BISPHOSPHONIC ACIDS FOR THE TREATMENT AND PREVENTION OF OSTEOPOROSIS

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 medicaments for the prevention or the treatment of disorders characterized by pathologically increased bone resorption, especially for the prevention and treatment of osteoporosis.

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, WO-A-90/00798, etc., 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. In 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 RGG, Rogers MJ. Bisphosphonates: From the laboratory to the clinic and back again. Bone 25(1):97-106 (1999); Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J, Frith JC. 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. BM 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 mineralisation (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. Intermittend regimens such as for example once weekly administration have been described in the art, but such intermittent treatments do not result in the desired results.

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 medicaments for the prevention or the treatment of disorders characterized by pathologically increased bone resorption, wherein the medicament

a) comprises about 50 to 250 mg, preferably about 100 to 150 mg of a bisphosphonic acid or a acceptable salt thereof and
b) the medicament is orally administered on 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 dose offers incremental patient benefits with respect to convenience and compliance as well as superior results. The "expected dose" (100%) corresponds to the cumulated efficacious daily doses. 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 on one, two or three consecutive days per month.

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 exemplified in Formula I below. It should be noted that the term "bisphosphonic acids" as used herein in referring to the therapeutic agents of the present invention are meant to also encompass bisphosphonates, biphosphonic acids, and bisphosphonic acids, as well as salts and derivatives of these materials. 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 withor without identifiable cause (such as post-menopausal osteoporosis, idiopathic juvenile osteoporosis, osteoporosis associated with Klinefelter's syndrome, male osteoporosis, osteoporosis due to nutritional factors, organ transplant related osteoporosis, immobilisation 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 medicaments 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%, most preferred 120% to 150% of the efficacious dose of bisphosphonic acids or pharmaceutically acceptable salts thereof, more preferably of ibandronic acid or pharmaceutically acceptable salts thereof.

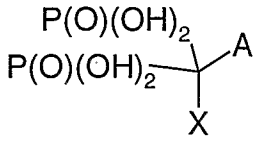
The term " efficacious dose" refers to about 50 to about 250 mg, more preferably to about 100 to about 150 mg, of a bisphosphonate or a pharmaceutically acceptable salt thereof for example of ibandronic acid or a pharmaceutically acceptable salt thereof. As noted, the efficacious dose may be a single 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 US Patent Nos. 4,509,612, 4,666,895, 4,719,203, 4,777,163, 5,002,937, 4,971,958 and 4,958,839 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., US Patent 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, 4,922,077, 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. The 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 US Patent No. 4,922,077, incorporated herein by reference.

Preferably, the medicament comprises 100 to 150 mg of a ibandronic acid or a pharmaceutically acceptable salt thereof. 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, EB-1053, tiludronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, risedronate, piridronate, pamidronate, zolendronate 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 US Patent Nos. 6,143,326 and 6,294,196, herein incorporated by reference.

For the preparation of tablets, coated tablets, dragées 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, dragées 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, solubilising 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 US Patent 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. Especially 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, EB-1053, tiludronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, risedronate, piridronate, pamidronate, zolendronate 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 US Patent 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

CLAIMS

1. Use of a bisphosphonic acid or pharmaceutically acceptable salt 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 at least 120% of the expected efficacious daily dose of a bisphosphonic acid or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients thereof; and
   b) the medicament is orally administered on one, two or three consecutive days per month.

2. The use of claim 1 wherein the disease is osteoporosis.

3. The use according to any of claims 1 to 2 wherein the efficacious dose is about 100 mg to about 150 mg of a bisphosphonic acid or a pharmaceutically acceptable salt thereof.

4. The use according to any of claims 1 to 3, wherein the bisphosphonic acid is ibandronic acid or a pharmaceutically acceptable salt thereof.

5. The use according to any of claims 1 to 4 wherein the efficacious dose is about 100 mg of a bisphosphonic acid or a pharmaceutically acceptable salt thereof.

6. The use according to any of claims 1 to 4 wherein the efficacious dose is about 150 mg of a bisphosphonic acid or a pharmaceutically acceptable salt thereof.

7. The use according to any one of claims 1 to 6, wherein the bisphosphonic acid or a pharmaceutically acceptable salt thereof is ibandronic acid, monosodium salt, monohydrate.

8. The use according to any one of claims 1 to 7, wherein the medicament is a film coated tablet wherein the tablet core comprises 50 to 250 mg of a bisphosphonic acid or a pharmaceutically acceptable salt thereof as defined in claims 1 to 7 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.

9. The use according to any of claims 1 to 8 wherein the medicament is administered as a single dose.

10. The use according to any of claims 1 to 8 wherein the medicament is administered as multiple sub-doses.

11. A method for treating 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 50 to 250 mg of a bisphosphonic acid or a pharmaceutically acceptable salt thereof is administered on one, or two consecutive days per month.

12. The method according to claim 11 wherein the bisphosphonic acid is ibandronic acid or a pharmaceutically acceptable salt thereof.

13. The method according to any of claims 11 and 12 wherein the bisphosphonic acid or a pharmaceutically acceptable salt thereof is administered as defined in any of claims 1 to 10.

13. The invention as hereinbefore defined.