

AUSTRALIA
Patents Act 1990

NOTICE OF ENTITLEMENT

We THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
of 22nd Floor, 300 Lakeside Drive, OAKLAND, CA 94612, U.S.A.

being the Applicant and Nominated Person, in respect of Application No. 64940/94, entitled
METHOD AND COMPOSITION FOR TREATMENT OF OSTEOPOROSIS state the following:

R Curtis Morris, Jr. and Anthony Sebastian are the actual inventors of the invention the subject
of the Application.

The applicant and nominated person is the assignee of the invention from the inventors.

Convention priority is claimed from the following basic application(s) referred to in the
declaration under Article 8 of the PCT:

Basic Applicants	Application No.	Application Date	Country	Country Code
R Curtis Morris Jnr and Anthony Sebastian	08/042,296	2 April 1993	United States of America	US

The basic application referred to in the declaration under Article 8 of the PCT was the first
application made in a Convention country in respect of the invention the subject of the
Application.

DATED this 13th day of May 1998

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

By their Patent Attorney



GRIFFITH HACK



AU9464940

(12) PATENT ABRIDGMENT (11) Document No. AU-B-64940/94
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 694112

- (54) Title
METHOD AND COMPOSITION FOR TREATMENT OF OSTEOPOROSIS
- International Patent Classification(s)
(51)⁶ **A61K 033/00 A61K 031/40 A61K 031/54**
- (21) Application No. : **64940/94** (22) Application Date : **29.03.94**
- (87) PCT Publication Number : **WO94/22312**
- (30) Priority Data
- (31) Number (32) Date (33) Country
042296 02.04.93 US UNITED STATES OF AMERICA
- (43) Publication Date : **24.10.94**
- (44) Publication Date of Accepted Application : **16.07.98**
- (71) Applicant(s)
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
- (72) Inventor(s)
R. CURTIS MORRIS JR.; ANTHONY SEBASTIAN
- (74) Attorney or Agent
GRIFFITH HACK , GPO Box 4164, SYDNEY NSW 2001
- (56) Prior Art Documents
US 4966776
US 4965282
- (57) Claim

1. A pharmaceutical composition of two drugs for treating osteoporotic disease in a human being subject thereto, which comprises:

a) a pharmacologically-acceptable alkalinizing potassium salt capable of reducing the acidity of tissue fluids or urine, said alkalinizing potassium salt being selected from the group consisting of potassium bicarbonate and potassium salts of carboxylic acids which alkalinize *in vivo*; and

b) a thiazide diuretic;

wherein the alkalinizing potassium salt and thiazide diuretic are present in synergistically effective amounts.

7. A method for treating osteoporotic disease in a patient, the method comprising administering synergistically effective amounts of:

(a) a pharmacologically acceptable alkalinizing potassium salt capable of reducing the acidity of tissue fluids or urine, said alkalinizing potassium salt being selected from the group consisting of a potassium bicarbonate and potassium salts of carboxylic acids which alkalinize *in vivo*; and

(b) a thiazide diuretic.

OPI DATE 24/10/94 APPLN. ID 64940/94
AOJP DATE 08/12/94 PCT NUMBER PCT/US94/03403



AU9464940

D.

(51) International Patent Classification⁵ : A01N 59/00	A1	(11) International Publication Number: WO 94/22312 (43) International Publication Date: 13 October 1994 (13.10.94)
(21) International Application Number: PCT/US94/03403 (22) International Filing Date: 29 March 1994 (29.03.94) (30) Priority Data: 08/042,296 2 April 1993 (02.04.93) US (60) Parent Application or Grant (63) Related by Continuation US 08/042,296 (CON) Filed on 2 April 1993 (02.04.93) (71) Applicant (for all designated States except US): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 22nd floor, 300 Lakeside Drive, Oakland, CA 94612 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MORRIS, R., Curtis, Jr. [US/US]; 1958 Vallejo Street, San Francisco, CA 94123 (US). SEBASTIAN, Anthony [US/US]; 40 Craggs Court, San Francisco, CA 94131 (US).	(74) Agents: PARMELEE, Steven, W. et al.; Townsend and Townsend Kourie and Crew, 20th floor, Steuart Street Tower, One Market Plaza, San Francisco, CA 94105 (US). (81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TT, UA, US, UZ, VN, 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, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

694112

(54) Title: METHOD AND COMPOSITION FOR TREATMENT OF OSTEOPOROSIS

(57) Abstract

A combination of the following active ingredients for treating osteoporosis: (a) a pharmacologically-acceptable alkalinizing potassium salt which produces hydroxyl ions and is thereby capable of reducing the acidity of tissue fluids or urine and which is selected from the group consisting of potassium bicarbonate and potassium salts of carboxylic acids which are transformed to bicarbonate and thus alkalinize *in vivo*; and (b) a thiazide diuretic.

METHOD AND COMPOSITION FOR
TREATMENT OF OSTEOPOROSIS

This is a continuation-in-part of U.S. application Serial No. 420,597, filed on October 17, 1989, now U.S. Patent No. 5,171,583 granted December 15, 1992, which was a continuation-in-part of U.S. application Serial No. 260,856, filed October 21, 1988, now abandoned.

FIELD OF THE INVENTION

This invention concerns novel methods for treating osteoporosis in humans and, more particularly, involves a method and composition for treating osteoporosis with a combination of an alkalinizing potassium salt and a thiazide diuretic which is effective in such treatment, which drug combination reduces the health risks or side effects associated with thiazide treatment.

BACKGROUND OF THE INVENTION

Osteoporosis is a metabolic bone disease characterized pathologically by an absolute decrease in the amount of bone, and clinically by increased susceptibility to fractures. Riggs et al., N. Engl. J. Med. (1986), 314:1676; Rusbach et al., in: Textbook of Endocrinology, Ed(s) Williams, (1981), p. 922; Riggs, in: Cecil Textbook of Medicine, Ed(s) Wyngaarden et al., (1985), p. 1456; Riggs et al., Am. J. Med., (1983), 75:899.

There are several biochemical markers which taken together, can be used to either diagnose a patient as osteoporotic, or to study the efficacy of treatments for osteoporosis. For example, urinary hydroxyproline excretion rate is widely used as a marker for bone resorption. Klein et al., Metabolism 2, Vol. 13, No. 3, March 1964, 272-285; Charles et al., J. Clin. Invest., Vol. 76, December 1985 2254-2258; and Deacon et al., Clin. Chim. Acta., 1987, 297-306.

Pyridinoline and deoxy-pyridinoline, two types of collagen crosslinks present in bone, which can be detected in urine, are also markers for bone resorption. Robins, et al., European Journal of Clinical Investigation (1991), 21:310-315.

5 Serum concentrations of osteocalcin serve as a biochemical marker of the rate of bone formation. Osteocalcin is an integral protein of the organic matrix of bone synthesized by bone-forming cells (osteoblasts) during the process of bone formation. A small fraction of the newly
10 synthesized osteocalcin escapes into the circulatory system, thus providing a blood marker of the rate of bone formation. The osteocalcin concentration increases when the bone formation rate increases, and decreases when the bone formation rate decreases. Brown, et al., The Lancet, May 19,
15 1984, p. 1091, "Serum Bone GLA-Protein: A Specific Marker For Bone Formation in Postmenopausal Osteoporosis". Another reflection of bone resorption/bone formation are changes in calcium and phosphorus balances (positive or negative) which are determined by measuring the difference between the total
20 excretion (feces and urine) and the dietary intake of calcium or phosphorus ion. (These balances are positive when the total excretion is less than the dietary intake.)

Thiazide diuretics are widely used for the treatment of hypertension. In recent years a number of studies have
25 suggested that they may also have a potential role in the prevention of bone loss and osteoporotic fracture, leading to several recent proposals for randomized, controlled clinical trials thereof (Lacroix, Comprehensive Therapy (1991), 17(8): 30-39; Editorial, "Thiazide Diuretics and Osteoporosis", BJCP, Autumn 1991, 45(3); Ray, W.A., Editorial, "Thiazide Diuretics and Osteoporosis: Time for a Clinical Trial?", 1 July 1991, Annals of Internal Medicine 115(1): 64-65).

The proposals that the thiazide diuretics may be effective in the treatment of osteoporosis are based on the
35 recognition that they reduce urinary calcium excretion (Adland-Davenport et al., Am. J. Obstet. Gynecol., (July 15, 1985), 152(6) Part 1: 630-634; Wasnich et al., Obstetrics and Gynecology, (April 1986), 67(4): 457-462; Ray et al., The

Lancet, (April 1, 1989): 687-690; Steiniche et al., APMIS, (1989), 97:302-308; and Lacroix et al., New Eng. J. Med., (Feb. 1, 1990): 286-290), improve calcium balance (Wasnich et al., New Eng. J. Med., (Aug. 11, 1983): 344-347; Hunt et al., 5 Am. J. Clin. Nutr., (1989), 50: 517-523; Steiniche et al., 1989; and La Croix et al., 1990) and decrease bone loss (Wasnich et al., Br. Med. J., (1990), 301: 1303-1305), coupled with the recent reported studies associating thiazide use with a decreased risk of hip fracture (Ray et al., 1989; LaCroix et 10 al., 1990; and Felson et al., JAMA, (1991), 265: 370-373).

The thiazide diuretics have, however, been associated with a recognized set of side effects, particularly when administered at higher doses. Administration of the thiazides commonly causes hypokalemia (Bloomfield et al., 15 J. Clin. Hypertens, 4:331-338; Solomon et al., J. Cardiovasc. Pharmacol. (1991) 17:854-859). They cause postural hypotension, resulting in increased frequency of fainting, dizziness and loss of consciousness in women (La Croix, 1991; Hale et al., J. Am. Geriatric Soc. (1984) 32:5- 20 10). In men, impotence commonly occurs (Papadopoulos, Arch. Intern. Med., Vol. 140, p. 1341 (1980); and Report of Medical Research Council Working Party on Mild to Moderate Hypertension, The Lancet, Sept. 12, 1981, pp. 539-543). In addition, they may adversely affect electrolytes, carbohydrate 25 metabolism, lipids and kidney function (Fried et al., in Diuretics Physiology Pharmacology and Clinical Use, 1986, Chapter 4, pp. 66-82).

It is therefore desirable to take advantage of the hypocalciuric properties of the thiazide diuretics in the 30 treatment of osteoporotic disease, while avoiding the multiple side effects thereof.

U.S. Patent No. 5,171,583, granted on December 15, 1992, the contents of which are incorporated herein by reference, discloses a method for ameliorating or preventing 35 osteoporosis in humans afflicted with or predisposed to osteoporosis, comprising administering a composition containing a therapeutically or prophylactically-effective amount of a composition of a pharmaceutically-acceptable

alkalinizing potassium salt. An effective dose of the alkalinizing potassium salt of 40-400 mmoles/70kg patient weight/day and preferably 40-250 mmoles/70kg/day is disclosed therein.

In accordance with the present invention, when the thiazide diuretics are used in combination with the foregoing alkalinizing potassium salts, a method and composition for treating osteoporosis is provided which reduces if not eliminates hypokalemia and the risks and side effects associated with the use of the thiazides.

SUMMARY OF THE INVENTION

The present invention thus involves a novel method for ameliorating or preventing osteoporosis in humans afflicted with or predisposed to osteoporosis, which comprises administering to a patient an effective dosage of a pharmaceutical composition comprising the following active ingredients:

(a) a pharmacologically-acceptable alkalinizing potassium salt which produces hydroxyl ions and is thereby capable of reducing the acidity (by increasing the alkalinity) of tissue fluids or urine and which is selected from the group consisting of potassium bicarbonate and potassium salts of carboxylic acids which are transformed (combusted) to bicarbonate and thus alkalinize in vivo; and

(b) a thiazide diuretic.

Preferably, the alkalinizing potassium salt is administered in an amount of about 60 to 180 milliequivalents/70 kg patient weight/day, and the thiazide diuretic is administered in amounts ranging from about 10% to about 90% of the minimum usual daily oral diuretic dose in humans.

By combining the pharmacologically-acceptable alkalinizing potassium salt and the thiazide diuretic, unexpectedly superior results are obtained in the treatment of osteoporosis as compared with the results obtained by treatment with either such active ingredient alone. Otherwise stated, it is possible in some instances to decrease the amount of the thiazide diuretic ingredient by as much as 90%



without materially diminishing the hypocalciuric effect obtained by it when administered as the sole active ingredient. The combination drug of the present invention thus provides the significant benefit of reducing, if not eliminating, the health risks and side effects which may be associated with administration of the thiazide diuretic.

DETAILED DESCRIPTION OF THE INVENTION

10 The two active ingredients of the combination drug invention, i.e., (a) the pharmacologically acceptable
alkalinizing potassium salt and (b) the thiazide diuretic, may
be administered as separate dosage forms in conjunction with
one another. Alternatively, and preferably, as described more
fully below, the alkalinizing potassium salt may be combined
with the thiazide in a unitary dosage form which can be
administered to subjects without the need for independent
administration of these active ingredients.

As used herein, the terms "treatment" or "treating"
cover any treatment of osteoporotic disease, and include:
20 (1) preventing osteoporosis from occurring in a subject who
does not have osteoporosis or who has not yet been diagnosed
as having it; (2) inhibiting or arresting the development of
the disease; or (3) regressing or reversing the osteoporotic
state.

As further used herein, the combination drug of the
invention is utilized in an "effective dosage" when it causes
the following effects in the patient:

- (a) it reduces the urinary hydroxyproline excretion
rate;
- (b) it reduces the urinary collagen crosslink
30 excretion rate; and
- (c) it increases calcium and phosphorus balances,
i.e., makes them less negative or more positive.

As also used herein, the term "collagen crosslinks"
means pyridinoline and deoxy-pyridinoline crosslinks.

Finally, as used herein the term "calcium balance"
means the difference between the total excretion (feces and
urine) of calcium and the dietary intake of calcium ion.

Similarly, the term "phosphorus balance" means the difference between the total excretion (feces and urine) of phosphorus and the dietary intake of phosphorus ion.

In the specification and claims, the term "minimum usual daily oral diuretic dose in humans" means the dose of thiazide which is required to achieve the following effects:

(a) a reduction in the urinary hydroxyproline excretion rate by more than 10%;

(b) a reduction in the urinary collagen cross-link excretion rate by more than 10%; and

(c) an increase in calcium and phosphorus balances, for example, by as much as 10% or more; when the thiazide is administered in the absence of other pharmaceutical compounds.

In the specification and claims, the term "synergistically effective amounts" means an amount of thiazide diuretic which is less than the minimum usual daily oral diuretic dose in humans and an amount of alkalinizing potassium salt which when combined together with the aforementioned amount of thiazide, and administered to a patient achieve the following effects:

a) a reduction in the urinary hydroxyproline excretion rate by more than 10%;



- b) a reduction in the urinary collagen cross-link excretion rate by more than 10%; and
- c) an increase in calcium and phosphorus balances, for example by as much as 10% or more,

5 which are normally achieved when the thiazide diuretic is administered in the minimum usual daily oral diuretic dose in humans.

The alkalinizing potassium salts which may be employed in the process of the present invention are those which, when present in
10 the body fluids, produce hydroxyl ions and are thereby capable of reducing the acidity (increasing the alkalinity) of tissue fluids or urine. A number of pharmaceutically-acceptable alkalinizing potassium salts are known, several of which are set forth in Berg et al., J. Pharmaceut. Sci. (1977) 66:1, which is incorporated herein by
15 reference. Given the disclosure herein, it will be well within the ability of one skilled in the art to select and screen pharmaceutically-acceptable alkalinizing salts for the ability to treat osteoporosis using well known methods and techniques. Desirably, a salt will be selected which is therapeutically effective in amounts readily
20 achievable in humans while being relatively well tolerated. Different salts may be chosen depending on particular routes of administration and preferred modes of formulation.



The alkalinizing potassium salts which may be thus administered are preferably selected from the group consisting of potassium bicarbonate (KHCO_3) and pharmacologically acceptable, non-toxic potassium salts of carboxylic acids such as potassium gluconate ($\text{C}_6\text{H}_{11}\text{KO}_7$) and potassium citrate ($\text{C}_6\text{H}_5\text{K}_3\text{O}_7$). The use of potassium bicarbonate is particularly preferred. The preparation, isolation and purification of these salts are well known to those skilled in the art, as they are commonly employed in a therapeutic setting for a variety of uses other than described herein. Specific procedures for the preparation of such salts are described in general terms in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 16th Ed., 1982, which is incorporated herein by reference.

The thiazide diuretics useful in the method and composition of the present invention comprise any of those conventionally utilized in the treatment of hypertension. Such agents are identified in Goodman and Gilman, The



Pharmacological Basis of Therapeutics, Eighth Edition, 1990, pp. 718-721 and 785-788; and in Drug Evaluations Subscription, AMA Div. of Drugs and Toxicology, 1992, Vol. II - Renal-Urologic Drugs, in Table 5. The disclosures of these references are incorporated by this reference. As used herein, the "thiazide diuretics" include the sulfonamide diuretics, e.g., chlorthalidone, whose pharmacological action is indistinguishable from that of the thiazides (See Goodman and Gilman, supra, at page 718). Preferred thiazide diuretics useful herein include chlorothiazide, hydrochlorothiazide, and chlorthalidone.

The thiazide diuretics are believed to be especially effective in the treatment of osteoporotic disease, in combination with the alkalinizing potassium salts, since they are weak carbonic anhydrase inhibitors which impair hydrogen ion secretion and thus decrease osteoclast resorption of bone. Although carbonic anhydrase inhibitors also produce acidosis, it is believed that the alkalinizing potassium salt prevents acidotic conditions and thus acts synergistically with the preferred thiazide diuretics, minimizing the amount of the latter required to produce a hypocalciuric effect. It should, however, be understood that the present invention is not limited by the foregoing hypothesized mechanism of co-action between the active ingredients of the preferred composition.

Administration of the pharmacologically acceptable alkalinizing potassium salt or the thiazide diuretic ingredients of the combination drug of the present invention may be in pharmaceutical compositions described hereinafter and can be via any of the accepted modes of administration for agents which are known to be useful in the treatment of osteoporosis. Each such ingredient may be administered orally, parenterally, or otherwise. Different active alkalinizing potassium salts or thiazide diuretics may be admixed and simultaneously administered, or benefit may be gained in some instances by their separate, sequential administration.

Depending on the intended mode, the alkalinizing potassium salt ingredient may be in the form of solid, semi-

solid or liquid dosage forms, such as, for example, tablets, capsules, pills, powders, granules, crystals, liquids, suspensions, or the like, preferably in unit-dosage forms suitable for administration of relatively precise dosages. Similarly, the thiazide diuretic ingredient may be in the form of a solid tablet, capsule or pill, preferably in unit-dosage forms suitable for administration of relatively precise dosages.

10 Preferably, the alkalinizing salt and the thiazide active ingredients are combined in a solid unitary dosage form in a tablet, capsule or pill, thus obviating the need for separate administration of these ingredients. The solid combined dosage form may include conventional pharmaceutical carriers or excipients, and, in addition, may include other pharmaceutical agents. Thus, the unit dosage form may be compounded with conventional nontoxic solid carriers such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. Such compositions
20 may contain about 50-90% of the active ingredients of the present invention, preferably about 70-90%.

Alternatively, the alkalinizing potassium salt ingredient may be administered as a separate dosage form, in conjunction with the administration of the thiazide diuretic. The two drugs may thus be administered on the same schedule or on different schedules in accordance with the normal modes of administration thereof. When the alkalinizing potassium salt ingredient is administered as a separate dosage form, it may be in the form of tablets, pills, capsules, powders, granules, crystals, sustained-release formulations, and the like, with
30 any of the previously listed excipients, or may be administered in a liquid pharmaceutically-administrable composition. Such liquid compositions can be prepared, for example, by dissolving the salt, such as potassium bicarbonate, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, aqueous dextrose, glycerol, and the like, to thereby form a solution or suspension. If desired, the separate alkalinizing salt dosage

form may also contain minor amounts of nontoxic auxiliary substances such as pH buffering agents and the like, for example, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; see, for example, the aforesaid Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 16th Ed., 1982. An active potassium salt ingredient of the combination drug, such as potassium bicarbonate, for example, may be provided as a dietary supplement supplied as pills, as granules or powder applied directly to foodstuffs, or dissolved in drinking water, as convenient means of administration.

Preferably, the thiazide ingredient of the combination drug is administered in a daily dosage equivalent to about 3 to 20 mg of hydrochlorothiazide and the alkalinizing potassium salt is administered in a daily dosage of about 60-180, preferably 60 to 120 milliequivalents. At these levels, the following relative effects are observable in comparison to the effects when the same amount of the thiazide diuretic is separately administered:

- (a) a reduction in the urinary hydroxyproline excretion rate (measured as described in the Klein, Charles et al. and Deacon et al. publications described above) by more than 10%;
- (b) a reduction in the urinary collagen crosslink excretion rate (measured as described in the Robins et al. publication described above) by more than 10%; and
- (c) an increase in calcium and phosphorus balances (measured as described in conventional manner), for example, by as much as 10%, or more.

As can be seen from the foregoing, the combination drug of the present invention exhibits a synergistic effect in treating osteoporosis, i.e., the combination of the two drugs is substantially more effective than the same amount of the thiazide when independently administered. Most preferably, the thiazide diuretic ingredient of the combination drug may be administered in an amount equivalent to the daily oral

administration of 3 to 20 mg of hydrochlorothiazide, appreciably lower than the usual daily oral diuretic dose in humans. The combination of the present invention incorporating these lower dosages of the thiazide is not only effective in treating osteoporosis, but also significantly reduces the health risks and side effects associated with thiazide diuretics at higher doses. It is generally convenient to supply the foregoing daily dosages in multiple (e.g., 3 to 5) tablets incorporating the active ingredients in suitable excipients and coated with a suitable sustained release coating.

The amount of the thiazide diuretic administered in accordance with the present invention will, of course, be dependent on the potency of the particular thiazide used and the mode of administration. The relative and equivalent potencies of various thiazide diuretics are well known to those skilled in the art. (The equivalent daily diuretic doses of hydrochlorothiazide and other thiazide diuretics are disclosed in Fried et al., 1986, supra, at pp. 68-70 and in Drug Evaluations Subscription, supra; those disclosures are incorporated by reference herein.) For example, 500 mg of chlorothiazide are equivalent to 75 mg of hydrochlorothiazide in terms of hypocalciuric potency and ability to treat osteoporosis. Given the disclosure herein, it will be well within the ability of one skilled in the art to select a thiazide diuretic and a dose level equivalent to the dosages of the particular thiazides described herein.

It will also be appreciated by those having skill in the art that in addition to administering the combination drug described herein, it may be desirable to supplement the patient's calcium intake, if necessary, to maintain it at about 1500 mg of calcium per day.

The following examples illustrate some particularly preferred, non-limiting embodiments of the present invention.

EXAMPLE I

A combination drug tablet is prepared containing the following active ingredients: 3 mg of hydrochlorothiazide and

1.5 grams of potassium bicarbonate. Four such tablets are administered daily, to provide a daily dose of 12 mg of the hydrochlorothiazide and 6.0 grams (60 milliequivalents) of the potassium bicarbonate.

EXAMPLE II

A combination drug tablet is prepared containing the same ingredients as Example I, except that the tablet contains only 0.75 mg of hydrochlorothiazide. Again, four such tablets are administered daily for effective treatment of osteoporosis.

From the foregoing, it will be appreciated that the present invention provides a novel method and composition which effectively treats/prevents osteoporosis in human subjects, with lower health risks and incidence of side effects than would be associated with thiazide diuretics.

Although the present invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A pharmaceutical composition of two drugs for treating osteoporotic disease in a human being subject thereto, which comprises:

5 a) a pharmacologically-acceptable alkalinizing potassium salt capable of reducing the acidity of tissue fluids or urine, said alkalinizing potassium salt being selected from the group consisting of potassium bicarbonate and potassium salts of carboxylic acids which alkalinize *in vivo*; and

10 b) a thiazide diuretic; wherein the alkalinizing potassium salt and thiazide diuretic are present in synergistically effective amounts.

2. The composition of claim 1, wherein the thiazide diuretic is selected from the group consisting of chlorothiazide, hydrochlorothiazide and chlorothalidone.

15 3. The composition of claim 1, in which the thiazide is incorporated in amounts ranging from about 10% to about 90% of its minimum usual daily oral diuretic dose in humans.

4. The composition of claim 3, wherein the alkalinizing potassium salt is present in the composition in an amount such that the composition

20 a) reduces the urinary hydroxyproline excretion rate of the human being treated more than 10% relative to the urinary hydroxyproline excretion rate of the human being observed when the same amount of the thiazide diuretic is independently administered;

25 b) reduces the urinary collagen crosslink excretion rate of the human being treated by more than 10% relative to the urinary collagen crosslink excretion rate of the human being when the same amount of the thiazide diuretic is independently administered; and

30 c) increases the serum osteocalcin concentration of the human being treated by more than 10% relative to the serum osteocalcin concentration of the human being when the same amount of the thiazide diuretic is independently administered.



5. The composition of claim 4, which further comprises a pharmaceutically-acceptable carrier.

6. The composition of claim 5, wherein the alkalinizing potassium salt is potassium bicarbonate.

5 7. A method for treating osteoporotic disease in a patient, the method comprising administering synergistically effective amounts of:

(a) a pharmacologically acceptable alkalinizing potassium salt capable of reducing the acidity of tissue fluids or urine, said alkalinizing potassium salt being selected from the group consisting of a potassium bicarbonate and potassium salts of carboxylic acids which alkalinize *in vivo*; and

10

(b) a thiazide diuretic.

8. The method of claim 7, wherein the thiazide diuretic is selected from the group consisting of chlorothiazide, hydrochlorothiazide and chlorthalidone.

15

9. The method of claim 7, wherein the alkalinizing potassium salt and the thiazide diuretic are administered in a plurality of unit dosage forms equivalent to a daily dosage of from 30 to 120 milliequivalents of the alkalinizing potassium salt and an amount of the thiazide diuretic equivalent to from 3 to 20 mgs of hydrochlorothiazide.

20

10. The method of claim 9, wherein the alkalinizing potassium salt is administered in an amount such that the administration of the combination of active ingredients

a) reduces the urinary hydroxyproline excretion rate of the human being treated more than 10%

25



relative to the urinary hydroxyproline excretion rate of the human being when the same amount of the thiazide diuretic is independently administered;

5 (b) reduces the urinary collagen crosslink excretion rate of the human being treated by more than 10% relative to the urinary collagen crosslink excretion rate of the human being when the same amount of the thiazide diuretic is separately administered; and

10 (c) increases the calcium and phosphorus balances of the human being treated by more than 10% relative to the balances when the same amount of the thiazide diuretic is independently administered.

15 11. The method of claim 9, wherein the alkalinizing potassium salt and the thiazide diuretic are administered in separate unit dosage forms.

12. The method of claim 9, wherein the alkalinizing potassium salt and the thiazide diuretic are administered in admixture in a unitary dosage form.

20 13. The method of claim 12, wherein the unitary dosage form further comprises a pharmaceutically-acceptable carrier.

14. The method of claim 9, wherein the alkalinizing potassium salt is potassium bicarbonate.

15. A composition of two drugs for treating osteoporotic disease in a human being subject thereto, said composition substantially as herein fully described with reference to Example 1 or Example 2.

5

DATED this 29th day of May 1998

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

By their Patent Attorneys

GRIFFITH HACK

E C C C
E C C C
E C C C
E C C C
E C C C
E C C C
E C C C
E C C C
E C C C
E C C C

E C C C
E C C C
E C C C
E C C C
E C C C
E C C C
E C C C
E C C C



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/03403

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A01N 59/00
US CL : 424/717

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. : 424/717

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

NONE

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

APS: "OSTEOPOROSIS"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,966,776 (PAK) 30 October 1990, see entire document.	1-14
Y	US, A, 4,965,282 (TAKAMURA ET AL) 23 October 1990, see entire document.	1-14

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be part of particular relevance	"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
"E" earlier document published on or after the international filing date	"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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"G"	document member of the same patent family
"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		

Date of the actual completion of the international search 24 JUNE 1994	Date of mailing of the international search report 07 SEP 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer <i>Lene Leava for</i> PETER KULKOSKY Telephone No. (703) 308-2351