IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WARNER CHILCOTT COMPANY, LLC and HOFFMANN-LA ROCHE INC., Plaintiffs, v. SUN PHARMA GLOBAL FZE Defendant.	Lead Case C.A. No. 08-627-LPS (Member Case C.A. No. 10-1085-LPS)

AMENDED COMPLAINT

Plaintiffs Warner Chilcott Company, LLC ("Warner Chilcott") and Hoffmann-La Roche Inc. ("Roche"), by their attorneys, hereby allege as follows:

Nature of the Action

This is an action for patent infringement of U.S. Patent No. 7,718,634 (the "'634 Patent"), arising under the patent laws of the United States, Title 35, United States Code, 35 U.S.C. §§ 271 and 281. This action relates to an amended Abbreviated New Drug Application ("ANDA") originally filed by Sun Pharma Global, Inc. (ANDA No. 90-886) with the U.S. Food and Drug Administration ("FDA") for approval to market 150 mg risedronate sodium tablets ("Sun 150 mg Risedronate Sodium Tablets"), which are a generic version of a 150 mg form of Warner Chilcott's ACTONEL® drug product ("Once-a-Month ACTONEL®"). Sun Pharma Global FZE is the successor in interest to Sun Pharma Global, Inc. and is now the applicant of record for ANDA No. 90-886.

Related Actions

This action is related to seven patent infringement actions currently pending before this Court, (1) *Warner Chilcott Company, LLC and Hoffmann-La Roche Inc. v. Teva*

Pharmaceuticals U.S.A., Inc. (C.A. No. 08-627-LPS) (the "Teva '938 Action"), involving U.S. Patent No. 7,192,938 (the "'938 Patent" and two other patents), (2) *Warner Chilcott Company, LLC and Hoffmann-La Roche Inc. v. Apotex Inc. and Apotex Corp.* (C.A. No. 09-143-LPS) (the "Apotex '938 Action"), also involving the '938 Patent (and one other patent), (3) *Warner Chilcott Company, LLC and Hoffmann-La Roche Inc. v. Mylan Pharmaceuticals* (C.A. No. 10-285-LPS) (the "Mylan '938 Action"), also involving the '938 Patent, (4) *Warner Chilcott Company, LLC and Hoffmann-La Roche Inc. v. Sun Pharma Global, Inc.* (C.A. No. 09-61-LPS) (the "Sun '938 Action"), also involving the '938 Patent, (5) *Warner Chilcott Company, LLC and Hoffmann-La Roche Inc. v. Teva Pharmaceuticals U.S.A., Inc.* (C.A. No. 11-81-LPS) (the "Teva '634 Action"), also involving the '634 Patent, (6) *Warner Chilcott Company, LLC and Hoffmann-La Roche Inc. v. Apotex Inc. and Apotex Corp.* (C.A. No. 10-1111-LPS), also involving the '634 Patent (the "Apotex '634 Action"), and (7) *Warner Chilcott Company, LLC and Hoffmann-La Roche Inc. v. Mylan Pharmaceuticals* (C.A. No. 11-236-LPS), also involving the '634 Patent (the "Mylan '634 Action").

The above Actions also arise under 35 U.S.C. §§ 271 and 281 and relate to ANDA's filed by the defendants in those actions for approval to market generic versions of Once-a-Month ACTONEL®. The Sun '938 Action relates to Sun's ANDA 90-886, which is the same ANDA implicated in this action. This action was previously consolidated with the above Actions for all pretrial purposes.

Parties

1. Plaintiff Warner Chilcott Company, LLC is a corporation organized and existing under the laws of Puerto Rico, having offices at Union St., Road 195, Km 1.1, Fajardo, Puerto Rico.

2. Plaintiff Hoffmann-La Roche Inc. is a corporation organized and existing under the laws of the State of New Jersey, with its principal place of business at 340 Kingsland Street, Nutley, New Jersey 07110.

3. Upon information and belief, Sun Pharma Global FZE is a corporation organized and existing under the laws of the United Arab Emirates, having a principle place of business in at Office #43, SAIF Zone, P.O. Box 122304, Sharjah, U.A.E., and is a wholly owned subsidiary of Sun Pharma Global, Inc., which is in turn a wholly-owned subsidiary of Sun Pharmaceutical Industries, Ltd. (a corporation organized and existing under the laws of India, having a principle place of business in Mumbai, India).

Jurisdiction and Venue

4. This action arises under the patent laws of the United States of America and this Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 1400(b), 2201, and 2202.

5. This Court has personal jurisdiction over Sun Pharma Global FZE by virtue of, *inter alia*, its systematic and continuous contacts with Delaware, including through its ultimate parent corporation, Sun Pharmaceutical Industries, Ltd.

6. This Court also has personal jurisdiction over Sun Pharma Global FZE because Sun Pharma Global, Inc. has committed an act of patent infringement in filing ANDA No. 90-886 that has led to foreseeable harm and injury to two corporations actively engaged in business in Delaware, Warner Chilcott and Roche, and Sun Pharma Global FZE is now the owner of ANDA No. 90-886 and successor in interest to Sun Pharma Global, Inc. in this action by virtue of Sun Pharma Global, Inc.'s transfer of ANDA No. 09-886 to Sun Pharma Global FZE. On September 14, 2009, Sun Pharma Global, Inc. notified the U.S. Food and Drug Administration

that Sun Pharma Global, Inc. transferred its ownership of ANDA No. 09-886 to Sun Pharma Global FZE. On August 8, 2010, the FDA acknowledged receipt of Sun Pharma Global, Inc.'s September 14, 2009 letter and transferred ANDA No. 09-886 from Sun Pharma Global, Inc. to Sun Pharma Global FZE.

7. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

Once-a-Month ACTONEL®

8. The 150 mg commercial formulation of risedronate sodium known as "Once-a-Month ACTONEL®" is manufactured, marketed, and sold by Warner Chilcott. Once-a-Month ACTONEL® (150 mg) was approved by the FDA on April 22, 2008.

9. On August 24, 2009, Warner Chilcott plc, which is the parent company of Plaintiff Warner Chilcott, and Procter and Gamble ("P&G")[1] entered into a Purchase Agreement by which Warner Chilcott plc acquired the worldwide prescription pharmaceuticals business of P&G and its affiliates, including the Once-a-Month ACTONEL® business. The acquisition of P&G's pharmaceutical business by Warner Chilcott plc was officially completed on October 30, 2009.

The '634 Patent

10. Roche is the owner by assignment of the '634 Patent entitled "Method of Treatment Using Bisphosphonic Acid," which the United States Patent and Trademark Office duly and legally issued on May 18, 2010. A true and correct copy of the '634 Patent is attached hereto as Exhibit A. The claims of the '634 Patent are valid and enforceable. The '634 Patent expires on May 6, 2023. The FDA-approved dosing regimen for Once-a-Month Actonel® is

[1] Once-a-Month ACTONEL® was originally developed, manufactured, marketed, and sold by P&G, the original NDA holder, prior to the sale of P&G's pharmaceutical business in 2009 to Warner Chilcott.

covered by certain claims of the '634 Patent. The FDA's official publication of approved drugs (the "Orange Book") includes Actonel® in its 150 mg dosage form listed together with the '634 Patent.

11. Roche is the assignee of the '634 Patent and has all rights needed to bring this action in Roche's name except as licensed to Warner Chilcott, and has the right to sue for and obtain equitable relief and damages for infringement; under Warner Chilcott's license, Warner Chilcott has the right to sue for and obtain equitable relief and damages for infringement of the '634 Patent.

Infringement by Sun

12. By letter dated December 12, 2008 ("First Sun Notice Letter"), Sun Pharma Global, Inc. notified P&G and Roche that Sun had submitted ANDA No. 90-886 to the FDA under Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking approval to engage in the commercial manufacture, use, and sale of the Sun 150 mg Risedronate Sodium Tablets, a generic version of FDA-approved Once-a-Month ACTONEL®, before the expiration date of Roche's U.S. Patent No. 7,192,938, which is related to the '634 Patent. Sun Pharma Global, Inc. subsequently transferred its ownership of ANDA No. 09-886 to Sun Pharma Global FZE and notified the FDA, which acknowledged the transfer. Upon information and belief, Sun intends to engage in commercial manufacture, use, and sale of the Sun 150 mg Risedronate Sodium Tablets promptly upon receiving FDA approval to do so.

13. By letter dated October 27, 2010 ("Second Sun Notice Letter"), Sun Pharma Global, Inc. notified Warner Chilcott and Roche that its ANDA No. 90-886 contained a "Paragraph IV certification" asserting that, in Sun's opinion, the commercial manufacture, use or

sale of Sun 150 mg Risedronate Sodium Tablets will not infringe any valid and enforceable claim of the '634 Patent.

14. By filing ANDA No. 90-886, Sun Pharma Global, Inc. and Sun Pharma Global FZE have necessarily represented to the FDA that the components of the Sun 150 mg Risedronate Sodium Tablets have the same active ingredients as those of the corresponding components of the Once-a-Month ACTONEL®, have the same route of administration, dosage form, and strengths as the corresponding components of Once-a-Month ACTONEL®, are bioequivalent to the corresponding components of Once-a-Month ACTONEL®, and that Sun 150 mg Risedronate Sodium Tablets have substantially the same proposed labeling as Once-a-Month ACTONEL®.

15. The original version of this complaint was filed before the expiration of forty-five days from the date Warner Chilcott and Roche received the Second Sun Notice Letter.

Count I

16. Each of the preceding paragraphs 1 to 15 is incorporated as if fully set forth.

17. Sun Pharma Global, Inc.'s submission of ANDA No. 90-886 to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of Sun 150 mg Risedronate Sodium Tablets prior to the expiration of the '634 Patent constitutes infringement of one or more of the valid claims of the '634 Patent under 35 U.S.C. § 271(e)(2)(A), and as the successor in interest to Sun Pharma Global, Inc. in this action, Sun Pharma Global FZE now infringes one or more of the valid claims of the '634 patent.

18. Upon FDA approval of Sun Pharma Global FZE's ANDA No. 90-886, Sun Pharma Global FZE will further infringe, directly or indirectly, the '634 Patent by making, using, offering to sell, and selling Sun 150 mg Risedronate Sodium Tablets in the United States, and by

actively inducing and contributing to infringement by others, in violation of 35 U.S.C. § 271(a)-(c) unless enjoined by this Court.

19. If Sun Pharma Global FZE's infringement of the '634 patent is not enjoined, Warner Chilcott and Roche will suffer substantial and irreparable harm for which there is no adequate remedy at law.

Prayer for Relief

WHEREFORE, Warner Chilcott and Roche pray that this Court grant the following relief:

(a) A declaration that the '634 Patent is valid and enforceable;

(b) A judgment that one or more claims of the '634 Patent is infringed by the Sun 150 mg Risedronate Sodium Tablets, that Sun Pharma Global Inc.'s submission of ANDA No. 90-886 was an act of infringement, and that Sun Pharma Global FZE's making, using, offering to sell, selling, or importing Sun 150 mg Risedronate Sodium Tablets will infringe the '634 Patent;

(c) An Order pursuant to 35 U.S.C. § 271(e)(4) providing that the effective date of any FDA approval of Sun Pharma Global FZE's ANDA No. 90-886 shall be a date that is not earlier than the expiration date of the '634 Patent;

(d) A judgment that Sun would infringe, either directly or indirectly, the '634 Patent upon marketing of the Sun 150 mg Risedronate Sodium Tablets after grant of FDA approval and during the unexpired term of the '634 Patent;

(e) An Order permanently enjoining Sun Pharma Global FZE, and its affiliates and subsidiaries, and each of their officers, agents, servants and employees and those persons in active concert or participation with any of them, from making, using, offering to sell, selling within the United States, or importing into the United States Sun 150 mg Risedronate Sodium Tablets until after the expiration date of the '634 Patent;

(f) Damages or other monetary relief to Warner Chilcott and Roche if Sun Pharma Global FZE engages in the commercial manufacture, use, offer to sell, sale, or importation of the Sun 150 mg Risedronate Sodium Tablets prior to the expiration of the '634 Patent;

(g) Reasonable costs of suit incurred by Warner Chilcott and Roche in this action; and

(h) Such further and other relief as this Court deems proper and just.

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EXHIBIT A

US007718634B2

(12) **United States Patent**
Bauss et al.

(10) **Patent No.: US 7,718,634 B2**
(45) **Date of Patent: *May 18, 2010**

(54) **METHOD OF TREATMENT USING BISPHOSPHONIC ACID**

(75) Inventors: **Frieder Bauss**, Neuhofen (DE); **Bernhard Pichler**, Ketsch (DE); **Stephen Turley**, Bottmingen (CH)

(73) Assignee: **Hoffman-La Roche Inc.**, Nutley, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/139,587**

(22) Filed: **Jun. 16, 2008**

(65) **Prior Publication Data**

US 2008/0249069 A1 Oct. 9, 2008

Related U.S. Application Data

(63) Continuation of application No. 10/430,007, filed on May 6, 2003, now Pat. No. 7,410,957.

(30) **Foreign Application Priority Data**

May 10, 2002 (EP) 02010136

(51) **Int. Cl.**
A61K 31/675 (2006.01)

(52) **U.S. Cl.** **514/108**

(58) **Field of Classification Search** 514/108
See application file for complete search history.

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(57) **ABSTRACT**

The present invention refers to a pharmaceutical composition of a bisphosphonic acid or salt thereof, and an excipient thereof, and a method of treating disorder characterized by pathologically increased bone resorption comprising orally administering at least 150% of the expected efficious daily dose of a bisphosphonic acid or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients thereof and administering the dose at a period of one two or three consecutive days per month.

10 Claims, No Drawings

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METHOD OF TREATMENT USING BISPHOSPHONIC ACID

PRIORITY TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 10/430,007, filed May 6, 2003, now allowed; which claims the benefit of European Application No. 02010136.6, filed May 10, 2002. The entire contents of the above-identified applications are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention refers to the use of bisphosphonic acids, especially of (1-hydroxy-3-(N-methyl-N-pentyl)aminopropylidene-1,1-bisphosphonic acid (ibandronic acid) or pharmaceutically acceptable salts thereof for the manufacture of pharmaceutical compositions for the prevention or the treatment of disorders characterized by pathologically increased bone resorption, especially for the prevention and treatment of osteoporosis.

BACKGROUND OF THE INVENTION

Bones serve mainly as a support, and consequently bone is frequently regarded as a simple building material. However, bone is a complicated biomaterial adapted to a wide variety of requirements, stimuli and noxae to which it is exposed. Endoprostheses are available as substitutes for bones and joints. However, endoprostheses, even when biomechanically highly refined, do not have an active effect on the environmental and load factors.

A variety of disorders in humans and mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, and hypercalcemia of malignancy and metastatic bone disease. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Because osteoporosis, as well as other disorders associated with bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

Bisphosphonates, i.e. bisphosphonic acids or pharmaceutically acceptable salts thereof, are synthetic analogs of the naturally occurring pyrophosphate. Due to their marked affinity for solid-phase calcium phosphate, bisphosphonates bind strongly to bone mineral. Pharmacologically active bisphosphonates are well known in the art and are potent inhibitors of bone resorption and are therefore useful in the treatment and prevention of diseases involving abnormal bone resorption, especially osteoporosis, Paget's disease, hypercalcemia of malignancy, and metastatic and metabolic bone diseases.

Bisphosphonates as pharmaceutical agents are described for example in EP-A-170,228; EP-A-197,478; EP-A-22,751; EP-A-252,504; EP-A-252,505; EP-A-258,618; EP-A-350,002; EP-A-273,190; and WO-A-90/00798, each of which are incorporated herein by reference.

Pharmaceutical forms of currently marketed bisphosphonates are oral formulations (tablets or capsules) or solutions for intravenous injection or infusion. They are systemically well tolerated when administered at therapeutic doses. However, bisphosphonates as a class are irritant to skin and mucous membranes and when given orally on a continuous basis may result in digestive tract side effects, e.g., esophageal adverse events or gastrointestinal disturbances. As a consequence, and due to their low oral bioavailability, the oral route of administration has, to date, had to follow inconvenient recommendations of use for the patient.

Bisphosphonates can be classified into two groups with different modes of action. Ibandronate belongs to the more potent nitrogen-containing bisphosphonates [Russell 1999 Russell R G G, Rogers M J. Bisphosphonates: From the laboratory to the clinic and back again. Bone 25(1):97-106 (1999); Rogers M J, Gordon S, Benford H L, Coxon F P, Luckman S P, Monkkonen J, Frith J C. Cellular Molecular mechanisms of action of bisphosphonates. Cancer 88 (12) Suppl:2961-2978 (2000)]. Ibandronate is one of the most potent bisphosphonates currently under clinical development in osteoporosis and metastatic bone diseases. In animal models of bone resorption, ibandronate is 2, 10, 50 and 500 times more potent than risedronate, alendronate, pamidronate, and clodronate respectively [Mühlbauer R. C., F. Bauss, R. Schenk, M. Janner, E. Bosies, K. Strein, and H. Fleisch. B M 21.0955 a potent new bisphosphonate to inhibit bone resorption. J. Bone Miner. Res. 6: 1003-1011 (1991)].

Ibandronate inhibits bone resorption without any impairment of mineralization (Mühlbauer et al Mühlbauer R. C., F. Bauss, R. Schenk, M. Janner, E. Bosies, K. Strein, and H. Fleisch. BM 21.0955 a potent new bisphosphonate to inhibit bone resorption. J. Bone Miner. Res. 6: 1003-1011 (1991).). It has been shown to decrease osteoclastic activity, thus inhibiting bone destruction. At high doses it also reduces the number of osteoclasts (Mühlbauer et al. Mühlbauer R. C., F. Bauss, R. Schenk, M. Janner, E. Bosies, K. Strein, and H. Fleisch. BM 21.0955 a potent new bisphosphonate to inhibit bone resorption. J. Bone Miner. Res. 6: 1003-1011 (1991)).

As described, bisphosphonates are accepted as providing strong efficacy in the management of osteoporosis. However, given the administration restrictions related to low oral bioavailability and potential for gastro-intestinal effects, there is a clear opportunity for regimens which offer improved convenience and flexibility, leading to a higher level of compliance and superior patient management/satisfaction. Intermitted regimens such as, for example, once weekly administration have been described in the art.

SUMMARY OF THE INVENTION

. It has now been found that the prevention or the treatment of disorders characterized by pathologically increased bone resorption such as osteoporosis, can be improved by a monthly administration of 50 to 250 mg of a bisphosphonate or pharmaceutical acceptable salt thereof, especially by a monthly administration of ibandronate, i.e., ibandronic acid or a pharmaceutically acceptable salt thereof.

The present invention is thus concerned with the use of a bisphosphonic acid or a pharmaceutical acceptable salt thereof, especially with the use of ibandronic acid or a pharmaceutical acceptable salt thereof, for the preparation of pharmaceutical compositions for the prevention or the treatment of disorders characterized by pathologically increased bone resorption, wherein the medicament comprises about 50 to 250 mg, preferably about 100 to 150 mg, of a bisphosphonic acid or a acceptable salt thereof, and orally administered in a period of one, two or three consecutive days per month.

Monthly oral treatment by administration of at least 120%, especially of 120% to 200%, of the expected efficacious daily dose offers incremental patient benefits with respect to convenience and compliance as well as superior results. Prior to the completion of the ibandronate clinical development program, no bisphosphonate had prospectively demonstrated fracture reduction efficacy with a drug-free interval beyond daily administration. In summary, it is quite unexpected that

fracture reduction benefit can be derived from a monthly administration of an oral bisphosphonate with a single or multiple tablet administration scheme.

Accordingly, the present invention relates to the use of bisphosphonic acids or pharmaceutically acceptable salts, especially ibandronic acid or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the prevention or treatment of disorders characterized by pathologically increased bone resorption, e.g. osteoporosis, wherein the medicament comprises at least 120% of the expected efficacious daily dose of a bisphosphonic acids or acceptable salts thereof and is administered on one, two or three consecutive days per month.

More preferably the invention comprises the use of ibandronic acid or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the prevention or the treatment of disorders characterized by pathologically increased bone resorption wherein the medicament

a) comprises about 100 to about 150 mg of ibandronic acid or a pharmaceutically acceptable salt thereof and

b) is orally administered in a period of one, two or three consecutive days per month.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The term "bisphosphonic acid" means compounds characterized by two phosphonate groups linked by phosphoether bonds to a central (geminal) carbon atom. Such a P—C—P structure is represented by compound I (see, page 6). The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated.

The term "pharmaceutically acceptable" as used herein means that the salts or chelating agents are acceptable from a toxicity viewpoint.

The term "pharmaceutically acceptable salt" refers to ammonium salts, alkali metal salts such as potassium and sodium (including mono, di- and tri-sodium) salts (which are preferred), alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

The term "disorders characterized by pathologically increased bone resorption" refers to medically defined conditions with or without identifiable cause (such as post-menopausal osteoporosis, idiopathic juvenile osteoporosis, Klinefelter's syndrome; male osteoporosis; osteoporosis due to nutritional factors; organ transplant related osteoporosis; immobilization associated osteoporosis; inflammatory condition and cortico-steroid induced osteoporosis).

The term "one, two or three consecutive days per month" means administration of one to three dose proportional or non-dose proportional tablets on one, two or three consecutive days of the month, preferably on one day per month. As used herein, the term "month" is used in accordance with the generally accepted meaning as a measure of time amounting to approximately four (4) weeks, approximately 30 days, or approximately 1/12 of a calendar year.

The term "medicament" refers to a pharmaceutical composition. The term encompasses single or multiple administration schemes.

Preferably, the medicament is administered on one day per month. Preferably, the medicament is administered as a single dose, however, the scope of the present invention includes pharmaceutical compositions administered as multiple sub-doses such as on two consecutive day per month or on three consecutive days per month.

Preferably, the medicament comprises at least 100%, preferably 120% to 200% of the efficacious dose of bisphosphonic acids or pharmaceutically acceptable salts thereof, more preferably of ibandronic acid or pharmaceutically acceptable salts thereof.

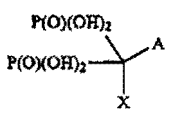
The term "efficacious dose" refers to about 50 to about 250 mg, more preferably to about 100 to about 150 mg, of a bisphosphonate or a pharmaceutically acceptable salt thereof, for example, of ibandronic acid or a pharmaceutically acceptable salt thereof. As noted, the efficacious dose may be a single dose or multiple sub-doses. For example, if the efficacious dose is 150 mg, the dose may be one (1) 150 mg dose, two (2) 75 mg sub-doses administered on one day or on two consecutive days, or three (3) 50 mg sub-doses administered on one day or on two or three consecutive days; if the efficacious dose is 100 mg, the dose may include one (1) 100 mg dose, two (2) 50 mg sub-doses administered on one day or two consecutive days, preferably on two consecutive days.

"Bisphosphonic acids and pharmaceutically acceptable salts thereof" as pharmaceutical agents are described for example in U.S. Pat. Nos. 4,509,612; 4,666,895; 4,719,203; 4,777,163; 5,002,937 and 4,971,958 and in European Patent Applications Nos. 252,504 and 252,505, herein incorporated by reference for such description.

Methods for the preparation of bisphosphonic acids and pharmaceutically acceptable salts thereof may be found in, e.g., U.S. Pat. Nos. 3,962,432; 4,054,598; 4,267,108; 4,327,039; 4,407,761; 4,621,077; 4,624,947; 4,746,654; 4,970,335; 5,019,651; 4,761,406; 4,876,248; in J. Org. Chem. 32, 4111 (1967) and European Patent Application 252,504, herein incorporated by reference. The pharmaceutically acceptable salts of bisphosphonic acids may also be employed in the instant invention. Examples of base salts of bisphosphonic acids include ammonium salts, alkali metal salts such as potassium and sodium (including mono, di- and tri-sodium) salts (which are preferred), alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Non-toxic, physiologically acceptable salts are preferred. The salts may be prepared by methods known in the art, such as described in European Patent Application 252,504 or in U.S. Pat. No. 4,922,077, incorporated herein by reference.

In this invention, the medicament comprises 100 to 150 mg of a ibandronic acid or a pharmaceutically acceptable salt thereof. The pharmaceutical composition comprises at least 150% of a bisphosphonic acid or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients thereof. In one embodiment, the bisphosphonic acid is ibandronic acid. Preferably, the medicament is administered as a single dose.

In a preferred embodiment of the present invention, the term "bisphosphonate" of the present invention corresponds to compounds of general formula



(I)

wherein A and X are independently selected from the group consisting of hydrogen, hydroxy, halogen, amino, SH, phenyl, alkyl, mono- or dialkylamino, mono- or dialkylaminoalkyl, alkoxy, thioalkyl, thiophenyl, and aryl or heteroaryl moieties selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, and benzyl, wherein the aryl or heteroaryl moiety is optionally substituted with alkyl.

In the foregoing chemical formula, A can include X, and X include A such that the two moieties can form part of the same cyclic structure.

The foregoing chemical formula is also intended to encompass carbocyclic, aromatic and heteroaromatic structures for the A and/or X substituents, e.g. naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Preferred structures are those in which A is selected from the group consisting of hydrogen, hydroxy, and halogen, an X is selected from the group consisting of alkyl, halogen, thiophenyl, thioalkyl and dialkylaminoalkyl.

More preferred structures are those in which A is selected from the group consisting of hydrogen, hydroxy, and Cl and X is selected from the group consisting of alkyl, Cl, chlorophenylthio and dialkylaminoalkyl.

The preferred bisphosphonic acid or pharmaceutically acceptable salt is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, risedronate, pamidronate, piridronate, zolendronate, EB-1053 or acceptable salts thereof, e.g., ibandronic acid, monosodium salt, monohydrate.

Ibandronic acid (1-hydroxy-3-(N-methyl-N-pentyl)aminopropylidene-1,1-bisphosphonic acid) or physiologically compatible salts thereof are particularly preferred, e.g., ibandronic acid, monosodium salt, monohydrate.

The bisphosphonates and pharmaceutically acceptable salts may be administered alone or in combination with other bone active drugs, either in fixed combinations or separately both physically and in time, including hormones, such as a steroid hormone, e.g., an estrogen; a partial estrogen agonist, or estrogen-gestagen combination; a calcitonin or analogue or derivative thereof, e.g., salmon, eel or human calcitonin parathyroid hormone or analogues thereof, e.g., PTH (1-84), PTH (1-34), PTH (1-36), PTH (1-38), PTH (1-31)NH2 or PPTS 893; a SERM (Selective Estrogen Receptor Modulator), e.g., raloxifene, lasofoxifene, TSE-434, FC1271, tibolone, vitamin D or an analog. Such additional bone active drugs may be administered more frequently than the bisphosphonate.

Appropriate pharmaceutical compositions are known in the art and have been described e.g., in U.S. Pat. Nos. 6,143,326 and 6,294,196, herein incorporated by reference.

For the preparation of tablets, coated tablets, dragees or hard gelatine capsules, the compounds of the present invention may be admixed with pharmaceutically inert, inorganic or organic excipients. Examples of suitable excipients for tablets, dragees or hard gelatine capsules include lactose, maize starch or derivatives thereof, talc or stearic acid or salts thereof.

The pharmaceutical compositions may also contain preserving agents, solubilizing agents, stabilizing agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, salts for the variation of osmotic pressure, buffers, coating agents or antioxidants. They may also contain other therapeutically valuable agents. Preferably, the pharmaceutical composition is a film coated tablet wherein the tablet core comprises 50 to 200 mg of a bisphosphonic acid or a pharmaceutically acceptable salt thereof as defined above and one or more pharmaceutically acceptable excipients selected from the group consisting of lactose, polyvinylpyrrolidone, microcrystalline cellulose, crospovidone, stearic acid, silicon dioxide and the tablet core comprises one or more pharmaceutically acceptable excipients selected from the group consisting of hydroxypropyl methylcellulose, titanium dioxide, talc and polyethylene glycol 6000. These compositions are known in the art and described for example in U.S. Pat. Nos. 6,143,326 and 6,294,196.

Another aspect of the present invention is a method for treating, reducing or preventing disorders characterized by pathologically increased bone resorption comprising to a mammal administration of an effective amount of bisphosphonic acids or acceptable salts thereof. In particular, the invention refers to a method for treating, reducing or preventing disorders characterized by pathologically increased bone resorption comprising oral administration of an effective amount of a bisphosphonic acid or a pharmaceutically acceptable salt thereof, wherein approximately 50 to 250 mg bisphosphonic acid or a pharmaceutically acceptable salt thereof are administered on one, two or three consecutive days per month. As noted above, the effective amount of bisphosphonic acid or pharmaceutically acceptable salt thereof may be administered as a single dose or as multiple sub-doses.

Preferably, in the method comprises administration of about 50 to 250 mg, preferably about 100 to 150 mg, of a bisphosphonate or a pharmaceutically acceptable salt thereof on one, two or three consecutive days per month. While the method includes administration of the dose through multiple sub-dosing, the preferred method provides a single dose. Examples for administration of the dose through multiple sub-dosing are as follows, if the efficacious dose is 150 mg, the dose may be two (2) 75 mg sub-doses administered on one day or on two consecutive days, or three (3) 50 mg sub-doses administered on one day or on two or three consecutive days; if the efficacious dose is 100 mg, the dose may be two (2) 50 mg sub-doses administered on one day or two consecutive days, preferably on two consecutive days. The preferred bisphosphonate is ibandronate or a pharmaceutically acceptable salt thereof, e.g., ibandronic acid, monosodium salt, monohydrate.

Preferably, in the method according to the present invention, the bisphosphonic acid is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, risedronate, pamidronate, piridronate, zolendronate, EB-1053 or pharmaceutical acceptable salts thereof. More preferably, the bisphosphonic acid is ibandronate or a pharmaceutically acceptable salt thereof, e.g. ibandronic acid, monosodium salt, monohydrate.

The invention will now be explained with reference to exemplified embodiments.

EXAMPLES

Example 1

Pharmaceutical Composition

The Example shows the composition of a 50 mg tablet. The composition and preparation of these tablets is known in the art and described for example in U.S. Pat. Nos. 6,143,326 and 6,294,196.

Other compositions may be prepared by adjusting the ingredients according to the amount of bisphosphonate, e.g. ibandronic acid, monosodium salt, monohydrate.

50 mg film-coated tablet

Components	mg per tablet
Tablet core:	
Ibandronic acid, monosodium salt, monohydrate	56.250
Lactose monohydrate	92.750
Povidone K 25	5.000
Microcrystalline cellulose	30.000
Crospovidone	10.000
Purified stearic acid	4.000
Colloidal silicon dioxide	2.000
Tablet coat:	
Hydroxypropyl methylcellulose	5.1425
Titanium dioxide	2.4650
Talc	0.8925
Polyethylene glycol 6,000	1.5000
Final weight:	210.000

What is claimed is:

1. A method for treating or inhibiting postmenopausal osteoporosis in a postmenopausal woman in need of treatment or inhibition of postmenopausal osteoporosis by administration of a pharmaceutically acceptable salt of ibandronic acid, comprising:

(a) commencing the administration of the pharmaceutically acceptable salt of ibandronic acid by orally administering to the postmenopausal woman, on a single day, a first dose in the form of a tablet, wherein the tablet comprises an amount of the pharmaceutically acceptable salt of ibandronic acid that is equivalent to about 150 mg of ibandronic acid; and

(b) continuing the administration by orally administering, once monthly on a single day, a tablet comprising an amount of the pharmaceutically acceptable salt of ibandronic acid that is equivalent to about 150 mg of ibandronic acid.

2. The method of claim 1, wherein the pharmaceutically acceptable salt is a sodium salt of ibandronic acid.

3. The method of claim 2 wherein the pharmaceutically acceptable sodium salt is a monosodium salt of ibandronic acid.

4. The method of claim 3 wherein the pharmaceutically acceptable monosodium salt of ibandronic acid is a monohydrate.

5. A method for treating or inhibiting postmenopausal osteoporosis in a postmenopausal woman in need of treatment or inhibition of postmenopausal osteoporosis by administration of a pharmaceutically acceptable salt of ibandronic acid, consisting essentially of orally administering to the postmenopausal woman, once monthly on a single day, a tablet comprising an amount of the pharmaceutically acceptable salt of ibandronic acid that is equivalent to about 150 mg of ibandronic acid.

6. The method of claim 5, wherein the pharmaceutically acceptable salt is a sodium salt of ibandronic acid.

7. The method of claim 6 wherein the pharmaceutically acceptable sodium salt is a monosodium salt of ibandronic acid.

8. The method of claim 7 wherein the pharmaceutically acceptable monosodium salt of ibandronic acid is a monohydrate.

9. A method for treating or inhibiting postmenopausal osteoporosis in a postmenopausal woman in need of treatment or inhibition of postmenopausal osteoporosis by administration of a pharmaceutically acceptable salt of risedronic acid, comprising:

(a) commencing the administration of the pharmaceutically acceptable salt of risedronic acid by orally administering to the postmenopausal woman, on a single day, a first dose in the form of a tablet, wherein the tablet comprises an amount of the pharmaceutically acceptable salt of risedronic acid that is equivalent to about 150 mg of risedronic acid; and

(b) continuing the administration by orally administering, once monthly on a single day, a tablet comprising an amount of the pharmaceutically acceptable salt of risedronic acid that is equivalent to about 150 mg of risedronic acid.

10. A method for treating or inhibiting postmenopausal osteoporosis in a postmenopausal woman in need of treatment or inhibition of postmenopausal osteoporosis by administration of a pharmaceutically acceptable salt of risedronic acid, consisting essentially of orally administering to the postmenopausal woman, once monthly on a single day, a tablet comprising an amount of the pharmaceutically acceptable salt of risedronic acid that is equivalent to about 150 mg of risedronic acid.

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