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2317/P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

INDUSTRIA Y COMERCIO
EXEDIENTE 00015567 Folios: 21
RECIBIDO 17 13:33:00
DE PATENTES D 1 REGISTRO/ 444 RESPUESTA
DIVISION DE NUEVAS CREACIONES

Re: Expediente No. 00015567
Solicitud de Patente en nombre de
THE PROCTER & GAMBLE COMPANY.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 A No. 94-76, of. 305-306, obrando como apoderada de la sociedad The Procter & Gamble Company, domiciliada en Cincinnati, Ohio, Estados Unidos de América, solicitante de la patente de la referencia, en respuesta al auto No. 620 del 4 de mayo de 2000, relacionado con el concepto técnico 627 del 26 de abril de 2000, me permito manifestar lo siguiente:

Anexo al presente memorial copia certificada de la solicitud de Patente Número 60/122,923 presentada en la Oficina de Patentes de los Estados Unidos de América el día 5 de marzo de 1999, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio.

Espero con esto haber dado cabal cumplimiento a lo solicitado por ese despacho. En caso de que la anterior respuesta no se adecue técnica o jurídicamente al requerimiento, solicito atentamente que ese despacho proceda de conformidad con lo indicado en la Circular Interna No. 001 del 13 de febrero de 1997 expedida por la Delegatura para la Propiedad Industrial de la Superintendencia de Industria y Comercio y que de conformidad con lo indicado en los artículos 3º., inciso 3, 35 inciso 2 y 59 inciso 2 del CCA, al analizar este memorial, se traten todas las cuestiones planteadas con motivo del mismo.

Señor Superintendente,



JIMENA ESCOBAR URIBE
C.C.39.779.452 de usaquén
T.P. 68228
Cód. 5376

ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE LLEGUE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos

Febrero 14, 2000

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 60/122,923

Fecha de Presentación: Marzo 05, 1999

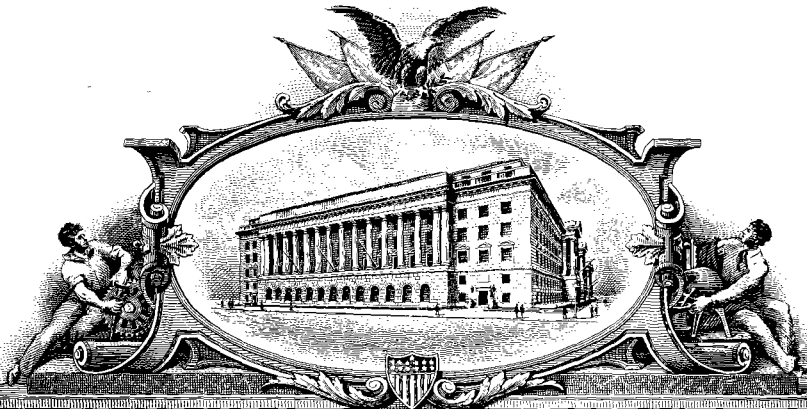
Por la autoridad del
Comisionado de Patentes y Marcas

(fdo) W. MONTGOMERY
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América.

REIVINDICACION

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1. Un método para incrementar el volumen óseo, que comprende administrar a un sujeto una cantidad segura y efectiva de un compuesto antireabsorbente y una cantidad segura y efectiva de un agonista selectivo FP de ocurrencia no natural.



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 14, 2000

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.**

APPLICATION NUMBER: 60/122,923

FILING DATE: *March 05, 1999*



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

W. Montgomery
W. MONTGOMERY
Certifying Officer

Date of Deposit March 5, 1999

I hereby certify that this paper/fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents Washington D.C. 20231

James C. Kellerman B43.708

Attorney mailing application

Signature of Attorney mailing application

PTO/SB/16 (2-98)

Approved for use through 01/31/2001 OMB 0651-0037
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL PATENT APPLICATION under 37 CFR §1.53(c).

Docket Number	7465P	Type a plus sign (+) inside this box ⇒	+
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INVENTOR(s) / APPLICANT(s)			
FAMILY NAME OR SURNAME	GIVEN NAME (first name)	MIDDLE INITIAL (if any)	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Hartke Lundy	James Mark	R. W.	West Chester, OH Cincinnati, OH
TITLE OF THE INVENTION (280 characters max)			
Methods Of Increasing Bone Volume Using Non-Naturally-Occurring FP Selective Agonists And Antiresorptive Compounds			
CORRESPONDENCE ADDRESS			
James C. Kellerman The Procter & Gamble Company Health Care Research Center 8700 Mason Montgomery Road Mason			
STATE	OH	ZIP CODE	45040-8006
COUNTRY		USA	
ENCLOSED APPLICATION PARTS (check all that apply)			
☒ Specification	Number of Pages: 22	+ Abstract	☐ Small Entity Statement
☐ Drawing(s)	Number of Sheets: _	☐ Other (specify) _	
METHOD OF PAYMENT (check one)			
☐ A check or money order is enclosed to cover the Provisional filing fees		PROVISIONAL FILING FEE AMOUNT(S)	\$150.00
☒ The Commissioner is hereby authorized to charge filing fees specified under 37 CFR §1.19(f) and credit Deposit Account Number. 16-2480			

The invention was made by an agency of the United States Government or under a contract with an agency of United States Government.

☒ No

☐ Yes, the name of the U. S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE

Date March 5, 1999

TYPED or PRINTED NAME James C. Kellerman

REGISTRATION NO. P43.708

(if appropriate)

☐ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL PATENT APPLICATION FILING ONLY

Burden Hour Statement: This form is estimated to take .2 hours to complete. Time will vary depending upon the needs of the individual cases. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistance Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-0037), Washington, DC 20503. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Patent Application; Assistant Commissioner for Patents, Washington, D.C. 20231.

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52

**METHODS OF INCREASING BONE VOLUME USING
NON-NATURALLY-OCCURRING FP SELECTIVE AGONISTS AND
ANTIRESORPTIVE COMPOUNDS**

James Richard Hartke

Mark Walden Lundy

TECHNICAL FIELD

The present invention provides novel methods of increasing bone volume comprising the administration of a non-naturally-occurring FP selective agonist and an antiresorptive compound to a subject in need of such treatment. This invention further provides methods of treating or preventing bone disorders comprising the administration of a non-naturally-occurring FP selective agonist and an antiresorptive compound to a subject in need of such treatment.

BACKGROUND OF THE INVENTION

The most common metabolic bone disorder is osteoporosis. Osteoporosis can be generally defined as a reduction in the quantity of bone, or as 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." Primary osteoporosis includes post menopausal 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 post menopausal osteoporosis. Kyphosis (abnormally increased curvature of the thoracic spine) may also result.

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 bone by an organized group of cells called "basic multicellular units" or "BMUs." BMUs primarily consist of osteoclasts and 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.

In osteoporotics an imbalance in the bone remodeling process develops in which bone is resorbed at a rate faster than it is being made resulting in bone loss. Although this imbalance occurs to some extent in most individuals, both male and female, as they age, it is much more severe among those who develop the post menopausal form of the condition. Accelerated bone loss may also result from drug administration, such as corticosteroids; prolonged bed rest; disuse of a limb; and microgravity. A consequence of this loss of bone is the complete removal of trabeculae and a deterioration of bone architecture such that the remaining bone is disproportionately decreased in strength (See, Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 3rd Edition (M.J. Favus, Editor, 1996).

It is thought that to completely return the bone to normal strength, new trabeculae should be formed to restore architecture and increase bone mass. It is further thought that when the restoration of normal architecture is associated not only with an increase in the strength, but also a return to normal stiffness and shock absorbing capability, the bone is less likely to fracture. Subjects suffering from other bone disorders such as rheumatoid arthritis, periodontal disease, and fractures may also benefit from treatments that restore bone mass and normal architecture to bone.

There have been many attempts to treat bone disorders with a variety of pharmacologic agents with the goal being to either slow further bone loss or to produce a net gain in bone mass. For example, there are antiresorptive agents, such as bisphosphonates, estrogen, calcitonin, and SERMs, which slow further bone loss by inhibiting osteoclasts. Additionally, there are anabolic agents, such as PTH, fluoride, and prostaglandins, which build bone. However, none of these agents build bone that is substantially similar, i.e. structurally or architecturally, to the type of bone lost.

The treatment of bone disorders with pharmacological agents is discussed in the following references: The Pharmacological Basis of Therapeutics, 9th Edition (A.G. Gilman, L.S. Goodman et al., Editors, 1996); W.A. Peck, et al., Physicians Resource Manual on Osteoporosis (1987), published by the National Osteoporosis Foundation; and Principles of Bone Biology (J.P. Bilezikian et al., Editors, 1996).

Among the treatments for osteoporosis suggested in the literature is the administration of bisphosphonates or other bone-active phosphonates. See, for example, Herbert Fleisch, Bisphosphonates in Bone Disease, 3rd Edition (1997); Storm et al., "Effect of Intermittent Cyclical Etidronate Therapy on Bone Mineralization and Fracture Rate in Women with Post-Menopausal Osteoporosis",

322 New England Journal of Medicine 1265 (1990); and Watts et al., "Intermittent Cyclical Etidronate Treatment of Post-Menopausal Osteoporosis", 323 New England Journal of Medicine 73 (1990). Such treatments using a variety of bisphosphonates are described in U.S. Patent 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 4,812,311, Uchtman, issued March 14, 1989; and U.S. Patent 4,822,609, Flora, issued April 18, 1989. The use of bisphosphonates for the treatment of osteoporosis, and other disorders involving abnormal calcium and phosphate metabolism, is also described in U.S. Patent 3,683,080, Francis, issued August 8, 1972; U.S. Patent 4,330,537, Francis, issued October 28, 1980; U.S. Patent 4,267,108, Blum et al., issued May 12, 1981; European Patent Publication 298,553, Ebetino, published January 11, 1989; and Francis et al., "Chemical, Biochemical, and Medicinal Properties of the Diphosphonates", The Role of Phosphonates in Living Systems, Chapter 4 (1983).

Administration of estrogen is also used as a means to prevent osteoporosis in post menopausal 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 estrogenic hormones. Estrogen may also be used to treat osteoporosis. See, for example, Barzel, "Estrogens in the Prevention and Treatment of Post-Menopausal Osteoporosis: a Review", 85 American Journal of Medicine 847 (1988); Barzel, "Estrogen Therapy for Osteoporosis: Is it Effective?", Hospital Practice 95 (1990); Ettinger, et al., "Post-Menopausal Bone Loss is Prevented by Treatment with Low-Dosage Estrogen with Calcium", 106 Annals in Internal Medicine 40 (1987); Lindsay, et al., "The Minimum Effective Dose of Estrogen for Prevention of Post-Menopausal Bone Loss", 63 Obstetrics and Gynecology 759 (1984); "Estrogen", Drug Information 1765 (1990); and World Patent Publication 92 14474, McOske, published September 3, 1992. 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).

PTH and prostaglandins, especially prostaglandins of the E series (e.g. PGE₂), are known to be potent stimulators of bone resorption and formation. The acceleration in turnover seen with these known bone anabolic agents may be detrimental to an already osteoporotic skeleton since the increased resorption may cause perforation and loss of trabeculae, or may weaken the existing trabecular structure. In addition, increased resorption may occur in cortical bone. These effects may in turn lead to increased fracture incidence at some sites.

PGF_{2α} has also been shown to be a stimulator of bone resorption, but it is not as potent as PGE₂. It has been suggested that some of the effects of PGF_{2α} on bone resorption, formation, and cell replication may be mediated by an increase in endogenous PGE₂ production.

Prostaglandins, in addition, have several drawbacks which limit their desirability for systemic administration. For example, although prostaglandins are characterized by their activity at a particular prostaglandin receptor, they often bind to and stimulate other prostaglandin receptors. Thus, systemic administration of prostaglandins is known to cause side effects such as inflammation, as well as smooth muscle contraction, bronchoconstriction, and vasoconstriction. Systemic administration of non-selective prostaglandin analogs can likewise cause side effects.

Applicants have previously disclosed in U.S. Patent Application Serial No. 09/148,105 that systemic administration of non-naturally-occurring FP selective agonists results in a bone anabolic effect and that the quality of bone formed by the administration of non-naturally-occurring FP selective agonists is superior to that formed by the administration of other anabolic agents, including prostaglandins of the E series.

Therefore, there is a continuing need to develop methods for treating bone disorders that (1) prevent further bone loss and (2) build bone that is substantially similar, structurally and architecturally, to the type of bone lost with a bone-specific agent.

SUMMARY OF THE INVENTION

The present invention provides novel methods of increasing bone volume, methods of increasing trabecular number, and methods of treating or preventing bone disorders comprising the administration of a non-naturally-occurring FP selective agonist and an antiresorptive compound to a subject in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides methods of increasing bone volume, methods of increasing trabecular number, and methods of treating or preventing bone disorders by administering to a subject a safe and effective amount of an antiresorptive compound and a safe and effective amount of a non-naturally-occurring FP selective agonist.

Definitions and Usage of Terms

"Bone disorder" means the need for bone repair or replacement. Conditions in which the need for bone repair or replacement may arise include: osteoporosis (including post menopausal osteoporosis, male and female senile osteoporosis and corticosteroid induced osteoporosis), rheumatoid arthritis, osteomalacia, multiple myeloma and other forms of cancer, prolonged bed rest, chronic disuse of a limb, anorexia, microgravity, exogenous and endogenous gonadal insufficiency, bone fracture, non-union, defect, prosthesis implantation and the like.

"Bone turnover rate" is the amount of bone resorption and formation per unit time measured or estimated using incorporation of fluorescent labels into bone, fluorescent and bright field microscopy, and histomorphometric techniques or by measurement of bone metabolism markers. For example, a subject may resorb and replace (turn over) approximately 3% of its skeleton over a 3 month period. A further description of histomorphometric techniques can be found in Bone Histomorphometry, 1994, by Eriksen et al., Raven Press.

"Bone volume" is the percentage of the bone occupied by a mineralized matrix. Measurement or estimation of the mineralized matrix volume can be accomplished using histomorphometry, computed tomography, or magnetic resonance imaging. Two dimensional measurements may be used to estimate the three dimensional volume. A further description of histomorphometric techniques can be found in Bone Histomorphometry, 1994, by Eriksen et al., Raven Press.

"Excitatory prostaglandin receptor" means prostanoid receptors which cause contraction of smooth muscle or release of internal calcium stores. Such receptors include but are not limited to FP, EP₁, EP₃, TP₁ and TP₂.

"FP" is an abbreviation for F prostanoid.

"FP agonist" is a compound with affinity for the FP receptor that results in measurable biological activity (including but not limited to an elevation in intracellular calcium or the contraction of smooth muscle) in cells, tissues, or organisms which contain the FP receptor. Whole cell, tissue, and organism assays which demonstrate FP activity of compounds are well known in the art. One particularly useful assay is the R-SAT™ Assay described by Brann, et al. in J. Biomole. Screen., Vol. 1, Number 1, 1996.

"FP receptor" refers to known human FP receptors, their splice variants, and undescribed receptors that preferentially bind PGF_{2α}. A human FP receptor is disclosed in PCT Publication WO 95/00551.

"Measurable" means the biologic effect is both reproducible and significantly different from the baseline variability of the assay.

"Non-naturally-occurring" means an agent that is not biologically derived in mammals.

"Prostaglandin analog" is a non-naturally-occurring compound which is structurally similar to a prostaglandin.

"Prostaglandin receptor" or "prostanoid receptor" is a naturally-occurring protein that binds prostaglandins, which when bound alters the function of a cell. Prostaglandin receptors may be characterized as either excitatory or relaxant. Such receptors include but are not limited to FP, EP₁, EP₂, EP₃, EP₄, DP, IP, TP₁ and TP₂. These receptors are further discussed by Coleman et al., in Pharmacological Reviews, 1994, Volume 6, No. 2, pages 205 - 229.

"Selective" means having an activation preference for a specific receptor over other receptors which can be quantified based upon whole cell, tissue, or organism assays which demonstrate receptor activity, such as the R-SATTM Assay disclosed above. A compound's selectivity is determined from a comparison of its EC₅₀ (or ED₅₀ if using an organism assay) at the relevant receptors. For example, a compound having an EC₅₀ of 8nM at the FP receptor and an EC₅₀ of 80 nM at the EP₁ receptor has a selectivity ratio for the FP receptor over the EP₁ receptor of 1:10.

"Subject" is a living vertebrate animal such as a mammal (especially human) in need of treatment.

"Trabecular number" is the number of individual trabeculae of bone per unit volume of cancellous bone measured or estimated from a two dimensional representation or a three dimensional specimen using histomorphometry, computed tomography, or magnetic resonance imaging.

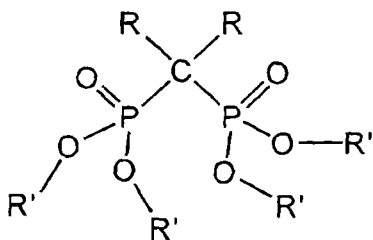
Antiresorptive Compounds

The methods of the present invention involve administering one or more antiresorptive compounds. As used herein, an "antiresorptive compound" is a compound that, when administered to a human or other animal subject, prevents bone loss by direct or indirect effect on the number of osteoclasts and/or their metabolism. Preferred antiresorptive compounds include those selected from the group consisting of bisphosphonates, estrogen compounds, SERMs, calcitonin compounds, antagonists of the SRC pathway, osteoprotegerin compounds, cathepsin K inhibitors, and mixtures thereof. Particularly preferred antiresorptive compounds include bisphosphonates, estrogen compounds, and SERMs.

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58

Bisphosphonates:

Preferred antiresorptive compounds useful in the methods of this invention include bisphosphonates. As used herein, "bisphosphonate" means an analog of pyrophosphate that contains a carbon atom connecting the two phosphorus atoms instead of an oxygen atom. Thus, bisphosphonates have the following general structure:



Specific examples of bisphosphonates useful in the present invention are described in the following references, all of which are incorporated by reference herein: Herbert Fleisch, Bisphosphonates in Bone Disease, 3rd Edition (1997); European Patent Publication 298,553, Ebetino, published January 11, 1989; European Patent Publication 298,555, Ebetino, published January 11, 1989; 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 3,899,496, 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, 1986; U.S. Patent 4,621,077, Rosini et al., issued November 4, 1986; U.S. Patent 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

62
59

4,719,203, Bosies et al., issued January 12, 1988; U.S. Patent 4,868,164 Ebetino et al., issued September 19, 1989; U.S. Patent 4,927,814, Gall et al., issued May 22, 1990; U.S. Patent 4,963,681 Ebetino et al., issued October 16, 1990; U.S. Patent 4,990,503, Isomura et al., issued February 5, 1991; U.S. Patent 5,071,840 Ebetino et al., issued December 10, 1991; U.S. Patent 5,128,244 Poland et al., issued July 7, 1992; U.S. Patent 5,137,880 Ebetino et al., issued August 11, 1992; U.S. Patent 5,334,586 Ebetino et al., issued August 2, 1994; U.S. Patent 5,391,743 Ebetino et al., issued February 21, 1995; U.S. Patent 5,393,746 Ebetino et al., issued February 28, 1995; U.S. Patent 5,519,013 Ebetino et al., issued May 21, 1996; U.S. Patent 5,574,024 Ebetino et al., issued November 12, 1996; U.S. Patent 5,583,122 Bendict et al., issued December 10, 1996; U.S. Patent 5,731,299 Ebetino et al., issued March 24, 1998; U.S. Patent 5,753,634 Ebetino et al., issued May 19, 1998; U.S. Patent 5,760,021 Ebetino et al., issued June 2, 1998; U.S. Patent 5,763,611 Ebetino et al., issued June 9, 1998; U.S. Patent 5,770,586 Ebetino et al., issued June 23, 1998; U.S. Patent 5,856,314 Ebetino et al., issued June 5, 1999; 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, Breliere 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 88/00590, Gall et al., published January 28, 1988.

Preferred bisphosphonates 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-amino-2-methyl-1-oxo)-pentyl)aminomethane phosphonomethylphosphinic acid; N-(2'-(3'-methyl)-piperidinylidene)aminomethane phosphonobutylphosphinic acid; S-(2'-pyridinyl)thiomethane phosphonomethylphosphinic acid; 2-(2-pyridyl)-1-hydroxyethane-1-phosphono-1-methyl phosphinic acid; 2-(3-pyridyl)-1-hydroxyethane-1-phosphono-1-methylphosphinic acid; 2-(N-imidazolyl)-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-cycloheptylaminomethanephosphonomethylphosphinic 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-pyrrolopyridine)-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-1,1-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) aminomethane-bisphosphonic 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-

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61

hydroxyethane-1,1-bisphosphonic acid; N-(2-(5-amino)-pyridyl)-aminomethane bisphosphonic acid; N-(2-(5-chloro)-pyridyl)-aminomethane bisphosphonic acid; N-(2-(3-picolyl))-aminomethane bisphosphonic acid; N-(2-(4-picolyl))-aminomethane bisphosphonic acid; N-(2-(5-picolyl))-aminomethane bisphosphonic acid; N-(2-(6-picolyl))-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-picolyl))-oxaethane-1,1-bisphosphonic acid; 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid; 2-(N-imidazolyl)-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-cycloheptylaminoethane 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 bisphosphonates useful in the methods of this invention include: 1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate); dichloromethylene bisphosphonic acid (clodronate); 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate); 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate); 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate); 2-(3-pyridinyl)-1-hydroxyethylidene-1,1-bisphosphonic acid (risedronate); 2-(N-imidazolyl)-1-hydroxyethylidene-1,1-bisphosphonic acid (zoledronate); 3-(N-pentyl-N-methylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (ibandronate); 3-(N-pyrrolidino)-1-hydroxypropylidene-1,1-bisphosphonic acid; N-cycloheptylaminoethylene bisphosphonic acid (incadronate); S-(p-chlorophenyl) thiomethylene bisphosphonic acid (tiludronate); (7-dihydro-1-pyridine)methylene bisphosphonic acid; (7-dihydro-1-pyridine)hydroxymethylene bisphosphonic acid; (6-dihydro-2-pyridine)hydroxymethylene bisphosphonic acid; 2-(6-pyrolopyridine)-1-hydroxyethane-1,1-bisphosphonic acid; 3-dimethylamino-1-hydroxypropylidene bisphosphonic acid (olpadronate); 1-hydroxy-2-imadazo(1, 2-a) pyridin-3-ylethylidene bisphosphonic acid; and pharmaceutically-acceptable salts and esters thereof.

65
62

Estrogen Compounds

Preferred antiresorptive compounds useful in the methods of this invention include estrogen compounds. As referred to herein, an "estrogen compound" refers to naturally occurring hormones, synthetic steroidal compounds, and non-steroidal compounds, and conjugates, metabolites, phytoestrogens and derivatives thereof, that have estrogenic activity. Naturally-occurring estrogens are steroids which contain a cyclopentanoperhydrophenathrene ring system. Such naturally-occurring estrogens are obtained from pregnant mares' urine or prepared synthetically, using methods well-known in the art. See: "Estrogens", Drug Information 1765 (1990); and Rudy, "Hormone Replacement Therapy - How to Select the Best Preparation and Regimen," 88 Postgraduate Medicine 157 (1990); and C. Christiansen et al., "Estrogens, Bone Loss and Prevention," 1 Osteoporosis Int. 7 (1990); all of which are incorporated by reference herein.

Estrogen compounds useful in the methods of this invention include, for example, estradiol, estrone, estriol, equilin, equilenin, estradiol cypionate, estradiol valerate, ethinyl estradiol, polyestradiol phosphate, estropipate, diethylstilbestrol, dienestrol, chlorotrianisene, and mixtures thereof. A preferred estrogen hormone useful herein is "conjugated estrogen", which is a mixture of sodium salts of the water-soluble sulfate esters of estrone and equilin. Such conjugated estrogens may also contain other estrogenic substances found in pregnant mares' urine, such as 17-a-dihydroequiline, 17-a-estradiol, equilenin, and 17-a-dihydroequilenin.

SERMs

Preferred antiresorptive compounds useful in the methods of this invention include Selective Estrogen Receptor Modulators ("SERMs"). As referred to herein, a "SERM" is a compound which has the estrogen agonist activity of inhibition of bone resorption, but which has estrogen antagonist activity on other tissues, notably breast and uterine tissue. SERMs may be steroids or non-steroids. Steroidal SERMs are exemplified by tamoxifen and related compounds. Non-steroidal SERMs include, for example, raloxifene, and related compounds disclosed in U.S. Patent 4,418,068, issued November 29, 1983 (incorporated by reference herein). Other SERMs are described in Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 3rd Edition (M.J. Favus, Editor, 1996) and "Basic Guide To The Mechanisms Of Antiestrogen Action", J.I. MacGregor et al., Pharmacological Review, 1998, both of which are incorporated herein by reference.

68
63

Calcitonin Compounds

Among the antiresorptive compounds useful in this invention are calcitonin compounds. As referred to herein, "calcitonin compounds" are calcium regulating hormones whose essential biological activity is to oppose the bone and renal effects of parathyroid hormone, i.e., to inhibit bone resorption and reduce urinary calcium excretion. Natural calcitonin is a 32 amino acid polypeptide hormone secreted from the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish. The linear amino acid sequence varies between species as does the potency but when the various calcitonins are administered at similar International Unit equivalents, all such calcitonins will provide equivalent efficacy as an antiresorptive compound.

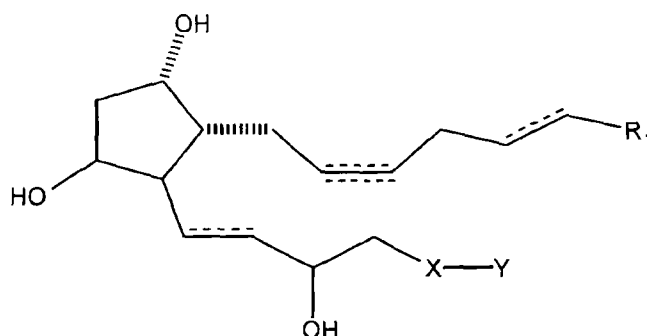
Natural calcitonin can be isolated from mammalian glands, i.e., from pig, cow, human, etc., or from salmon, eel and other sources by a procedure similar to that described in Behrens, Grinnans Ann Rev Biochem 38, 83, 1969. In addition to the isolation of the peptide from glands, any of the calcitonin sequences may be manufactured by synthetic processes such as by solid phase synthesis (J Hirt, et al., Rec Trav Chim 98, 143, 1979), or produced by recombinant methods (J W Jacobs et al., J Biol Chem 254, 10600, 1979). Calcitonin compounds also include synthetic-natural hybrids, and analogues, mixtures, peptidomimetics and other variants of the natural calcitonin molecule (See, Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 3rd Edition (M.J. Favus, Editor, 1996), incorporated herein by reference.

Non-naturally-occurring FP Selective Agonists

The methods of the present invention involve administering a non-naturally-occurring selective FP agonist. Particularly preferred non-naturally-occurring FP agonists are selective for the FP receptor over other excitatory prostaglandin receptors in a ratio of at least about 1:10, more preferably at least about 1:20, and most preferably at least about 1:50. Still more preferred non-naturally-occurring FP agonists are selective for FP receptors over all other prostanoid receptors in a ratio of at least about 1:10, more preferably at least about 1:20, and most preferably at least about 1:50.

Particularly useful non-naturally-occurring selective FP agonists are prostaglandin analogs. Examples of such compounds are prostaglandin analogs having the following general structure:

64



wherein:

R_1 is CO_2H , $\text{C}(\text{O})\text{NHOH}$, CO_2R_2 , CH_2OH , $\text{S}(\text{O})_2\text{R}_2$, $\text{C}(\text{O})\text{NHR}_2$, $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_2$, or tetrazole; characterized in that R_2 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

X is $(\text{CH}_2)_n$, where n is 0 to 3, NH , S , or O ; and

Y is a cycloalkyl or aromatic moiety, either substituted or unsubstituted.

Prostaglandin analogs of the above structure include: cloprostenol (Estrumate®), fluprostenol (Equimate®), tiaprost, alfaprostol, delprostenate, froxiprost, latanoprost, 13,14-dihydro-16-((3-trifluoromethyl)phenoxy)-16-tetranor prostaglandin $F_{1\alpha}$, 17-((3-trifluoromethyl)phenyl)-17-trinor-prostaglandin $F_{2\alpha}$, 13,14-dihydro-18-thienyl-18-dinor prostaglandin $F_{1\alpha}$ and their analogs.

Other prostaglandin analogs of the present invention include 9- α , 11- α , 15- α -trihydroxy-16-(3-chlorophenoxy)- ω -tetranor-prosta-4-cis-13-trans-dienoic acid and its analogs. Additional prostaglandin analogs are also disclosed in CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids, Volume I, Chemical and Biochemical Aspects, Part B. Ed. by Anthony L. Willis, CRC Press (Boca Raton, 1987) Table Four pp. 80-97 (incorporated herein by reference), and references therein.

The non-naturally-occurring FP selective agonists described above are useful in increasing bone volume, increasing trabecular number through formation of new trabeculae, increasing bone mass without increasing the bone turnover rate, and increasing formation at the endosteal surface without removing bone from the existing cortex. Additionally, the quality of bone formed by the administration of these compounds is superior to that formed by the administration of other bone anabolic agents, including prostaglandins of the E series. Bone quality refers to the

combination of bone matrix (inorganic and organic), bone mass or volume, and bone architecture which impart overall strength and fracture resistance to bone.

Methods of Use

The present invention provides novel methods of increasing bone volume, methods of increasing trabecular number, and methods of treating or preventing bone disorders comprising the administration of a non-naturally-occurring FP selective agonist and an antiresorptive compound to a subject in need of such treatment. The non-naturally-occurring FP selective agonist and the antiresorptive compound can be administered concurrently or sequentially.

The methods provided by the invention prevent further bone loss through slowing of resorption and stimulate formation of new bone. Additionally, methods provided by the invention may stimulate formation of new bone and maintain gains in bone volume and/or trabecular number. Because it is believed that administration of a non-naturally-occurring FP selective agonist does not result in upregulation of resorption, it is expected that the dosages of both the antiresorptive compound and the non-naturally-occurring FP selective compound will not require adjustment to compensate for the increase in resorption that results from the administration of other bone anabolic agents such as PTH.

In a preferred embodiment of the invention, the non-naturally-occurring FP selective agonist is first administered to the subject for the period of time required to restore the subject's bone volume to the desired level. This period can last from about 1 month to about 36 months, preferably from about 6 months to about 36 months, and more preferably from about 6 months to about 24 months. Upon discontinuation of the non-naturally-occurring FP selective agonist, the antiresorptive compound is then administered to the subject to maintain the bone volume at the desired level. This may be indefinitely.

In another preferred embodiment of the invention, the antiresorptive compound is administered to the subject for some period of time and then discontinued. The non-naturally-occurring FP selective agonist is then administered to the subject for the period of time required to restore the subject's bone volume to the desired level. This period can last from about 1 month to about 36 months, preferably from about 6 months to about 36 months, and more preferably from about 6 months to about 24 months. Upon discontinuation of the non-naturally-occurring FP selective agonist, an antiresorptive compound (the antiresorptive compound previously administered or a different antiresorptive

66

compound) is then administered to the subject to maintain the bone volume at the desired level. This may be indefinitely.

In another embodiment of the invention, the antiresorptive compound and the non-naturally-occurring FP selective agonist are administered to the subject at the same time for the period of time required to restore the subject's bone volume to the desired level. This period can last from about 1 month to about 36 months, preferably from about 6 months to about 36 months, and more preferably from about 6 months to about 24 months. At such time, (1) only the non-naturally-occurring FP selective agonist may be discontinued, (2) both the antiresorptive compound and the non-naturally-occurring FP selective agonist may be discontinued and a new antiresorptive compound administered to the subject, or (3) both the antiresorptive compound and the non-naturally-occurring FP selective agonist may be discontinued.

Dosages

The antiresorptive compound and the non-naturally-occurring FP selective agonist compound are both administered in a "safe and effective amount." The phrase "safe and effective amount", as used herein means an amount of a compound or composition high enough to significantly positively modify the symptoms and/or condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of an agent for use in the methods of the invention herein will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular agent being employed, the particular pharmaceutically-acceptable excipients utilized, and like factors within the knowledge and expertise of the attending physician.

The specific amount and dosage regimen of a particular compound administered pursuant to the methods of this invention is a function of the potency of the compound, the patient being treated, the condition being treated, the severity of the condition being treated, and the route of administration to achieve the desired effect, as well as other factors. Preferably, the compound is administered in amounts and in regimens recognized in the art as useful for treating bone disorders in accordance with sound medical practice.

The appropriate amount of the antiresorptive compound selected can be determined from the references previously cited and incorporated herein by

70
67

reference. For clinically approved antiresorptive compounds, the appropriate dose can be found in the product's labeling.

The appropriate amount of the non-naturally-occurring FP selective agonist compound to be used may be determined by routine experimentation with animal models. Such a model includes, but is not limited to, the intact and ovariectomized rat models of osteoporosis, the ferret, canine, and non human primate models of osteoporosis, as well as disuse models of osteoporosis.

The dosage range for systemic administration of the non-naturally-occurring FP agonists of the present invention is from about 0.01 to about 1000 $\mu\text{g/kg}$ body weight per day, preferably from about 0.05 to about 100 $\mu\text{g/kg}$ per body weight per day, most preferably from about 0.1 to about 50 $\mu\text{g/kg}$ body weight per day. Plasma levels are expected to be in the range of about 0.01 to about 500 ng/ml, more preferably from about 0.05 to 100 ng/ml, and most preferably from about 0.1 to 50 ng/ml.

While these dosages are based upon a daily administration rate, weekly or monthly accumulated dosages may also be used to calculate the clinical requirements. The non-naturally-occurring FP agonists of the present invention may be administered, based on a weekly dosage, more frequently than once daily. The non-naturally-occurring FP agonists of the present invention may also be administered, based on a weekly dosage, less frequently than once daily. Hence, the weekly dosage may be divided into 3, 4, 5, 6, or 7 daily dosages, preferably 5, 6, or 7 daily dosages.

Prolonged delivery (also referred to as "prolonged administration") of the non-naturally-occurring FP selective agonist results in improved dose separation between side effects and the desired bone effect. As used herein, "prolonged delivery" or "prolonged administration" means that the total daily dosage is delivered into the subject's circulation over a period of at least about 6 hours and up to 24 hours. Preferred prolonged delivery periods are for at least about 12 hours and up to 24 hours. Examples of prolonged delivery include administration of the non-naturally-occurring FP agonist via a transdermal patch or a subcutaneous pump that delivers the total daily dosage over a twenty-four hour period.

It is believed that the flattening of the plasma concentration curve resulting from prolonged delivery mitigates side effects while maintaining bone efficacy. It is further believed that the administration of non-naturally-occurring FP selective agonists with extended half-lives will likewise result in a flattening of the plasma concentration curve without prolonging the administration.

74
63

Dosage Forms and Methods of Administration

The antiresorptive compound and the non-naturally-occurring FP selective agonist compound may each be administered in any of a variety of pharmaceutically-acceptable compositions. In addition to the active compound, pharmaceutically-acceptable compositions contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a subject. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the 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 subject being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as cornstarch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid, magnesium stearate; calcium sulfate; 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; alginic acid; emulsifiers, such as the Tweens®; wetting agents such as sodium lauryl sulfate; coloring agents; flavoring agents, excipients; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with a compound is basically determined by the way the compound is to be administered. The compounds of the present invention may be administered systemically, including transdermally, orally and/or parenterally, including subcutaneous or intravenous injection, and/or intranasally.

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) and by intravenously. Preferred unit dosage forms for bisphosphonate include tablets, capsules, suspensions, and solutions, comprising a safe and effective amount of active.

42
69

Preferred methods of administering estrogen compounds are orally and transdermally, 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 estrogen compounds include tablets, capsules, suspensions, solutions, and transdermal patches comprising a safe and effective amount of active.

A preferred methods of administering SERMs are orally and transdermally, 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 SERMs include tablets, capsules, suspensions, solutions, and transdermal patches comprising a safe and effective amount of active.

A preferred method of administering calcitonin compounds is via subcutaneous injection in a unit dosage form. Preferred unit dosage forms for injection include sterile solutions of water, physiological saline, or mixtures thereof. The pH of said solutions should be adjusted to about 7.4. Other preferred dose forms for calcitonin compounds include nasal, transdermal, rectal, sublingual, and oral. Preferred oral forms include, for example, liposomes, lipid emulsions, and proteinaceous cages.

A preferred method of administering non-naturally-occurring FP selective agonists is via transdermal delivery. Preferred transdermal dosage forms include transdermal patches, creams, ointments, gels and the like. Another preferred method of administering non-naturally-occurring FP selective agonists is via subcutaneous injection in a unit dosage form. Preferred unit dosage forms for injection include sterile solutions of water, physiological saline, or mixtures thereof. The pH of said solutions should be adjusted to about 7.4. Yet, another preferred method of administering non-naturally-occurring FP selective agonists is via subcutaneous implant or other subcutaneous slow release dosage forms.

Other preferred dose forms of non-naturally-occurring FP selective agonists include nasal, rectal, sublingual, and oral. Suitable carriers for injection or surgical implants include hydrogels, controlled- or sustained-release devices, polylactic acid, and collagen matrices. Implant devices may be coated with the non-naturally-occurring FP agonist. The non-naturally-occurring prostaglandin FP agonist may be dissolved in a buffer and may be mixed with a collagen gel which is then coated onto the porous end of the implant device.

The following non-limiting examples illustrate formulations of the subject invention.

Example I

The FP agonist, fluprostenol, and the bisphosphonate, risedronate (Actonel™), are administered to a 65 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated daily with a transdermal patch that delivers 10 µg/kg fluprostenol over a 24 hour period and a 5 mg risedronate tablet. This treatment is continued for 24 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA).

Example II

The FP agonist, fluprostenol, and the bisphosphonate, risedronate (Actonel™), are administered to a 65 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated daily with a transdermal patch that delivers 10 µg/kg fluprostenol over a 24 hour period and a 5 mg risedronate tablet. This treatment is continued for 24 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA). At this time, she is administered a 5 mg risedronate tablet by mouth once a day to maintain the bone gains produced by fluprostenol for 2 years or as required as determined by yearly DXA measurements.

Example III

The FP agonist, fluprostenol, is administered to a 65 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated daily with a transdermal patch that delivers 10 µg/kg fluprostenol over a 24 hour period. This treatment is continued for 24 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA). At this time, she is administered a 5 mg risedronate (Actonel™) tablet by mouth once a day to maintain the bone gains produced by fluprostenol for 2 years or as required as determined by yearly DXA measurements.

74
71

Example IV

The bisphosphonate, risedronate (Actonel™), is administered to a 65 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated daily with a 5 mg tablet. This treatment is continued for 24 months. At this time, as measured by dual energy X-ray absorptiometry (DXA), no further vertebral bone loss is occurring, but the spine is still considered osteoporotic. She is then treated daily with a transdermal patch that delivers 10 µg/kg fluprostenol over a 24 hour period. This treatment is continued for 24 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA).

Example V

The estrogen supplement Premarin, is administered to a 65 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated daily with a 0.625 mg tablet. This treatment is continued for 24 months. At this time, as measured by dual energy X-ray absorptiometry (DXA), the spine is still considered osteoporotic. She is then treated daily with both estrogen as a 0.625 mg tablet and a transdermal patch that delivers 10 µg/kg fluprostenol over a 24 hour period. This combined treatment is continued for 24 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA).

Example VI

The estrogen supplement Premarin, is administered to a 65 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated daily with a 0.625 mg tablet. This treatment is continued for 24 months. At this time, as measured by dual energy X-ray absorptiometry (DXA), the spine is still considered osteoporotic. She is then treated daily with a transdermal patch that delivers 10 µg/kg fluprostenol over a 24 hour period. This treatment is continued for 24 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA). At this time, she is administered a 5 mg risedronate (Actonel™) tablet by mouth once a day to maintain the bone gains produced by fluprostenol for 2 years or as required as determined by yearly DXA measurements.

75
72

Example VII

The FP agonist, fluprostenol, is administered to a 63 year old woman who has decreased bone mass and has been diagnosed with osteoporosis by her physician. She is treated with an implantable subcutaneous pump that delivers 10 $\mu\text{g/kg}$ fluprostenol over a 24 hour period. This treatment is continued for 6 months, at which time, vertebral bone mass is increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA). At this time, she is administered a 5 mg risedronate (ActonelTM) tablet by mouth once a day to maintain the bone gains produced by fluprostenol for 6 months. At this time, to further increase bone mass as measured by dual energy X-ray absorptiometry (DXA), she is again treated with an implantable subcutaneous pump that delivers 10 $\mu\text{g/kg}$ fluprostenol over a 24 hour period. This treatment is continued for 6 months, at which time, vertebral bone mass is substantially increased compared to her vertebral bone mass at the onset of therapy as measured by dual energy X-ray absorptiometry (DXA). At this time, she is administered a 5 mg risedronate (ActonelTM) tablet by mouth once a day to maintain the bone gains produced by fluprostenol for 2 years or as required as determined by yearly DXA measurements.

While particular embodiments of the subject invention have been described, it would be obvious to those skilled in the art that various changes and modifications to the compositions disclosed herein can be made without departing from the spirit and scope of the invention.

What is claimed is:

1. A method of increasing bone volume, comprising administering to a subject a safe and effective amount of an antiresorptive compound and a safe and effective amount of a non-naturally-occurring FP selective agonist.

75
74

METHOD OF INCREASING BONE VOLUME USING
NON-NATURALLY-OCCURRING FP AGONISTS AND
ANTIRESORPTIVE COMPOUNDS

ABSTRACT OF THE INVENTION

The present invention provides novel methods of increasing bone volume, methods of increasing trabecular number, and methods of treating or preventing bone disorders comprising the administration of a non-naturally-occurring FP selective agonist and an antiresorptive compound to a subject in need of such treatment.

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