ALENDRONATE (Systemic)

Introduction

Revised: 01/10/2001

VA CLASSIFICATION (Primary/Secondary)¾HS301/HS303

Commonly used brand name(s):Fosamax.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Bone resorption inhibitor 1.

Indications

Accepted

Osteoporosis, male (treatment)¾Alendronate is indicated for the use in treatment of osteoporosis in men to increase bone mass. 34

Osteoporosis, glucocorticoid-induced (treatment adjunct)¾Alendronate is indicated for the treatment of osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 milligrams or more of prednisone and who have a low bone mineral density. 33 Alendronate should be used in conjunction with adequate amounts of vitamin D and calcium. 33

Osteoporosis, postmenopausal (treatment adjunct)¾Alendronate is indicated for the treatment of osteoporosis in postmenopausal women, as confirmed by the finding of low bone mass (at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture [1, 4, 5, 6, 12, 13, 20].

Alendronate should be used in conjunction with adequate intake of calcium (1 to 1.5 grams of elemental calcium a day [21]) and vitamin D (400 to 800 Units a day [22]) to aid in the prevention of progressive loss of bone mass [18, 19].

Osteoporosis, postmenopausal (prophylaxis)¾Alendronate is indicated for the prevention of osteoporosis in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture [32].

Alendronate should be used in conjunction with adequate intake of calcium (1 to 1.5 grams of elemental calcium a day [21]) and vitamin D (400 to 800 Units a day [22]) to aid in the prevention of progressive loss of bone mass [18, 19].

Paget's disease of bone (treatment)¾Alendronate is indicated for the treatment of Paget's disease in patients with alkaline phosphatase concentrations at least two times the upper limit of normal, those who are symptomatic, or those at risk for future complications from the disease [1, 2, 3, 20, 26].

Signs and symptoms of Paget's disease may include bone pain, deformity, and/or fractures; increased concentrations of N-telopeptide of type I collagen, serum alkaline phosphatase, and/or urinary hydroxyproline; neurologic disorders associated with skull lesions and spinal deformities; and elevated cardiac output and other vascular disorders associated with increased vascularity of bones [15, 16, 26].

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾325.12 [1]

Mechanism of action/Effect:

Animal studies indicate that alendronate shows preferential localization to sites of bone resorption where it inhibits osteoclast activity, but does not interfere with osteoclast recruitment or attachment [1].

Studies in rats and mice showed that normal bone mass was formed on top of alendronate, thereby incorporating alendronate in the bone matrix [1].

Alendronate is not pharmacologically active when incorporated; therefore, it must be administered continuously to suppress osteoclasts on newly formed resorption surfaces [1].

Studies in baboons and rats indicate that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled) [1].

In addition, bone formation exceeds bone resorption at these remodeling sites, leading to increased bone mass [1].

Data from long-term animal studies indicate that the bone formed during alendronate therapy is of normal quality [1, 9].

Absorption:

Studies in humans showed that mean oral bioavailability in women was 0.7% for doses ranging from 5 to 40 mg when alendronate was administered after an overnight fast and 2 hours before a standardized breakfast [1].

Oral bioavailability in men was 0.59% following administration of a 10-mg dose 2 hours before the first meal of the day 1.

In postmenopausal women, bioavailability was decreased by approximately 40% when 10 mg of alendronate was given either 30 minutes or 1 hour before a standardized breakfast, when compared with dosing 2 hours before eating 1.

Bioavailability was negligible when alendronate was administered with or up to 2 hours after a standardized breakfast 1.

Concomitant administration with coffee or orange juice reduced bioavailability by approximately 60% 1.

Distribution:

Studies in male rats given an intravenous dose of 1 mg per kilogram of body weight (mg/kg) showed that alendronate was transiently distributed to soft tissue, but was then rapidly redistributed to bone or excreted in the urine 1.

Vol D¾At least 28 L in humans 1.

Protein binding:

High (approximately 78% in human plasma) 1.

Biotransformation:

There is no evidence that alendronate is metabolized in humans or animals 1.

Duration of action:

In osteoporosis¾Six weeks after a single 5-mg intravenous dose 17.

In Paget's disease of bone¾Six months after a single 5-mg intravenous dose 17.

Elimination:

Renal; approximately 50% of an intravenous dose was excreted in urine within 72 hours, with little or none of the dose recovered in the feces 10.

Following a single 10-mg intravenous dose, the renal clearance of alendronate was 71 mL per minute (mL/min); the systemic clearance did not exceed 200 mL/min 1.

Plasma concentrations fell by more than 95% within 6 hours following intravenous alendronate administration 1.

Precautions to Consider

Carcinogenicity/Tumorigenicity

In a 92-week carcinogenicity study in mice given alendronate at doses of 1, 3, and 10 mg per kilogram of body weight (mg/kg) per day (males) or 1, 2, and 5 mg/kg per day (females) (0.5 to 4 times the 10-mg human dose based on body surface area), harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose females 1.

In a 2-year carcinogenicity study in rats, parafollicular cell (thyroid) adenomas were increased in high-dose males at doses of 1 and 3.75 mg/kg (1 and 3 times the 10-mg human dose, respectively, based on body surface area) 1.

Mutagenicity

Alendronate was not genotoxic in the in vitro microbial mutagenesis assay with and without metabolic activation, in an in vitro mammalian cell mutagenesis assay, in an in vitro alkaline elution assay in rat hepatocytes, and in an in vivo chromosomal aberration assay in mice 1.

However, in an in vitro chromosomal aberration assay in Chinese hamster ovary cells, alendronate was weakly positive at concentrations ³ 5 mmol in the presence of cytotoxicity 1.

Pregnancy/Reproduction

Fertility¾Studies in male and female rats given oral alendronate doses of up to 5 mg/kg per day (4 times the 10-mg human dose based on body surface area) found no effect on fertility 1.

Pregnancy¾Adequate and well-controlled studies in humans have not been done 1.

Reproduction studies in rats given alendronate doses ranging from 1 to 10 mg/kg (1 to 9 times the 10-mg human dose based on body surface area) showed decreased postimplantation survival at 2 mg/kg per day and decreased body weight gain in normal pups at 1 mg/kg per day 1.

Sites of incomplete fetal ossification of vertebrae (cervical, thoracic, and lumbar), skull, and sternebrae were statistically significantly increased in rats beginning at doses of 10 mg/kg per day 1.

No similar fetal effects were seen when pregnant rabbits were treated at doses of up to 35 mg/kg per day (50 times the 10-mg human dose based on body surface area) 1.

Both total and ionized calcium decreased in pregnant rats at doses of 15 mg/kg per day (13 times the 10-mg human dose based on body surface area), resulting in delays and failures of delivery 1.

Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg per day (0.5 times the recommended human dose) when rats were treated from before mating through gestation 1.

Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg per day for varying periods of time, ranging from treatment only during premating to treatment only during early, middle, or late gestation; these deaths were decreased but not eliminated by cessation of treatment 1.

Calcium supplementation, either in the drinking water or by minipump, did not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; intravenous calcium supplementation prevented maternal, but not fetal, deaths 1.

FDA Pregnancy Category C 1.

Breast-feeding

It is not known whether alendronate is distributed into human breast milk 1.

Alendronate was distributed into the milk of rats after an intravenous dose 1.

Pediatrics

No information is available on the relationship of age to the effects of alendronate in pediatric patients. Safety and efficacy have not been established 1.

Geriatrics

Appropriate studies performed to date have not demonstrated geriatrics-specific problems that would limit the usefulness of alendronate in the elderly 1.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Dietary supplements (including calcium) or 9

Food and beverages or 9

Medications, oral (including antacids)

(simultaneous use may interfere with the absorption of alendronate; patients should be advised to take alendronate at least 30 minutes before taking other medications, food, or beverages 1)

Ranitidine

(intravenous ranitidine was shown to double the bioavailability of oral alendronate; the clinical significance of this increased bioavailability is not known 1, 9)

>>

Salicylates or salicylate-containing compounds

(an increased incidence of upper gastrointestinal adverse events was reported in individuals taking more than 10 mg of alendronate a day concurrently with salicylates or salicylate-containing compounds 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

With physiology/laboratory test values

Calcium, serum, and

Phosphate, serum

(alendronate has been reported to cause a 2% reduction in serum calcium concentrations and a 4 to 6% reduction in serum phosphate concentrations in the first month after initiation of therapy; no further decreases have been observed during the 3-year duration of therapy 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist

>> Gastrointestinal diseases such as duodenitis, dysphagia, symptomatic esophageal diseases, frequent heartburn, gastritis, gastroesophageal reflux disease, hiatal hernia, or ulcers 27

(alendronate may exacerbate these conditions 14)

>> Renal function impairment when creatinine clearance is < 35 mL per minute (0.58 mL/sec)

(use is not recommended because elimination of alendronate may be reduced; greater accumulation of alendronate in the bone may be expected 1)

>> Sensitivity to alendronate 1

Risk-benefit should be considered when the following medical problems exist

Hypocalcemia or

Vitamin D deficiency

(alendronate may exacerbate these conditions; hypocalcemia and vitamin D deficiency should be corrected before alendronate therapy is begun 1)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

For Paget's disease

Alkaline phosphatase, serum or 1

Hydroxyproline, urinary 2, 3

(serum alkaline phosphatase determinations recommended every 3 to 6 months; urinary hydroxyproline determinations recommended every 6 to 12 months; values should decrease with treatment [1], [25])

Calcium, serum

(determinations recommended every 3 to 4 months; values should increase with treatment [31])

N-telopeptide of type I collagen, urinary

(determinations recommended every 3 to 6 months; values should decrease with treatment [26], [28])

For postmenopausal osteoporosis

Bone mineral density

(determinations recommended every 1 to 2 years to assess effectiveness of therapy; clinicians recommend monitoring hip, femur, or spine; values should increase with treatment)

Calcium, serum or [29]

Creatinine, serum [30]

(determinations recommended every 6 to 12 months; serum calcium values should increase with treatment)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence more frequent

Abdominal pain 1, 5

Incidence less frequent

Dysphagia (difficulty swallowing) 1, 7, 11; heartburn 1; irritation, pain, or ulceration of the esophagus 2, 4, 5, 6, 7, 11, 23, 24; muscle pain 1

Note: There have been reports of severe irritation, pain, or ulceration of the esophagus in some patients 7, 11.

Presenting symptoms may include dysphagia and/or heartburn7, 8, 11.

Alendronate therapy should be discontinued if these symptoms develop 14.

Incidence rare

Skin rash 1, 6

Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

Abdominal distension (full or bloated feeling) 1; constipation 1, 5; diarrhea 1, 5; flatulence (gas); headache 1; nausea 1

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Alendronate (Systemic) .

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to alendronate

Pregnancy¾Studies in animals showed decreased weight gain, incomplete fetal ossification, decreased survival of the fetus, and delays in delivery

Breast-feeding¾Should not be given to nursing women because alendronate is distributed in milk of rats

Other medications, especially aspirin or compounds that contain aspirin

Other medical problems, especially gastrointestinal diseases or severe renal function impairment

Proper use of this medication

>> Taking with 6 to 8 ounces of plain water on empty stomach, at least 30 minutes before first food, beverage, or medication of the day

>> Not lying down for at least 30 minutes after taking alendronate

Possible need for calcium and vitamin D supplementation

>> Proper dosing

Missed dose: Not taking later in the day; continuing usual schedule the next morning

>> Proper storage

Side/adverse effects

Signs of potential adverse effects, especially abdominal pain; heartburn; dysphagia; irritation, pain, or ulceration of the esophagus; muscle pain; and skin rash

General Dosing Information

To facilitate delivery of alendronate to the stomach and reduce esophageal irritation, patients should not lie down for at least 30 minutes after taking alendronate 1 and until after their first food of the day 34.

Safety of treatment for longer than 4 years has not been studied 1.

Diet/Nutrition

Alendronate should be taken with 6 to 8 ounces of plain water 1.

Absorption of alendronate is best when taken in the morning, at least 30 minutes before the first food, beverage, or medication of the day 1.

Food and beverages such as mineral water, coffee, tea, or juice will decrease the absorption of alendronate 1.

Waiting longer than 30 minutes will improve the absorption of alendronate 1.

Alendronate should not be taken at bed time or before arising for the day. 34

Some patients may be instructed to take calcium or vitamin D supplements if their diet is inadequate 1.

These supplements should be taken 30 minutes or longer after taking alendronate 1.

Oral Dosage Forms

ALENDRONATE TABLETS

Usual adult dose

Glucocorticoid-induced osteoporosis; men and women (treatment)¾Oral, 5 mg once a day in the morning, at least thirty minutes before the first food, beverage, or medication. 33 In postmenopausal women not receiving estrogen, the dosage is 10 mg once a day in the morning, at least thirty minutes before the first food, beverage, or medication. 33 The dose should be taken with six to eight ounces of plain water. 33, 34

Osteoporosis, male (treatment)¾Oral, 10 mg once a day in the morning, at least thirty minutes before the first food, beverage, or medication. 34 34

Paget's disease of bone (treatment)¾Oral, 40 mg once a day in the morning 2, 3 , at least thirty minutes before the first food, beverage, or medication 1.

Treatment should continue for six months 1.

Re-treatment may be considered for certain patients following a six-month post-treatment evaluation period [1].

Postmenopausal osteoporosis (treatment) ¾Oral, 10 mg once a day in the morning [4, 5, 6 or 70 mg once a week in the morning, administered at least thirty minutes before the first food, beverage, or medication [1].

The dose should be taken with six to eight ounces of plain water [1, 34].

Postmenopausal osteoporosis (prophylaxis) ¾Oral, 5 mg once a day in the morning or 35 mg once a week in the morning, administered at least thirty minutes before the first food, beverage, or medication [34, 32].

The dose should be taken with six to eight ounces of plain water [32].

Usual pediatric dose

Safety and efficacy have not been established [1].

Strength(s) usually available

U.S.¾5 mg (Rx)[Fosamax (anhydrous lactose) (croscarmellose sodium) (magnesium stearate) (microcrystalline cellulose)]

10 mg (Rx)[Fosamax (anhydrous lactose) (croscarmellose sodium) (carnauba wax) (magnesium stearate) (microcrystalline cellulose)]

35 mg (Rx)[Fosamax (anhydrous lactose) (croscarmellose sodium) (magnesium stearate) (microcrystalline cellulose)] 34

40 mg (Rx)[Fosamax (anhydrous lactose) (croscarmellose sodium) (magnesium stearate) (microcrystalline cellulose)] 1, 34

70 mg (Rx)[Fosamax (anhydrous lactose) (croscarmellose sodium) (magnesium stearate) (microcrystalline cellulose)] 34

Canada¾10 mg (Rx)[Fosamax (lactose)] 20

40 mg (Rx)[Fosamax (lactose)] 20

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer 1, 20.

Auxiliary labeling:

· Take on empty stomach 1.

References

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21 Reviewer comments, 1996.

22 Reviewer comments, 1996.

23 de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. N Engl J Med 1996; 335: 1016-21.

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27 Panel comment, 1996.

28 Panel comment, 1996.

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34 Product Information: FosamaxÒ, alendronate sodium. Merck & Co., Inc., Whitehouse Station, NJ (PI issued 10/2000) PI reviewed 12/2000.