METHODS FOR THE TREATMENT OF OSTEOPOROSIS USING BONE-active PHOSPHONATES AND PARATHYROID HORMONE

The present invention provides methods of treating a human or other animal subject having a bone metabolism disorder, comprising the steps of: (a) administering to said subject a safe and effective amount of a bone active phosphonate during a period of at least about 5 months; (b) administering to said subject a safe and effective amount of a parathyroid hormone, during a period of from about 3 to about 12 months.
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METHODS FOR THE TREATMENT OF OSTEOPOROSIS USING BONE
ACTIVE PHOSPHONATES AND PARATHYROID HORMONE

BACKGROUND OF THE INVENTION

This invention relates to methods of increasing bone mass in humans and
other animals, i.e., for the treatment of osteoporosis and related bone metabolic
disorders. In particular, this invention relates to such methods of treatment by the
administration of a bone active phosphonate and parathyroid hormone.

The most common metabolic bone disorder is osteoporosis. Osteoporosis
can be generally defined as the reduction in the quantity of bone, or the atrophy of
skeletal tissue. In general, there are two types of osteoporosis: primary and
secondary. "Secondary osteoporosis" is the result of an identifiable disease
process or agent. However, approximately 90% of all osteoporosis cases is
"primary osteoporosis". Such primary osteoporosis includes postmenopausal
osteoporosis, age-associated osteoporosis (affecting a majority of individuals over
the age of 70 to 80), and idiopathic osteoporosis affecting middle-aged and
younger men and women.

For some osteoporotic individuals the loss of bone tissue is sufficiently
great so as to cause mechanical failure of the bone structure. Bone fractures often
occur, for example, in the hip and spine of women suffering from postmenopausal
osteoporosis. Kyphosis (abnormally increased curvature of the thoracic spine) may
also result.

The mechanism of bone loss in osteoporotics is believed to involve an
imbalance in the process of "bone remodeling". Bone remodeling occurs
throughout life, renewing the skeleton and maintaining the strength of bone. This
remodeling involves the erosion and filling of discrete sites on the surface of bones,
by an organized group of cells called "basic multicellular units" or "BMUs". BMUs primarily consist of "osteoclasts", "osteoblasts", and their cellular
precursors. In the remodeling cycle, bone is resorbed at the site of an "activated"
BMU by an osteoclast, forming a resorption cavity. This cavity is then filled with
bone by osteoblasts.

Normally, in adults, the remodeling cycle results in a small deficit in bone,
due to incomplete filling of the bone resorption cavity. Thus, even in healthy
adults, age-related bone loss occurs. However, in many people, particularly in
post-menopausal osteoporotics, there is an increase in the number of BMUs that
are activated. This increased activation accelerates bone remodeling, resulting in abnormally high bone loss.

Although its etiology is not fully understood, there are many risk factors thought to be associated with osteoporosis. These include low body weight, low calcium intake, physical inactivity, and estrogen deficiency.


Administration of estrogen is also used as a means to prevent osteoporosis in postmenopausal women. This therapy typically involves daily administration of from about 0.625 milligrams to about 1.25 milligrams of conjugated estrogens, or equivalent amounts of other estrogen hormones. Estrogen may also be used to treat osteoporosis (i.e., actual building of bone in osteoporotics), although this has

Furthermore, the use of estrogen has been associated with certain side effects, such as uterine bleeding. See, Rudy, "Hormone Replacement Therapy - How to Select the Best Preparation and Regimen," 88 Postgraduate Medicine 157 (1990).


Applicant has found, surprisingly, that the administration of parathyroid hormone after administration of an a bone active phosphoante provides benefits not recognized in the art. Accordingly, the methods of this invention provide
effective methods of preventing and treating osteoporosis, with improved efficacy and reduced side effects compared to methods among those known in the art.

SUMMARY OF THE INVENTION

The present invention provides methods of treating a human or other animal subject having a bone metabolism disorder, comprising the steps of:

(a) administering to said subject a safe and effective amount of a bone active phosphonate, during a period greater than about 6 months;

(b) administering to said subject a safe and effective amount of a parathyroid hormone, during a period of from about 3 to about 12 months.

DESCRIPTION OF THE INVENTION

The methods of the present invention comprise the administration of a bone active phosphonate and parathyroid hormone compound to a human or other animal subject. Specific compounds and compositions to be used in these processes must, accordingly, be pharmaceutically-acceptable. As used herein, such a "pharmaceutically-acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

Bone-Active Phosphonates:

The methods of this invention comprise administration of one or more bone-active phosphonates. As referred to herein, a "bone-active phosphonate" includes one or more compounds of the general formula

\[
\begin{array}{c}
\text{PO}_3\text{H}_2 \\
\text{A}---\text{C}---\text{B} \\
\text{O}=\text{P}---\text{R} \\
\mid \\
\text{OH}
\end{array}
\]

and pharmaceutically-acceptable salts and esters thereof, wherein A, B, and R are as defined hereinafter.

In Formula (1), "R" is hydroxy (for bisphosphonates), or hydrogen or alkyl (for phosphonoalkylphosphinates). In the phosphonoalkylphosphinates, R is preferably unsubstituted alkyl, especially lower alkyl. When R is substituted alkyl, preferred substituents include halogen, unsubstituted or substituted phenyl, unsubstituted or substituted pyridinyl, unsubstituted amino, amino substituted with
one or two lower alkyl groups, hydroxy, or carboxy. More preferred substituents are fluoro, phenyl, unsubstituted amino, and hydroxy; most preferred are fluoro (especially when present as trifluoromethyl) and phenyl.

Particularly preferred R moieties in the phosphonoalkylphosphinates are unsubstituted lower alkyl groups, especially unsubstituted, straight-chain, saturated lower alkyl groups. Also preferred R moieties are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and n-hexyl. More preferably, R is methyl, ethyl, n-propyl, or n-butyl. Most preferably, R is methyl.

In Formula (1), "A" is hydrogen; halogen; nitro; alkyl; heterocycle; aryl; heteroaryl; unsubstituted amino, or the amide thereof derived from a carboxylic acid of a substituent group; amino substituted with one substituent group, or the amide thereof derived from a carboxylic acid of a substituent group; amino substituted independently with one alkyl group and one substituent group; hydroxy, or the ester thereof derived from a carboxylic acid of a substituent group; ether having a substituent group; thiol, or the thiol ester thereof derived from a carboxylic acid of a substituent group; thioether having a substituent group, or the sulfoxide and sulfone derivative thereof; \(-\text{SO}_3\text{H}\), the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of a substituent group, the unsubstituted amide thereof, or the amide thereof substituted with one or two alkyl groups; \(-\text{CO}_2\text{H}\), the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of a substituent group, the unsubstituted amide thereof, or the amide thereof substituted with one or two alkyl groups; aldehyde; ketone having a substituent group; carbamate, unsubstituted or substituted with one or two alkyl groups; peptides having from about 1 to about 100 amino acid moieties; or the A and B moieties are covalently linked to form a ring having from 3 to 7 atoms with from 0 to 3 heteroatoms selected from the group consisting of nitrogen, sulfur, phosphorus and oxygen, the ring being unsubstituted or substituted with one or more of the above substituents of A; or the A and B moieties are replaced by an unsubstituted or substituted alkyl moiety attached to the geminal carbon (the carbon shown in structure (1) hereinabove) by a double bond.

Preferably, A is one of the following moieties.

1. hydrogen
2. halogen (preferably fluoro or chloro, more preferably fluoro)
3. substituted or unsubstituted alkyl having the general structure
wherein:

(a) \( n \) is an integer from 1 to 10, preferably from 1 to 5, more preferably 1 or 2, more preferably 1;

(b) each \( R^1 \) is, independently, hydrogen, halogen, lower alkyl, unsubstituted amino or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted independently with two lower alkyl groups, hydroxy or the ester thereof derived from a carboxylic acid of a lower alkyl group, \(-\text{CO}_2\text{H}\) or the pharmaceutically-acceptable salts thereof or the ester thereof derived from an alcohol of a lower alkyl group or the unsubstituted amide thereof or the amide thereof substituted with one or two lower alkyl groups, ether having a lower alkyl group, \(-\text{PO}_3\text{H}_2\) or the pharmaceutically-acceptable salts thereof, and nitro, or two \( R^1 \)'s on the same carbon atom are \( =\text{O} \) or \( =\text{NR}^9 \) (where \( \text{R}^9 \) is lower alkyl or may be hydrogen when there is another nitrogen atom attached to the same carbon atom as the \( =\text{NR}^9 \) moiety), or two \( R^1 \)'s on adjacent carbon atoms may be replaced by an additional bond between the carbon atoms, or an \( R^1 \) on the first carbon atom (from the right side of structure (2) hereinabove) and B (see structure (1) hereinabove) may be replaced by an additional bond; and

(c) \( Y \) is halogen; nitro; cyano; heterocycle; aryl; heteroaryl; unsubstituted amino, and the amide thereof derived from a carboxylic acid of an alkyl, heterocycle, aryl or heteroaryl group; amino substituted with one alkyl, heterocycle, aryl or heteroaryl group and the amide thereof derived from a carboxylic acid of an alkyl group; amino substituted independently with one alkyl group and one alkyl, heterocycle, aryl or heteroaryl group; hydroxy, and the ester thereof derived from a carboxylic acid of an alkyl, heterocycle, aryl or heteroaryl group; ether having an alkyl, heterocycle, aryl or heteroaryl group; thiol, and the thiol ester thereof derived from a carboxylic acid of an alkyl, heterocycle, aryl or heteroaryl group; thioether having an alkyl, heterocycle, aryl or heteroaryl group, and the sulfoxide and sulfone derivatives thereof; \(-\text{SO}_3\text{H}\), the pharmaceutically-acceptable salts
thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups; -CO₂H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups; PO₃H₂, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups; -(R⁸)PO₂H (where R⁸ is hydrogen or unsubstituted lower alkyl), the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups; aldehyde; ketone having an alkyl group; carbamate, unsubstituted or substituted with one or two alkyl groups; or peptidyl. For bisphosphonates, Y is preferably a heterocycle (preferably 5 to 7 membered heterocycles having one or two nitrogen atoms); amino; and substituted amino. Particularly preferred Y moieties include pyridyl, amino, and amino substituted with one or two lower alkyl groups. Preferably, for phosphonoalkylphosphinates, Y is halogen (preferably fluoro); trifluoromethyl; ether having a lower alkyl group; unsubstituted amino, and the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group and the amide thereof derived from carboxylic acid of a lower alkyl group; amino substituted independently with two lower alkyl groups; or peptidyl having from one to about six amino acid moieties.

(4) cycloalkyl having from 4 to 10 carbon atoms, preferably 5 or 6 carbon atoms
(5) heterocycle having 5 or 6 atoms in the ring; more preferably one or two nitrogen atoms in the ring, more preferably having one nitrogen atom in the ring. Particularly preferred heterocycles are unsubstituted or substituted piperidinyl, pyrrolidinyl, piperazinyl, and morpholinyl.
(6) unsubstituted and substituted phenyl and naphthyl
(7) unsubstituted and substituted 5 and 6 membered ring heteroaryls having one or two heteroatoms (especially nitrogen heteroatoms), preferably pyridinyl
(8) an amine-containing moiety having the general structure:
wherein

(a) $m$ is an integer from 0 to 10, preferably from 0 to 5, more preferably 0 or 1, more preferably 0;

(b) $R^1$ and $Y$ are as described hereinbefore; and

(c) $R^2$ is hydrogen, lower alkyl or acyl derived from a carboxylic acid of a lower alkyl

(9) an oxygen-containing moiety having the general structure:

wherein

(a) $m$ is an integer from 0 to 10, preferably from 0 to 5, more preferably 0 or 1, more preferably 0; and

(b) $R^1$ and $Y$ are as described hereinbefore

(10) sulfur-containing moiety having the general structure:

wherein

(a) $m$ is an integer from 0 to 10, preferably from 0 to 5, more preferably 0 or 1, more preferably 0; and

(b) $R^1$ and $Y$ are as described hereinbefore
In Formula (1), "B" is hydrogen; halogen; unsubstituted or substituted lower alkyl; unsubstituted or substituted cycloalkyl having from 3 to 7 atoms in the ring; unsubstituted or substituted heterocycle having from 3 to 7 atoms in the ring; unsubstituted or substituted phenyl; hydroxy, or the ester thereof derived from a carboxylic acid of a lower alkyl group; thiol; unsubstituted amino, or the amide thereof derived from a carboxylic acid of a lower alkyl group; amino substituted with one lower alkyl group, or the amide thereof derived from a carboxylic acid of a lower alkyl group; amino substituted independently with two lower alkyl groups; or -CO₂H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of a lower alkyl group, the unsubstituted amide thereof, or the amide thereof substituted with one or two lower alkyl groups.

To maintain chemical stability of these compounds, the A and B moieties preferably do not both have heteroatoms (nitrogen, oxygen or sulfur), or a heteroatom and a halogen, bonded to the phosphonate moiety (i.e., the carbon atom geminally substituted with the phosphorous atoms). Thus, when the A moiety has an oxygen, sulfur, nitrogen, or halogen atom bonded to the phosphorus-substituted methylene carbon, then B is selected from hydrogen; unsubstituted or substituted lower alkyl, cycloalkyl, heterocycle (where a carbon atom of the heterocycle is bonded to the geminal carbon atoms), or phenyl, -COOH, the pharmaceutically-acceptable salts thereof; the ester thereof derived from an alcohol of a lower alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two lower alkyl groups.

Preferably B is hydrogen, halogen, unsubstituted or substituted lower alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted benzyl, hydroxy or the ester thereof derived from a carboxylic acid of a lower alkyl group, thiol, unsubstituted amino or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted independently with two lower alkyl groups, or -COOH or the pharmaceutically-acceptable salts thereof and the ester thereof derived from an alcohol of a lower alkyl group and the unsubstituted amide thereof or the amide thereof substituted with one or two lower alkyl groups.

More preferably, B is hydrogen, chloro, methyl, ethyl, hydroxy, thiol, unsubstituted amino, (N-methyl)amino, (N,N-dimethyl)amino, -COOH or the pharmaceutically-acceptable salts thereof, -COOCH₂, or -CONH₂. More preferably, B is hydrogen, methyl, chloro, amino, or hydroxy; more preferably hydrogen, or hydroxy, or amino, or thiol; more preferably hydroxy. Particularly
preferred bone-active phosphonates include those wherein A is a moiety of groups (3) or (8) above, and B is hydroxy.

Particularly preferred bisphosphonates useful herein are of the formula:

\[
\begin{align*}
R^2 - X & \quad \Bigg( \begin{array}{c} R^3 \\ \downarrow \\ C \end{array} \Bigg) \\ C & \quad R^1 \\ \Bigg( \begin{array}{c} R^3 \\ \downarrow \\ n \end{array} \Bigg) \quad PO_3H_2
\end{align*}
\]

wherein: n is an integer from 0 to 7 (preferably from 0 to 3, more preferably 1); \( R^1 \) is hydrogen, chloro, amino, or hydroxy (preferably hydrogen or hydroxy); X is \(-\text{NH}_2\text{-},\) quaternary amine, oxygen, sulfur, or a single bond (preferably \(-\text{NH}_2\text{-}\) or single bond); \( R^2 \) and \( R^3 \) is a substituted or unsubstituted 5- to 7-membered carbo cyclic (preferably 6- to 7-membered, more preferably benzene or cycloheptyl), a substituted or unsubstituted 5- to 7-membered heterocycle having from 1 to 3 heteroatoms (preferably a 6-membered heterocycle having 1 or 2 nitrogen atoms, wherein a ring nitrogen may be quaternarized), \(-\text{NH}_2\text{-},\) amino substituted with one alkyl or two alkyl (preferably \( C_1-C_5 \)) groups to give a secondary or tertiary amine, respectively, quaternary amino, or hydrogen; wherein if \( R^2 \) is a substituted 5- to 7-membered carbo cyclic or heterocycle, the substituent is one or more substituents selected from the group consisting of substituted and unsubstituted, saturated or unsaturated alkyl having from 1 to about 6 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted benzyl, hydroxy, halogen, carboxyl, alkoxy, nitro, amido, amino, substituted amino, carboxylate, and combinations thereof, hydrogen being preferred; each \( R^3 \) is, independently, hydrogen, or substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 4 carbon atoms; and their pharmaceutically-acceptable salts and esters.

The term "pharmaceutically-acceptable salts and esters", as used herein, means hydrolyzable esters and salts of the bone-active phosphonates which have the same general pharmacological properties as the acid form from which they are derived, and which are pharmaceutically acceptable. Pharmaceutically-acceptable salts include, for example, alkali metals (e.g., sodium and potassium), alkaline earth metals (e.g., calcium and magnesium), non-toxic heavy metals (e.g., stannous and indium), and ammonium and low molecular weight substituted ammonium (e.g., mono-, di- and triethanolamine) salts. Preferred compounds are the sodium, potassium, and ammonium salts. Pharmaceutically-acceptable esters include unsubstituted and substituted alkyl, aryl and phosphoryl esters. Nonlimiting examples of pharmaceutically-acceptable esters include, for example, isopropyl,
tertiarybutyl, 2-chloroethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, p-
toluenesulfonylthethyl, glycyll, sarcosyl, benzyl, phenyl, 1,2-hexanoylglyceryl, p-
nitrophenyl, 2,2 dimethyl-1,3-dioxolene-4-methyl, isopenetyl, o-
carbomethoxyphenyl, piraloyloxymethylsalicylyl, diethylamidophosphoryl,
pivaloyloxymethyl, acyloxyethyl, propionyloxymethyl, isobutyryloxymethyl,
dodecyl, octadecyl, and isopropylloxymethyl.

Specific examples and definitions for substituents useful in the compounds
of Formulas (1) through (6) are described in European Patent Publication 298,553,
application also describes phosphonoalkylphosphinates useful in the methods of
this invention (wherein R is hydrogen or alkyl), and methods for making such
compounds. Methods of making phosphonoalkylphosphinates are also described
(incorporated by reference herein).

Bisphosphonates useful in the methods of this invention (wherein R is
hydroxy), and methods for making such compounds, are described in the following
patent documents, all incorporated by reference herein: U.S. Patent 3,553,314,
Francis, issued January 5, 1971; U.S. Patent 3,683,080, Francis, issued August 8,
1972; U.S. Patent 3,846,420, Wollmann et al., issued November 5, 1974; U.S.
Patent 3,899,490, Schindler et al., issued August 12, 1975; U.S. Patent 3,941,772,
Ploger et al., issued March 2, 1976; U.S. Patent 3,957,160, Ploger et al., issued
May 18, 1976; U.S. Patent 3,962,432, Schmidt-Dunker, issued June 8, 1976; U.S.
Patent 3,979,385, Wollmann et al., issued September 7, 1976; U.S. Patent
3,988,443, Ploger et al., issued October 26, 1976; U.S. Patent 4,054,598, Blum et
al., issued October 18, 1977; U.S. Patent 4,113,861, Fleisch et al., issued
September 12, 1978; U.S. Patent 4,117,090, Ploger, issued September 26, 1978;
U.S. Patent 4,134,969, Schmidt-Dunker, issued January 16, 1979; U.S. Patent
4,267,108, Blum et al., issued May 12, 1981; U.S. Patent 4,304,734, Jary et al.,
issued December 8, 1981; U.S. Patent 4,330,537, Francis, issued May 18, 1982;
U.S. Patent 4,407,761, Blum et al., issued October 4, 1983; U.S. Patent
4,469,686, Andrews, issued September 4, 1984; U.S. Patent 4,578,376, Rosini,
issued March 25, 1986; U.S. Patent 4,608,368, Blum et al., issued August 26,
4,687,767, Bosies et al., issued August 18, 1987; U.S. Patent 4,687,768, Benedict
et al., issued October 18, 1987; U.S. Patent 4,711,880, Stahl et al., issued
December 8, 1987; U.S. Patent 4,719,203, Bosies et al., issued January 12, 1988;
U.S. Patent 4,927,814, Gall et al., issued May 22, 1990; U.S. Patent 4,990,503,
Isomura et al., issued February 5, 1991; German Offenlegungsschrift 2,104,476,
Worms, published August 17, 1972; German Offenlegungsschrift 2,343,147,
Ploeger et al., published April 3, 1975; German Offenlegungsschrift 2,360,798,
Worms et al., published June 26, 1975; German Offenlegungsschrift 2,513,966,
Schmidt-Dunker, published October 7, 1976; German Offenlegungsschrift
2,541,981, Eimers et al., published March 24, 1977; German Offenlegungsschrift
3,334,211, Blum, published April 4, 1985, Japanese Patent Publication 78/59,674,
Suzuki et al., published May 29, 1978; Japanese Patent Publication 79/135,724,
Suzuki et al., published October 22, 1979; Japanese Patent Publication 80/98193,
Suzuki et al., published July 25, 1980; European Patent Publication 88,359, Blum
et al., published September 14, 1983; European Patent Publication 100,718,
Breilere et al., published February 15, 1984; European Patent Publication 186,405,
Benedict et al., published July 2, 1986; European Patent Publication 197,478,
Bosies et al., published October 15, 1986; European Patent Publication 230,068,
Benedict et al., published July 29, 1987; European Patent Publication 273,514,
Ebetino et al., published July 6, 1988; European Patent Publication 274,158,
Ebetino et al., published July 13, 1988; European Patent Publication 282,309,
Sakamoto et al., published September 14, 1988; European Patent Publication
282,320, Isomura et al., published September 14, 1988; PCT Patent Publication
87/03598, Binderup et al., published June 18, 1987; and PCT Patent Publication

Preferred bone-active phosphonates useful in the methods of this invention
include: N-(2'-(3'-methyl)-pyridinyl)aminomethane phosphonomethylphosphinic
acid; N-(2'-(5'-methyl)-pyridinyl)amino methane phosphonomethylphosphinic acid;
N-(2'-(3'-methyl)-piperidinylidene)aminomethane phosphonomethylphosphinic
acid; N-(2'-(5'-methyl)-piperidinylidene)aminomethane phosphonomethylphosphinic
acid; 2-(2'-pyridinyl)ethane-1-phosphono-1-methylphosphinic acid; 2-(2'-
piperidinyl)ethane-1-phosphono-1-methylphosphinic acid; 2-(p-aminophenyl)-1-
hydroxy-ethane-1-phosphono-1-methylphosphinic acid; 2-(m-aminophenyl)-1-
hydroxy-ethane-1-phosphono-1-methylphosphinic acid; N-(1-(5-aminophenyl-1-
1-oxo)-pentyl)aminomethane phosphonomethylphosphinic acid; N-(2'-(3'-methyl-
piperidinylidene)aminomethane phosphonomethylphosphinic acid; S-(2'-
pyridinyl)thiomethane phosphonomethylphosphinic acid; 2-(2'-pyridyl)-1-
hydroxyethane-1-phosphono-1-methyl phosphonic acid; 2-(3'-pyridyl)-1-
hydroxyethane-1-phosphono-1-methyl phosphonic acid; 2-(N-imidazoyl)-1-
hydroxyethane-1-phosphono-1-methylphosphinic acid; 3-(N-pentyl-N-
methylamino)-1-hydroxypropane-1-phosphono-1-methylphosphinic acid; 4-amino-
1-hydroxybutane-1-phosphono-1-methylphosphinic acid; 3-(N-pyrrolidino)-1-hydroxypropane-1-phosphono-1-methylphosphinic acid; N-cycloheptyl aminomethanephosphonomethylphosphinic acid; S-(p-chlorophenyl) thiomethanephosphonomethylphosphinic acid; (7-dihydro-1-pyridine)methanephosphonomethylphosphinic acid; (7-dihydro-1-pyridine)hydroxymethanephosphonomethylphosphinic acid; (6-dihydro-2-pyridine)hydroxymethanephosphonomethylphosphinic acid; 2-(6-pyrolopyridine)-1-hydroxyethane-1-phosphono-1-methyl phosphinic acid; 1-hydroxyethane-1,1-bisphosphonic acid; 1-hydroxy pentane-1,1-bisphosphonic acid; methane bisphosphonic acid; dichloromethanebisphosphonic acid; hydroxymethanebisphosphonic acid; 1-aminoethane-1,1-bisphosphonic acid; 2-aminoethane-1,1-bisphosphonic acid; 3-aminopropane-1-hydroxy-1,1-bisphosphonic acid; 3-(dimethylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 3,3-dimethyl-3-amino-1-hydroxypropane-1,1-bisphosphonic acid; phenylaminomethane bisphosphonic acid; N,N-dimethylaminomethane bisphosphonic acid; N-(2-hydroxyethyl) aminomethanebisphosphonic acid; 4-amino-1-hydroxybutane-1,1-bisphosphonic acid; 5-amino-1-hydroxypentane-1,1-bisphosphonic acid; 6-amino-1-hydroxyhexane-1,1-bisphosphonic acid; indan-2,2-bisphosphonic acid; hexahydroindan-2,2-bisphosphonic acid; 2-methylcyclobutane-1,1-bisphosphonic acid; 3-chlorocyclopentane-1,1-bisphosphonic acid; cyclohexane-1,1-bisphosphonic acid; 2-(2-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; N-(2-(5-amino)-pyridyl)-aminomethane bisphosphonic acid; N-(2-(5-chloro)-pyridyl)-aminomethane bisphosphonic acid; N-(2-(3-picoly))-aminomethane bisphosphonic acid; N-(2-(4-picoly))-aminomethane bisphosphonic acid; N-(2-(5-picoly))-aminomethane bisphosphonic acid; N-(2-(6-picoly))-aminomethane bisphosphonic acid; N-(2-(3,4-lutidine))-aminomethane bisphosphonic acid; N-(2-pyrimidyl)-aminomethane bisphosphonic acid; N-(2-pyridyl)-2-aminoethane-1,1-bisphosphonic acid; 2-(2-pyridyl)-ethane-1,1-bisphosphonic acid; 2-(3-pyridyl)-ethane-1,1-bisphosphonic acid; 2-(4-pyridyl)-ethane-1,1-bisphosphonic acid; 2-(2-(3-picoly))-oxaethane-1,1-bisphosphonic acid; 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; 2-(N-imidazoyl)-1-hydroxyethane-1,1-bisphosphonic acid; 3-(N-pentyl-N-methylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 3-(N-pyrrolidino)-1-hydroxypropane-1,1-bisphosphonic acid; N-cycloheptylaminomethane bisphosphonic acid; S-(p-chlorophenyl) thiomethanebisphosphonic acid; (7-dihydro-1-pyridine)methanebisphosphonic acid; (7-dihydro-1-pyridine)hydroxymethanebisphosphonic acid; (6-dihydro-2-pyridine)hydroxymethanebisphosphonic acid; 2-(6-pyrolopyridine)-1-
hydroxyethane-1,1-bisphosphonic acid; and pharmaceutically-acceptable salts and esters thereof.

Particularly preferred bone-active phosphonates useful in the methods of this invention include: 1-hydroxyethane-1,1-bisphosphonic acid; dichloromethane bisphosphonic acid; 3-amino-1-hydroxypropane-1,1-bisphosphonic acid; 6-amino-1-hydroxyhexane-1,1-bisphosphonic acid; 4-amino-1-hydroxybutane-1,1-bisphosphonic acid; 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; 2-(N-imidazoyl)-1-hydroxyethane-1,1-bisphosphonic acid; 3-(N-pentyl-N-methylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 3-(N-pyrrolidino)-1-hydroxypropane-1,1-bisphosphonic acid; N-cycloheptylaminomethanebisphosphonic acid; S-(p-chlorophenyl) thiomethanebisphosphonic acid; (7-dihydro-1-pyridine)methane bisphosphonic acid; (7-dihydro-1-pyridine)hydroxymethane bisphosphonic acid; (6-dihydro-2-pyridine)hydroxymethanebisphosphonic acid; 2-(6-pyrolopyridine)-1-hydroxyethane-1,1-bisphosphonic acid; and pharmaceutically-acceptable salts and esters thereof.

**Parathyroid Hormone**

The methods of this invention also comprise administration of a parathyroid hormone. As referred to herein, "parathyroid hormone" refers to the naturally occurring human parathyroid hormone, synthetic analogs thereof, parathyroid hormone and parathyroid hormone fragments manufactured by recombinant DNA technology, and parathyroid hormone fragments and parathyroid hormone fragment analogs. Parathyroid hormone useful in the methods of this invention includes, for example hPTH (1-38), hPTH (1-34), hPTH (1-37), hPTH (2-34), and hPTH (2-38). Detailed descriptions of the types of parathyroid hormones available and methods for manufacturing parathyroid hormone are disclosed in the following references, all incorporated by reference herein, U.S. Patent 4,105,602, Colescott, et al., issued August 8, 1978; U.S. Patent 4,698,328, Neer, et al., issued October 6, 1987; U.S. Patent 4,833,125, Neer, et al., issued May 23, 1987; DE 32 43 358, Hesch, publication date May 24, 1984; and DE 39 35 738, Forssmann, et al., publication date May 8, 1991.

**Methods of Treatment**

This invention provides methods for treating a human or other animal subject having a bone metabolism disorder, comprising the steps of:

(a) administering to said subject a safe and effective amount of a bone active phosphonate, during a period of greater than about 6 months;
(b) administering to said subject a safe and effective amount of a parathyroid hormone, during a period of from about 3 to about 12 months.

Preferably, in step (a), said bone active phosphonate is administered for greater than about 8 months. Also preferably, in step (b), said parathyroid hormone is administered for from about 4 months to about 8 months, more preferably for about 6 months. Preferably steps (a) and (b) are repeated from 1 to 5 times (i.e., so the entire method comprises performance of each step, in sequence, 2 to 6 times).

In a preferred method of this invention, the bone active phosphonate is administered during the treatment period of step (b); i.e., the phosphonate is administered concurrently with the parathyroid hormone.

The bone active phosphonate and parathyroid hormone are administered in a "safe and effective amount", which, as referred to herein, is the quantity of a material which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed.

The specific amount and dosage regimen of a particular bone active phosphonate administered during the methods of this invention is a function of the potency of the compound, as well as other factors. Preferably, the phosphonate is administered in amounts and in regimens recognized in the art of useful for treating osteoporosis in accordance with sound medical practice.

Potency of a bone active phosphonate can be expressed in terms of its "LED" or "least effective dose", which is the minimum dose of compound that is effective, by itself, to cause a significant inhibition of bone resorption. Preferably, in the methods of this invention, the antiresorptive compound is administered at a level of at least about 0.8 LED of the compound, more preferably from about 0.8 LED to about 5 LED, more preferably from about 0.8 to about 3 LED.

The specific LEDs of a given bone active phosphonate will vary depending upon its chemical composition, and method of administration (i.e., oral or parenteral). The lower the LED, the more potent the compound. Generally, it is desirable to administer higher potency phosphonates in lower doses and on a fewer number of days in the period of treatment. Likewise, the higher the LED, the less potent the compound. Accordingly, then, in general, it is desirable to administer a
lower potency phosphonates in higher doses and on a greater number of days in the period of treatment.

In particular, the LEDs for the bone-active phosphonates may be determined using any of several art-recognized in vivo models. One such model is the thyroparathyroidectomized ("TPTX") rat model. In this model, compounds are evaluated for in vivo bone resorption inhibition potency, by measuring their ability to inhibit the increase of serum calcium levels caused by administration of parathyroid hormone in rats whose parathyroid gland has been removed. This model is described in Russell et al., 6 Calcified Tissue Research 183 (1970); Muhlbauder et al., 5 Mineral Electrolyte Metabolism 296 (1981); U.S. Patent 4,761,406, Flora et al., issued August 2, 1988, and European Patent Publication 298,553, Ebetino, published January 11, 1989; all of which are incorporated by reference herein.

Another model is the "Schenk Model", which measures the effects of bone-active phosphonates on bone growth in young rats. This model is described in Schenk et al., 11 Calcif. Tissue Res. 196 (1973); Shinoda et al., 35 Calcif. Tissue Int. 87 (1983); U.S. Patent 4,761,406, Flora et al., issued August 2, 1988; and European Patent Publication 298,553, Ebetino, published January 11, 1989; all of which are incorporated by reference herein.

Another model is the "ovariectomized" or "OVX" rat model, which measures the ability of bone-active phosphonates to prevent loss of bone in female rates induced by ovariectomy. This model is described in Wronski et al., 125 Endocrinology 810 (1989), incorporated by reference herein.

The LEDs for bone active phosphonates are conveniently expressed in "mgP/kg", which, as referred to herein, is the amount of compound, expressed as milligrams phosphorus in the compound, per kilogram weight of the subject to be treated. Because the bone active phosphonates vary in molecular weight, expressing the amount administered in mg P/kg normalizes the comparison between compounds of varying potencies. In order to determine the mg P/kg administered to a patient according to the methods of this invention, the following conversion formula is used:

\[
\text{mg/kg compound administered} = \left( \frac{\text{mg phosphorus}}{\text{kg}} \right) \times \left( \frac{\text{molecular weight of compound}}{62} \right)
\]

(For example, 2-(3-pyridinyl)-1-hydroxyethane-1,1-bisphosphonate has a molecular weight of 350. Two phosphorus atoms have a molecular weight of 62.)
Thus, if a patient is dosed at 0.01 mg/kg of the compound, then about 0.002 mg P/kg was administered.

The LEDs for parenteral dosing of preferred bone-active phosphonates useful herein are: 1.0 mg P/kg, for 1-hydroxyethane-1,1-bisphosphonic acid; 0.5 mg P/kg, for dichloromethane bisphosphonic acid; 0.03 mg P/kg, for 3-amino-1-hydroxypropane-1,1-bisphosphonic acid; 0.001 mg P/kg, for 4-amino-1-hydroxybutane-1,1-bisphosphonic acid; 0.1 mg P/kg, for 6-amino-1-hydroxyhexane-1,1-bisphosphonic acid; 0.01 mg P/kg, for N-(2-pyridyl) aminomethane-1,1-bisphosphonic acid; 0.0003 mg P/kg, for 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; 0.0001 mg P/kg, for N-cycloheptylaminomethanebisphosphonic acid; 0.0001 mg P/kg, for 3-(N-pentyl-N-methylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 0.01 mg P/kg, for 3-(dimethylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 0.01 mg P/kg, for 3-(N-pyrolidino)-1-hydroxypropane-1,1-bisphosphonic acid; 0.03 mg P/kg, for N-cycloheptylaminomethanebisphosphonic acid; and 0.3 mg P/kg for S-(p-chlorophenyl)thiomethanebisphosphonic acid. (The LEDs for oral dosing would be higher, depending upon the systemic absorption of the phosphonate. Typically, absorption from oral administration is from about 1% to about 10%. Thus, oral LEDs are typically about ten- to one hundred-fold higher than the parenteral LEDs.)

Parathyroid hormone is routinely dosed in International Units (IU). In the methods of this invention, parathyroid hormone is preferably administered at levels of from about 100 to about 700 IU per day, more preferably from about 200 to about 600 IU per day, more preferably from about 400 to about 500 IU per day.

During the treatment period of step (a), and optionally the treatment period of step (b), the bone active phosphonate can be administered daily, or in a cyclical fashion. Such cyclical regimens are generally described in U.S. Patents 4,761,406, Flora et al., issued August 2, 1988; U.S. Patent 4,812,304, Anderson et al., issued March 14, 1989; U.S. Patent 4,822,609, Flora, issued April 18, 1989; World Patent Publication 93 11786, Geddes and Boyce, published June 29, 1993; and World Patent Publication 92 11474, McOsker, published September 3, 1992; all of which are incorporated by reference herein. For methods using a bisphosphonate, the bisphosphonate must be given at least one day of every thirty(30)-days of said treatment period. Preferably, the bisphosphonate may be given every day, every second day, every third day, every fourth day, every fifth day, or every sixth day, of said treatment period.
During the treatment period of step (b), the parathyroid hormone must be
given at least one day every seven days of every thirty(30)-days. Preferably, the
parathyroid hormone is administered at least about 50% of the days during the
period of step (b).

The methods of this invention comprise treatment of osteoporosis at all
stages of the disorder. Since osteoporosis is an ongoing process of bone loss,
rather than a disorder having a discrete beginning- or end-point, "treatment", as
referred to herein, consists of any method which stops, slows, or reverses the
process of bone loss which occurs in osteoporosis.

Preferred methods of this invention comprise treatment of osteoporosis in
subjects who have already lost skeletal mass (herein referred to as "established
osteoporosis"). Such methods of this invention for the treatment of established
osteoporosis preferably comprise administering the actives for a period of time
sufficient to achieve an increase in the net skeletal mass of said subject. The
increase in mass may be in cortical bone, trabecular bone, or both. Preferably, the
net skeletal mass is increased by at least about 5% per year, preferably by at least
about 10% per year.

The specific period of time sufficient to achieve an increase in the net
skeletal mass of the subject may depend on a variety of factors. Such factors
include, for example, the specific actives employed, the amount of actives
administered, the age and sex of the subject, the specific disorder to be treated,
concomitant therapies employed (if any), the general physical health of the subject
(including the presence of other disorders), the extent of bone loss in the
individual, and the nutritional habits of the individual.

The therapeutic regimen utilizing the methods of this invention are
preferably continued for at least about twelve months. Of course, a therapeutic
regimen may be continued indefinitely, according to sound medical practice.
Preferably the subject is treated until a net skeletal mass is obtained commensurate
with reduced fracture risk as assessed by the patient's physician.

Also, preferably, the subject is administered nutritional and other
therapeutic agents to aid in the increase of bone mass. Such optional agents
include, for example, Vitamin D and calcium.

In the methods of this invention, "administering" refers to any method
which, in sound medical practice, delivers the actives used in this invention to the
subject to be treated in such a manner so as to be effective in the building of bone.
The actives may be administered by any of a variety of known methods of
administration, e.g., orally, dermamucosally (for example, dermally, sublingually,
intranasally, and rectally), parenterally (for example, by subcutaneous injection, intramuscular injection, intra-articular injection, intravenous injection), and by inhalation. Thus, specific modes of administration include, but are not limited to, for example, oral, transdermal, mucosal, sublingual, intramuscular, intravenous, intraperitoneal, subcutaneous administration, and topical application.

A preferred method for the treatment of osteoporosis includes an initial diagnostic step, to determine the presence of the disorder. Thus, a preferred method of this invention comprises the steps of performing a diagnostic on a human subject for the detection of osteoporosis and, upon obtaining a positive result from said diagnostic, administering the actives according to the methods of this invention. For such methods for treatment of postmenopausal female subjects prior to significant bone loss, said initial diagnostic step comprises performing a diagnostic for determining menopause. Such methods are well known in the art, and include, for example, determination of the bone mass and rate of bone remodeling. The rate of bone remodeling can be determined by measurement of biochemical markers. See, Hui, et al., "The Contribution of Bone Loss to Postmenopausal Osteoporosis," J Osteoporosis Int, 30 (1990), incorporated by reference herein.

Suitable diagnostics for the detection of established osteoporosis are also well known in the art. Such methods include the measurement of the radiodensity of skeletal radiographs, quantitative computerized tomography, single energy photon absorptiometry, dual-energy photon absorptiometry, dual energy X-ray absorptiometry, and quantitative digital radiography. Diagnostic techniques among those useful herein are described in W. A. Peck et al., Physician's Resource Manual on Osteoporosis (1987), published by the National Osteoporosis Foundation (incorporated by reference herein).

Dosage Forms:

The bone active phosphonate and parathyroid hormone may be administered in any of a variety of pharmaceutically-acceptable compositions. Such compositions may comprise an active and a pharmaceutically-acceptable carrier. Pharmaceutically-acceptable carriers include solid or liquid filler diluents or encapsulating substances, and mixtures thereof, that are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components of the pharmaceutical composition are capable of being commingled with the actives, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the
pharmaceutical composition under ordinary use situations. Pharmaceutically-
acceptable carriers must, of course, be of sufficiently high purity and sufficiently
low toxicity to render them suitable for administration to the human or lower
animal being treated.

Some examples of the substances which can serve as pharmaceutical
carriers are: sugars, such as lactose, glucose and sucrose; starches, such as corn
starch and potato starch; cellulose and its derivatives, such as sodium
carboxymethylcellulose, ethylcellulose, cellulose acetate, powdered tragacanth;
malt; gelatin; talc; stearic acid; magnesium stearate; vegetable oils, such as peanut
oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such
as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; agar;
algic acid; pyrogen-free water; isotonic saline; phosphate buffer solutions;
 wetting agents and lubricants such as sodium lauryl sulfate; coloring agents;
flavoring agents; and preservatives. Other compatible pharmaceutical additives
and actives may be included in the pharmaceutically-acceptable carrier for use in
the compositions of the present invention.

The choice of a pharmaceutically-acceptable carrier to be used in
conjunction with the active is determined by the way the active is to be
administered. If the active is to be injected, the preferred pharmaceutical carrier is
sterile water, physiological saline, or mixtures thereof. The pH of such parenteral
composition is preferably adjusted to about 7.4. Suitable pharmaceutically-
acceptable carriers for topical application include those known in the art for use in
creams, gels, tapes, patches, and similar topical delivery means.

The pharmaceutically-acceptable carrier employed in conjunction with the
actives is used at a concentration sufficient to provide a practical size to dosage
relationship. The pharmaceutically-acceptable carriers, in total, may comprise from
about 0.1% to about 99.9% by weight of the pharmaceutical compositions of the
present invention, preferably from about 5% to about 80%, and most preferably
from about 10% to about 50%.

A preferred method of administering bisphosphonates is orally, in a unit-
dosage form (i.e., a dosage form containing an amount of active suitable for
administration in one single dose, according to sound medical practice). Preferred
unit dosage forms for bisphosphonate include tablets, capsules, suspensions, and
solutions, comprising a safe and effective amount of active. Pharmaceutically-
acceptable carriers suitable for the preparation of unit dosage forms for oral
administration are well known in the art. Their selection will depend on secondary
considerations like taste, cost, shelf stability, which are not critical for the purposes
of the present invention, and can be made without difficulty by a person skilled in the art. Preferably, oral unit dosage forms of the bone-active phosphonate comprise from about 0.0005 mgP/kg oral per day to about 1.0 mgP/kg oral per day of the phosphonate.

Preferred dose forms for parathyroid hormone include subcutaneous, nasal, transdermal, rectal, sublingual, and oral. Preferred oral forms include, for example, liposomes, lipid emulsions, and proteinaceous cages.

Kits:

This invention also provides kits for conveniently and effectively implementing the methods of this invention. Such kits comprise one or more unit doses of bone active phosphonate, one or more unit doses of parathyroid hormone, and a means for facilitating compliance with methods of this invention. Such kits provide a convenient and effective means for assuring that the subject to be treated takes the appropriate active in the correct dosage in the correct manner. The compliance means of such kits includes any means which facilitates administering the actives according to a method of this invention. Such compliance means includes instructions, packaging, and dispensing means, and combinations thereof. Examples of packaging and dispensing means are well known in the art, including those described in U.S. Patents 4,761,406, Flora et al., issued August 2, 1988; and U.S. Patent 4,812,311, Uchtmann, issued March 14, 1989 and U.S. 4,833,125, Neer et al., issued May 23, 1989, all incorporated by reference herein.

The following non-limiting examples illustrate the compositions, processes and uses of the present invention.

**EXAMPLE 1**

An Asian male human patient weighing approximately 65 kg and diagnosed with idiopathic osteoporosis is treated by a method of this invention. Specifically, for a period of eight months, the patient is administered the bisphosphonate, 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid. The patient is orally administered one tablet per day, with each tablet containing 0.002 mgP/kg per day of the bisphosphonate. The bisphosphonate treatment is discontinued. Then, for the next six months, the patient is administered parathyroid hormone (human synthetic fragment 1-34, or hPTH 1-34). The hormone is subcutaneously administered at a dose of 13 IU/kg via insulin syringe to the anterior thigh for five days out of every week during the six-month period.
A biopsy of iliac crest bone is taken and reveals an increase in mean wall thickness of the remodeling units (BMU) compared to her baseline biopsy. The activation frequency and depth of resorption cavities on cancellous, cortical and endocortical surfaces are not significantly increased above the values observed at baseline. Bone mineral density is measured, indicating an increase of 11%.

EXAMPLE 2

A human Caucasian female patient weighing approximately 60 kg and diagnosed with postmenopausal osteoporosis is treated by a method of this invention. Specifically, the patient is administered the bisphosphonate 4-amino-1-hydroxy-butane-1,1-bisphosphonic acid for a period of one year. After the one year period, the bisphosphonate is continued. However, the patient is then also administered parathyroid hormone (human synthetic fragment 1-34, or h PTH 1-34) for six months, as a daily nasal spray delivering 5 IU/kg.

A blood sample is then obtained and analyzed for the bone specific marker, osteocalcin, and bone-derived and total alkaline phosphatase. Osteocalcin values are increased by 57% and both bone and total alkaline phosphatase are slightly elevated compared to pretreatment values. Base mineral density is measured, indicating an increase of 10%.
WHAT IS CLAIMED IS:

1. A method of treating a human or other animal subject having a bone metabolism disorder, comprising the steps of:

   (a) administering to said subject a safe and effective amount of a bone active phosphonate, during a period of greater than about 6 months.
   
   (b) administering to said subject a safe and effective amount of a parathyroid hormone, during a period of from about 3 to 12 months.

2. A method of treating a human or other animal subject, according to Claim 1, wherein, in step (b), said parathyroid hormone is administered for about 6 months.

3. A method of treating a human or other animal subject, according to Claim 1, wherein said steps (a) and (b) are repeated from 1 to 6 times.

4. A method of treating a human or other animal subject, according to Claim 3, additionally comprising administration of a bone active phosphonate during step (b).

5. A method of treating a human or other animal subject, according to Claim 2, wherein said phosphonate compound is a bisphosphonate selected from the group consisting of oxyethane-1,1-bisphosphonic acid; dichloromethane bisphosphonic acid; 3-amino-1-hydroxypropane-1,1-bisphosphonic acid; 6-amino-1-hydroxyhexane-1,1-bisphosphonic acid; 4-amino-1-hydroxybutane-1,1-bisphosphonic acid; 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; 2-(N-imidazoyl)-1-hydroxyethane-1,1-bisphosphonic acid; 3-(N-pentyl-N-methylamino)-1-hydroxypropane-1,1-bisphosphonic acid; 3-(N-pyrrolidino)-1-hydroxypropane-1,1-bisphosphonic acid; N-cycloheptylaminomethanebisphosphonic acid; S-(p-chlorophenyl) thiomethanebisphosphonic acid; (7-dihydro-1-pyridine)methane bisphosphonic acid; (7-dihydro-1-pyridine)hydroxymethane bisphosphonic acid; (6-dihydro-2-pyridine)hydroxymethanebisphosphonic acid; 2-(6-pyrolopyridine)-1-hydroxyethane-1,1-bisphosphonic acid; and pharmaceutically-acceptable salts and esters thereof.
6. A method of treating a human or other animal subject, according to Claim 5, wherein said bisphosphonate is 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : A61K 31/66; 38/29.
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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US, A, 4,812,304 (ANDERSON ET AL.) 14 MARCH 1989, SEE ENTIRE DOCUMENT.</td>
<td>1-6</td>
</tr>
<tr>
<td>Y</td>
<td>WO, A, 93/11786 (GEDDES ET AL.) 24 JUNE 1993, SEE ENTIRE DOCUMENT.</td>
<td>1-6</td>
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</table>

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

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