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(54) Title: PHARMACEUTICAL COMPOSITIONS OF ALENDRONIC ACID AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The present invention relates to pharmaceutical compositions of alendronic acid and pharmaceutically acceptable salts thereof, and processes for their preparation.

PHARMACEUTICAL COMPOSITIONS OF ALENDRONIC ACID AND PROCESSES FOR THEIR PREPARATION

Field of the Invention

The present invention relates to pharmaceutical compositions of alendronic acid and pharmaceutically acceptable salts thereof, and processes for their preparation.

Background of the Invention

A variety of bisphosphonic acids have been disclosed as being useful in the treatment and prevention of diseases involving bone resorption. Representative examples may be found in the following: US 3,962,432; US 4,054,598; US 4,267,108; US 4,327,039; US 4,621,077; US 4,624,947; US 4,746,654; US 4,922,077; and WO 02/03963. Various methods for tablet formulation of bisphosphonic acids have been employed, however, they are not entirely satisfactory.

For example, the use of the common diluent lactose, when employed in a solid dosage form of an active ingredient having a basic nitrogen-containing functionality, can result in discoloration, chemical instability and loss of potency of the dosage form. The mechanism responsible for the incompatibility of lactose with basic nitrogen-containing active ingredients is believed to be due to the Maillard (or "browning") reaction in which the basic nitrogen (typically a primary or secondary amino group) of the active ingredient reacts with the "glycosidic" hydroxyl group of lactose ultimately resulting in the formation of brown pigmented degradation products. Other sugars having a "glycosidic" hydroxyl group, such as glucose, also stimulate this degradation when employed as excipients in dosage forms of basic nitrogen-containing actives. Degradation of the active ingredient is particularly pronounced in the presence of water and/or elevated temperature.

The above problem can be solved by making a composition which is free of such excipients.

Attempts have been made to formulate bisphosphonates bearing a basic nitrogen-containing functionality with lactose as a diluent by eliminating water from the formulation process. A dry mix process using anhydrous lactose as a diluent avoids the enhanced degradation which occurs in the presence of water. Solid dosage forms prepared by such a process are exemplified in US 5,882,656.

Summary of the Invention

In one general aspect there is provided a pharmaceutical composition suitable for oral administration to a human. The composition consists essentially of (a) from about 0.5% to about 60% by weight of alendronic acid or a pharmaceutically acceptable salt thereof; (b) from about 10% to about 95% by weight of microcrystalline cellulose; (c) from about 0.5% to about 20% by weight of a disintegrant selected from the group consisting of starch, modified starch, croscarmellose sodium, crospovidone, sodium starch glycolate, and mixtures thereof; and (d) from about 0.1% to about 10% by weight of lubricant/glidant selected from the group consisting of colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated vegetable oil, sodium stearyl fumarate, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and mixtures thereof. The composition is optionally film coated.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the composition may be in the form of a tablet. The pharmaceutically acceptable salts may include ammonium salts, alkali metal salts, alkaline earth metal salts, salts with organic bases, N-methyl-D-glucamine, and salts with amino acids. The pharmaceutically acceptable salt may be the sodium salt. The sodium salt may be the monohydrate, trihydrate, anhydrous or other polymorphic form.

The lubricant/glidant may be one or more of colloidal silicon dioxide, magnesium stearate and talc.

In another general aspect there is provided a process for the preparation of a pharmaceutical composition. The process includes the steps of (a) blending alendronic acid or pharmaceutically acceptable salt thereof and microcrystalline cellulose, (b) optionally milling the blend, (c) mixing the blend of step a) with a disintegrant and lubricant/glidant, (d) optionally granulating the blend, (e) optionally blending the granules with extragranular excipients, (f) lubricating the blend of step a) or granules of step b), and (g) compressing into or filling into a suitable size solid dosage form.

Embodiments of the process may include one or more of the following features. For example, the extragranular excipients may be one or more of microcrystalline cellulose, disintegrant, glidant and lubricant. The granulation may be carried out by wet or dry granulation technique. The wet granulation may be carried out with a granulating

fluid or solution/dispersion of binder. The dry granulation may be carried out by roller compactor or slugging.

The composition may consist essentially of (a) from about 0.5% to about 60% by weight of alendronic acid or a pharmaceutically acceptable salt thereof; (b) from about 10% to about 95% by weight of microcrystalline cellulose; (c) from about 0.5% to about 20% by weight of a disintegrant selected from the group consisting of starch, modified starch, croscarmellose sodium, crospovidone, sodium starch glycolate, and mixtures thereof; and (d) from about 0.1% to about 10% by weight of lubricant/glidant selected from the group consisting of colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated vegetable oil, sodium stearyl fumarate, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and mixtures thereof.

In another general aspect there is provided a method of treating or preventing osteoporosis comprising administering a pharmaceutical composition consist essentially of (a) from about 0.5% to about 60% by weight of alendronic acid or a pharmaceutically acceptable salt thereof; (b) from about 10% to about 95% by weight of microcrystalline cellulose; (c) from about 0.5% to about 20% by weight of a disintegrant selected from the group consisting of starch, modified starch, croscarmellose sodium, crospovidone, sodium starch glycolate, and mixtures thereof; and (d) from about 0.1% to about 10% by weight of lubricant/glidant selected from the group consisting of colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated vegetable oil, sodium stearyl fumarate, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and mixtures thereof.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Description of the Invention

The inventors have developed pharmaceutical compositions suitable for oral administration to a human. The compositions include alendronic acid, microcrystalline cellulose, disintegrant and lubricant/glidant, wherein the composition is free of sugars.

Microcrystalline cellulose used in the composition serves various functions such as diluent and lubricant, as well as binder. The increasing microcrystalline cellulose content

in a composition results in lowering of the requirement for a diluent as microcrystalline cellulose also has good compressibility. Hence, in some cases it can completely replace the diluent, e.g., as in the case of this invention. Additionally, microcrystalline cellulose is not known to interact with alendronic acid.

The term 'pharmaceutical composition' as used herein includes solid dosage forms such as tablet, capsule, pill and the like. The tablets can be prepared by techniques known in the art such as wet granulation, dry granulation and direct compression, and may contain a therapeutically useful amount of the alendronic acid or salts thereof and such excipients as are necessary to form the tablet by such techniques. Tablets and pills can additionally be given enteric coatings and other release-controlling coatings for the purpose of acid protection, easing swallowability, etc.

The pharmaceutically acceptable salts of alendronic acid include ammonium salts, alkali metal salts such as potassium and sodium (including, but not limited to, mono-, di- and tri-sodium) salts, 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 and lysine. The sodium salt may exist in any of the solid states, including the monohydrate, trihydrate, anhydrous, or any other polymorphic forms.

In one general aspect, the pharmaceutical composition may be prepared by a dry granulation technique comprising the steps of blending alendronic acid or pharmaceutically acceptable salts thereof, microcrystalline cellulose and disintegrant; dry granulating the blend by roller compactor or slugging; optionally blending with pharmaceutically acceptable inert excipients; lubricating the granules/blend; compressing the lubricated blend into suitable sized tablets; and, optionally, coating the tablets with film forming polymers and coating additives.

In another general aspect, the pharmaceutical composition may be prepared by a direct compression technique comprising the steps of blending alendronic acid or pharmaceutically acceptable salts thereof, microcrystalline cellulose and disintegrant; lubricating the blend; directly compressing the lubricated blend into suitable sized tablets; and, optionally, coating with film forming polymers and coating additives.

In addition to the active ingredient, diluent, disintegrant and lubricant/glidant, the composition may comprise coloring agents. Coloring agents that may be used include any

FDA approved colors for oral use.

The pharmaceutical composition may optionally be coated with functional and/or non-functional layers comprising film-forming polymers. Examples of film-forming polymers include ethylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethyl cellulose, hydroxymethylcellulose, hydroxyethylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate; waxes such as polyethylene glycol; methacrylic acid polymers such as Eudragit ® RL and RS; and the like. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry® may also be used for coating the tablets.

The invention is further illustrated by the following examples, which are for illustrative purpose only and should not be considered as limiting the scope of the invention.

EXAMPLES 1-3

	Example 1	Example 2	Example 3
Ingredients	Quantity (mg)		
Intragranular			
Sodium alendronate trihydrate	76.43	10.92	6.526
Microcrystalline cellulose	88.45	12.636	41.974
Croscarmellose sodium	10.5	1.5	0.5
Magnesium stearate	1.75	0.25	0.25
Extragranular			
Microcrystalline cellulose	147.87	21.124	21.124
Croscarmellose sodium	10.5	1.5	1.5
Talc	3.5	0.5	0.5
Colloidal silicon dioxide	3.5	0.5	0.5

Magnesium stearate	7.5	1.07	1.07
Total	350.0	50.0	50.0

Process:

1. Sodium alendronate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate were sifted through a sieve and geometrically blended.
2. The blend of step 1 was passed through a roller compactor and the compacts were passed through a sieve.
3. Croscarmellose sodium, microcrystalline cellulose, talc and colloidal silicon dioxide were sifted through a sieve and added to the blend of step 2 and thoroughly mixed.
4. Magnesium stearate was sifted through a sieve and added to the blend of step 3 and thoroughly mixed.
5. The blend of step 4 was compressed into tablets.

EXAMPLE 4-6

	Example 4	Example 5	Example 6
Ingredients	Quantity (mg)		
Intragranular			
Sodium alendronate trihydrate	76.78	10.96	5.48
Microcrystalline cellulose	105.47	15.067	20.556
Croscarmellose sodium	12.0	1.71	1.714
Magnesium stearate	1.75	0.25	0.25
Extragranular			
Microcrystalline cellulose	168.0	24.0	24.0
Croscarmellose sodium	12	1.714	1.714
Talc	4.0	0.571	0.571
Colloidal silicon dioxide	4.0	0.571	0.571

	Example 4	Example 5	Example 6
Magnesium stearate	8.0	1.142	1.142
Total	392.0	56.0	56.0

Process:

1. Sodium alendronate and microcrystalline cellulose were milled through a suitable sieve.
2. Croscarmellose sodium and magnesium stearate were sifted through sieve and geometrically blended.
3. The blend of step 1 was passed through a roller compactor and the compacts were passed through a sieve.
4. Croscarmellose sodium, microcrystalline cellulose, talc and colloidal silicon dioxide were sifted through a sieve and added to the blend of step 2 and thoroughly mixed.
5. Magnesium stearate was sifted through a sieve and added to the blend of step 3 and thoroughly mixed.
6. The blend of step 4 was compressed into tablets.

Upon stability testing of the tablets made according to the above examples, no discoloration was observed when the tablets were subjected to 40°C/75% relative humidity for six months.

While there have been shown and described what are the preferred embodiments of the invention, one skilled in the pharmaceutical formulation art will appreciate that various modifications in the formulations and process can be made without departing from the scope of the invention as it is defined by the appended claims.

We claim:

1 1 A pharmaceutical composition suitable for oral administration to a human, the
2 composition consisting essentially of:

3 a) from about 0.5% to about 60% by weight of alendronic acid or a
4 pharmaceutically acceptable salt thereof;

5 b) from about 10% to about 95% by weight of microcrystalline cellulose;

6 c) from about 0.5% to about 20% by weight of a disintegrant selected from
7 the group consisting of starch, modified starch, croscarmellose sodium,
8 crospovidone, sodium starch glycolate, and mixtures thereof; and

9 d) from about 0.1% to about 10% by weight of lubricant/glidant selected from
10 the group consisting of colloidal silicon dioxide, stearic acid, magnesium
11 stearate, calcium stearate, talc, hydrogenated vegetable oil, sodium stearyl
12 fumarate, sucrose esters of fatty acid, microcrystalline wax, yellow
13 beeswax, white beeswax, and mixtures thereof;

14 wherein the composition is optionally film coated.

1 2. The pharmaceutical composition of claim 1, wherein the composition is in the form
2 of a tablet.

1 3. The pharmaceutical composition according to claim 1, wherein the
2 pharmaceutically acceptable salts include ammonium salts, alkali metal salts,
3 alkaline earth metal salts, salts with organic bases, N-methyl-D-glucamine, and
4 salts with amino acids.

1 4. The pharmaceutical composition according to claim 3, wherein the
2 pharmaceutically acceptable salt comprises the sodium salt.

1 5. The pharmaceutical composition according to claim 4, wherein the sodium salt
2 comprises the monohydrate, trihydrate, anhydrous or other polymorphic form.

1 6. The pharmaceutical composition according to claim 1, wherein the
2 lubricant/glidant comprise one or more of colloidal silicon dioxide, magnesium
3 stearate and talc.

1 7. A process for the preparation of pharmaceutical composition, the process

comprising the steps of:

a) blending alendronic acid or pharmaceutically acceptable salt thereof and microcrystalline cellulose,

b) optionally milling the blend,

c) mixing the blend of step a) with a disintegrant and lubricant/glidant,

d) optionally granulating the blend,

e) optionally blending the granules with extragranular excipients,

f) lubricating the blend of step a) or granules of step b), and

g) compressing into or filling into a suitable size solid dosage form.

8. The process for the preparation of a pharmaceutical composition according to claim 7, wherein the extragranular excipients comprise one or more of microcrystalline cellulose, disintegrant, glidant and lubricant.

9. The process for the preparation of a pharmaceutical composition according to claim 7, wherein the granulation is carried out by wet or dry granulation technique.

10. The process for the preparation of a pharmaceutical composition according to claim 9, wherein the wet granulation is carried out with a granulating fluid or solution/dispersion of binder.

11. The process for the preparation of a pharmaceutical composition according to claim 9, wherein the dry granulation is carried out by roller compactor or slugging.

12. The process of the preparation of a pharmaceutical composition according to claim 9, wherein the composition consists essentially of:

a) from about 0.5% to about 60% by weight of alendronic acid or a pharmaceutically acceptable salt thereof;

b) from about 10% to about 95% by weight of microcrystalline cellulose;

c) from about 0.5% to about 20% by weight of a disintegrant selected from the group consisting of starch, modified starch, croscarmellose sodium, crospovidone, sodium starch glycolate, and mixtures thereof; and

d) from about 0.1% to about 10% by weight of lubricant/glidant selected from the

group consisting of colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated vegetable oil, sodium stearyl fumarate, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and mixtures thereof.

13. A method of treating or preventing osteoporosis comprising administering a pharmaceutical composition according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003471

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/20 A61K31/66 A61P19/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/075828 A (LEK PHARMACEUTICALS D. D.) 10 September 2004 (2004-09-10) page 4, line 21 - page 5, line 22 page 8, line 3 - page 9, line 4 page 11, line 6 - page 12, line 19 page 15 - page 18; examples 3-6	1-13
X	US 2003/161878 A1 (JASPROVA DAGMAR) 28 August 2003 (2003-08-28) page 3, paragraphs 39,40 page 4, paragraph 55 page 5, paragraph 73; example 3 page 7, paragraph 113-115; example 6	1-13

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2006	14/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gomez Gallardo, S

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003471

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001/007863 A1 (KATDARE ASHOK V ET AL) 12 July 2001 (2001-07-12)	7-11
A	page 1, paragraphs 5-9,19-27 claims 1-25	1-6,12, 13
P,X	US 2005/181043 A1 (NANDI INDRANIL ET AL) 18 August 2005 (2005-08-18) page 1, paragraph 23 page 2, paragraph 49-55 page 3 - page 4; examples 1-5	1-7,13

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/003471

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2005/003471

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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US 2005181043 A1	18-08-2005	NONE		