Med Choice

Alendronic Acid

70 mg Film-coated Tablet

Calcium citrate / Cholecalciferol (Vitamin D3)

1.5 g / 200 IU Tablet

Fosdin® Pack

Anti-osteoporosis / Mineral / Vitamin

Formulation

Each weekly film-coated tablet contains:
Alendronate monosodium trihydrate, USP..... 91.37 mg
(equivalent to 70 mg of free acid)
Excipients..... q.s.p.
Each daily tablet contains:
Calcium (as citrate tetrahydrate), USP.....1.5 g
(equivalent to 315 mg of calcium ion)
Cholecalciferol (Vitamin D3), USP..... 200 IU
Excipients..... q.s.p.

Product Description

Alendronic acid 70 mg film-coated tablet: creamy white rounded tablet.
Calcium citrate / Cholecalciferol (Vitamin D3) 1.5 g / 200 IU tablet: white to creamy white oblong tablet.

Pharmacological actions

Pharmacodynamics
Alendronic acid

The bone tissue is reabsorbed by osteoclasts within the normal cellular process. Alendronic acid is a synthetic bisphosphonate located in the bone resorption zones that inhibits the activity of the osteoclasts reducing bone turnover; therefore, an increase in bone mass is obtained. Under therapy, normal bone tissue develops, and alendronate is deposited in the bone-matrix in pharmacologically inactive form. Likewise, a binding ten times higher than that of osteoclasts has been observed resulting in reduced bone turnover.

Calcium citrate and vitamin D3

Calcium is an essential component for the function of various systems and organs of the human body (muscles, nervous system, cardiovascular, renal), among others. The bone is the biggest calcium deposit in the human body in the form of hydroxyapatite. There is an active calcium exchange among the bones and plasma fluid. As calcium is pivotal for the functioning of our organism, when there is a deficiency in plasma due to low intake or some organic alterations, the main need is met by the bone which gives its calcium to the blood stream. To maintain normal calcium levels and bone quality, it is necessary to have an adequate calcium supplementation daily.
Vitamin D is a significant factor in calcium homeostasis; 20% or 30% of the calcium absorption in the small intestine depends on the presence of this vitamin. Vitamin D3 is necessary for the formation of the normal bone tissue. The absence of this vitamin may be due to lack of exposure to the sunlight and inadequate food intake. Vitamin D, calcitonin, and paratohormone regulate the calcium level in blood according to the needs of the body.

Pharmacokinetics
Alendronic acid

Preclinically, alendronate is not metabolised in animals and is cleared from the plasma by uptake into the bone and elimination via renal excretion. Although soon after administration, the drug distributes widely in the body. This transient state is rapidly followed by a nonsaturable redistribution to skeletal tissues. Oral bioavailability is about 0.9% to 1.8%, and food markedly inhibits oral absorption. Removal of the drug from bone reflects the underlying rate of turnover of the skeleton. Renal clearance appears to involve both glomerular filtration and a specialised secretory pathway. Clinically, the pharmacokinetics of alendronate have been characterised almost exclusively based on urinary excretion data because of the extremely low concentrations achieved after oral administration. After intravenous administration of radiolabelled alendronate to women, no metabolites of the drug were detectable and urinary excretion was the sole means of elimination. About 40% to 60% of the dose is retained for a long time in the body, presumably in the skeleton, with no evidence of saturation or influence of one intravenous dose on the pharmacokinetics of subsequent doses. The oral bioavailability of alendronate in the fasted state is about 0.7%, with no significant difference between men and women. Absorption and disposition appear independent of dose. Food substantially reduces the bioavailability of oral alendronate; otherwise, no substantive drug interactions have been identified.

Calcium citrate and Vitamin D3

Calcium absorption from the GI tract requires Vitamin D. Available elemental calcium depends on the salt form used, dose administered and the presence of an acid environment in the stomach. Elimination is primarily in the feces as unabsorbed calcium and the kidneys eliminate 20%.

Many vitamin D analogs are readily absorbed from the GI tract following oral administration if fat absorption is normal. The presence of bile is required for absorption of ergocalciferol and the extent of GI absorption may be decreased in patients with hepatic, biliary, or GI disease (e.g., Crohn's disease, Whipple's disease, sprue). Because vitamin D is fat soluble, it is incorporated into chylomicrons and absorbed via the lymphatic system; approximately 80% of ingested vitamin D appears to be absorbed systemically through this mechanism, principally in the small intestine. Although some evidence suggested that intestinal absorption of vitamin D may be decreased in geriatric adults, other evidence did not show clinically important age-related alterations in GI absorption of the vitamin in therapeutic doses. It currently is not known whether aging alters the GI absorption of physiologic amounts of vitamin D/Vitamin D analogs.

After absorption, ergocalciferol and cholecalciferol enter the blood via chylomicrons of lymph and then associate mainly with a specific alpha-globulin (vitamin D-binding protein). The hydroxylated metabolites of ergocalciferol and cholecalciferol also circulate associated with the same alpha-globulin. 25-Hydroxylated ergocalciferol and cholecalciferol are stored in fat and muscles for prolonged periods. Once vitamin D enters systemic circulation from lymph via the thoracic duct or from skin, it accumulates in the liver within a few hours.

The metabolites of vitamin D analogs are excreted principally in bile and feces. Although some vitamin D that is excreted in bile is reabsorbed in the small intestine, enterohepatic circulation does not appear to be an important mechanism for conservation of the vitamin.

Indications and uses

For the treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis.

Interactions with Drugs or Food
Alendronic Acid:

Its absorption may be interfered if taken with food, nutritional supplements (calcium) or drugs (antacids) so intake of alendronic acid must be done 30 minutes apart. Intravenous ranitidine doubles the bioavailability of oral alendronic acid; its clinical significance is unknown.
Salicylate compounds: increased incidence of adverse events of the upper gastrointestinal tract was reported on individuals taking more than 10 mg of alendronic acid daily with salicylate compounds.
Aminoglycosides: Increased risk of hypoglycemia.
Calcium and iron salts reduce absorption of alendronic acid.

Calcium citrate and vitamin D3:

Absorption of some drugs may be modified due to the presence of calcium in high doses, that is why these medications should be taken 1 or 2 hours from the calcium citrate/vitamin D3 dose.
Alcohol and caffeine intake and tobacco use in high amounts may decrease calcium citrate/vitamin D3 absorption.
Antacids containing aluminum: concomitant use may increase aluminum absorption.
Calcium channel blockers: response of verapamil et al to the body may be reduced.
High amounts of food intake with fiber, grains, cereals or phytates may lead to a reduced calcium absorption forming non-resolvable complexes by enteral route.
Calcitonin: Its administration must have 4 or more hours difference from the calcium citrate/vitamin D3 dose. Otherwise, hypercalcemia treatment with calcitonin may be antagonized.
Thiazide diuretics: may induce hypercalcemia by reducing calcium excretion.
Estrogens: increase calcium absorption.
Bisphosphonates: calcium citrate/vitamin D3 can decrease absorption of bisphosphonates. Patients are advised to take bisphosphonates at 30 minutes before calcium citrate/vitamin D3 dose.
Phenytoin: reduced bioavailability of both. Doses of calcium citrate/vitamin D3 and phenytoin should be taken at least 2 hours apart.
Fluoroquinolones: absorption may be reduced due to its chelation effect, thus reducing quinolone concentrations in serum and urine.
Sodium fluoride: forms non-resolvable complexes decreasing absorption of both. These medications should be administered 2 hours apart.
Cellulose sodium phosphate: its co-administration may diminish the effect of cellulose sodium phosphate for the prevention of hypercalciuria.
Potassium phosphate – sodium phosphate: concomitant use may increase the potential of calcium deposits in soft tissues if serum calcium is high.
Iron: decreases absorption of calcium supplements.
These medications should be administered 2 hours apart.
Gallium nitrate: reduces calcium levels in the blood.
Calcium or magnesium-containing preparations: serum concentrations of calcium or magnesium may increase in patients with renal failure leading to hypercalcemia or hypermagnesemia.
Dairy products and Sodium bicarbonate: excessive and long concurrent use with calcium supplements may result to milk-alkali syndrome.
Tetracyclines: its absorption may be reduced by the formation of non-resolvable complexes or increase in gastric pH.
These medications should be administered 1 to 2 hours apart.
Vitamin A: doses higher than 7500 RE or 25000 IU daily may stimulate bone loss and counteract the effects of calcium supplementation and may cause hypercalcemia.
Vitamin D, calciferol and calcitriol, in large doses may result to an increased intestinal absorption of calcium.
Serum phosphate: (laboratory tests) shows a decrease from normal levels on prolonged calcium administration.

Contraindications
Alendronic Acid:

Except under special circumstances, alendronic acid should not be used when the following medical problems exist: Gastrointestinal diseases such as duodenitis, dysphagia, symptomatic gastroesophageal reflux disease, pyrosis, gastritis, gastroesophageal reflux, hiatal hernia and peptic ulcer.
Alendronic acid may exacerbate the symptoms.
Patients with a creatinine clearance lower than 35 mL per minute (0.58 mL/sec): alendronate is not recommended since its elimination may be reduced.
Hypersensitivity to alendronic acid.
Risk-benefit factors must be considered when the following medical problems exist:
Hypocalcemia (primary or secondary) or vitamin D deficiency (alendronic acid may exacerbate these conditions). Hypocalcemia and Vitamin D deficiency must be corrected before starting therapy with alendronic acid.

Calcium citrate and Vitamin D3:

Except under special circumstances this medication should not be used when the following problems exist:
Hypercalcemia (primary or secondary), hypercalciuria, kidney calculus. There is a risk of exacerbation when taking this medication.
Sarcoidosis. It may potentiate hypercalcemia.
Risk–benefit factors must be considered when the following medical problems exist: Dehydration or electrolyte imbalance.
Chronic diarrhea or gastrointestinal malabsorption.
Hypercalcemia.
Patients with end stage renal failure may develop hypercalcemia when given calcium with meals. Serum calcium levels must be monitored during the dose adjustment period. History of kidney stones.
Patients with idiosyncrasy and hypersensitivity to any component.

Precautions
Alendronic Acid:

Carcinogenicity/Tumorigenicity: In a 2-year oral carcinogenicity study, parafollicular cell (thyroid) adenomas were increased in high-dose male rats at doses of 1 and 3.75 mg/kg body weight.
These doses are equivalent to approximately 0.3 and 1 times a 40 mg human daily dose based on surface area, mg/m^2.
Mutagenicity: Alendronic acid was not genotoxic in the in vitro microbial mutagenesis assay with and without metabolic activation. In an in vitro chromosomal aberration assay in Chinese hamster ovary cells, however, alendronic acid was weakly positive at concentrations ≥ 5 mm in the presence of cytotoxicity.

Pregnancy/reproduction:
Fertility: Alendronic acid had no effect on the fertility or reproductive performance (male or female) in rats at oral doses up to 5 mg/kg/day.
Pregnancy: no proper and well-controlled studies have been conducted for alendronic acid. Reproductive studies in rats showed decreased post-implantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/sq m. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/sq m). Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/sq m) resulting in delays and failures of delivery.
Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment.
Pregnancy Category C.
Nursing: It is not known whether alendronic acid is excreted into human breast milk. Given the indication, alendronic acid should not be used by breast-feeding women.
Pediatrics: Safety and efficacy have not been established. Alendronic acid is not indicated for use in children.
Elderly: In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronic acid. Therefore no dosage adjustment is necessary for the elderly.

Adverse reactions
Alendronic acid:

Reactions requiring medical care:
More frequent incidence: abdominal pain
Less frequent incidence: dysphagia, gastric pyrosis, irritation, pain or ulceration of esophagus, muscle pain
Rare incidence: rash
Reactions requiring medical care, only if they are uncomfortable or recurrent;
Less frequent incidence: distended abdomen, constipation, diarrhea, flatulence, headache, nausea

Calcium citrate and vitamin D3:
For vitamin D:

Early symptoms of vitamin D toxicity related to hypercalcemia:
Bone pain, constipation (usually more frequent in children and teenagers), diarrhea, somnolence, dry mouth, continuous headache, increased thirst, increased frequency (especially at night) or increased quantity of urine, irregular heartbeats, loss of appetite, metallic taste, muscle pain, nausea and vomiting (usually more frequent in children and teenagers), pruritus, unusual fatigue.
Late symptoms of vitamin D toxicity related to hypercalcemia:
Bone pain, cloudy urine, conjunctivitis, decreased libido, ectopic calcification, high fever, high blood pressure, increased sensitivity of eyes to the light or eye irritation. Irregular heartbeats, itching, lethargy, loss of appetite, muscle pain, nausea and vomiting and pancreatitis, psychosis, rhinorrhea, loss of weight.

For Calcium:

Rare incidence:
Syndrome of acute hypercalcemia, calcified renal calculus, and vomiting, unusually large amount of urine or increased frequency of urination.
Early symptoms of hypercalcemia:
Severe constipation, dry mouth, continuous headache, increased thirst, irritability, loss of appetite, mental depression, metallic taste, unusual tiredness.
Late symptoms of hypercalcemia:
Confusion, somnolence, high blood pressure, increased sensitivity of eyes or skin to light, especially with hemodialysis patients.
Irregular, rapid or slow heartbeats, nausea.

Possible side effects

Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Patients are advised to contact a physician if pain, weakness or discomfort in the thigh, hip or groin is experienced. This may be an early indication of a possible fracture of the thigh bone.

Posology and method of administration

The optimal duration of bisphosphate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Fosdin® pack on individual patient basis, particularly after 5 or more years of use.

Dosing and route of administration

Usual dose in adults:
Treatment of osteoporosis in men and post-menopausal women:
Weekly tablet (70 mg alendronic acid) should be taken once a week without food, at least 30 minutes before the first food, drink or drug.
Daily tablet (calcium citrate and vitamin D3) should be taken every day, preferably with food (lunch or dinner), never with the weekly tablet (70 mg alendronic acid).

NOTE: The weekly tablet (70 mg alendronic acid) should be taken without food at least 30 minutes before taking any food or drug by oral route. The weekly tablet (70 mg alendronic acid) should only be taken with a glass of plain water (not mineral water).

After the intake of the weekly tablet (70 mg alendronic acid), the patient should stay sitting or standing up and avoid lying down.
The weekly tablet (70 mg alendronic acid) should not be chewed or dissolved in the mouth.
It is not necessary to make adjustments to the dosage in elderly patients or patients with mild or moderate renal failure (clearance of creatinine from 35 to 60 mL/min).
The daily tablet (calcium citrate and vitamin D3) should be taken once a day for 7 days.
Usual Pediatric dose:
Safety and efficacy have not been established for alendronic acid.

Treatment of overdosage
Alendronic acid:

No specific information is available on the treatment of overdosage with alendronic acid. Oral overdosage may cause hypocalcemia, hypophosphatemia and adverse gastrointestinal reactions such as gastric discomfort, pyrosis, esophagitis, ulcer.
Administration of milk or antacids should be considered for overdosage of alendronic acid. Vomiting should not be induced since gastroesophagic irritation may occur. Patient should remain fully upright.

Calcium citrate + Vitamin D3:

If serum calcium concentration is more than 2.9 mmol per liter (12 mg per 100 mL) immediate measures may be required: Hydrate patient with 0.9% sodium chloride injection and induce diuresis with furosemide or ethacrynic acid. Monitor the patient with ECG.

Presentation

Each pvc/pvdc amber thermo-sealed aluminum blister pack of Fosdin® for weekly treatment contains:
1 film-coated tablet for weekly consumption of Alendronic acid and 7 tablets for daily consumption of:
Calcium (as citrate tetrahydrate) + Cholecalciferol (Vitamin D3).
(Box of 8 tablets)

Storage conditions

Keep in a cool and dry place.
Store at temperatures not exceeding 30°C.
Keep out of reach of children.

"For suspected drug reaction, report to the FDA at www.fda.gov.ph. The patient is advised to seek immediate medical attention at the first sign of any adverse drug reaction."

Caution: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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