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(54) Title
COMBINATIONS OF ACE INHIBITORS AND DIURETICS

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(56) Prior Art Documents
**JOURNAL OF HYPERTENSION, 1983, ANDREN ET AL; ENALAPRIL WITH
EITHER A VERY LOW OR LOW WAS DOSE OF HYDROCHLOROTHIAZIDE
IS EQUALLY EFFECTIVE IN ESSENTIAL HYPERTENSION, PAGES 384-386**

(57) Claim

1. A pharmaceutical formulation comprising a pharmaceutical carrier and dispersed therein 20mg of enalapril maleate and 6mg of hydrochlorothiazide.

2. A method of treating hypertension, which comprises the administering to a patient in need of such treatment a pharmaceutical formulation comprising 20mg of enalapril maleate and 6mg of hydrochlorothiazide.

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(21) International Application Number: PCT/US93/01813 (22) International Filing Date: 2 March 1993 (02.03.93) (30) Priority data: 849,554 11 March 1992 (11.03.92) US (71) Applicant: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors: KRISTIANSON, J. Krister ; Olofsgatan 13, S-193 00 Sigtuna (SE). WOLDOLSEN, Per ; 454-191 Prospect Avenue, West Orange, NJ 07052 (US). (74) Agent: NICHOLSON, William, H.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published <i>With international search report.</i> 686097
(54) Title: COMBINATIONS OF ACE INHIBITORS AND DIURETICS (57) Abstract Pharmaceutical formulations comprising as active ingredients an angiotensin converting enzyme (ACE) inhibitor at a dose level normally found effective as an antihypertensive and a diuretic at a dose level below its minimum effective dose, demonstrate greater efficacy than would be expected in returning the blood pressure of hypertensive patients to normotensive values.		

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- 1 -

10 TITLE OF THE INVENTION
COMBINATIONS OF ACE INHIBITORS AND DIURETICS

BACKGROUND OF THE INVENTION

Both diuretics and ACE-inhibitors have an
15 effect on the renin-angiotensin-aldosterone system.
ACE-inhibitors act by inhibiting the conversion of
angiotensin I to angiotensin II. Diuretics regulate
the sodium-balance, and thereby also fluid volume.
The decrease, both in sodium as well as volume,
20 following therapy with diuretics increases plasma
renin activity and thereby activates the
renin-angiotensin-aldosterone system. This effect
will to some degree counteract the blood-pressure
lowering effect of the diuretic. When a diuretic and
25 an ACE-inhibitor are combined the different
pharmacological actions of these two drugs will,

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- 2 -

influence the effect of the other. There is accordingly a logical rationale for combining these two pharmacological principles.

5 It is possible to establish the highest non-pharmacological active dose of diuretic, i.e. a dose that is so low that it has no effect on blood pressure, and no apparent adverse effects. The highest non-effective dose of diuretic will still trigger the renin-angiotensin-aldosterone system and
10 although it has no physiological effect of its own, it will nonetheless have a potentiating effect on an ACE-inhibitor.

In a recently completed study by us of the effects of different doses of HCTZ on blood pressure and various metabolic parameters, doses ranging from
15 3 mg to 25 mg were investigated. 25 mg HCTZ produced significant effects on blood pressure and the metabolic parameters. 12.5 mg of HCTZ was found to be at the threshold of an effective antihypertensive response, and changes were seen in the metabolic
20 parameters. Contrary to this, the doses of 3 and 6 mg were demonstrated not to be different from placebo in effects on blood pressure and various metabolic parameters.

25 Based on this study it can be concluded that 6 mg has been established as the highest non-pharmacological dose of HCTZ.

In a study by Andren et al., J. Hypertension 1 (suppl. 2) 384-386 (1983) doses of 6.25, 12.5 and
30 25 mg of hydrochlorothiazide (HCTZ) were combined with 10 and 40 mg of enalapril respectively. The authors concluded that: "the five combinations were equally effective in reducing blood pressure, and when given with enalapril the dose of HCTZ can be very low". When the Andren study was performed, it

was not known by him that 6.25mg is or is close to the non-pharmacological dose.

Summary of the Invention

This invention is concerned with pharmaceutical formulations for the treatment of essential hypertension and disorders associated therewith such as congestive heart failure 5 which have as active ingredients an angiotensin converting enzyme (ACE) inhibitor and a diuretic wherein the diuretic is at a dose level below the recognised pharmacological dose.

With these formulations the ACE inhibitor is found to have greater efficacy in reducing elevated blood pressure to normal levels than it would have if used at the same dose in monotherapy. At the same time the diuretic is being administered at dose levels 10 that would be ineffective as an antihypertensive if used alone and similarly ineffective in causing adverse reactions.

In a particularly preferred embodiment, the invention provides a pharmaceutical formulation comprising a pharmaceutical carrier and dispersed therein 20mg of enalapril maleate and 6mg of hydrochlorothiazide, and a method of treating hypertension 15 comprising the administration to a patient in need of such treatment of a pharmaceutical formulation comprising 20mg of enalapril maleate and 6mg of hydrochlorothiazide.

Detailed Description of the Invention

The novel pharmaceutical formulations of this invention comprise: a pharmaceutical carrier; an ACE inhibitor at the dose level normally employed in monotherapy, which is 20 usually about 5-50mg, depending on the ACE inhibitor; and a diuretic at a dose level which is the highest non-pharmacological dose.

The formulation is designed for oral administration and is presented as tablets, capsules, gel caps, caplets or as a sustained release formulation. It may also be designed as an elixir

- 4 -

for oral administration, or a suppository for rectal administration.

Illustrative of the excipients which can be incorporated in tablets, capsules and the like are:

5 a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a

10 sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as

15 fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening

20 agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

The novel formulations of this invention are useful in the treatment of essential hypertension, and congestive heart failure.

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21 APR 1994

- 5 -

The ACE inhibitors useful in the novel formulation and method of treatment of this invention are enalapril, lisinopril, captopril, alacipril, benazapril, cilazapril, delapril, fosinopril, perindopril, quinapril, ramipril, moveltipril, spirapril, ceronapril, imidapril, temocapril, trando-lopril, utilbapril, zofenopril, (R)-3-[(S)-1-carboxy-5-(4-piperidyl)pentyl]-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid, libenz-april, zalicipril, n-octyl 2-[N-[(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-(1S,3S,5S)-2-azabicyclo[3.3.0]octane-3-carboxylate maleate salt, 7-[(S)-1-carboxy-3-phenylpropyl]amino[4S-[4 α ,7 α (R*),12b β]]-1,2,3,4,5,6,7,8,12b-octahydro-6-oxopyrido-[2,1-a][2]benzazepine-4-carboxylic acid, N-[8-amino-1(S)-carboxy-octyl]-L-alanyl-L-proline, 3-pyridylcarbonyl-Lys- α -D-Glu-perhydroindole-2-carboxylic acid, benzhydryl[4 α ,7 α (R),12b β]-7-[[1-(ethoxycarbonyl)phenylpropyl]amino]-1,2,3,4,6,7,12a,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylate, and 1-(N-((1S)-1-carboxy-3-phenylpropyl)-(S)-alanyl-4-(N-methyl-N-(6-chloro-7-sulfamoyl)-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)methyl)-aminoproline.

Preferred ACE inhibitors are enalapril, lisinopril, captopril, perindopril, benzapril, quinapril, and cilazapril, especially enalapril.

The diuretics useful in the novel formulation and method of treatment of this invention are: hydrochlorothiazide (HCTZ), furosemide, altizide, trichlormethazide, triflumethazide, bemetizide, cyclothiazide, methylchlothiazide, azosemide, chlorothiazide, butizide, bendroflumethazide, cyclopenthiazide, benzclortriazide, polythiazide, hydroflumethazide, benzthiazide, ethiazide, penflutazide.

Preferred diuretics for incorporation in the novel formulation of this invention are hydrochlorothiazide, trichlormethazide, furosemide and altizide, especially hydrochlorothiazide.

PCT/US 93/01813

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In the specification and claims hereof, the naming of an
ACE inhibitor or diuretic such as enalapril or hydrochlorothiazide
respectfully is meant to include salts thereof such as enalapril maleate.

5 The novel method of treatment of this invention comprises
the administration of a unit dose of the novel pharmaceutical
formulations, one to three

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AMENDED SHEET

- 6 -

times a day depending on the patient and the severity of the indication being treated. Usually once or twice a day is adequate.

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EXAMPLE 1

	<u>Component</u>	<u>Amount (mg)</u>		
		A	B	C
	enalapril maleate	20	10	5
10	hydrochlorothiazide	6	6	6
	sodium bicarbonate	10	5	2.5
	lactose	154	164.1	198.1
	starch NF	22	22	22.77
	pregelatinized starch NF	2.2	2.2	5.06
15	magnesium stearate	1.1	1.0	0.90

The excipients shown in Example 1 are exemplary of the substituents used in each of the other examples that follow.

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EXAMPLE 2

	<u>Component</u>	<u>Amount (mg)</u>		
		1	2	3
25	lisinopril	20	10	5
	hydrochlorothiazide	6	6	6

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- 7 -

EXAMPLE 3

	<u>Component</u>	<u>Amount (mg)</u>		
		<u>1</u>	<u>2</u>	<u>3</u>
5	Captopril	50	25	12.5
	hydrochlorothiazide	6	6	6

EXAMPLE 4

10	<u>Component</u>	<u>Amount (mg)</u>		
		<u>1</u>	<u>2</u>	<u>3</u>
	Benazapril	40	20	10
	hydrochlorothiazide	6	6	6
15				

EXAMPLE 5

	<u>Component</u>	<u>Amount (mg)</u>		
20		<u>1</u>	<u>2</u>	<u>3</u>
	Quinapril	20	10	5
	hydrochlorothiazide	6	6	6

EXAMPLE 6

	<u>Component</u>	<u>Amount (mg)</u>		
		<u>1</u>	<u>2</u>	<u>3</u>
	Cilazapril	50	25	12.5
30	hydrochlorothiazide	6	6	6

The claims defining the invention are as follows:

1. A pharmaceutical formulation comprising a pharmaceutical carrier and dispersed therein 20mg of enalapril maleate and 6mg of hydrochlorothiazide.
2. A method of treating hypertension, which comprises the administering to a
5 patient in need of such treatment a pharmaceutical formulation comprising 20mg of enalapril maleate and 6mg of hydrochlorothiazide.

Dated 29 July, 1997

Merck & Co., Inc.

Patent Attorneys for the Applicant/Nominated Person

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/01813

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/54,31/40,

US CL :514/223.5,423 -

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

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

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

APS and Cas Online:ACE inhibitors, diuretic, hypertension, heart, cardio?, enalapril, hydrochlorothiazide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of Hypertension, 1983, Andren et al., Enalapril with either a 'verylow' or 'low' dose of hydrochlorothiazide is equally effective in essential hypertension, pages 384-386.	1-10
Y	Chemical Abstract, volume 111, no. 9, Becker et al.; "Loop diuretics combined with an ACE inhibitor for treatment of hypertension: a study with furosemide, piretanide, and ramipil in spontaneously hypertensive rats", abstract no. 70668h, J. Cardiovasc. Pharma col., 1989, 13 (Suppl. 3), p. 535-539.	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

"T"

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

"X"

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

"Y"

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

"Z"

document member of the same patent family

Date of the actual completion of the international search

01 MAY 1993

Date of mailing of the international search report

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