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Ksander et al.

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(54) **METHODS OF TREATMENT AND PHARMACEUTICAL COMPOSITION**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,610,816	A	9/1986	Berger	549/452
4,722,810	A	2/1988	Delaney et al.	260/402.5
4,740,499	A	4/1988	Olins	514/13
4,749,688	A	6/1988	Haslanger et al.	514/19
4,929,641	A	5/1990	Haslanger et al.	514/506
5,217,996	A	6/1993	Ksander	514/533
5,223,516	A	6/1993	Delaney et al.	514/339
5,273,990	A	12/1993	De Lombaert	514/381
5,294,632	A	3/1994	Erion et al.	514/381
5,399,578	A	3/1995	Bühlmayer et al.	514/381
5,520,522	A	5/1996	Rathore et al.	417/322

FOREIGN PATENT DOCUMENTS

EP	0 342 850	11/1989
EP	0 343 911	11/1989
EP	0 361 365	4/1990
EP	0 443 983	8/1991
EP	0 498 361	8/1992
EP	555175	1/1993
EP	0 636 621	2/1995
EP	0726072	2/1996
EP	0 726 072	8/1996
EP	0636621 B1	3/1997
GB	2 218 983	11/1989
WO	90/09374	8/1990
WO	92/14706	9/1992
WO	93/09101	5/1993
WO	93/10773	6/1993
WO	94/15908	7/1994
WO	01/74348	10/2001
WO	02/06253	1/2002
WO	02/092622	11/2002
WO	03/066606	8/2003

OTHER PUBLICATIONS

Almeida et al., "Clearance Function of Type C Receptors of Atrial Natriuretic Factor in Rats", *Am J Physiol*, vol. 256, pp. R469-R475 (1989).
Bazil, Krulan and Webb, "Telemetric Monitoring of Cardiovascular Parameteres in Conscious Spontaneously Hypertensive Rats", *J Cardiovasc Pharmacol*, vol. 22, pp. 897-905 (1993).
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).
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).
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).
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).
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).
Needleman et al., "The Biochemical Pharmacology of Atrial Peptides", *Annu Rev Pharm Tox*, vol. 29, pp. 23-54 (1989).
Stephenson and Kenny, "Metabolism of Neuropeptides", *Biochem J*, vol. 241, pp. 237-247 (1987).

(Continued)

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(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