(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 August 2010 (12.08.2010)

PCT

(10) International Publication Number
WO 2010/090613 A1

(51) International Patent Classification:
A61K 31/663 (2006.01) *A61K 45/06* (2006.01)
A61K 31/593 (2006.01) *A61P 19/10* (2006.01)
A61K 33/06 (2006.01)

(21) International Application Number:
PCT/TR2010/000024

(22) International Filing Date:
2 February 2010 (02.02.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2009/00880 5 February 2009 (05.02.2009) TR

(72) Inventor; and
(71) Applicant : **BILGIC, Mahmut** [TR/TR]; Tozkoparan Mah. General Ali Riza Gurcan Cad. Merter Is, Merkezi Bagimsiz Bolum No:2/8 Merter, Istanbul 34173 (TR).

(74) Agent: **HATICE GULBEN YILMAZ KARLIDAG**; Tozkoparan Mah. General Ali Riza Gurcan Cad. Merter Is, Merkezi Bagimsiz Bolum No:2/8 Merter, Istanbul 34173 (TR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2010/090613 A1

(54) Title: THE COMBINED PHARMACEUTICAL COMPOSITION IN A SINGLE DOSAGE FORM

(57) Abstract: The present invention relates to a stabilized pharmaceutical composition comprising combination of active agents in a single dosage form so as to increase patients' compliance and as a result the success of the treatment.

THE COMBINED PHARMACEUTICAL COMPOSITION IN A SINGLE DOSAGE FORM

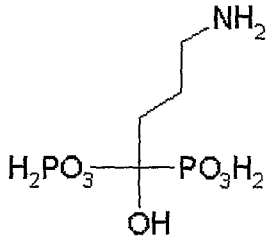
Field of the invention

This invention is directed to a stable combined pharmaceutical composition in a single dosage form so as to enhance the patient's treatment compliance and hence the success of the treatment.

Background of the invention

The present invention provides an effective combination for the prevention and/or treatment and/or supplement of diseases and conditions associated with the abnormal bone resorption. The effect caused by the combination prepared according to the present invention as named as "desired effect" thoughout this document. The combination of the present invention includes a calcium salt, vitamin-D and alendronate or pharmaceutically acceptable salt, derivative or hydrate thereof.

Alendronic acid is a bisphosphonate which has a chemical name of sodium [4-amino-1-hydroxybutylidene) biphosphonic acid (Formula I).



(I)

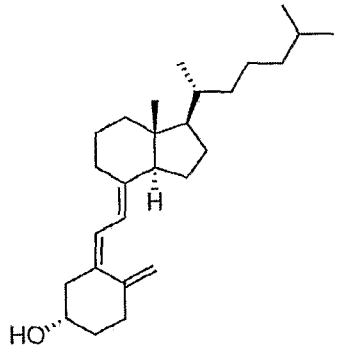
Alendronic acid is firstly disclosed in patent numbered US4705651 A. In this patent, manufacturing processes and the usage of alendronic acid in osteopathy treatment are included.

Although alendronate is a second generation diphosphonate, it is also the first drug of its general group which is capable of the reinforcing of the bone as well as inhibiting the bone loss. Alendronate, is a biphosphonate which connects to hydroxyapatite in the bone and inhibits osteoclast (a kind of bone cell which destroys bone tissue by destroying bone matrix) mediated bone resorption. Bone resorption occurs by ruffled edges of osteoclasts in contact with the bone which are capable of making resorption. Alendronate inhibits the resorption by localizing specially under the resorption area of osteoclasts. In time, normal bone tissues which are produced by osteoblasts plank down onto alendronate. The activity of alendronate continues until it sinks inside the matrix where it shows no activity. However, alendronate will be connected to

hydroxyapatite for years. Alendronate shoud be used continually to maintain the octeoclast inhibition on newly formed resorption surface.

Alendronate decreases the turnover of the bone. It increases the mass of bone wherein the bone formation exceeds the bone resorption. It also decreases the direct resorption of bone in Paget disease which is a progressive and idiopathic disease wherein the bone metabolism is accelarated and re-shaped. After the six months treatment, deformed bone is transformed into the normal bone structure. It sharply increases the bone mineral density in postmenopausal osteoporosis which is characterized with progressive loss of bone causing increase in fragility of bone mass. This increases in bone mass can be seen in spine and hip after three months of treatment. After a year of treament, bone return back to its normal structure by means of both structure and the mineral content. It cause an improtant decrease in serum calcium and uriner calcium level at malignant hypercalsemia which is believed to be a result of increased bone resorption in patients with metastatic cancer. It inhibits the progress of osteolytic diseases and relieves severe bone pain. In order to obtain optimum efficiency of normal bone production, calcium and vitamin D supplement is needed in treatments.

Vitamin D is a group of fat-soluble prohormones, the two major forms of which are vitamin D_2 (or ergocalciferol) and vitamin D_3 (or cholecalciferol).Vitamin D3 is a form of vitamin D with the chemical name of (3β,5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-3-ol (Formul II).



(II)

Vitamin D3 is a form of Vitamin D that is synthesized in human body naturally. Vitamin D3 is occured naturally in the mammal skin from 7-dehydrocholesterol under the action of UV light. It can be partially provided by animal products. Vitamin D3 undergoes biotransformation in kidney and liver and turn into its active form of 1,25-dihydroxycholecalciferol ([1,25-$(OH)_2$ D_3] veya calcitriol).

It plays an important role on the maintance of calcium balance and regulation of parathyroid hormone. It stimulates the renal re-absorption of calcium, increases the absorption of calcium

and phosphorus from intestine and transition from bone to plasma. It is believed that the calcium absoprtion from intestine is achieved by binding of calcitriol to spesific receptors found on cytoplasm of intestine mucosa cells. After that, calcium is absorbed by production of a calcium binding protein. When calcium and phosphorus levels of plasma reach to a saturated level, mineralization occurs in the bone.

Calcium is the chemical element with the symbol "Ca". It is the most abundant mineral found in the human body. 99% of body calcium is found in bone tissue. It plays an important role on bone structure and muscle contractions. The blood coagulation, neural transmission and the provision of electrical conduction in the heart depends on calcium. Parathyroid hormone, vitamin D, calcitonin, glucocorticoids can affect the balance of calcium and magnesium.

Calcium and its salts are used for treatment or prophylaxis of calcium deficiency. Calcium can be administered by oral route in carbonate, chloride, citrate, glubionate, gluceptate, gluconate, lactate, or phosphate salt forms; and it can be administered by parenteral route in acetate, chloride, gluceptate, gluconate, and glycerophosphate / lactate salt forms.

Minimum daily requirement of calcium in the postmenopausal women is 1500 mg. In the premenopausal women, this amount is 1000 mg. This indicates that in the in the post menopausal period a woman needs at least 500 mg / day of additional calcium supplementation. Vitamin D is required for absorption of calcium. It was determined that vitamin D deficiency and osteoporosis that develops as a result of this is a risk factor for falls and fractures. In the postmenopausal women, due to vitamin D deficiency, calcium absorption is reduced. Various clinical studies have showed that daily calcium and vitamin D intake in men, just like in women, is lower than the recommended dose. This increases the probability of ratio of diseases (osteoporosis, osteomalacia, etc.) originating from vitamin D and calcium deficiency in adults of advanced age. Therefore, attention to dietary factors, as well as the use of various drugs supplements are also recommended.

Dietary calcium plays an important role in preventing osteoporosis. However, using calcium alone is not possible to treat osteoporosis. Recently, it is a common opinion that in the active period of bone loss the use of calcium alone does not prevent bone loss. However, when calcium is combined with some drugs (vitamin D or biphosphonates such as alendronate) it increasingly exhibits a synergistic effect. For example, calcium requirements for the new bone after the use of alendronate should be provided with calcium supplementation. As for the absorption of calcium vitamin D is needed. In conclusion, vitamin D and calcium supplementation must also be included in the context of a treatment in which biphopshonates, such as alendronate, is used.

The synergistic effect of alendronate, calcium and vitamin D in various combinations (a combination of calcium and vitamin D or a combination of alendronate and vitamin D or a combination of alendronate and calcium or a simultaneous use of alendronate, calcium and vitamin D combination, etc.) in treatment of osteoporosis and falling and fractures depending on osteoporosis was demonstrated in various pre-clinical studies.

- McComsey G. A. et al. Alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in HIV. *AIDS* (2007) 21(18): 2473-82
- Mondy K. Alendronate, vitamin D, and calcium for the treatment of osteopenia/osteoporosis associated with HIV infection. *J Acquir Immune Defic Syndr.* (2005) 38(4): 426-31
- Ho A., Kung A. Efficacy and Tolerability of Alendronate Once Weekly in Asian Postmenopausal Osteoporotic Women. *The Annals of Pharmacotherapy*: Vol. 39, No. 9, pp. 1428-1433
- Recker R. Alendronate with and without cholecalciferol for osteoporosis: results of a 15-week randomized controlled trial. *Curr Med Res Opin.* (2006) 22 (9): 1745-55
- Chapuy M. C. Vitamin D_3 and calcium to prevent hip fractures in elderly women. *The New England Journal of Medicine* (1992) 327, 1637-42

The following patents of the state of art below show an orientation of various combinations of the active agents.

The patent numbered US20050261250 A1 discloses a pharmaceutical composition which comprises a biphosphonate or pharmaceutically acceptable salts, derivatives or hydrates or a mixture thereof and a vitamin D compound.

In patent numbered WO03086415 A1, a pharmaceutical composition of an inactive metabolite of vitamin D2 and/or D3 and at least one biphosphonate is disclosed.

The patent numbered WO2005027921 A1 describes a pharmaceutical composition which includes 2-methylene-19-nor-20(S)- 1α,25-dihydroxyvitamin D3 and a biphosphonate.

In WO2004022068 A1, an administration method for giving a toxic dose of vitamin D which can not cause hypercalcemia comprising administering to said mammal in an appropriate dosage schedule an effective amount of a bone calcium resorption inhibitor has been described.

In aforementioned patents, importance of calcium in the treatment is emphasized but a combination with biphosphonates such as alendronate and vitamin D in the same preparation was not considered.

In patent numbered WO9906051 A1, a pharmaceutical composition which is characterized in that it comprises a binding agent chosen in the group consisting of propylene glycol, a polyethylene glycol with a molecular weight between 300 and 1500, liquid paraffin or silicone oil and that the Vitamin D is present at the rate of 1 - 2 g of calcium for 500 1000 I.U. of Vitamin D.has been described.

Patent numbered EP0969849 B1 describes pharmaceutical preparations containing a combination of an active form of vitamin D3 and tricalcium phosphate.

In patent with the number of EP0583378 B1, a bone mineral supplement which comprises calcium in the form of calcium citrate maleate in the range of 100-1000 mg (on an elemental basis), and vitamin D wherein said vitamin D is administered as its biologically active metabolites and precursors selected from 1α, 25- $(OH)_2$ vitamin D; 25 OH vitamin D, 1α OH vitamin D_2 veya D_3, or analogues of the dihydroxy compound in amounts equivalent to 0.60-30 μg vitamin D has been described.

In patent numbered EP1651191 A2, an oral pharmaceutical composition comprising vitamin D combined with a calcium phosphate, characterised in that the composition is of the effervescent type, and the calcium is present in a concentration of between 1 and 2 g of calcium ion per posological unit. has been described.

In all of these patents, only calcium and vitamin D combination has been described, however combination of calcium and vitamin D with bisphosphonates, such as alendronate, in a single preparation was not considered.

When the state of art is examined, the binary combinations are observed as a solution for providing a synergistic effect. However, the necessity of combining two active agents that show synergistic effect in a single dosage form is more important. The reason for this requirement is disclosed in patent numbered US20050261250 A1 as patients receive medication in two separate time periods can not be able to adjust this time periods and therefore they are unable to adapt to the treatment. In the same patent, a marketing study which was done in 1998 is given as an example. According to the study, 75-85% of the doctors which have prescribed alendronate also

recommend vitamin D supplement. However, only 57% of osteoporosis patients are able to implement this proposal.

According to researchs, only 50% of patients with chronic diseases in developed countries fulfill the treatment requirements. [Sabaté, E. "Adherence to Long term Therapies: Evidence for Action". *World Health Organization*. Geneva, 2003. 212 pp. ISBN 92-4-154599-2]. More generally, it is determined that 40-60% of people do not take their medication as prescribed and this causes bad consequences[Heneghan CJ, Glasziou P, Perera R The Cochrane Library, ISSN 1464-780X].

Patients usually skip taking their medications with the reasons of forgetfulness, busy life, different time schedules of used drugs, not finding the proper environment to drink in everytime, not understanding the illness and treatment, communication problems with the doctor, the doctor's low ability to control the patient efficiently, patients' mistrust to the doctors or the treatment, side effects, treatment perspective of the patients to illness and the treatment, depression, cognitive disorders, financial problems and a complicated treatment regimens.

A complicated dose regime, especially multiple drug use in several times a day is one of the most significant factor to prevent the patient's complience to treatment. The patient compliance and therefore the success of treatment will be higher if the treatment regimen is much simpler. For example, the combination of the active ingredients in a single dosage form will simplify treatment and increase patient's complience to treatment[Blonde L. Compliance and Persistence With Medication Therapy. *Managed Care* (2000). Volume 9, Number 9; archives.who.int/icium/icium2004/resources/ppt/AC016.ppt.]. The negative impact of taking multiple drug on patients will also be eliminated by the use of a combined medication in the form of a single dosage form.

The present invention is directed to obtain a triple combination of alendronate (or pharmaceutically acceptable salts, derivatives or hydrates thereof), a calcium salt and vitamin D in a single dosage form so as to increase patient complience to the treatment and thus the treatment success.

The invention is characterized in that alendronate (or pharmaceutically acceptable salts, derivatives or hydrates thereof), a calcium salt and pharmaceutically acceptable, non-toxic and therapeutic amount of vitamin D are combined in a single dosage form to achieve desired effect by providing a suitable formulation of these three active agents.

However, formulations containing vitamin D are faced with stability problems because vitamin D tends to degrade upon exposure to heat, light, air, moisture, oxidizing agents or when exposed to an environment with acidic pH. This condition brings along the necessity of the selection of suitable excipients so as to ensure stability of vitamin D in tablet.

The present invention provides a stabilized pharmaceutical composition wherein alendronate (or pharmaceutically acceptable salts, derivatives or hydrates thereof), a calcium salt and vitamin D are combined in a single dosage form so as to obtain desired effect starting from increasing patient's compliance and thus the success of the treatment. The pharmaceutical preparations of the present invention may include at least one stabilizing agent to ensure stability of vitamin D.

Summary of the invention

The present invention relates to a pharmaceutical composition for use in the treatment and/or prophylaxis of diseases and conditions associated with abnormal bone resorption and/or used as a supplement characterized in that the pharmaceutical composition comprises therapeutically effective amount of alendronate or pharmaceutically acceptable salt, derivative or hydrate thereof, therapeutically effective amount of a calcium salt and therapeutically effective amount of vitamin D combined in a single dosage form.

Detailed description of the invention

The present invention provides a stabilized pharmaceutical composition in a single dosage form which comprises alendronate or pharmaceutically acceptable salt, derivative or hydrates thereof, a calcium salt and vitamin D to increase patient compliance and thus the success of treatment and to achieve the desired effect.

According to the invention, the formulations in a single dosage form comprise a certain proportion of alendronate (or pharmaceutically acceptable salt, derivative or hydrate thereof), a certain proportion of calcium salts and a certain proportion of vitamin D, and optionally one or more pharmaceutically acceptable excipients selected from diluent, binder, disintegrant, lubricant, glidant, surface active agent, stabilizing agent, sweetener and flavoring agent in which the formulation is effective for the prevention and/or treatment and/or supplementation of diseases associated with abnormal bone resorption and mentioned formulations increase the compliance of patient to treatment and thus the success of the treatment.

The term of "the use for the prevention and/or treatment and/or supplementation of disease and conditions associated with abnormal bone resorption" in the invention means in osteoporosis

treatment; to reduce the risk of fracture in bones including vertebra and hip in the postmenopausal women; to reduce the risk of bone fractures in men in the treatment of osteoporosis; Idiopathis osteoporosis; various diseases caused by osteoporosis, and glucocorticoid and steroid mediated osteoporosis, osteopenia, osteomalacia, osteogenesis imperfecta, osteocondrodysplasia, Sudek's atrophy, rheumatoid arthritis, Paget's disease, malignant tumors of bone metastases, hypercalcaemia, or in the treatment of diseases such as hyperthyroidism; and nutritional supplements especially for woman which are in growth, pregnant or breast-feeding in the period before and after menopause to maintain bone health, but the explained usage areas are not limited with these.

The terms of "a certain proportion" and "optionally" mean that in order to obtain the desired therapeutic effect, preferred amount of alendronate (or pharmaceutically acceptable salt, derivative or hydrate thereof) in the range of 0.1-980 mg, an amount of calcium salt(on the basis of elemental calcium) in the range of 250-5000 mg, an amount of vitamin D in the range of 100-100000 IU and one or more pharmaceutically acceptable excipients to be used when necessary which are selected from a group of a diluent, binder, disintegrant, lubricant, glidant, surface active agent, sweetener and flavoring agent.

The term of " a pharmaceutically acceptable salt, derivative or hydrate of alendronate" implies that salts can be selected from sodium, potassium, calcium, magnesium and ammonium salts; derivatives can be selected from ester and amide derivatives; hydrates can be selected from monohydrates, dihydrates, trihydrates, hemihydrates, ¼ hydrate, ⅓ hydrate, ⅔ hydrate, ¾ hydrate, $^{5}/_{4}$ hydrate, $^{4}/_{3}$ hydrate, $^{5}/_{2}$ hydrate and $^{3}/_{2}$ hydrate; preferably alendronate is alendronate monosodium trihydrate.

The term of "calcium salt" implies that it can be selected from carbonate, chloride, citrate, glubionat, gluceptate, gluconate, lactate, phosphate, maleate, glycerophosphate, bicarbonate or tartarate salts.

The pharmaceutically acceptable diluents can be selected from a group consisting of lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, calcium phosphate (dibasic and / or tribasic), calcium sulfate trihydrate, calcium sulfate dihydrate, calcium carbonate, kaolin, lactilol, powdered cellulose, dextrose, dextares, dextrin, sucrose, maltose, fructose, mannitol, sorbitol, xylitol. The diluent is present in the formulations preferably in the range of 0-85% by weight and more preferably 0.1-75% by weight.

The pharmaceutically acceptable binder can be selected from a group consisting of starch (potato starch, corn starch, wheat starch, etc.), sugars such as sucrose, glucose, dextrose, lactose, maltodextrin, natural and synthetic gums (e.g. acacia), gelatin, cellulose derivatives (e.g. microcrystalline cellulose, HPC, HEC, HPMC, carboxymethylcellulose, methylcellulose, ethylcellulose), polyvinylpyrollidone, polyethylene glycol, waxes, calcium carbonate, calcium phosphate, alcohols (e.g. sorbitol, xylitol, mannitol) and water. The binder is present in the formulations preferably in the range of 0-10% by weight and more preferably in the range of 0.1-5% by weight.

The pharmaceutically acceptable disintegrants can be selected from a group consisting of starch (corn starch, potato starch), sodium starch glycolate, pregelatinized starch, cellulose derivatives (e.g. croscarmellose sodium or microcrystalline cellulose), polyvinylpyrollidone, crospovidone, alginic acid, sodium alginat, clays (e.g. xanthan gum or veegum), ion-exchange resins and effervescent systems (alkali or alkaline earth metal carbonates [e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, potassium hydrogen carbonate, calcium carbonate]; sodium hydrogen sulfate, potassium hydrogen sulfate, sodium dihydrogen phosphate, succinic acid, tartaric acid, adipic acid, citric acid, water soluble polybasic organic acids or salts thereof. The disintegrant is present in the formulations preferably in the range of 0-85% by weight and more preferably in the range of 0.1-75% by weight.

Pharmaceutically acceptable lubricants can be selected from a group consisting of metallic stearates (magnesium stearate, calcium stearate, aluminum stearate, etc.), fatty acid esters (e.g. sodium stearyl fumarate), fatty acids (such as stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates (sodium lauryl sulfate, magnesium lauryl sulfate, etc.), sodium chloride, sodium benzoate, sodium acetate and talk. The lubricant is present in the formulations preferably in the range of 0-10% by weight and more preferably in the range of 0.1-5% by weight.

The pharmaceutical acceptable glidants can be selected from a group consisting of silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, tribasic calcium phosphate, metallic stearates, calcium silicate and metallic lauryl sulfate. The glidant is found in a range below 1% by weight in the formulations.

The pharmaceutically acceptable surface active agents can be selected from a group consisting of polyoxyethylene-sorbitane-fatty acid esters (polysorbates), sodium lauryl sulfate, sodium stearyl fumarate, polyoxyethylene alkyl ethers, sorbitane fatty acid esters, polyethylene glycols, polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds,

aminoacids like L-leucine, sugar esters of fatty acids, glycerides of fatty acids. The surface active agent is present in the formulations preferably in the range of 0-10% by weight and more preferably in the range of 0.1-5% by weight.

The stabilizing agent and/or agents can be selected from a group consisting of antioxidants, chelating agents, alkaline agents and photo-protectors. The stabilization agent and/or agents is present in the formulations preferably in the range of 0-85% by weight and more preferably in the range of 0.1-75% by weight.

The antioxidants can be selected from a group consisting of butylated hydroxyanisole (BHA), sodium ascorbate, butylated hydroxytoluene (BHT), sodium sulfite, gallates (e.g. propyl gallate), tocopherol, citric acid, malik acid, ascorbic acid, acetylcysteine, fumaric acid, lecithin, ascorbil palmitate, ethylenediamine tetraacetate.

The chelating agents can be selected from a group consisting of disodium EDTA, edetic acid, citric acid, sodium citrate, potassium citrate or combinations thereof.

The alkalizing agents can be selected from a group consisting of sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, sodium silicate, disodium hydrogen ortophosphate, alkali metal salts such as sodium aluminate; calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulfate, magnesium acetate, magnesium silicate, earth alkali metal salts like magnesium aluminate and primary, secondary and tertiary amines, cyclic amines, organic compounds such as N-N'-dibenzylethylenediamine, diethanoleamine, ethylenediamine, meglumine, monosodium glucamate, polyacryline sodium, sodium alginate.

The photo-protector agents can be selected from a group consisting of metal oxides such as titanium oxide, iron oxide or zinc oxide.

The pharmaceutically acceptable sweeteners can be selected from a group consisting of sucralose, sucrose, fructose, glucose, galactose, xylose, dextrose, levulose, lactose, maltose, maltodextrin, mannitol, maltitol, maltol, sorbitol, xylitol, erytritol, lactitol, isomalt, corn syrup, saccharin, saccharin salts, acesulphame potassium, aspartam, D-tryptophan, monoammonium glycerrizinate, neohesperidin dihydrochalcone, taumatine, neotam, alitam, steviosite and cyclamates. The sweetener is present in the formulations preferably in the range of 0-5% by weight and more preferably in the range of 0.1-3% by weight.

The pharmaceutically acceptable flavoring agents can be selected from a group consisting of natural, aroma oils (peppermint oil, partridge currant oil, clove bud oil, parsley oil, eucalyptus oil, lemon oil, orange oil, etc.), menthol, menthan, anetole, methyl salicylate, ocaliptole, cinnamon, 1-methyl acetate, ogenol, oxanone, alpha-irisone, marjoram, lemon, orange, propenyl guaetol acetyl, sinnamon, vanilla, timole, linalol, cinnamaldehyde glycerol acetal, N-substituted p-mentane-3-carboxyamide,3,1-methoxy propane 1,2-diol. The flavoring agent is present in the formulations preferably in the range of 0-5% by weight and more preferably in the range of 0.1-3% by weight.

In addition to these agents, pharmaceutically acceptable other excipients which are selected from resolution modulators, electrolytes, colorants and coating agents may be used in formulations.

According to the invention, the dosage form can be in the form of tablets, capsules, soluble tablets, fast-dissolving tablets, effervescent tablets, effervescent granules, fast-dissolving powder mixtures or dry powder mixture for preparation of syrup.

The formulation examples of the invention are given below. These examples are given only to explain the invention and invention is not limited to these examples.

EXAMPLES

Example 1.

Content	**Amount (mg)**
Alendronate monosodium trihydrate *	13.05
Calcium Carbonate **	2497.30
Vitamin D_3 Type 100 CWS ***	8.80
Citric Acid	985.45
Sodium Hydrogen Carbonate	720.40
Aspartam	20.00
Lemon flavor	20.00
Total weight of tablet	4265

* Equivalent to 10 mg Alendronic Acid

** Equivalent to 1000 mg Calcium

*** Equivalent to 880 IU Vitamin D_3

Granule includes approximately 100,000 IU per 1 gr

Example 2.

Content	**Amount (mg)**
Alendronate monosodium trihydrate *	45.68
Calcium Carbonate **	2497.30
Vitamin D_3 Type 100 CWS ***	14.00
Citric Acid	1290.30
Sodium Hydrogen Carbonate	912.72
Aspartam	20.00
Lemon flavor	20.00
Total weight of tablet	4800

* Equivalent to 35 mg Alendronic Acid

** Equivalent to 1000 mg Calcium

*** Equivalent to 1400 IU Vitamin D_3

Example 3.

Content	**Amount (mg)**
Alendronate monosodium trihydrate *	91.36
Calcium Carbonate **	2497.30
Vitamin D_3 Type 100 CWS ***	28
Citric Acid	1416.82
Sodium Hydrogen Carbonate	1020.52
Aspartam	20.00
Lemon flavor	20.00
Total weight of tablet	5094

* Equivalent to 70 mg Alendronic Acid

** Equivalent to 1000 mg Calcium

*** Equivalent to 2800 IU Vitamin D_3

CLAIMS

1. A pharmaceutical composition for use in the treatment and/or prophylaxis of diseases and conditions associated with abnormal bone resorption and/or used as a supplement, characterized in that the pharmaceutical composition comprises therapeutically effective amount of alendronate or a pharmaceutically acceptable salt, derivative or hydrate thereof, therapeutically effective amount of a calcium salt and therapeutically effective amount of vitamin D combined in a single dosage form.
2. The use of a pharmaceutical composition according to claim 1 characterized in that the pharmaceutical composition comprises
   - Alendronate or a pharmaceutically acceptable salt, derivative or hydrate thereof in the range of 0.1-980 mg
   - A calcium salt (on elemental calcium basis) in the range of 250-5000 mg
   - Vitamin D in the range of 100-100,000 IU and optionally one or more pharmaceutically acceptable excipients selected from a group of comprising, diluent, binder, disintegrant, lubricant, glidant, surface active compound, stabilizing agent, sweetener and flavoring agent.

3. The use of a composition according to claim 1 characterized in that the composition provides an effective combination for the prevention and/or treatment and/ or supplement of diseases and conditions associated with the abnormal bone resorption in osteoporosis treatment; to reduce the risk of fracture in bones including vertebra and hip in the postmenopausal women; to reduce the risk of bone fractures in men in the treatment of osteoporosis; Idiopathis osteoporosis; various diseases caused by osteoporosis, and glucocorticoid and steroid mediated osteoporosis, osteopenia, osteomalacia, osteogenesis imperfecta, osteocondrodysplasia, Sudek's atrophy, rheumatoid arthritis, Paget's disease, malignant tumors of bone metastases, hypercalcaemia, or in the treatment of diseases such as hyperthyroidism; and nutritional supplements especially for woman which are in growth, pregnant or breast-feeding in the period before and after menopause to maintain bone health,
4. The use of a composition according to claim1 or 2 characterized in that a pharmaceutically acceptable salt of alendronate is selected from, salts such as sodium, potassium, calcium, magnesium and ammonium salts; a pharmaceutically acceptable dertivative of alendronate is selected from derivatives, such as ester and amide

derivatives; a pharmaceutically acceptable hydrate of alendronate is selected from hydrates such as monohydrates, dihydrates, trihydrates, hemihydrates, ¼ hydrate, ⅓ hydrate, ⅔ hydrate, ¾ hydrate, $^{5}/_{4}$ hydrate, $^{4}/_{3}$ hydrate, $^{5}/_{2}$ hydrate and $^{3}/_{2}$ hydrate.

5. The use of a composition according to claim 4 characterized in that the composition comprises alendronat monosodium trihydrate as a pharmaceutically acceptable salt, derivative or hydrate of alendronate.

6. The use of a compositon according to claim 1 or 2 characterized in that the calcium salt is selected from a group consisting of carbonate, chloride, citrate, glubionate, gluceptate, gluconate, lactate, or phosphate, maleate, glycerophosphate, bicarbonate or tartarate salts.

7. The use of a compositon according to claim 1 or 2 characterized in that vitamin D is in the from of vitamin D_3.

8. The use of a compositon according to claim 1 or 2 characterized in that the diluent is selected from lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, calcium phosphate (dibasic and / or tribasic), calcium sulfate trihydrate, calcium sulfate dihydrate, calcium carbonate, kaolin, lactilol, powdered cellulose, dextrose, dextrates, dextrin, sucrose, maltose, fructose, mannitol, sorbitol, xylitol.

9. The use of a compositon according to claim 8 wherein the diluent is present in a composition preferably in the range of 0-85% by weight and more preferably 0.1-75% by weight.

10. The use of a compositon according to claim 1 or 2 characterized in that the binder is selected from starch (potato starch, corn starch, wheat starch, etc.), sugars such as sucrose, glucose, dextrose, lactose, maltodextrin, natural and synthetic gums (e.g. acacia), gelatin, cellulose derivatives such as microcrystalline cellulose, HPC, HEC, HPMC, carboxymethylcellulose, methylcellulose, ethylcellulose), polyvinylpyrollidone, polyethylene glycol, waxes, calcium carbonate, calcium phosphate, alcohols (e.g. sorbitol, xylitol, mannitol) and water.

11. The use of a composition according to claim 10 characterized in that the binder is present in a composition preferably in the range of 0-10% by weight and more preferably in the range of 0.1-5% by weight.

12. The use of a composition according to claim 1 or 2 characterized in that the disintegrant is selected from a group consisting of starch (corn starch, potato starch), sodium starch glycolate, pregelatinized starch, cellulose derivatives (such as croscarmellose sodium or microcrystalline cellulose), polyvinylpyrollidone, crospovidone, alginic acid, sodium alginat, clays (such as xanthan gum or veegum), ion-exchange resins and effervescent

systems (alkali or alkaline earth metal carbonates [such as sodium carbonate, sodium hydrogen carbonate, potassium carbonate, potassium hydrogen carbonate, calcium carbonate]; sodium hydrogen sulfate, potassium hydrogen sulfate, sodium dihydrogen phosphate, succinic acid, tartaric acid, adipic acid, citric acid, water soluble polybasic organic acids or salts thereof.

13. The use of a composition according to claim 12 characterized in that the disintegrant is present in a composition preferably in the range of 0-85% by weight and more preferably in the range of 0.1-75% by weight.

14. The use of a composition according to claim 1or 2 characterized in that the lubricant is selected from a group consisting of metallic stearates (magnesium stearate, calcium stearate, aluminum stearate, etc.), fatty acid esters(such as sodium stearil fumarate), fatty acids (such as stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates (sodium lauryl sulfate, magnesium lauryl sulfate, etc.), sodium chloride, sodium benzoate, sodium acetate and talk.

15. The use of a composition according to claim 14 characterized in that the lubricant is present in a composition preferably in the range of 0-10% by weight and more preferably in the range of 0.1-5% by weight.

16. The use of a composition according to claim 1 or 2 characterized in that the glidant is selected from a group consisting of silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, tribasic calcium phosphate, metallic stearates, calcium silicate and metallic lauryl sulfate.

17. The use of a composition according to claim 16 characterized in that the glidant is found in a range below 1% by weight.

18. The use of a composition according to claim 1 or 2 characterized in that the surface active agent is selected from a group consisting of polyoxyethylene-sorbitane-fatty acid esters(polysorbates), sodium lauryl sulfate, sodium stearil fumarate, polyoxyethylene alkyl ethers, sorbitane fatty acid esters, polyethylene glycols, polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, amino acids like L-leucine, sugar esters of fatty acids, glycerides of fatty acids.

19. The use of a composition according to claim 18 characterized in that the surface active agent is present in a composition preferably in the range of 0-10% by weight and more preferably in the range of 0.1-5% by weight.

20. The use of a composition according to claim 1 or 2 characterized in that the stabilizing agent and/or agents is selected from a group antioxidants consisting of butylated hydroxyanisole (BHA), sodium ascorbate, butylated hydroxytoluene (BHT), sodium sulfite, gallates (e.g. propyl gallate), tocopherol, citric acid, malik acid, ascorbic acid, acetylcysteine, fumaric acid, lecithin, ascorbil palmitate, ethylenediamine tetraacetate.
21. The stabilizing agent and/or agents is present in the formulations preferably in the range of 0-85% by weight and more preferably in the range of 0.1-75% by weight.
22. The use of a composition according to claim 1 or 2 characterized in that the stabilizing agent is selected from a group of the chelating agents consisting of disodium EDTA, edetic acid, citric acid, sodium citrate, potassium citrate or combinations thereof.
23. The use of a composition according to claim 1 or 2 characterized in that the stabilizing agent is selected from a group of the alkalizing agents consisting of sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, sodium silicate, disodium hydrogen ortophosphate, alkali metal salts such as sodium aluminate; alkali metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulfate, magnesium acetate, magnesium silicate, magnesium aluminate and primary, secondary and tertiary amines, cyclic amines, organic compounds such as N-N'-dibenzylethylenediamine, diethanoleamine, ethylenediamine, meglumine, monosodium glucamate, polyacryline sodium, sodium alginate.
24. The use of a composition according to claim 1 or 2 characterized in that the stabilizing agent is selected from a group of the photo-protector agents consisting of metal oxides such as titanium oxide, iron oxide or zinc oxide.
25. The use of a composition according to claim 20 or 23 characterized in that the stabilizing agent is present in a composition preferably in the range of 0-85% by weight and more preferably in the range of 0.1-75% by weight.
26. The use of a composition according to claim 1 or 2 characterized in that the sweetener is selected from sucralose, sucrose, fructose, glucose, galactose, xylose, dextrose, levulose, lactose, maltose, maltodextrin, mannitol, maltitol, maltol, sorbitol, xylitol, erythritol, lactitol, isomalt, corn syrup, saccharin, saccharin salts, acesulphame potassium, aspartam, D-tryptophan, monoammonium glycerrizinate, neohespheridin dihydrochalcon, taumatine, neotam, alitam, steviosite and cyclamates.

27. The use of a composition according to claim 25 characterized in that the sweetener is present in a composition preferably in the range of 0-5% by weight and more preferably in the range of 0.1-3% by weight.

28. The use of a composition according to claim 1 or 2 characterized in that the flavoring agent is selected from natural, aroma oils (peppermint oil, partridge currant oil, clove bud oil, parsley oil, eucalyptus oil, lemon oil, orange oil, etc.), menthol, menthan, anetole, methyl salicylate, ocaliptole, cinnamon, 1-methyl acetate, ogenol, oxanone, alpha-irisone, marjoram, lemon, orange, propenyl guaetol acetyl, sinnamon, vanilla, timole, linalol, cinnamaldehyde glycerol acetal, N-substituted p-mentane-3-carboxyamide,3,1-methoxy propane 1,2-diol.

29. The use of a composition according to claim 27 characterized in that the flavoring agent is present in a composition preferably in the range of 0-5% by weight and more preferably in the range of 0.1-3% by weight.

30. The use of a composition according to any of the preceeding claims characterized in that the dosage form is in the form of tablets, capsules, fast dissolving tablets, effervescent tablets, effervescent granules, fast dissolving granules, fast-dissolving powder mixtures or dry powder mixture for preparation of a syrup.

31. The use of a composition according to any preceeding claims characterized in that the composition combines three active agents together in a single dosage form and so the composition increases the patient's compliance to the treatment and thus the success of the treatment.

32. The use of a composition according to any of the preceeding claims characterized in that the composition comprises,

Alendronate monosodium trihydrate in the range of 0.1-980 mg

Calcium carbonate in the range of 250- 5000 mg

Vitamin D in the range of 100-100,000 IU

Citric acid in the range of 0-85% by weight

Sodium hydrogen carbonate in the range of 0-85% by weight

Aspartame in the range of 0-5% by weight

Lemon flavor in the range of 0-5% by weight.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2010/000024

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/663 A61K31/593 A61K33/06 A61K45/06 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

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, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 200649 Thomson Scientific, London, GB; AN 2006-472934 XP002576493 & CN 1 729 995 A (SHIJIAZHUANG PHARM GROUP OUYI PHARM CO) 8 February 2006 (2006-02-08) abstract	1,2,30, 31
X	WO 2004/087038 A1 (PROCTER & GAMBLE [US]; CAWTHRAY RICHARD JAMES [FR]; DIFABRITUS VINCENT) 14 October 2004 (2004-10-14) example 4	1-32

-/--

[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
12 April 2010	28/04/2010

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, Fax: (+31–70) 340–3016	Baurand, Petra

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2010/000024

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MONDY K, POWDERLY W G, CLAXTON S A, YARASHESKI K H, ROYAL M, STONEMAN J S, HOFFMANN M E, TEBAS P: "Alendronate, vitamin D, and calcium for the treatment of osteopenia/osteoporosis associated with HIV infection" JAIDS JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, vol. 38, no. 4, 1 April 2005 (2005-04-01), pages 426-431, XP002576494 page 426, abstract	1-32
Y	BRAZIER M ET AL: "BIOLOGICAL EFFECTS OF SUPPLEMENTATION WITH VITAMIN D AND CALCIUM IN POSTMENOPAUSAL WOMEN WITH LOW BONE MASS RECEIVING ALENDRONATE" CLINICAL DRUG INVESTIGATION, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 22, no. 12, 1 January 2002 (2002-01-01), pages 849-857, XP008033378 ISSN: 1173-2563 page 850, right-hand column, paragraph 4	1-32
Y	Merck & Co., Inc.: "Fosamax Plus D"[Online] 2005, XP002576495 HIGHLIGHTS OF PRESCRIBING INFORMATION Retrieved from the Internet: URL:www.fosamax.com> [retrieved on 2010-04-06] the whole document	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2010/000024

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 1729995 A	08-02-2006	NONE	
WO 2004087038 A1	14-10-2004	AU 2004226326 A1	14-10-2004
		BR PI0408770 A	04-04-2006
		CA 2517102 A1	14-10-2004
		CN 1764430 A	26-04-2006
		EP 1605890 A1	21-12-2005
		HR 20050824 A2	28-02-2006
		HU 3526 U	29-12-2008
		IS 8019 A	12-09-2005
		JP 2006520615 T	14-09-2006
		KR 20050111610 A	25-11-2005
		MA 27723 A1	02-01-2006
		MX PA05010198 A	08-11-2005
		NZ 541856 A	30-03-2007
		RU 2314786 C2	20-01-2008