P/00/008
Section 29(1)
Regulation 3.1(2)

AUSTRALIA
Patents Act 1990

NOTICE OF ENTITLEMENT

We THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

of 22nd Floor, 300 Lakeside Drive, Oakland, California 94612, United States of America

being the Applicant and Nominated Person, in respect of Application No. 66219/94, 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 actual inventors.

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

Basic Applicants	Applicationn Number	Application Date	Country	Country Code
R Curtis Morris, Jr. and Anthony Sebastian	08/042,349	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 1st day of April 1998

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
By their Patent Attorney

GRIFFITH HACK

AU9466219

(12) PATENT ABRIDGMENT (11) Document No. AU-B-66219/94
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 692155

(54) Title
METHOD AND COMPOSITION FOR TREATMENT OF OSTEOPOROSIS

International Patent Classification(s)
(51)[5] A61K 033/00
(51)[6] A61K 031/565

(21) Application No. : 66219/94 (22) Application Date : 29.03.94

(87) PCT Publication Number : WO94/22457

(30) Priority Data

(31) Number	(32) Date	(33) Country
042349	02.04.93	US UNITED STATES OF AMERICA

(43) Publication Date : 24.10.94

(44) Publication Date of Accepted Application : 04.06.98

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(57) Claim

1. A combination 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) an estrogen which is effective in the treatment of osteoporosis;

wherein the alkalinizing potassium salt and estrogen are present together in synergistically effective amounts.

OPI DATE 24/10/94 APPLN. ID 66219/94
AOJP DATE 08/12/94 PCT NUMBER PCT/US94/03402
AU9466219

INTEI ... PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 33/00 — A1

(11) International Publication Number: WO 94/22457

(43) International Publication Date: 13 October 1994 (13.10.94)

(21) International Application Number: PCT/US94/03402

(22) International Filing Date: 29 March 1994 (29.03.94)

(30) Priority Data:
08/042,349 2 April 1993 (02.04.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/042,349 (CON)
Filed on 2 April 1993 (02.04.93)

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(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
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.

692155

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

(57) Abstract

The 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) an estrogen which is effective in the treatment of osteoporosis, in an amount of as little as 1/10 its normal recommended dose; the alkalinizing potassium salt being present in an amount such that the combination is substantially more effectie in treating osteoporosis than the same amount of the estrogen when independently administered.

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 alkalinizing potassium salt and an estrogen which is effective in such treatment and which reduces the health risks or side effects associated with conventional estrogen treatment of osteoporosis.

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.

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 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, 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 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.)

In post-menopausal women, estrogen deficiency has been identified as a major predisposing factor for osteoporosis. It has been reported that long-term estrogen replacement therapy can arrest the progression of osteoporosis in post-menopausal women. Johansen, et al., (1990) Metabolism Vol. 39, No. 11, pp. 1122-1126; Ettinger, Obstetrics & Gynecology, (1988), 72: 12s-17s; Ettinger et al., Annals of Internal Medicine (1985), 102:319-324.

The lowest dosage of estrogen which has been approved by the FDA as being effective in the prevention or treatment of osteoporosis is 0.625 mg of conjugated estrogens, or equivalent doses of other estrogens. However, long-term use of estrogen at this level poses serious health risks. Three independent studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens at this dosage level for prolonged

periods. Ziel, et al. (1975) New England Journal of Medicine, 293:1167-1170; Smith, et al. (1975) New England Journal of Medicine, 293:1164-1167; Mack, et al. (1976) New England Journal of Medicine, 294:1262-1267. These three studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in non-users. The risk appears to depend on both duration of treatment, Ziel et al., Id., and on estrogen dose. Mack et al., Id.

In addition to the documented risk of endometrial cancer from estrogen therapy, at least one study suggests that estrogens given to postmenopausal women increase the risk of breast cancer. New England Journal of Medicine (1974) 290:15-19. It has also been reported that the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens increases two to threefold. Id. Moreover, postmenopausal women who undergo estrogen therapy may have an increased risk of thromboembolic and thrombotic vascular diseases and high blood pressure. Pfeffer et al., (1976) Am. J. Epidemiology 103:445-456. Thus, at the dosage levels required for the effective treatment of osteoporosis, estrogens may pose serious health risks and side effects.

One study suggests that the addition of progestins to estrogen replacement therapy provides protection from estrogen-induced endometrial cancer and may improve bone metabolism. Williams et al. (1990), Am. J. Obstet. Gynecol., Vol. 162, pp. 438-446. However, the addition of a progestational agent causes a high incidence of side effects, including monthly bleeding and premenstrual symptoms. Id. Although the study indicates that these side effects can be reduced by administering the progestin in combination with the estrogen on a continuous daily basis as opposed to administering the estrogen and progestin on a sequential cyclical basis, the study noted that 3 of the 65 patients who received continuous doses of estrogen and progestin developed endometrial polyps. Id.

Another study, Ettinger, (1988), Obstetrics & Gynecology 72: 12s-17s suggests that the usual dosage of estrogen, e.g., approximately 0.6 mg of the conjugated

estrogens discussed below, for treating osteoporosis may be cut in half by augmenting the calcium intake of patients to at least 1500 mg/day. However, the study suggests that even half of the usual dosage of estrogen is likely to cause menstrual bleeding and other undesirable side effects.

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 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.

It is among the objects of the present invention to provide a method and composition for treating osteoporosis which is more effective than treatment with estrogens alone.

It is a further object of the present invention to provide a method and composition for treating osteoporosis which reduces if not eliminates the risks and side effects associated with treatment with estrogens.

SUMMARY OF THE INVENTION

The present invention involves a novel method for ameliorating or preventing osteoporosis in humans afflicted with or predisposed to osteoporosis, which comprises administering the combination of 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) an estrogen which is effective in the treatment of osteoporosis, said estrogen being administered in an amount as small as 1/10 its normal recommended dose, preferably in an amount of from about 1/10 the normal recommended dose to the recommended dose or higher;

the alkalinizing potassium salt being administered in an amount such that the combination of the two drugs is substantially more effective, generally from about 10% to as much as 50% or more, effective in treating osteoporosis than the same amount of the estrogen when independently administered.

Evidence that the combination of the pharmacologically-acceptable alkalinizing potassium salt with an estrogen would have been unobvious to those having ordinary skill in the art prior to the present invention is the synergism achieved by the combination in treating osteoporosis. Thus, the present invention provides a more effective treatment for osteoporosis than conventional estrogen treatments. Moreover, if desired, in accordance with the present invention, the amount of estrogen administered in the combination drug may be as low as about 1/10 the normal recommended dose of estrogen, as defined below. The combination of the lower dosages of estrogen, in conjunction with the alkalinizing potassium salts, in accordance with the present invention, is effective in the treatment of osteoporosis, and provides the significant benefit of reducing, if not eliminating, the health risks and side effects associated with conventional treatments with estrogen. Use of the alkalinizing potassium salt with the estrogen may obviate the necessity of co-administration of the estrogen with progestins; alternatively, the natriuretic properties of the alkalinizing potassium salt may offset the sodium-retaining characteristics of the progestins and thereby enhance the results obtained by combined estrogen-progestin-alkalinizing potassium salt therapy.

DETAILED DESCRIPTION OF THE INVENTION

The two active ingredients of the combination of the invention, i.e., (a) the pharmacologically acceptable alkalinizing potassium salt and (b) an estrogen which is effective in the treatment of osteoporosis, may be administered as separate dosage forms in conjunction with one another, i.e., either at the same time or on different schedules. Alternatively, and preferably, as described more fully below, the alkalinizing potassium salt may be combined with the estrogen in a unitary dosage form which can be administered to subjects without the need for separate administration of these active ingredients.

As used herein, the terms "treatment" or "treating" cover any treatment of osteoporotic disease, and include: (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 used herein, the term "normal recommended dose" when used to refer to estrogen, means an amount of estrogen which, when administered to a human being subject to osteoporosis is effective in treating osteoporosis, i.e., it causes the following effects in a human being:

(a) reduces the urinary hydroxyproline excretion rate;

(b) reduces the urinary collagen crosslink excretion rate; and

(c) increases calcium and phosphorus balances, i.e., makes them less negative or more positive.

For example, the normal recommended dose of the estrogen known as conjugated estrogens (which is defined below) in the treatment of osteoporosis is 0.625 mg, administered on a cyclical basis, i.e., three weeks on, and one week off. See the Physicians Desk Reference, 1993 Edition, pages 2624-25. (The foregoing effects occur whether or not the estrogen is simultaneously administered with progestin.)

As used herein, references to the "same amount of said estrogen when independently administered" means an identical amount of the identical estrogen used in the combination drug of the present invention, which estrogen is administered without also administering the alkalinizing potassium salt ingredient of the combination drug of the present invention.

In the specification and claims, "synergistically effective amounts" means an amount of estrogen no less than 1/10 of the normal recommended dose and less than the normal recommended dose, and an amount of alkalinizing potassium salt which when combined with the before-mentioned amount of estrogen, and administered to a patient achieves the following effects:

(a) reduces the urinary hydroxyproline excretion rate;

(b) reduces the urinary collagen crosslink excretion rate; and

(c) increases calcium and phosphorus balances,

which are normally achieved when the estrogen is administered in a normal recommended dose.

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

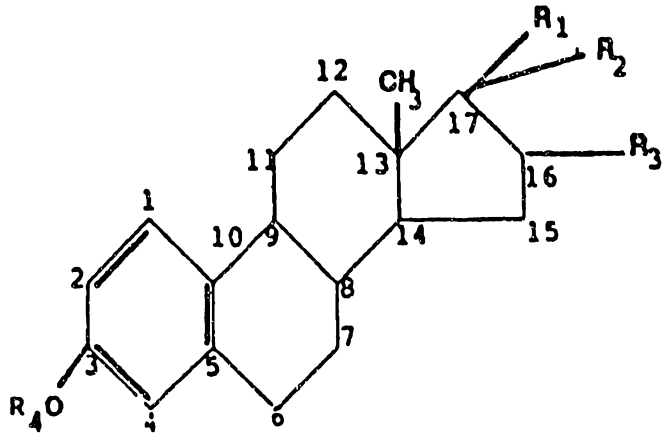
As used herein, the term "calcium balance" means the difference between the total excretion (feces and urine) of calcium and the dietary intake of calcium. Similarly, the term "phosphorus balance" means the difference between the total excretion (feces and urine) of phosphorus and the dietary intake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

The alkalinizing potassium salts which may be employed in the process of the present invention are those which, when present in 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 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 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 ($C_6H_{11}KO_7$) and potassium citrate ($C_6H_5K_3O_7$). 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 term "estrogen" as used herein means any natural or synthetic substance possessing the biological activity of estrus-producing hormones, and which is useful in the treatment of osteoporosis. Estrogens useful in the practice of the present invention preferably comprise those of the following formula, including pharmaceutically acceptable salts and esters thereof:



wherein R_1 is a hydroxyl group and R_2 is selected from the group consisting of H, -C=C, and -C≡C, or

R_1 and R_2 together represent an oxygen which is bound to the molecule by a double bond,

R_3 is either hydrogen or a hydroxyl group, and

R_4 is selected from the group consisting of H, methyl, and cyclopentyl groups, and

wherein the estrogen has either a double bond at the 6-7 and 8-9 positions, a double bond at the 7-8 position, or no double bonds at the 6, 7, 8 and 9 positions.

The estrogens which may be thus administered in accordance with this invention include, but are not limited to all of the following estrogens and mixtures thereof: estrone

(3-hydroxyestra-1, 3, 5 (10)-triene-17-one); 17β-estradiol (17β-estra-1,3,5(10)-triene-3,17-diol); 17α-estradiol (estra-1,3,5(10)-triene-3,17α-diol); ethinyl estradiol (17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol); equilin (3-hydroxyestra-1,2,5(10),7-tetraen-17-one); equilenin (3-hydroxyestra-1,2,3,5,7,9-pentaen-17-one); 17α-dihydroequilin (17α-estra-1,3,5(10),7-tetraene-3,17-diol); 17β-dihydroequilin (17β-estra-1,3,5(10),7-tetraene-3,17-diol); 17α-dihydroequilenin (17-estra-1,3,5,7,9-pentaene-3,17,diol); 17β-dihydroequilenin (17β-estra-1,3,5,7,9-pentaene-3,17,diol); mestranol (17-α-ethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol); quinestradiol (estriol 3-cyclopentyl ether); quinestrol (17α-ethinylestradiol 3-cyclopentyl ether); estradiol benzoate (17β-estra-1,3,5(10)-triene-3,17-diol 3-benzoate); estradiol 17β-cypionate (17β-estra-1,3,5(10)-triene-3,17-diol 17-cyclopentanepropanoate); and conjugated estrogens.

As used herein, the term "conjugated estrogens" means a mixture of conjugated estrogens from natural sources occurring as sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine, the principal component of which is sodium estrone sulfate. Conjugated estrogens are sold under the trademark "PREMARIN" by Wyeth-Ayerst Laboratories. See the Physicians Desk Reference, 1993 Edition pages 2624-26.

The preparation, isolation, and purification of each of the foregoing estrogens are well known to those skilled in the art. Numerous literature descriptions of how to prepare these estrogens are cited in The Merck Index (11th Ed. 1989) under descriptions of the foregoing estrogens. The Merck Index and the cited literature descriptions for preparing the estrogens are incorporated herein by reference.

Administration of the pharmacologically acceptable alkalinizing potassium salt or the estrogen 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.

For the alkalinizing potassium salt, these methods include oral, parenteral, and other modes of systemic administration. Different alkalinizing potassium salts may be admixed and simultaneously administered, or benefit may be gained in some instances by their separate, sequential administration. For the estrogen, these methods include oral, parenteral, transdermal, and other modes of systemic 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 estrogen 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.

Preferably, the alkalinizing salt and estrogen 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 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 estrogen active ingredient. 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 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.

The estrogen ingredient of the combination drug of the present invention may be administered in an amount of as little as about 1/10 of its normal recommended dose. The alkalinizing potassium salt ingredient of the combination drug is administered in an amount such that the combination drug is about 10% more, or as much as 50% or more, effective in treating osteoporosis than the same amount of the estrogen when independently administered.

Preferably, the estrogen ingredient is orally administered in an amount equivalent (on a daily basis) to about 0.06 to 1.25 mg, preferably about 0.06 to 0.625 mg of the conjugated estrogens. The amount of the alkalinizing potassium salt administered in the combination drug is about 30-120, preferably about 30 to 60, milliequivalents. At these levels, the following relative effects are observable in comparison to the effects when the same amount of the estrogen is independently 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 in conventional manner), for example, by as much as 10%, or more.

As can be seen from the foregoing, the combination of the active ingredients 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 estrogen when independently administered. Most preferably, the estrogen ingredient may be administered in an amount equivalent to the oral administration of as little as about 0.06 mg of conjugated estrogens. When used in the combination of this invention, the lower dose of estrogen is not only effective in treating osteoporosis, but also significantly reduces the health risks and side effects associated with estrogens at conventional doses.

The amount of the estrogen ingredient administered in accordance with the present invention will, of course, be dependent on the potency of the particular estrogen(s) used and the mode of administration. The relative and equivalent potencies of various estrogens are well known to those skilled in the art. For example, 0.6 mg of conjugated estrogens are equivalent to 2.0 mg of micronized 17β-estradiol in terms of estrogenic 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 an estrogen and a dose level equivalent to the estrogens and the dose levels described herein.

The combination drug of the present invention may be administered on a daily basis continuously, or instead, may be administered on a cyclical basis, i.e., three weeks on, and

one week off. 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 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: 0.156 mg of conjugated estrogens and 1.5 grams of potassium bicarbonate. Four such tablets may be suitably administered daily.

EXAMPLE II

A combination drug tablet is prepared containing the same ingredients as Example I and administered in accordance with the same protocol, except that each tablet contains only 0.08 mg of conjugated estrogens and 0.75 grams of potassium bicarbonate.

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 associated with conventional hormonal treatments for osteoporosis.

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:

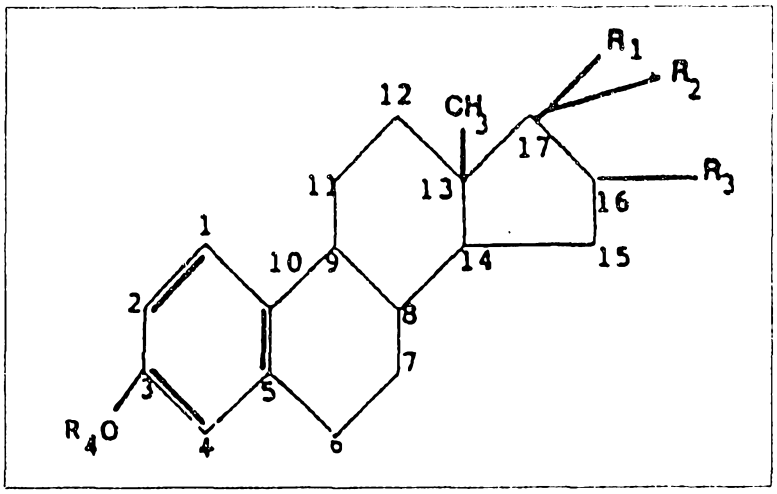
1. A combination of two drugs for treating osteoporotic disease in a human being subject thereto, which comprises:

(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) an estrogen which is effective in the treatment of osteoporosis;

wherein the alkalinizing potassium salt and estrogen are present together in synergistically effective amounts.

2. The combination of claim 1, wherein the estrogen comprises a compound having the following formula, including pharmaceutically acceptable salts and esters thereof:



wherein R_1 is a hydroxyl group and R_2 is selected from the group consisting of H, -C=C and -C≡C, or

R_1 and R_2 together represent an oxygen which is bound to the molecule by a double bond,

R_3 is either hydrogen or a hydroxyl group,

R_4 is selected from the group consisting of H, methyl and cyclopentyl groups, and

wherein the estrogen has either a double bond at the 6-7 and 8-9 positions, a double bond at the 7-8 position, or no double bonds at the 6, 7, 8, and 9 positions.

3. The combination of claim 2, wherein the alkalinizing potassium salt and the estrogen are incorporated in amounts proportional to daily doses of from 30-120 milliequivalents of the alkalinizing potassium salt and daily doses of the estrogen equivalent to 0.06 to 1.25 mg of conjugated estrogens.

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

a. reduces the urinary hydroxyproline excretion rate of the human being treated more than 10% relative to the urinary hydroxyproline excretion rate of that human being when the same amount of said estrogen is independently administered;

b. reduces the urinary collagen crosslinks excretion rate of the human being treated by more than 10% relative to the urinary collagen crosslinks excretion rate of that human being when the same amount of said estrogen is independently administered; and

c. increases the calcium and phosphorus balances of the human being.

5. The combination of claim 4, wherein the alkalinizing potassium salt and the estrogen are incorporated in a unitary dosage form which further comprises a pharmaceutically-acceptable carrier therefor.

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

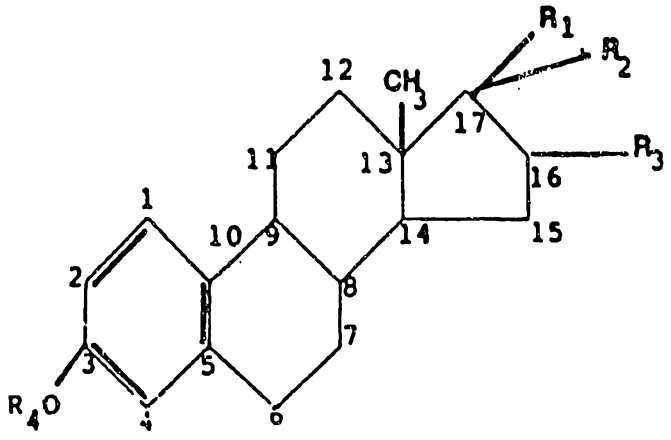
7. A method for treating osteoporotic disease in a human being subject thereto, which comprises administering the combination of the following active ingredients:

(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) an estrogen which is effective in the treatment of osteoporosis, in an amount of as little as 1/10 its normal recommended dose;

the alkalinizing potassium salt being administered in an amount such that the combination drug is at least 10% more effective in treating osteoporosis than the same amount of said estrogen when independently administered.

8. The method of claim 7, wherein said estrogen comprises a compound having the following formula, including pharmaceutically acceptable salts and esters thereof:



wherein R_1 is a hydroxyl group and R_2 is selected from the group consisting of H, -C=C, and -C≡C, or

R_1 and R_2 together represent an oxygen which is bound to the molecule by a double bond,

R_3 is either hydrogen or a hydroxyl group,

R_4 is selected from the group consisting of H, methyl and cyclopentyl groups, and

wherein the estrogen has either a double bond at the 6-7 and 8-9 positions, a double bond at the 7-8 position, or no double bonds at the 6, 7, 8, and 9 positions.

9. The method of claim 8, wherein the alkalinizing potassium salt is administered in an amount, per day, of from 30-120 milliequivalents and the estrogen is administered in an amount equivalent to 0.06 to 1.25 mg of conjugated estrogens.

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% relative to the urinary hydroxyproline excretion rate of that human being treated when the same amount of said estrogen is independently administered;

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 that human being treated when the same amount of said estrogen is independently administered; and

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 said estrogen is independently administered.

11. The method of claim 9, wherein the alkalinizing potassium salt and the estrogen are administered in eparate dosage forms.

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

13. The method of claim 11, 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. The use of the combination of claim 1 for treating osteoporotic disease in a human being.

16. A combination of two drugs for treating osteoporotic disease in a human being, the combination being substantially as described herein with reference to the accompanying Examples.

DATED this 1st day of April 1998

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

By their Patent Attorneys

GRIFFITH HACK

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/03402

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K 33/00
US CL :424/717, 222
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, 722

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: OSTEOPOROSIS, POTASSILIM

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, 4,814,177 (WALSDORF ET AL) 21 March 1989, see entire document.	1-14
Y	EP, A, 0 011 818 (CIBA GEIGY AG) 11 June 1980, see Abstract.	1-14
Y	US, A, 4,078,060 (BENSON ET AL) 07 March 1978, 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)	"&"	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	Date of mailing of the international search report
17 JUNE 1994	AUG 11 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 PETER KULKOSKY Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*