Our Ref 302970

FORM 1

AUSTRALIA
Patents Act

629288

APPLICATION FOR A STANDARD PATENT

Ciba-Geigy AG, of Klybeckstrasse 141, 4002 BASLE, SWITZERLAND

hereby applies for the grant of a standard patent for an invention entitled

Low dose benazepril and thiazide diuretic composition

which is described in the accompanying complete specification.

Details of basic application(s):

Basic Application:	Country:	Date:
300,383	UNITED STATES OF AMERICA	23 January 1989

The address for service is:

ARTHUR S. CAVE & CO.
Patent & Trade Mark Attorneys
Level 10, 10 Barrack Street
SYDNEY NSW 2000

DATED this TWENTY SECOND day of JANUARY 1990

Ciba-Geigy AG
By Its Patent Attorneys
ARTHUR S. CAVE & CO.

HECTOR CUMMING, FIPAA

TO:
The Commissioner of Patents
COMMONWEALTH OF AUSTRALIA

FEE: 192.00

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5010

AU Case 4-17427/=/CGC 1398 FORM 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952 - 1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made by CIBA-GEIGY AG for a patent for an invention entitled:

Low dose benazepril and thiazide diuretic composition.

I, Werner Waldegg of CIBA-GEIGY AG, Klybeckstrasse 141, 4002 Basle, Switzerland do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 on the Act was (were) made in USA
on January 23, 1989

by Armel Rosselet

3. Armel Rosselet, Guntengarten 46, 4107 Ettingen, Switzerland

is (are) the actual inventor(s) of the invention and the facts upon which the applicant is entitled to make the application are as follows: The said applicant is the assignee of the actual inventor(s).

4. The basic application(s) referred to in paragraph 2 of this Declaration was (were) the first application(s) made in a Convention country in respect of the invention the subject of the application.

DECLARED at Basle, Switzerland on November 28, 1989

CIBA-GEIGY AG

Werner Waldegg
Single Signature, by special power

To: The Commissioner of Patents

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-48703/90
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 629288

(54) Title
LOW DOSE BENAZEPRIL AND THIAZIDE DIURETIC COMPOSITION

International Patent Classification(s)
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(56) Prior Art Documents
US 4470380
US 4217347

(57) Claim

1. A low dose pharmaceutical composition for treating mild to moderate hypertension comprising 4 to 6 mg of benazepril or a pharmaceutically acceptable salt of benazepril and a thiazide diuretic in an amount of 80 % to 120 % of $^1/_8$ of the minimum recommended initial antihypertensive dose of said thiazide diuretic when used alone, each amount being per unit dose of said composition.

2. The composition of claim 1 wherein said thiazide diuretic is selected from bendroflumethiazide, chlorthalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, polythiazide, trichlormethiazide, benzthiazide, and cyclothiazide.

13. A method of treating mild to moderate hypertension comprising administering a composition of claim 1.

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AUSTRALIA
Patents Act

FORM 10

COMPLETE SPECIFICATION

(ORIGINAL)

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:
Related Art:

Applicant(s): Ciba-Geigy AG
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4002 BASLE
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Level 10, 10 Barrack Street
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Complete specification for the invention entitled

"Low dose benazepril/thiazide diuretic composition".

The following statement is a full description of this invention, including the best method of performing it known to me:-

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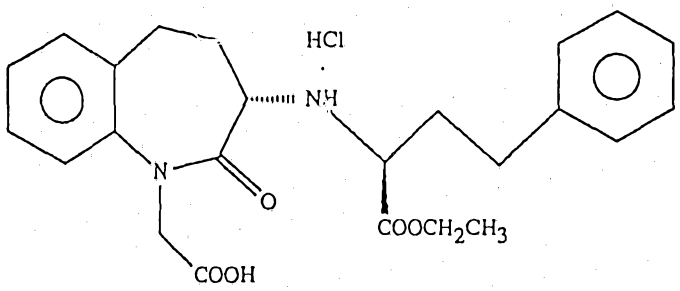
Low dose benazepril and thiazide diuretic composition

The invention relates to a pharmaceutical composition for treating mild to moderate hypertension containing the angiotensin converting enzyme inhibitor benazepril in combination with thiazide diuretics, and to a method of treatment of hypertension utilizing this composition.

Benazepril hydrochloride is a new orally active, non-sulfhydril containing, angiotensin converting enzyme inhibitor having the structure



The compound is described in U.S. 4,410,520. Thiazide diuretics, the second component of the instant combination, have long been a mainstay of antihypertensive therapy. All of the active agents of the instant invention are well known compounds in the art; their synthesis, routes of administration, etc. are well known. Additionally, there has been some literature published in recent years on combining angiotensin converting enzyme inhibitors with thiazide diuretics. See for example US 4,472,380, especially columns 9 and 10 and example 127 thereof; US 4,217,347, especially columns 2-3 and the examples; American J. Hypert. 1(1), 38-41 (1988); European patent application 0,215,357; J. Hypertension 1 (Suppl. 2), 384-386 (1983); and Amer. J. Hypert. 1 (3, part 2), 13A-14A, Abstract 1226 (1988). However, each of these deal with angiotensin converting enzyme inhibiting drugs other than benazepril and/or diuretics in amounts substantially greater than that in the present invention. Probably the most significant reference is Merck's South African Patent Application 83 3903, claiming priority of US Application 383,435. This reference discloses angiotensin converting enzyme inhibitors of benazepril type in amounts of 2.5-100 mg/day in combination with diuretics generically in the range of 0.5-100 mg/day. Hydrochlorothiazide is only mentioned in amounts of at least 10 mg/day.

It is an object of the present invention to provide a pharmaceutical composition to treat and a method of treating mild to moderate hypertension with a minimum amount of active agent while achieving pressure reductions not achievable with the individual active agents at the same dosage.

The invention is a fixed ratio low dose combination of 4-6 mg benazepril or a pharmaceutically acceptable salt thereof with 80-120 % of $^1/_8$ of the initial daily antihypertensive clinically recommended dose of a thiazide diuretic given as a once daily dosage. The inventive composition is a daily unit dose for administration to a human adult having mild to moderate hypertension comprising about 4 to about 6 mg, preferably about 5 mg, benazepril hydrochloride or any other pharmaceutically acceptable salt of benazepril and about 80 % to about 120 %, preferably about 100 %, of $^1/_8$ the usual initial antihypertensive adult clinical dose of a thiazide diuretic, when such diuretic is used alone.

Pharmaceutically acceptable salts of benazepril are acid addition salts with pharmacologically harmless acids, e.g. with inorganic acid, for example hydrochloric acid, sulfuric acid or phosphoric acid, or with organic carbonic, sulfonic or sulfo acids, for example acetic, propionic, glycolic, maleic, fumaric, tartaric, citric, benzoic, methanesulfonic, ethanesulfonic, or 2-hydroxyethanesulfonic acid. Preferred is the hydrochloride, i.e. the acid addition salt with hydrochloric acid.

Preferably the diuretic is selected from

bendroflumethiazide	(5 mg)	0.5 - 0.75 mg;
chlorthalidone	(25 mg)	2.5 - 3.75 mg;
chlorothiazide	(500 mg)	50 - 75 mg;
hydrochlorothiazide	(50 mg)	5 - 7.5 mg;
hydroflumethiazide	(50 mg)	5 - 7.5 mg;
methylchlorothiazide	(2.5 mg)	0.25 - 0.38 mg;
polythiazide	(2 mg)	0.2 - 0.3 mg;
trichlormethiazide	(2 mg)	0.2 - 0.3 mg;
benzthiazide	(50 mg)	0.5 - 0.75 mg;
cyclothiazide	(2 mg)	0.2 - 0.3 mg.

The usual minimum initial clinical antihypertensive adult dose is shown in parenthesis, followed by the dosage range useful in this invention. The initial clinical dose applied

nowadays may differ from the dose given in parenthesis in the list above for some cases. For example hydrochlorothiazide is often given in an initial dose of 25 mg.

More preferably, the thiazide diuretic is selected from chlorothiazide, hydrochlorothiazide, methylchlorothiazide, and chlorthalidone. Most preferably, the thiazide diuretic is selected from chlorothiazide and hydrochlorothiazide; it is in particular hydrochlorothiazide.

The most advantageous composition comprises benazepril hydrochloride and hydrochlorothiazide in a weight ratio of about 0.8 to 1, for example about 5 mg benazepril hydrochloride and about 6.25 mg hydrochlorothiazide.

In a clinical double-blind randomized trial with 334 men and women having a sitting diastolic blood pressure of 95-114 mmHg, the efficacy of the preferred combination of the invention comprising 5 mg benazepril hydrochloride and 6.25 mg hydrochlorothiazide given once daily was compared with the efficacy of other compositions and of the single drugs during six weeks. The results are summarized in the following table:

5 mg benazepril[a)] + 6.25 mg hydrochlorothiazide	- 9.9 mmHg[b)]
10 mg benazepril + 12.5 mg hydrochlorothiazide	- 9.6 mmHg
20 mg benazepril + 25 mg hydrochlorothiazide	-13.9 mmHg
20 mg benazepril	- 9.8 mmHg
25 mg hydrochlorothiazide	- 6.9 mmHg
20 mg benazepril + 6.25 mg hydrochlorothiazide	-10.3 mmHg
5 mg benazepril + 25 mg hydrochlorothiazide	-10.7 mmHg
placebo	- 3.9 mmHg

a) as the hydrochloride
b) reduction of sitting diastolic blood pressure

The clinical results demonstrate that the low dose composition of the invention has a surprising efficacy.

The composition can be put together by methods which are standard in the art in any convenient dosage form, including tablet, capsule, powder, etc. Any suitable pharmaceutical adjuvant or carrier may also be included. Administration may be by any route by which both benazepril and the thiazide diuretic may be simultaneously administered, but is most

preferably oral. The most suitable dosage form is a solid oral dosage form such as a tablet or capsule. While other antihypertensive active agents may be added, most preferably only benazepril and only one thiazide diuretic are present in any one composition.

The instant invention will be more fully understood by reference to the following example, which illustrates, but does not limit the invention.

Example: Film-coated tablets, containing 6.25 mg 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide and 5.00 mg 1-carboxymethyl-3S-(1S-ethoxycarbonyl-3-phenylpropylamino)-2,3,4,5-tetrahydro-1H-[1]benzazepine-2-one hydrochloride are prepared as follows:

Ingredients (for 2'000 tablets)

core materials

6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (micronized)	12.50 g
1-carboxymethyl-3S-(1S-ethoxycarbonyl-3-phenylpropylamino)-2,3,4,5-tetrahydro-1H-[1]benzazepine-2-one hydrochloride	10.00 g
hydroxypropylmethylcellulose	6.00 g
hydrogenated castor oil	12.00 g
lactose (ground)	423.50 g
polyvinyl-polypyrrolidone	20.00 g

Film materials

hydroxypropylmethylcellulose	7.34 g
polyethyleneglycol 8000 (flakes)	1.34 g
talcum	5.32 g
titanium dioxide	2.00 g

The 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide, the 1-carboxymethyl-3S-(1S-ethoxycarbonyl-3-phenylpropylamino)-2,3,4,5-tetrahydro-1H-[1]benzazepine-2-one hydrochloride and the core hydroxypropylmethylcellulose are mixed with part of the lactose. The remaining lactose is added and the mixture is granulated with water, dried, and milled. The remaining core ingredients are admixed therewith and the homogenous mixture is compressed into tablets, which are coated with an aqueous suspension of the above coating materials.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A low dose pharmaceutical composition for treating mild to moderate hypertension comprising 4 to 6 mg of benazepril or a pharmaceutically acceptable salt of benazepril and a thiazide diuretic in an amount of 80 % to 120 % of $^1/_8$ of the minimum recommended initial antihypertensive dose of said thiazide diuretic when used alone, each amount being per unit dose of said composition.

2. The composition of claim 1 wherein said thiazide diuretic is selected from bendroflumethiazide, chlorthalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlorothiazide, polythiazide, trichlormethiazide, benzthiazide, and cyclothiazide.

3. The composition of claim 2 wherein said thiazide diuretic is hydrochlorothiazide.

4. The composition of claim 1 wherein said thiazide diuretic is present in an amount which is $^1/_8$ of the minimum recommended initial antihypertensive dose when the thiazide diuretic is used alone.

5. The composition of claim 3 wherein said hydrochlorothiazide is present in an amount of 5 mg to 7.5 mg per dose.

6. The composition of claim 5 wherein said hydrochlorothiazide is present in an amount of 6.25 mg per dose.

7. The composition of claim 1 wherein said benazepril or pharmaceutically acceptable salt thereof is benazepril hydrochloride.

8. The composition of claim 7 wherein said benazepril hydrochloride is present in an amount of 5 mg per dose.

9. The composition of claim 1 comprising 5 mg benazepril hydrochloride and 6.25 mg hydrochlorothiazide per dose.

10. The composition of claim 1 which is a tablet, a powder, or a capsule.

11. The composition of claim 1 which is an oral tablet or oral capsule.

12. The composition of claim 1 substantially as herein described with reference to the example.

13. A method of treating mild to moderate hypertension comprising administering a composition of claim 1.

14. The method of claim 12 wherein said administration is once daily.

15. The method of claim 12 wherein said administration is orally.

16. A low dose pharmaceutical composition substantially as herein described with reference to any one of the foregoing Example.

Dated this 14th day of July, 1992

CIBA-GEIGY AG
By its Patent Attorneys
DAVIES COLLISON CAVE