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(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Plot No. 90, Sector - 32, 122 001 Guragaon, Haryana (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MEHTA, Kamal** [IN/IN]; 1-N-50, R.C. Vyas Colony, Bhilwara, 311001 Rajasthan (IN). **MATHUR, Rajeev, Shanker** [IN/IN]; 112/4, C3 Silver Oak Apartments, DLF City Phase-1, 122002 Gurgaon, Haryana (IN). **CHAROO, Naseem, Ahmad** [IN/IN]; House No. 27, Gopal Pora, Alamdar Colony, Wathora, District Badgam, 191111 Jammu & Kashmir (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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(54) Title: PHARMACEUTICAL COMPOSITION OF ALENDRONIC ACID

(57) Abstract: The present invention relates to a pharmaceutical composition of alendronic acid and pharmaceutically acceptable salts thereof.

PHARMACEUTICAL COMPOSITION OF ALENDRONIC ACID

The present invention relates to a pharmaceutical composition of alendronic acid and pharmaceutically acceptable salts thereof.

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; and US 4,922,077. Various methods for tablet formulation of bisphosphonic acids have been employed, however, they are not 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 apparent 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. This problem can be solved by making a composition which is free of such excipients.

Attempts have been made to formulate bisphosphonates bearing basic nitrogen-containing functionality with lactose as 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

The inventors have developed pharmaceutical composition suitable for oral administration to a human, comprising alendronic acid, non-reducing sugar or sugar alcohol, disintegrant and lubricant/glidant.

In one general aspect, there is provided a pharmaceutical composition suitable for oral administration to a human, comprising:

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

b) from about 10% to about 95% by weight of a non-reducing sugar or sugar alcohol such as mannitol, xylitol, sorbitol, inositol, sucrose and trehalose or mixtures thereof;

c) from about 0.5% to about 20% by weight of a disintegrant such as starch, modified starch, croscarmellose sodium, crospovidone and sodium starch glycolate or mixtures thereof; and

d) from about 0.1% to about 10% by weight of lubricant/glidant such as 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 or mixtures thereof.

In another general aspect, there is provided a process for the preparation of pharmaceutical composition comprising the steps of-

a) blending from about 0.5% to about 60% by weight of alendronic acid or pharmaceutically acceptable salt thereof; and from about 10% to about 95% by weight of a non-reducing sugar or sugar alcohol such as mannitol, xylitol, sorbitol, inositol, sucrose and trehalose or mixtures thereof,

b) mixing the blend of step a) with about 0.5% to about 20% by weight of a disintegrant such as starch, modified starch, croscarmellose sodium, crospovidone and sodium starch glycolate or mixtures thereof; and, about 0.1% to about 10% by weight of lubricant/glidant such as 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 or mixtures thereof,

c) optionally granulating the blend,

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

e) compressing into or filling into suitable size solid dosage form.

In one general aspect, there is provided a method of treating or preventing osteoporosis comprising administering a pharmaceutical composition comprising:

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

b) from about 10% to about 95% by weight of a non-reducing sugar or sugar alcohol such as mannitol, xylitol, sorbitol, inositol, sucrose and trehalose or mixtures thereof;

c) from about 0.5% to about 20% by weight of a disintegrant such as starch, modified starch, croscarmellose sodium, crospovidone and sodium starch glycolate or mixtures thereof; and

d) from about 0.1% to about 10% by weight of lubricant/glidant such as 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 or mixtures thereof.

In another general aspect, there is provided pharmaceutical composition suitable for oral administration to a human, comprising:

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

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

c) from about 0.5% to about 20% by weight of croscarmellose sodium;

d) from about 0.1% to about 5% by weight of magnesium stearate;

e) from about 0.1% to about 5% by weight of talc; and

f) from about 0.1% to about 5% by weight of colloidal silicon dioxide.

In another general aspect, there is provided a process for the preparation of pharmaceutical composition comprising the steps of:

a) blending alendronic acid or pharmaceutically acceptable salts thereof and mannitol,

b) mixing the blend of step a) with croscarmellose sodium, talc and colloidal silicon dioxide,

c) optionally granulating the blend,

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

e) compressing into or filling into suitable size solid dosage form.

Use of mannitol provides a dual advantage, firstly, being a non-reducing sugar alcohol, it does not undergo Maillard reaction with alendronic acid; and secondly, due to good compressibility characteristics, it facilitates fast disintegration of tablets with high hardness. Additionally, such tablets when made with a direct compression method do not require the use of binder.

The term 'pharmaceutical composition' as used herein includes solid dosage forms such as tablets, capsules, pills and the like. The tablets can be prepared by techniques known in the art and contain a therapeutically useful amount of the alendronic acid or salts thereof and such excipients as are desirable 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, lysine. The sodium salt may exist in any of the solid state

which includes monohydrate, dihydrate, trihydrate, anhydrous, or any other polymorphic forms.

The non-reducing sugar or sugar alcohol can act as diluent in the formulation. A "non-reducing sugar" as used herein refers to a sugar or sugar alcohol without a glycosidic hydroxyl group or a sugar (or sugar alcohol) which is otherwise incapable of reaction with the basic nitrogen of a basic nitrogen-containing compound in a Maillard-type reaction. Examples of non-reducing sugar or sugar alcohol include mannitol, xylitol, sorbitol, inositol, sucrose and trehalose.

In one general aspect, the pharmaceutical composition may be prepared by a wet granulation technique, comprising the steps of blending alendronic acid or pharmaceutically acceptable salts thereof, non-reducing sugar or sugar alcohol and disintegrant; granulating with a granulating fluid or solution/dispersion of binder; drying and sizing the granules; optionally blending with pharmaceutically inert extragranular excipients; lubricating the granules/blend; compressing the lubricated blend into suitable sized tablets; and optionally coating with film forming polymer and coating additives.

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, non-reducing sugaror sugar alcohol and disintegrant; dry granulating the blend by roller compactor or slugging; lubricating the granules/blend; compressing the lubricated blend into suitable sized tablets; and optionally coating with film forming polymer 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, non-reducing sugar or sugar alcohol and disintegrant; lubricating the blend; directly compressing the lubricated blend into suitable sized tablets; and optionally coating with film forming polymer and coating additives.

In addition to active ingredients, diluents, disintegrants and lubricants/glidants; the composition may comprise other pharmaceutically acceptable excipients such as binders, surfactants and coloring agents.

Surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical dosage forms. These include polyethoxylated fatty acids and its derivatives, for example, polyethylene glycol 400 distearate, polyethylene glycol – 20 dioleate, polyethylene glycol 4 –150 mono dilaurate, polyethylene glycol –20 glyceryl stearate; alcohol – oil transesterification products, for example, polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example, polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example, propylene glycol monocaprylate; mono and diglycerides, for example, glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example, polyethylene glycol – 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example, sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like.

Coloring agents 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, if desired.

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 invention is further illustrated by the following examples, which is for illustrative purpose only and do not limit the scope of invention .

EXAMPLE 1-5

	Example 1	Example 2	Example 3	Example 4	Example 5
Ingredients	**Quantity (mg)**				
Sodium Alendronate Trihydrate	91.37	52.21	45.68	13.05	6.53
Mannitol	248.13	141.79	124.07	35.45	41.97
Croscarmellose sodium	3.50	2.00	1.75	0.50	0.50
Magnesium stearate	3.50	2.00	1.75	0.50	0.50
Talc	1.75	1.00	0.88	0.25	0.25
Colloidal silicon dioxide (Aerosil)	1.75	1.00	0.88	0.25	0.25
Total	350.00	200.00	175.00	50.00	50.00

Process:

1. Sodium Alendronate and Mannitol were sifted through sieve and blended geometrically.
2. Croscarmellose sodium, talc and aerosil were also sifted through sieve and mixed with the blend of step 1.
3. Magnesium stearate was sifted through sieve and added to the step 2 and mixed thoroughly.
4. Blend of step 4 was compressed to tablets.

EXAMPLE 6-8

	Example 6	Example 7	Example 8
Ingredients	**Quantity (mg)**		
Intragranular			
Sodium Alendronate Anhydrous	76.43	10.92	5.46
Mannitol	88.45	12.64	18.10
Croscarmellose sodium	10.50	1.50	1.50
Magnesium stearate	1.75	0.25	0.25
Extragranular			
Mannitol	147.87	21.12	21.12
Croscarmellose	10.50	1.50	1.50

	Example 6	Example 7	Example 8
Ingredients	**Quantity (mg)**		
sodium			
Talc	3.50	0.50	0.50
Colloidal silicon dioxide	3.50	0.50	0.50
Magnesium stearate	7.50	1.07	1.07
Total	350.00	50.00	50.00

Process:

1. Sodium Alendronate, Mannitol, Croscarmellose sodium and Magnesium Stearate were sifted through sieve and mixed geometrically.
2. The blend was passed through roll compactor and the compacts obtained were passed through sieve.
3. Croscarmellose sodium, Mannitol, talc and colloidal silicon dioxide were sifted through sieve and mixed with the compact of step 2.
4. Magnesium stearate was sifted through sieve and added to the step 3 and mixed.
5. The blend was compressed into tablets.

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. A pharmaceutical composition suitable for oral administration to a human, comprising:

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

b) from about 10% to about 95% by weight of a non-reducing sugar or sugar alcohol selected from the group consisting of mannitol, xylitol, sorbitol, inositol, sucrose and trehalose or mixtures thereof;

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 and sodium starch glycolate or 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 or mixtures thereof.

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

3. The pharmaceutical composition according to claim 1, wherein pharmaceutically acceptable salts include ammonium salts, alkali metal salts such as potassium and 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, lysine.

4. The pharmaceutical composition according to claim 3, wherein pharmaceutically acceptable salt is sodium salt.

5. The pharmaceutical composition according to claim 4, wherein sodium salt is monohydrate, dihydrate or trihydrate, anhydrous or any other polymorphic form.

6. A pharmaceutical composition suitable for oral administration to a human, comprising:

a) from about 10% to about 60% by weight of alendronic acid or pharmaceutically acceptable salt thereof;

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

c) from about 0.5% to about 20% by weight of croscarmellose sodium;

d) from about 0.1% to about 5% by weight of magnesium stearate;

e) from about 0.1% to about 5% by weight of talc; and

f) from about 0.1% to about 5% by weight of colloidal silicon dioxide.

7. A process for the preparation of pharmaceutical composition of claim 1 comprising the steps of-

a) blending alendronic acid or pharmaceutically acceptable salt thereof and a non-reducing sugar or sugar alcohol,

b) mixing the blend of step a) with a disintegrant, lubricant/glidant.

c) optionally granulating the blend,

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

e) compressing into or filling into suitable size solid dosage form.

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

9. The process for the preparation of pharmaceutical composition according to claim 8 wherein wet granulation is carried out with a granulating fluid or solution/dispersion of binder.

10. The process for the preparation of pharmaceutical composition according to claim 8 wherein dry granulation is carried out by roller compactor or slugging.

11. A method of treating or preventing osteoporosis comprising administering pharmaceutical composition of claim 1.

INTERNATIONAL SEARCH REPORT

International application No
/IB2005/003099

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/20 A61K31/663 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	US 2004/138180 A1 (AHMED SALAH U ET AL) 15 July 2004 (2004-07-15) page 2, paragraph 11 - page 3, paragraph 19 page 3, paragraphs 42,43 page 5, paragraphs 58,60,69-72 page 7, paragraph 89-95; examples 4,5 claims 1-27	1-11
X	GR 1 004 660 B1 (FARMANEL FARMAKEFTIKI, EBORIKI KAI VIOMICHANIKI ANONYMOS ETAIREIA KAI) 25 August 2004 (2004-08-25) page 6, line 21 - page 7, line 21 page 13, line 32 - page 14, line 22; example 1 page 15; example 4 claims 1-6	1-11

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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
2 February 2006	16/02/2006

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

ational application No
. . ./IB2005/003099

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	-& EP 1 491 199 A (PHARMANEL PHARMACEUTICAL, COMMERCIAL AND INDUSTRIAL S.A) 29 December 2004 (2004-12-29) page 2, paragraph 1 page 4, paragraph 22-26 page 7, paragraph 33; example 1 page 8; example 4 claims 1-11	1-5,7,8, 10,11
X	WO 01/28564 A (YUYU INDUSTRIAL CO., LTD) 26 April 2001 (2001-04-26) page 8, line 14 - page 9, line 8 page 39 - page 40; examples 1-3	1-11
X	WO 01/85176 A (INSTYTUT FARMACEUTYCZNY; ADAMSKI, STANIS&LSTROK; ZAREMBA, ANDRZEJ; SZE) 15 November 2001 (2001-11-15) page 3, line 10 - page 4, line 23 page 5, line 13 - page 6, line 3 page 6, lines 19-26 page 10, lines 4-17; example claims 1-12	1-11
X	US 2003/161878 A1 (JASPROVA DAGMAR) 28 August 2003 (2003-08-28) page 3, paragraph 39 - page 4, paragraph 48 page 4, paragraph 56 page 5 - page 7; examples 2,3,5,7 claims 1-3	1-11
X	EP 1 407 766 A (VERISFIELD LTD) 14 April 2004 (2004-04-14) page 2, paragraph 1-4 page 2, paragraph 9 - page 3, paragraph 13 page 3, paragraph 16 - page 4, paragraph 24 page 4 - page 6; examples 1-5 claims 1-10	1-11
P,X	WO 2005/030177 A (CIPLA LIMITED) 7 April 2005 (2005-04-07) page 4, paragraph 2 page 6, paragraphs 1,2 page 7, last paragraph - page 8, paragraph 2 page 10 - page 11; example 1	1-5,7-9, 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/003099

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 11 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

national application No
T/IB2005/003099

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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