 (eCTD-seq0351).
12/11/2013	Novartis is providing to the FDA the initial Pediatric Study Plan (iPSP). (eCTD-seq0352)
12/16/2013	Safety Report PHHO2012HK007713; follow-up (eCTD-seq0353)
12/19/2013	Safety Report PHHO2013BR001096; follow-up (eCTD-seq0356)
12/19/2013	Safety Report PHHO2013TW011210 Follow-up (eCTD-seq0354)
12/31/2013	Safety Report PHHO2013ES016372; (eCTD-seq0357)
1/8/2014	New Investigators for Protocols CLCZ696B2228, CLCZ696D2301 and CLCZ696B2314 (eCTD-Seq0355)
1/16/2014	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0358)
2/5/2014	Safety Report PHHO2013TW011210; follow-up (eCTD-seq0359)
2/12/2014	New Investigator for Studies CLCZ696B2228 and CLCZ696B2314. (eCTD-seq0360)
2/27/2014	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0361)

FDA Interaction Date	Content Summary
2/27/2014	Safety Report PHHO2012ES004570; follow-up (eCTD-seq0362)
3/4/2014	Safety Report PHHO2011IS18084; follow-up (eCTD-seq0365)
3/7/2014	New Investigators for Protocol CLCZ696B2228 (eCTD-Seq0363)
3/7/2014	CMC Information Amendment (Seq 0364)
3/18/2014	Safety Report PHHO2011TW09929; follow-up (eCTD-seq0367)
3/26/2014	Safety Report PHHO2014IN003017;(eCTD-seq0368)
3/27/2014	Safety Report PHHO2011IN12674; follow-up (eCTD-seq0371)
3/29/2014	Safety Report PHHO2013TW011210; Follow-up (eCTD-seq0370)
4/1/2014	Clinical Information Amendment which provides an updated version of the Investigator's Brochure Edition 14, dated 20-Mar-2014 (eCTD-Seq0369).
4/1/2014	Novartis is notifying FDA that on the March 28, 2014, the DMC of the CLCZ696B2314 (PARADIGM-HF) study unanimously recommended early closure of the trial for reasons of compelling efficacy following a preplanned interim analysis. (eCTD-seq0372)
4/7/2014	Safety Report PHHO2013BR001096; Follow-up (eCTD-seq0366)
4/7/2014	Safety Report PHHO2012FR018676; follow-up (eCTD-seq0374)
4/7/2014	Safety Report PHHO2013BR001096; follow-up (eCTD-seq0373)
4/9/2014	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0375)
4/11/2014	New Investigator for protocol LCZ696B2228 (eCTD-seq0376)
4/14/2014	Submission is to provide the Agency with a proposed PARADIGM-HF Unblinding Plan for FDA review and comment. (eCTD-seq0377)
4/14/2014	FDA advice letter regarding agreement on iSPS.
4/14/2014	FDA advice information request for Novartis to submit an Agreed iPSP.
4/15/2014	Submission provides Amendment 4 to Protocol CLCZ696B2314, New Clinical Data from study CLCZ696A2126 and Pharmacology/Toxicology information. (eCTD-seq0379)
4/15/2014	The purpose of this submission is to provide the Agency with Amendment 1 to the PARADIGM-HF SAP. (eCTD-seq0378)
4/18/2014	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0380)
4/30/2014	Telecon with the FDA to discuss our proposed PARADIGM-HF unblinding plan to facilitate early discussions with FDA and other Health Authorities (HAs).
5/8/2014	Submission provides a request for a Pre-NDA meeting with FDA. (eCTD-seq0381)
5/8/2014	FDA advice information request regarding Novartis submission containing a Statistical Analysis Plan (SAP) for Protocol CLCZ696D2301.
5/8/2014	Safety Report PHHO2012BR003913; follow-up (eCTD-seq0386)
5/9/2014	Safety Report PHHO2013IN000955; follow-up (eCTD-seq0387)
5/12/2014	Safety Report PHHO2012GB001045, follow-up (eCTDseq 0388)
5/13/2014	FDA granting Novartis request for a Type B meeting scheduled for June 25, 2014 to obtain concurrence from the Division on the proposed presentation and format for an electronic NDA submission.
5/13/2014	Submission is to provide the Agreed iPSP in both WORD and PDF formats. (eCTD-seq0391)

FDA Interaction Date	Content Summary
5/15/2014	CMC information Amendment is submited to introduce information on a new formulation (LCZ696 3.125mg Film Coated Tablets) (eCTD-Seq0392)
5/15/2014	Submission to provide the Agency with a new protocol, CLCZ696B2126. (eCTD-seq0385)
5/20/2014	New Investigator(s) for protocol(s) CLCZ696B2228 and Revised 1572 for protocol(s) CLCZ696B2314 (eCTD-seq0390).
5/22/2014	Safety Report PHHO2012BR003913; follow-up (eCTD-seq0396)
5/22/2014	Safety Report PHHO2013BR001096; follow-up (eCTD-seq0394)
5/23/2014	The purpose of this submission is to provide the FDA with a Rolling Submission Request as well as a Fast Track Designation request. (eCTD-seq0397)
5/23/2014	Novartis is submitting the Briefing Book for the Pre-NDA Type B meeting scheduled for June 25,2014. (eCTD-seq0395)
5/28/2014	Safety Report PHHO2014IT007104 (eCTD-seq0398)
5/28/2014	Safety Report PHHO2011IN12674; follow-up (eCTD-seq0399)
5/28/2014	Safety Report PHHO2012BR003913; follow-up (eCTD-seq0400)
5/29/2014	Safety Report PHHO2012ZA008690; follow-up (eCTD-seq0401)
6/3/2014	Safety Report PHHO2014IN003017; follow-up (eCTD-seq0402)
6/9/2014	Email to FDA regarding information pertaining to question 2C of the Briefing Book sent in May for the pre-NDA meeting on June 25th.
6/10/2014	Safety Report PHHO2014IT007104; follow-up (eCTD-seq0404)
6/12/2014	Amendment 1 to protocol CLCZ696B2228 (eCTD-seq0403).
6/13/2014	FDA letter notifying Novartis of agreement to their Agreed iPSP.
6/16/2014	Novartis is submitting updated version of the Investigator's Brochure Edition 15 (eCTD-seq0405)
6/16/2014	Submission is to provide the Agency with the PARADIGM-HF (CLCZ696B2314) baseline characteristics publication in the European Journal of Heart Failure (2014). (eCTD-seq0407)
6/17/2014	Safety Report PHHO2013IN007292;follow-up(eCTD-seq0408)
6/18/2014	New Investigator for Study CLCZ696B2126, CLCZ696B2228 and CLCZ696B2314. (eCTD-seq0406)
6/19/2014	Submission is to provide the Agency with a request for a proprietary name review for Entresto. (eCTD-seq0410)
6/19/2014	FDA preliminary comments for the Type B meeting scheduled June 25, 2014 to obtain concurrence from the Division on the proposed presentation and format for an electronic NDA submission.
6/19/2014	Email correspondence from FDA regarding eDISH data set.
6/23/2014	FDA has reviewed Novartis request and conclude that the required criteria have been met and are designating as a Fast Track development program the investigation of LCZ696 for the treatment of patients with heart failure with reduced Ejection Fraction (HFrEF). We have also reviewed your request for submission of portions for review of your planned marketing.
6/26/2014	Amendment 1 to Protocol CLCZ696D2301. Submission also provides a response to the SAP comments received on 5/8/2014. (eCTD-seq0409)

FDA Interaction Date	Content Summary
6/30/2014	Response to FDA's Preliminary Comments dated June 19, 2014. (eCTD-seq0411)
6/30/2014	Safety Report PHHO2014US008920 (eCTD-seq0413)
7/7/2014	Novartis is requesting a CMC Type B meeting with FDA. (eCTD-seq0412)
7/9/2014	Safety Report PHHO2013IN007292; follow-up (eCTD-seq0414)
7/10/2014	Safety Report PHHO2013DE002628; follow-up (eCTD-seq0416)
7/11/2014	The purpose of this submission is to provide the Agency with Amendment 2 to the PARADIGM-HF SAP. (eCTD-seq0414)
7/14/2014	Email correspondence with FDA in regards to PARADIGM-HF SAP.
7/14/2014	FDA minutes from the Type C meeting dated June 25, 2014 to obtain concurrence on the proposed presentation and format for an electronic NDA submission.
7/14/2014	In preparation for the Type B CMC meeting, enclosed are the briefing book and 2 appendices. (eCTD-0417)
7/14/2014	Safety Report PHHO2010GB15448; follow-up (eCTD-seq0418)
7/15/2014	Safety Report PHHO2010GB16454; follow-up (eCTD-seq0421)
7/15/2014	Safety Report PHHO2010HU18329; follow-up (eCTD-seq0422)
7/15/2014	Safety Report PHHO2010IL18897; follow-up (eCTD-seq0419)
7/16/2014	Email to FDA with Novartis pre-NDA meeting minutes dated June 25, 2014.
7/16/2014	Safety Report PHHO2014US008920 Follow-up (eCTD-seq0425)
7/16/2014	Safety Report PHHO2012IL015128 Follow-up (eCTD-seq0423)
7/16/2014	Safety Report PHHO2012PL003313 follow-up (eCTD-seq0424)
7/19/2014	Safety Report PHHO2011BR09808 Follow-up (eCTD-seq0427)
7/21/2014	Novartis is requesting a Type C meeting with FDA to share the top line data from PARADIGM-HF and continue discussions related to data driven topics. (eCTD-seq0429)
7/21/2014	Safety Report PHHO2011FI06062 Follow-up (eCTD-seq0428)
7/22/2014	Safety Report PHHO2013BR001096; follow-up (eCTD-seq0431)
7/25/2014	FDA granting Novartis a Type C meeting scheduled September 22, 2014 to discuss the top line results of your pivotal phase III study, PARADIGM-HF.
7/25/2014	Submission is to provide the Agency with a new clinical study protocol, CLCZ696B2317. (eCTD-seq0426)
7/28/2014	New Investigator for protocol CLCZ696D2301 (eCTD-seq0430)
7/31/2014	Safety Report PHHO2012HK007713 Follow-up (eCTD-seq0433)
8/1/2014	Safety Report PHHO2013RU001322 7-Day Safety report (eCTD-seq0434)
8/4/2014	FDA granting Novartis request for a Type B meeting scheduled for Auguast 14, 2014 to discuss the Novartis approach for the supply of intermediates in the synthesis of LCZ696.
8/4/2014	Safety Report PHHO2010SK18613 7-Day Safety report (eCTD-seq0437)
8/4/2014	Safety Report PHHO2013IN010818 7-Day Safety report (eCTD-seq0438)
8/4/2014	Safety Report PHHO2013PH013229 7-day (eCTD-seq0436)
8/4/2014	Safety Report PHHO2013ZA015856 7-day (eCTD-seq0439)
8/5/2014	The purpose of this submission is to provide two clarifications in regards to the FDA meeting minutes dated June 25, 2014. (eCTD-seq0435)

FDA Interaction Date	Content Summary
8/5/2014	Safety Report PHHO2013PH013229 7-Day. (eCTD-seq0436)
c	Safety Report PHHO2012HK008472 7-Day Safety report (eCTD-seq0440)
8/5/2014	Safety Report PHHO2013SK004806 7-day (eCTD-seq0441)
8/6/2014	Novartis is submitting clinical study report for study CLCZ696A2126 (eCTD-seq0432)
8/7/2014	FDA preliminary comments to questions for the Type B meeting scheduled for August 14, 2014 to discuss the Novartis approach for the supply of intermediates in the synthesis of LCZ696.
8/7/2014	15-day IND Safety Reports for multiple Case Numbers. (eCTD-seq0447)
8/7/2014	Safety Report: PHHO2011US09057, PHHO2011DK15547, PHHO2011BR17438, PHHO2013US003391, PHHO2012US010292, PHHO2012US011722, PHHO2013ES002749, PHHO2013IN005416, PHHO2013PH000734, PHHO2013RU000937, PHHO2013EC015808, PHHO2013ES015219, PHHO2013DK004754, PHHO2013DE006467, PHHO2013CZ012058, PHHO2013CO012535, PHHO2013BR008240, PHHO2013BE006968, PHHO2012ZA017859, PHHO2012ZA009538, PHHO2012ZA001868, PHHO2012US015945, PHHO2012US008541, PHHO2012US005669, PHHO2012TW017726, PHHO2012BR007861 (eCTD-seq0445)
8/7/2014	Safety Report: PHHO2012RU012030, PHHO2012PL012082, PHHO2013IN015895, PHHO2013NL016945, PHHO2013NL007092, PHHO2012PL009369, PHHO2012PE008660, PHHO2012PE002268, PHHO2012PA012287, PHHO2012PA012287, PHHO2012MX012696, PHHO2012MX005808, PHHO2012KR013885, PHHO2012GB007230, PHHO2012GB002757, PHHO2012FR006226, PHHO2012FI005049, PHHO2012EE018381, PHHO2012DK013888, PHHO2012DE013416, PHHO2012DE011372, PHHO2012DE004433, PHHO2012CZ015409, PHHO2012CA010107, PHHO2012BR017241, PHHO2012BR016850, PHHO2012BR016818, PHHO2012BR008516, PHHO2012BR005262, PHHO2012BR002423, PHHO2012BE010457 (eCTD-seq0446)
8/7/2014	Safety Report PHHO2012BR007861 7-Day safty report (eCTD-seq0444)
8/11/2014	P Safety Report HHO2012RU017982; 7-Day report (eCTD-seq0448)
8/11/2014	Safety Report PHHO2013PH013229. (eCTD-seq0449)
8/11/2014	Safety Report PHHO2013CO005157 7-Day safety report (eCTD-seq0451)
8/12/2014	Safety Report PHHO2013IN010818 (eCTD-seq0455)
8/12/2014	Safety Report PHHO2010SK18613 (eCTD-seq0454)
8/12/2014	Safety Report PHHO2013TR009017 (eCTD-seq0452)
8/12/2014	Safety Report PHHO2013SK008706 (eCTD-seq0453)
8/12/2014	Safety Report PHHO2010HU17146 Follow-up (eCTD-seq0458)
8/12/2014	Safety Report PHHO2013ZA015856. (eCTD-seq0450)
8/13/2014	Novartis is informing the Agency that CMC information in referenced IND 77,318 has been updated. (eCTD-seq0457)

FDA Interaction Date	Content Summary
8/13/2014	Safety Report: PHHO2011TW05094,PHHO2013BR009267,PHHO2013IN001817,PHHO2013IN001851,PHHO2013IN013024,PHHO2013IN015054,PHHO2014PH000579 Follow-up (eCTD-seq0459)
8/14/2014	Safety Report PHHO2013SK004806 (eCTD-seq0460)
8/15/2014	Safety Report PHHO2010IN16648 (eCTD-seq0472)
8/15/2014	Safety Report PHHO2010IT15164 (eCTD-seq0471)
8/15/2014	Safety Report PHHO2011IN11799; follow-up (eCTD-seq0470)
8/15/2014	Safety Report PHHO2012AR010257; follow-up (eCTD-seq0469)
8/15/2014	Safety Report PHHO2012GB017225; follow-up (eCTD-seq0468)
8/15/2014	Safety Report PHHO2012IN017070 (eCTD-seq0466)
8/15/2014	Safety Report PHHO2014US008920 Follow-up (eCTD-seq0467)
8/17/2014	Safety Report PHHO2013CO005157 (eCTD-seq0474)
8/18/2014	Safety Report PHHO2014RU006393; 7-Day safety report (eCTD-seq0473)
8/20/2014	New Investigator LCZ696D2301 (Seq 0456)
8/20/2014	Safety Report: PHHO2011TW05094, PHHO2013BR009267, PHHO2013IN001817, PHHO2013IN001851, PHHO2013IN013024, PHHO2013IN015054, PHHO2014PH000579 (eCTD-seq0476)
8/20/2014	Safety Report PHHO2012RU017982 (eCTD-seq0475)
8/21/2014	This submission provides responses to FDA's preliminary comments to the pre-NDA Type B CMC briefing document. (eCTD-seq0464)
8/21/2014	Safety Report PHHO2012PH006218 (eCTD-seq0478)
8/21/2014	Safety Report PHHO2013DE015885 (eCTD-seq0479)
8/25/2014	Safety Report PHHO2013IN010949 (eCTD-seq0480)
8/25/2014	Safety Report PHHO2014RU006393 (eCTD-seq0481)
8/25/2014	Safety Report PHHO2012ZA008690; follow-up (eCTD-seq0482)
9/1/2014	Safety Report PHHO2012US009119 7-Day safety report (eCTD-seq0486)
9/3/2014	Safety Report PHHO2011PL08780 (eCTD-seq0489)
9/3/2014	Safety Report PHHO2011PL08780; 7-Day safety report (eCTD-seq0483)
9/4/2014	The purpose of this submission is to provide the FDA with a proposal for the 120 day safety update. (eCTD-seq0484)
9/4/2014	The purpose of this submission is to provide the Agency with the New England Journal of Medicine article titled 'Angiotensin'Neprilysin Inhibition versus Enalapril in Heart Failure'. (eCTD-seq0488)
9/4/2014	Novartis has some clarifications regarding the additional requests # 8, 18, and 30 contained in the Preliminary comments. (eCTD-seq0487)
9/5/2014	Safety Report PHHO2014US008920; follow-up (eCTD-seq0490)
9/8/2014	New Investigator(s) for protocol(s) CLCZ696D2301 (eCTD-seq0485)
9/8/2014	New protocol for CLCZ696B2318M (eCTD-seq0491)

FDA Interaction Date	Content Summary
9/8/2014	Submission provides an follow-up to the August 14th, Type B CMC meeting with FDA to discuss Novartis's approach for the supply of intermediates in the synthesis of LCZ696-ABA. (eCTD-seq0492)
9/8/2014	Safety Report PHHO2012US009119 (eCTD-seq0493)
9/12/2014	Novartis telecon report regarding the Extended Access Program.
9/15/2014	The purpose of this submission is to provide the Agency with slides for the PARADIGM-HF Top Line Data Review Meeting on September 22, 2014. (eCTD-seq0494)
9/15/2014	Safety Report PHHO2014ZA009494 (eCTD-seq0495)
9/17/2014	Email to and from FDA regarding follow-up on the CMC meeting.
9/18/2014	FDA acknowledgement letter of Novartis Treatment Protocol.
9/18/2014	FDA minutes from the Type B meeting dated August 14, 2014 with Novartis to seek an agreement with the Agency on Novartis' approach for the supply of intermediates in the synthesis of LCZ696-ABA.
9/24/2014	New Investigators for protocol CLCZ696D2301 (eCTD-seq0496)
9/24/2014	Safety Report PHHO2012EC015122; follow-up (eCTD-seq0497)
9/26/2014	Safety Report PHHO2013PH009418; follow-up (eCTD-seq0498)
9/29/2014	DSUR Annual report submission covering the period July 31, 2013 through July 30, 2014 (eCTD-Seq0477).
10/2/2014	FDA advice information request regarding amendment dated September 4, 2014, containing clarifications in response to FDA's pre-NDA preliminary comments dated June 19, 2014.
10/2/2014	Email from FDA with Advice-Information Request letter.
10/3/2014	New Investigator for Protocol CLCZ696D2301. (eCTD-seq0500)
10/7/2014	Novartis is submitting an amendment to the DSUR by providing Regional Appendix 2 (List of subjects who died during the reporting period) and Appendix 3 (List of subjects who dropped out of studies during the reporting period). (eCTD-seq0499)
10/8/2014	Novartis telecon report regarding the LCZ696 Extended Access Program (B2318M) is safe to proceed in the US.
10/9/2014	Safety Report PHHO2014GB004572 (eCTD-seq0501)
10/14/2014	Safety Report PHHO2011FI06062; follow-up (eCTD-seq0503)
10/15/2014	Safety Report PHHO2013CN003844 7-Day safety report (eCTD-seq0504)
10/15/2014	Safety Report PHHO2013CN003844 (eCTD-seq0505)
10/16/2014	Safety Report PHHO2013CO005157;follow-up (eCTD-seq0506)
10/21/2014	New Investigators for protocols CLCZ696D2301, CLCZ696D2314 (eCTD-seq0502)
10/22/2014	FDA minutes from the Type C Top-Line Results meeting dated September 22, 2014 to discuss top-line results of your pivotal phase III study, PARADIGMHF.
10/24/2014	Safety Report PHHO2012GB006694; follow-up (eCTD-seq0508)
10/27/2014	Slides for Friday's TC regarding Pediatric.
10/28/2014	20141028 0507 New Investigator D2301,B2314 (Seq 507)
10/31/2014	Novartis telecon report regarding the PPSR strategy for LCZ696.
11/10/2014	amended Treatment Protocol to protocol CLCZ696B2318M (eCTD-seq0509).

FDA Interaction Date	Content Summary
11/13/2014	The purpose of this submission is to provide the draft PARAGON-HF protocol amendment for FDA review. (eCTD-seq0512)
11/13/2014	Follow up to the August 14, 2014 Type B CMC Meeting.
11/18/2014	New Investigators for protocols CLCZ696D2301, CLCZ696B2317 (eCTD-seq0513)
11/21/2014	FDA letter for proprietary name Entresto accepted.
12/18/2014	New Investigator(s) for protocol(s) CLCZ696D2301, CLCZ696B2317 (eCTD-seq0515)
12/22/2014	Clinical information amendment to submit the Clinical Study Report for CLCZ696B2228 (eCTD-seq0516)
12/22/2014	Clinical Information Amendment to submit the Clinical Study Report for CLCZ696B2314 (Paradigm-HF) (eCTD-seq0517)
1/14/2015	New Investigator(s) for protocol(s) CLCZ696D2301 & CLCZ696B2317 (eCTD-seq0518).
1/23/2015	The purpose of this submission is to submit the Clinical Study Report for CLCZ696B2126 (eCTD-Seq0519)
1/26/2015	Amendment 2 for Protocol CLCZ696B2214. (eCTD-seq0520)
1/28/2015	FDA information request regarding study D2301.
1/29/2015	Submission of updated Transfer of Sponsor Obligations version 02, for Study LCZ696B2317. (eCTD-seq0521)
2/2/2015	New Investigator(s) for protocol(s) CLCZ696D2301 & CLCZ696B2317 (eCTD-seq0522).
2/6/2015	The purpose of this submission is to provide the Agency with a Proposed Pediatric Study Request (PPSR). (eCTD-seq0523)
2/24/2015	New Investigator(s) for protocol(s) CLCZ696D2301 & CLCZ696B2317 (eCTD-seq0524).
2/26/2015	Information Amendment to the IND 77,318 Seq No: 0273 (Cross-reference to IND 104,628) submitted on February 26, 2015 to inform the Agency regarding a typographical error in the description of Valsartan 80mg film-coated tablet that were used as a comparator in LCZ696 clinical study D2301 (eCTD-Seq0525)
3/4/2015	New Investigator(s) for protocol(s) CLCZ696D2301 & CLCZ696B2317 (eCTD-seq0526).
3/25/2015	Reference is also made to original protocol submission for study CLCZ696B2317, submitted to FDA on July 25, 2014 (S-0426).
3/26/2015	Clinical information amendment to submit the Clinical Study Report and Amendment 1 for CLCZ696A2201 and CLCZ696A2223 (eCTD-seq0527)
3/27/2015	Response to FDA request dated January 28, 2015 regarding PARAGON-HF cognitive function assessment. (eCTD-seq0530)
4/1/2015	Protocol Amendment- New Investigator (eCTD-seq 0529)
4/10/2015	Protocol amendment - New Protocol for the study CLCZ696B2132 (eCTD-seq0532)
4/13/2015	FDA has reviewed Novartis' proposed pediatric study request and are unable to issue a Written Request based on the submission.
4/17/2015	Clinical Information Amendment Updated IB Ed 16 (Seq 0531)

FDA Interaction Date	Content Summary
4/24/2015	New Investigator CLCZ696D2301 (Seq 0533)
5/14/2015	Submission provides Amendment 2 for Protocol CLCZ696D2301 along with revised TOO. (eCTD-seq0534)
5/14/2015	PROTOCOL AMENDMENT: Change in Protocol CLCZ696B2317 Amendment 2 (eCTD-seq0535)
5/18/2015	New Investigator(s) for protocol(s) CLCZ696D2301, CLCZ696B2317 and CLCZ696B2132 (eCTD-seq0536)
5/28/2015	PHHO2015GB008891. (eCTD-seq0538)
6/3/2015	Submission provides the response to the 'inadequate study request' letter and an updated PPSR that incorporates all of the changes from the response. (eCTD-seq0537)
6/8/2015	Submission is to provide a letter from Dr. Robert Shaddy, a pediatric cardiologist, sharing his perspective and support on the proposed Novartis pediatric study. (eCTD seq0540)
6/8/2015	Amendment 1 to protocol CLCZ696B2132 (eCTD-seq0539).
6/12/2015	Amendment to Protocol CLCZ696D2301 (eCTD-seq0541)
6/18/2015	Clinical Information Amendment (eCTDseq-0542)
7/6/2015	New Protocol CLCZ696B2130 (eCTD-seq0545)
7/13/2015	New Investigators for Protocol LCZ696D2301 and 1572 Changes (eCTD-Seq0546)

APPENDIX G

NDA Chronology

FDA Interaction Date	Content Summary
9/30/2014	Submission of part 1 Original NDA for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. (eCTD-seq0000)
10/29/2014	Novartis is submitting part 2 of the rolling NDA for LCZ696 for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. (eCTD-seq0001)
11/20/2014	FDA email request regarding an updated 356h form that list all manufacturing and testing sites with their current responsibilities.
11/25/2014	Response to FDA request dated November 20, 2014 regarding updated 356h form. (eCTD-seq0003)
12/15/2014	Amendment to pending application for NDA 207620 (eCTD-seq0004)
12/17/2014	Novartis is submitting part 3 of the rolling NDA for LCZ696 for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. LCZ696 was granted Fast Track designation on June 23, 2014. (eCTD-seq0002)
12/17/2014	FDA email request for CMC information.
1/5/2015	FDA acknowledgement letter for Original NDA Part 3 dated December 17, 2014.
1/6/2015	FDA request for Novartis to provide a description for categorical variables in your analysis datasets (e.g. BLFLG_1C, PSTB_1C, Period, Phase_1c, TRTC, TRT_1C in the AAEV dataset).
1/13/2015	Email correspondence with FDA in regards to Novartis' request for review of the proprietary name, Entresto.
1/15/2015	Reference is made to an email request received from the Agency on January 12, 2015 requesting a submission of the cover letter to include the statement 'REQUEST FOR PROPRIETARY NAME REVIEW' in bold, capital letters on the first page of each submission as outlined in the 'Guidance for Industry. (eCTD-seq0006)
1/16/2015	Response to FDA request dated December 16, 2014 regarding CMC information. (eCTD-seq0005)
1/16/2015	Submission is to provide updated stability data on LCZ696 film coated tablets. (eCTD-seq0007)
1/16/2015	Email request from FDA for Novartis to complete the ClinPharm and Cardiac Safety Table.
1/20/2015	Response to FDA request dated January 13, 2015 regarding dataset. (eCTD-seq0008)
1/22/2015	Response to FDA request dated January 16, 2015 regarding PK Datasets. (eCTD-seq0009)
1/28/2015	Response to FDA email request dated January 6, 2015 regarding Clinical/Stats. (eCTD0seq0010)
1/28/2015	Response to FDA email request dated January 16, 2015 requesting completion of the Clinical Pharmacology and Cardiac Safety Table. (eCTD-seq0011)
1/30/2015	Response to FDA request dated January 26, 2015 regarding Clinical Pharmacology information. (eCTD-seq0012)
2/2/2015	Response to FDA request dated January 27, 2015. (eCTD-seq0013)

FDA Interaction Date	Content Summary
2/5/2015	Response to FDA request dated February 29, 2015 regarding SAS Codes. (eCTD-seq0014)
2/9/2015	FDA is notifying Novartis that proprietary name Entresto is acceptable.
2/11/2015	Response to FDA request dated February 3, 2015 for clinical information. (eCTD-seq0016)
2/12/2015	FDA has completed their filing review and have determined that the application is sufficiently complete to permit a substantive review.
2/18/2015	Response to FDA request dated February 10, 2015 regarding Clinical information. (eCTD-seq0015)
2/20/2015	Response to FDA request dated February 13, 2015 regarding Clinical information. (eCTD-seq0017)
2/24/2015	Response to FDA request dated February 13, 2015 in regards to Biopharmaceutics. (eCTD-seq0018)
2/26/2015	Response to FDA request dated February 19, 2015 for Clinical information. (eCTD-seq0019)
3/3/2015	Response to FDA request dated February 19, 2015 for Clinical information. (eCTD-seq0020)
3/10/2015	Response to FDA request dated February 12, 2015 for Clinical information. (eCTD-seq0021)
3/12/2015	Response to FDA request dated February 27, 2015 regarding Clinical Information. (eCTD-seq0022)
3/13/2015	Response to FDA request dated February 19, 2015 for CMC information. (eCTD-seq0023)
3/17/2015	Response to FDA request dated March 9, 2015 for Clinical Information. (eCTD-seq0024)
4/2/2015	Response to FDA request dated March 26, 2015 for 10 patient narratives. (eCTD-seq0027)
4/3/2015	Response to FDA requests dated March 20th and March 30th 2015 regarding Clinical information. (eCTD-seq0026)
4/7/2015	FDA Mid-Cycle Communication letter regarding telecon dated March 19, 2015 to provide Novartis with an update on the status of the review of your application.
4/8/2015	Response to FDA request dated March 31, 2015 for CMC information. (eCTD-seq0028)
4/9/2015	Novartis telecon report regarding drug substance and labeling LCZ696 as a fixed dose combination.
4/15/2015	Response to FDA request dated March 27, 2015 for CMC information. (eCTD-seq0029)
4/15/2015	Submission is to provide the 120-Day Safety Update. (eCTD-seq0025)
4/16/2015	Novartis is submitting an request for a Type C CMC only meeting. (eCTD-seq0030)

FDA Interaction Date	Content Summary
4/20/2015	Response to FDA request dated April 14, 2015 to provide narratives for selected patients from PARADIGM-HF trial (CLCZ696B2314) with events of pregnancy and/or with spontaneous abortion. (eCTD-seq0031)
4/21/2015	Novartis is submitting the Briefing Book for the Type A CMC meeting. (eCTD-seq0032)
4/24/2015	Novartis is submitting a Request for Proprietary Name Review of Entresto. (eCTD-seq0033)
4/28/2015	Novartis telecon report regarding labeling LCZ696 as a fixed dose combination follow-up meeting.
4/29/2015	Response to FDA email request dated April 22, 2015 for Clinical information. (eCTD-seq0035)
5/1/2015	Response to FDA request dated April 21, 2015 regarding Clinical information. (eCTD-seq0034)
5/4/2015	Response to FDA request dated April 3, 2015 regarding updated labeling that removes reference to a MedGuide and replaces it with PPI. (eCTD-seq0036)
5/6/2015	Response to FDA request for Clinical information during the March 19, 2015 MCC meeting where FDA noted that a post marketing study may be needed to better characterize the risk of serious angioedema events in black patients treated with LCZ696 in the United States. (eCTD-seq0038)
5/7/2015	Response to FDA request dated April 24, 2015 for Clinical information. (eCTD-seq0037)
5/13/2015	Response to FDA request dated March 27, 2015 for updated CTD modules. (eCTD-seq0039)
5/15/2015	Response to FDA request dated March 27, 2015 requesting revised carton and container labeling. (eCTD-seq0040)
5/15/2015	Response to FDA request dated March 27, 2015 regarding labeling. (eCTD-seq0041)
5/20/2015	Email from FDA with attached labeling comments and PDF of labeling.
5/20/2015	FDA comments regarding labeling.
5/22/2015	Response to FDA request dated May 12, 2015 regarding labeling. (eCTD-seq0042)
5/26/2015	Response to FDA request dated May 15, 2015 for CMC information. (eCTD-seq0043)
5/26/2015	FDA Background Package for the LCM scheduled for June 8, 2015.
6/2/2015	Response to FDA request dated May 15, 2015 for updated CMC modules. (eCTD-seq0045)
6/3/2015	Response to FDA request dated May 21, 2015 to provide data needed to populate the ?Drug Trials Snapshots? website. (eCTD-seq0044)
6/4/2015	Submission provides Updated Proposed Labeling. (eCTD-seq0046)
6/8/2015	Email from FDA with comments regarding Novartis proposed post marketing study plan.

FDA Interaction Date	Content Summary
6/11/2015	Response to FDA request dated June 9, 2015 providing comments on Entresto carton, blister and container labeling. (eCTD-seq0048)
6/12/2015	Response to FDA request dated June 5, 2015 for Clinical information. (eCTD-seq0047)
6/15/2015	Submission is to follow-up to the clarification teleconference held on 11-June-2015 between FDA and Novartis representatives on the topic of LCZ696 50mg Film-coated tablets dissolution specifications. (eCTD-seq0049)
6/19/2015	The purpose of this submission is to send the final agreed timelines + rationale (already agreed via email with Alexis Childers on June 18th). (eCTD-seq0051)
6/19/2015	FDA has completed their review of the proposed proprietary name, Entresto and have concluded that it is conditionally acceptable.
6/23/2015	FDA request in regards to the PMC.
6/25/2015	Response to FDA request dated June 23, 2015 regarding CMC information. (eCTD-seq0052)
6/26/2015	Submission provides updated proposed labeling in response to FDA comments. (eCTD-seq0050)
7/1/2015	The purpose of this submission is to provide an official updated label in response to the comments. (eCTD-seq0053)
7/2/2015	The purpose of this submission is to provide updated labeling in response to FDA comments (eCTD-seq0054)
7/6/2015	Response to FDA request date July 6, 2015 requiring a post-marketing requirement (PMR) to assess cognitive function. (eCTD-seq0056)
7/7/2017	Approval of Entresto
7/9/2015	FDA approval of the shelf life for Entresto film-coated tablets packaged in HDPE bottles is 24 months and packaged in PVC blisters is 30 months.
7/16/2015	Submission of final printed labeling in SPL format. (eCTD-seq0055)
7/24/2015	FDA minutes from the LCM dated June 3, 2015.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

April 28, 2016

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 8,101,659 was filed on September 1, 2015, under 35 U.S.C. § 156. Please note that patent term extension applications for U.S. Patent No. 7,468,390, U.S. Patent No. 8,404,744, U.S. Patent No. 8,796,331 and U.S. Patent No. 8,877,938 for NDA 207620 for the human drug product ENTRESTO® (sacubitril and valsartan) were filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The assistance of your Office is requested in confirming that the product identified in the application, ENTRESTO® (sacubitril and valsartan), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080

Department of Health and Human Services | Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD 20993-0002

AUG 25 2016

Re: ENTRESTO
Patent Nos.; 7468,390; 8,101,659; 8,404,744;
8,796,331; and 8,877,938
Docket Nos.: FDA-2016-E-1851;
FDA-2016-E-1878; FDA-2016-E-1879;
FDA-2016-E-1880; and FDA-2016-E-1882

The Honorable Michelle K. Lee
UnderSecretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Lee:

This is concerning the applications for patent term extension for U.S. Patent Nos. 7468,390; 8,101,659; 8,404,744; 8,796,331; and 8,877,938, filed by Novartis Pharmaceuticals Corporation, under 35 U.S.C. 156. The human drug product claimed by the patent is ENTRESTO (sacubitril and valsartan), which was assigned new drug application (NDA) No. 207620.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. 156(a)(4). Our records also indicate that ENTRESTO (sacubitril and valsartan) is a combination product. One of the active ingredients, valsartan, has been previously approved for commercial marketing or use as a single ingredient, Novartis Pharmaceuticals, Diovan, NDA 20-665, or as a combination with other active ingredients in several products (e.g., Novartis Pharmaceuticals, Diovan HCT, NDA 20-818, ExForge, NDA 21-990, and others). The second active ingredient, sacubitil represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1).

The NDA was approved on July 7, 2015, which makes the submission of the patent term extension application on September 1, 2015, timely within the meaning of 35 U.S.C. 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936 1080

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
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Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

FEB 14 2017

Attention: Beverly Friedman

Dear Sir:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 8,101,659. The application was filed on September 1, 2015, under 35 U.S.C. § 156. Please note that patent term extension applications for U.S. Patent No. 8,877,938; U.S. Patent No. 7,468,390; U.S. Patent No. 8,796,331 and U.S. Patent No. 8,404,744 based on the regulatory review of NDA 207620 for the human drug product ENTRESTO® (sacubitril & valsartan) were filed concurrently, pursuant to the provisions of 37 C.F.R. § 1.785.

The patent claims a product which has been subject to review under the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080

RE: ENTRESTO® (sacubitril & valsartan)
Docket No. FDA-2016-E-1878

U.S. FOOD & DRUG ADMINISTRATION

AUG 14 2017

Re: ENTRESTO
Patent Nos.: 7,468,390;
8,101,659; 8,404,744; 8,796,331;
and 8,877,938
Docket Nos.: FDA-2016-E-1851;
FDA-2016-E-1878; FDA-2016-E-
1879; FDA-2016-E-1880; AND
FDA-2016-E-1882

Acting Director
United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Acting Director:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 7,468,390; 8,101,659; 8,404,744; 8,796,331; and 8,877,938, filed by Novartis Pharmaceuticals Corporation, under 35 U.S.C. section 156 et seq. We have reviewed the dates contained in the applications and have determined the regulatory review period for ENTRESTO (sacubitril and valsartan), the human drug product claimed by the patents.

The total length of the regulatory review period for ENTRESTO is 3,148 days. Of this time, 2,945 days occurred during the testing phase and 203 days occurred during the approval phase. These periods of time were derived from the following dates:

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: November 25, 2006.

   Novartis Pharmaceuticals Corporation claims that April 8, 2007, is the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was November 25, 2006, which was 30 days after FDA receipt of an earlier IND.

2. The date the application was initially submitted with respect to the new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act: December 17, 2014.

   FDA has verified the applicant's claim that the new drug application (NDA) for ENTRESTO (NDA 207620) was submitted on December 17, 2014.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD 20993-0002
www.fda.gov

3. The date the application was approved: July 7, 2015.

FDA has verified the applicant's claim that NDA 207620 was approved on July 7, 2015.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. section 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents PharmaOne Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080

so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of USPTO may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA has approved for marketing the human drug product ODOMZO (sonidegib phosphate). ODOMZO is indicated for the treatment of adult patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy. Subsequent to this approval, the USPTO received a patent term restoration application for ODOMZO (U.S. Patent No. 8,178,563) from Novartis AG, and the USPTO requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated July 28, 2016, FDA advised the USPTO that this human drug product had undergone a regulatory review period and that the approval of ODOMZO represented the first permitted commercial marketing or use of the product. Thereafter, the USPTO requested that FDA determine the product's regulatory review period.

II. Determination of Regulatory Review Period

FDA has determined that the applicable regulatory review period for ODOMZO is 2,414 days. Of this time, 2,112 days occurred during the testing phase of the regulatory review period, while 302 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(i)) became effective:* December 15, 2008. FDA has verified the applicant's claim that December 15, 2008, is the date the investigational new drug application (IND) became effective.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act:* September 26, 2014. FDA has verified the applicant's claim that the new drug application (NDA) for ODOMZO (NDA 205266) was initially submitted on September 26, 2014.

3. *The date the application was approved:* July 24, 2015. FDA has verified the applicant's claim that NDA 205266 was approved on July 24, 2015.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the USPTO applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 169 days of patent term extension.

III. Petitions

Anyone with knowledge that any of the dates as published are incorrect may submit either electronic or written comments and, under 21 CFR 60.24, ask for a redetermination (see **DATES**). Furthermore, as specified in § 60.30 (21 CFR 60.30), any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period. To meet its burden, the petition comply with all the requirements of § 60.30, including but not limited to: Must be timely (see **DATES**), must be filed in accordance with § 10.20, must contain sufficient facts to merit an FDA investigation, and must certify that a true and complete copy of the petition has been served upon the patent applicant. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Submit petitions electronically to *https://www.regulations.gov* at Docket No. FDA–2013–S–0610. Submit written petitions (two copies are required) to the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Dated: February 6, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–02658 Filed 2–8–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2016–E–1851; FDA–2016–E–1878; FDA–2016–E–1879; FDA–2016–E–1880; and FDA–2016–E–1882]

Determination of Regulatory Review Period for Purposes of Patent Extension; ENTRESTO

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or the Agency) has determined the regulatory review period for ENTRESTO and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of applications to the Director of the U.S. Patent and Trademark Office (USPTO), Department of Commerce, for the extension of a patent which claims that human drug product.

DATES: Anyone with knowledge that any of the dates as published (in the **SUPPLEMENTARY INFORMATION** section) are incorrect may submit either electronic or written comments and ask for a redetermination by April 10, 2018. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by August 8, 2018. See "Petitions" in the **SUPPLEMENTARY INFORMATION** section for more information.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before April 10, 2018. The *https://www.regulations.gov* electronic filing system will accept comments until midnight Eastern Time at the end of April 10, 2018. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

• *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*

• If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

• *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

• For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket Nos. FDA–2016–E–1851; FDA–2016–E–1878; FDA–2016–E–1879; FDA–2016–E–1880; and FDA–2016–E–1882 for "Determination of Regulatory Review Period for Purposes of Patent Extension; ENTRESTO." Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

• Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with § 10.20 (21 CFR 10.20) and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6250, Silver Spring, MD 20993, 301–796–3600.

SUPPLEMENTARY INFORMATION:

I. Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of USPTO may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA has approved for marketing the human drug product ENTRESTO (sacubitril and valsartan). ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (New York Heart Association Class II–IV) and reduced ejection fraction. Subsequent to this approval, the USPTO received patent term restoration applications for ENTRESTO (U.S. Patent Nos. 7,468,390; 8,101,659; 8,404,744; 8,796,331; and 8,877,938) from Novartis Pharmaceuticals Corporation, and the USPTO requested FDA's assistance in determining the patents' eligibility for patent term restoration. In a letter dated August 25, 2016, FDA advised the USPTO that this human drug product had undergone a regulatory review period and that the approval of ENTRESTO represented the first permitted commercial marketing or use of the product. Thereafter, the USPTO requested that FDA determine the product's regulatory review period.

II. Determination of Regulatory Review Period

FDA has determined that the applicable regulatory review period for ENTRESTO is 3,148 days. Of this time, 2,945 days occurred during the testing phase of the regulatory review period, while 203 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(i)) became effective:* November 25, 2006. Novartis Pharmaceuticals Corporation claims that April 8, 2007, is the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was November 25,

2006, which was 30 days after FDA receipt of an earlier IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the FD&C Act:* December 17, 2014. FDA has verified the applicant's claim that the new drug application (NDA) for ENTRESTO (NDA 207620) was initially submitted on December 17, 2014.

3. *The date the application was approved:* July 7, 2015. FDA has verified the applicant's claim that NDA 207620 was approved on July 7, 2015.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the USPTO applies several statutory limitations in its calculations of the actual period for patent extension. In its applications for patent extension, this applicant seeks 1,296 days, 732 days, 519 days, 270 days or 225 days of patent term extension.

III. Petitions

Anyone with knowledge that any of the dates as published are incorrect may submit either electronic or written comments and, under 21 CFR 60.24, ask for a redetermination (see **DATES**). Furthermore, as specified in § 60.30 (21 CFR 60.30), any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period. To meet its burden, the petition must comply with all the requirements of § 60.30, including but not limited to: Must be timely (see **DATES**), must be filed in accordance with § 10.20, must contain sufficient facts to merit an FDA investigation, and must certify that a true and complete copy of the petition has been served upon the patent applicant. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Submit petitions electronically to *https://www.regulations.gov* at Docket No. FDA–2013–S–0610. Submit written petitions (two copies are required) to the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Dated: February 5, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–02592 Filed 2–8–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2017–N–6145]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by the Center for Veterinary Medicine

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by March 12, 2018.

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202–395–7285, or emailed to *oira_submission@omb.eop.gov.* All comments should be identified with the OMB control number 0910–0566. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Ila S. Mizrachi, Office of Operations, Food and Drug Administration, Three White Flint North, 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 301–796–7726, *PRAStaff@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by the Center for Veterinary Medicine—21 CFR 10.75

OMB Control Number 0910–0566—Extension

The Center for Veterinary Medicine's (CVM's) Guidance for Industry (GIF) #79, "Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by the Center for Veterinary Medicine" (*https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052393.pdf*), describes the process by which CVM formally resolves disputes relating to scientific controversies. A scientific controversy involves issues concerning a specific product regulated by CVM related to matters of technical expertise and requires specialized education, training, or experience to be understood and resolved. The guidance details information on how CVM intends to apply provisions of existing regulations regarding internal review of Agency decisions. In addition, the guidance outlines the established procedures for persons who are sponsors, applicants, or manufacturers of animal drugs or other products regulated by CVM that wish to submit a request for review of a scientific dispute. When a sponsor, applicant, or manufacturer has a scientific disagreement with a written decision by CVM, they may submit a request for a review of that decision by following the established procedures discussed in the guidance.

CVM encourages applicants to begin the resolution of science-based disputes with discussions with the review team/group, including the Team Leader or Division Director. The Center prefers that differences of opinion regarding science or science-based policy be resolved between the review team/group and the applicant. If the matter is not resolved by this preferred method then CVM recommends that the applicant follow the procedures in GFI #79.

In the **Federal Register** of October 27, 2017 (82 FR 49836), FDA published a 60-day notice requesting public comment on the proposed collection of information. We received no comments.

FDA estimates the burden of this collection of information as follows:

U.S. FOOD & DRUG
ADMINISTRATION

Re: ENTRESTO
Patent Nos. 7,468,390; 8,101,659;
8,404,744; 8,796,331;
and 8,877,938
Docket Nos. FDA-2016-E-1851
FDA-2016-E-1878
FDA-2016-E-1879
FDA-2016-E-1880
FDA-2016-E-1882

The Honorable Andrei Iancu
Under Secretary of Commerce for Intellectual Property and
Director, United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

JUL 03 2019

Dear Director Iancu:

This is in regard to the patent term extension applications for U.S. Patent Nos. 7,468,390; 8,101,659; 8,404,744; 8,796,331; and 8,877,938 filed by Novartis Pharmaceuticals Corporation under 35 U.S.C. § 156. The patents claim ENTRESTO (sacubitril and valsartan), a human drug product reviewed in new drug application (NDA) 207620.

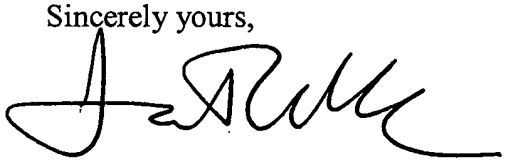
In the February 9, 2018, issue of the Federal Register (83 Fed. Reg. 5781), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before August 8, 2018, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

U.S. Food and Drug Administration
10903 New Hampshire Ave.
Building 51, Room 6250
Silver Spring, MD 20993
www.fda.gov

Please let me know if we can provide further assistance.

Sincerely yours,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: David Kurlandsky
Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	10/17/2019	for the District of Delaware

PLAINTIFF	DEFENDANT
Novartis Pharmaceuticals Corporation	See attachment

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,101,659	1/24/2012	Novartis Pharmaceuticals Corporation
2	8,796,331	8/5/2014	Novartis Pharmaceuticals Corporation
3	8,877,938	11/4/2014	Novartis Pharmaceuticals Corporation
4	9,388,134	7/12/2016	Novartis Pharmaceuticals Corporation
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

Attachment to Form AO 120

DEFENDANTS:

ALKEM LABORATORIES LTD., S&B PHARMA, INC., AUROBINDO PHARMA USA INC., AUROBINDO PHARMA LTD., BIOCON PHARMA LIMITED, BIOCON LIMITED, BIOCON PHARMA, INC., CRYSTAL PHARMACEUTICAL (SUZHOU) CO., LTD., LAURUS LABS LIMITED, LAURUS GENERICS INC., LUPIN ATLANTIS HOLDINGS, S.A., LUPIN LIMITED, LUPIN INC., LUPIN PHARMACEUTICALS, INC., NANJING NORATECH PHARMACEUTICAL CO., LIMITED, TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD.

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	10/24/2019	for the District of Delaware

PLAINTIFF	DEFENDANT
Novartis Pharmaceuticals Corporation	See attachment

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,101,659	1/24/2012	Novartis Pharmaceuticals Corporation
2	8,796,331	8/5/2014	Novartis Pharmaceuticals Corporation
3	8,877,938	11/4/2014	Novartis Pharmaceuticals Corporation
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Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

Attachment to Form AO 120

DEFENDANTS:

ALEMBIC PHARMACEUTICALS LIMITED, ALEMBIC GLOBAL HOLDING SA, ALEMBIC PHARMACEUTICALS, INC., MACLEODS PHARMACEUTICALS LTD., MACLEODS PHARMA USA, INC., NATCO PHARMA LIMITED, NATCO PHARMA, INC.

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	10/29/2019	for the District of Delaware

PLAINTIFF	DEFENDANT
Novartis Pharmaceuticals Corporation	See attachment

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,101,659	1/24/2012	Novartis Pharmaceuticals Corporation
2	8,796,331	8/5/2014	Novartis Pharmaceuticals Corporation
3	8,877,938	11/4/2014	Novartis Pharmaceuticals Corporation
4	9,388,134	7/12/2016	Novartis Pharmaceuticals Corporation
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

Attachment to Form AO 120

DEFENDANTS:

DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, MYLAN PHARMACEUTICALS INC., MYLAN INC., MYLAN LABORATORIES LIMITED, NOVUGEN PHARMA (MALAYSIA) SDN. BHD., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LTD.

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:19–cv–19345–FLW–DEA	10/25/2019	TRENTON, NJ
PLAINTIFF NOVARTIS PHARMACEUTICALS CORPORATION		DEFENDANT MACLEODS PHARMACEUTICALS LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,101,659 B2	01/24/2012	Gary M. ksander, Randy L. Webb
2 9388,134 B2	07/12/2016	Lilli Feng, Sven Erik Godtfredsen, Paul Allen Sutton, Mahavir Prashad, Michael J. Girgis, Bin Hu, Yugang Liu, Thomas J. Blacklock, Piotr Henryk Karpinski
3 8,877,938 B2	05/04/2014	Lilli Feng, Sven Erik Godtfredsen, Paul Allen Sutton, Mahavir Prashad, Michael J. Girgis, Bin Hu, Yugang Liu, Thomas J. Blacklock, Piotr Henryk Karpinski
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In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Alexandra Rufolo	10/25/2019

Copy 1––Upon initiation of action, mail this copy to Director Copy 3––Upon termination of action, mail this copy to Director
Copy 2––Upon filing document adding patent(s), mail this copy to Director Copy 4––Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the Northern District of West Virginia on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:19-CV-201	10/30/2019	for the Northern District of West Viriginia

PLAINTIFF	DEFENDANT
NOVARTIS PHARMACEUTICALS CORPORATION	MYLAN PHARMACEUTICALS INC., MYLAN INC., MYLAN LABORATORIES LIMITED

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,101,659	1/24/2012	Novartis Pharmaceuticals Corporation
2	8,796,331	8/5/2014	Novartis Pharmaceuticals Corporation
3	8,877,938	11/4/2014	Novartis Pharmaceuticals Corporation
4	9,388,134	7/12/2016	Novartis Pharmaceuticals Corporation
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**