PRODUCT MONOGRAPH

PrAPO-ALENDRONATE

Alendronate Sodium Tablets
Apotex Standard
5 mg, 10 mg, 40 mg, 70 mg Alendronate

Bone Metabolism Regulator

APOTEX INC.
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Toronto, Ontario
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Control No. 196029

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet / 5 mg, 10 mg, 40 mg, 70 mg	magnesium stearate, mannitol and microcrystalline cellulose

INDICATIONS AND CLINICAL USE[1]

APO-ALENDRONATE (alendronate sodium) is indicated for:

- The treatment and prevention of osteoporosis in postmenopausal women.
  - For the treatment of osteoporosis, APO-ALENDRONATE increases bone mass and prevents fractures, including those of the hip and spine (vertebral compression fractures).

    Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2.0 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture.
  - For the prevention of osteoporosis, APO-ALENDRONATE may be considered 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.

    Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass; thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of APO-ALENDRONATE for prevention of osteoporosis.
- The treatment of osteoporosis in men to reduce the incidence of fractures.
- The treatment and prevention of glucocorticoid-induced osteoporosis in men and women.
- The treatment of Paget's disease of bone in men and women.

[1] [Pr]FOSOMAX® Product Monograph dated May 26, 2017, page 3-4.

- Treatment is indicated in patients with Paget's disease of bone having serum alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

Geriatrics (≥65 years of age):
In clinical studies, there was no age-related difference in the efficacy or safety profiles of APO-ALENDRONATE.

Pediatrics (<18 years of age):
APO-ALENDRONATE is not indicated for use in children.

Important limitations of use: The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS[2]

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes.
- Hypocalcemia (see WARNINGS AND PRECAUTIONS).
- Renal insufficiency with creatinine clearance **<** 0.58 mL/s [< 35 mL/min] (see DOSAGE AND ADMINISTRATION).

WARNINGS AND PRECAUTIONS[3]

General
To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, patients should be instructed to swallow each tablet of APO-ALENDRONATE (alendronate sodium) with a full glass of water. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take APO-ALENDRONATE at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking APO-ALENDRONATE immediately and consult their physician.

Causes of osteoporosis other than estrogen deficiency, aging and glucocorticoid use should be considered.

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[2] PrFOSOMAX® Product Monograph dated May 26, 2017, page 4.
[3] PrFOSOMAX® Product Monograph dated May 26, 2017, page 4-7.

Osteonecrosis

Osteonecrosis of the jaw (ONJ) has been reported in patients receiving treatment regimens including bisphosphonates. The majority of reports occurred following tooth extractions with delayed healing and involved cancer patients treated with intravenous bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. However, some cases have also occurred in patients receiving oral bisphosphonate treatment for postmenopausal osteoporosis and other diagnoses. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection, including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors. Known risk factors for osteonecrosis of the jaw include a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors, immunosuppressive drugs), poor oral hygiene, co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, diabetes mellitus), smoking, and heavy alcohol use.

Patients who develop osteonecrosis of the jaw should receive appropriate antibiotic therapy and/or oral surgery and discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment. Dental surgery may exacerbate the condition. For patients requiring dental procedures (e.g. tooth extraction, dental implants), there are no definitive data available to establish whether discontinuation of bisphosphonate treatment reduces the risk of ONJ.

Cases of osteonecrosis of the external auditory canal (cholesteatoma) have been reported in patients treated with APO-ALENDRONATE.

Clinical judgment of the treating physician and/or oral surgeon should guide the management plan, including bisphosphonate treatment, of each patient based on individual benefit/risk assessment.

The following should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds).
- Route of administration (higher risk for parenteral administration).
- Cumulative dose of bone resorption therapy.
- Co-morbid conditions (e.g. anemia, coagulopathies) and smoking.
- Periodontal disease, poorly fitting dentures, history of dental disease.

Musculoskeletal

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs includes alendronate. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping the medication. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of alendronate, the percentages of patients with these symptoms were similar in the alendronate and placebo groups.

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in some long-term (time to onset in the majority of reports ranged from 18 months to 10 years) alendronate-treated patients. Some were stress fractures (some of which were reported as insufficiency fractures) occurring in the absence of apparent trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. Approximately one third of these fractures were bilateral; therefore the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. Poor healing of these fractures was also reported. Patients with suspected stress fractures should be evaluated, including evaluation for causes and risk factors of stress fractures (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, lower extremity arthritis or fracture, previous stress fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of alendronate therapy in patients with stress fractures should be considered based on individual benefit/risk assessment.

Endocrine and Metabolism

Hypocalcemia must be corrected before initiating therapy with APO-ALENDRONATE (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as Vitamin D deficiency) should be treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with APO-ALENDRONATE. Symptomatic hypocalcemia has been reported rarely, both in patients with predisposing conditions and patients without known predisposing conditions. Patients should be advised to report to their physicians any symptoms of hypocalcemia, such as paresthesias or muscle spasms. Physicians should carefully evaluate patients who develop hypocalcemia during therapy with APO-ALENDRONATE for predisposing conditions.

Due to the positive effects of APO-ALENDRONATE to increase bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated, and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and Vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Gastrointestinal

APO-ALENDRONATE, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with APO-ALENDRONATE. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue APO-ALENDRONATE immediately and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking APO-ALENDRONATE and/or who fail to swallow it with the recommended amount of water, and/or who continue to take APO-ALENDRONATE after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION).

Because of possible irritant effects of APO-ALENDRONATE on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when APO-ALENDRONATE is given to patients with active upper gastrointestinal problems, such as dysphagia, esophageal diseases (including known Barrett's esophagus), gastritis, duodenitis, or ulcers.

While no increased risk was observed in extensive clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications.

Ophthalmologic

Ocular disturbances including conjunctivitis, uveitis, episcleritis and scleritis have been reported with alendronate therapy. Patients with ocular events other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. If ocular inflammatory symptoms are observed, treatment may need to be discontinued.

Special Populations

Pregnant Women:

Alendronate has not been studied in pregnant women and should not be given to them.

Nursing Women:

Alendronate has not been studied in nursing mothers and should not be given to them.

Pediatrics (< 18 years of age):

APO-ALENDRONATE is not indicated for use in children.

Geriatrics (≥65 years of age):

In clinical studies, there was no age-related difference in the efficacy or safety profiles of alendronate.

Monitoring and Laboratory Tests:

Not Applicable

ADVERSE REACTIONS[4]

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical studies, alendronate was generally well tolerated. In studies of up to five years in duration, side effects, which usually were mild, generally did not require discontinuation of therapy.

[4] PrFOSOMAX® Product Monograph dated May 26, 2017, page 7-13.

Alendronate has been evaluated for safety in clinical studies in approximately 7200 postmenopausal women.

Treatment of Osteoporosis

Postmenopausal Women:
In two, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational) of virtually identical design, with a total of 994 postmenopausal women, the overall safety profiles of alendronate 10 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with alendronate 10 mg/day and 6.0% of 397 patients treated with placebo.

Adverse experiences considered by the investigators as possibly, probably, or definitely drug-related in ≥ 1% of patients treated with either alendronate 10 mg/day or placebo are presented in the following table.

Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients Treated for Osteoporosis

	Alendronate 10 mg/day % (n = 196)	Placebo % (n = 397)
Gastrointestinal		
Abdominal pain	6.6	4.8
Nausea	3.6	4.0
Dyspepsia	3.6	3.5
Constipation	3.1	1.8
Diarrhea	3.1	1.8
Flatulence	2.6	0.5
Acid regurgitation	2.0	4.3
Esophageal ulcer	1.5	0.0
Vomiting	1.0	1.5
Dysphagia	1.0	0.0
Abdominal distention	1.0	0.8
Gastritis	0.5	1.3
Musculoskeletal		
Musculoskeletal (bone, muscle or joint) pain	4.1	2.5
Muscle cramp	0.0	1.0
Nervous System/Psychiatric		
Headache	2.6	1.5
Dizziness	0.0	1.0
Special Senses		
Taste Perversion	0.5	1.0

* Considered possibly, probably, or definitely drug-related as assessed by the investigators.

One patient treated with alendronate (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant acetylsalicylic acid (ASA) developed an anastomotic ulcer with mild hemorrhage, which was considered drug-related. ASA and alendronate were discontinued and the patient recovered.

In the two-year extension (treatment years 4 and 5) of the above studies, the overall safety profile of alendronate 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued alendronate 10 mg/day due to any clinical adverse experience was similar to that during the first three years of the study.

In the Fracture Intervention Trial, discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with alendronate 5 mg/day for two years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo.

Discontinuations due to upper gastrointestinal adverse experiences were: alendronate, 3.2%; placebo, 2.7%. The overall adverse experience profile was similar to that seen in other studies with alendronate 5 or 10 mg/day.

In a one-year, double-blind multicenter study, the overall safety and tolerability profiles of alendronate 70 mg once weekly and alendronate 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug-related in ≥1% of patients in either treatment group are presented in the following table:

Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients Treated for Osteoporosis		
	Alendronate 70 mg Once weekly % (n = 519)	**Alendronate 10 mg/day % (n = 370)**
Gastrointestinal		
Abdominal pain	3.7	3.0
Dyspepsia	2.7	2.2
Acid regurgitation	1.9	2.4
Nausea	1.9	2.4
Abdominal distension	1.0	1.4
Constipation	0.8	1.6
Flatulence	0.4	1.6
Gastritis	0.2	1.1
Gastric ulcer	0.0	1.1
Musculoskeletal		
Musculoskeletal (bone, muscle or joint) pain	2.9	3.2
Muscle cramp	0.2	1.1

* Considered possibly, probably, or definitely drug-related as assessed by the investigators.

Men:
In two, placebo-controlled, double-blind, multicenter studies in men (a two-year study of alendronate 10 mg/day (n=146) and a one-year study of alendronate 70 mg once weekly (n=109)), the safety profile of alendronate was generally similar to that seen in postmenopausal women. The rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate 10 mg/day vs 10.5% for placebo and 6.4% for alendronate 70 mg once weekly vs 8.6% for placebo.

Other Studies in Men and Women:
In a ten-week endoscopy study in men and women (n **=** 277; mean age: 55) no difference was seen in upper gastrointestinal tract lesions between alendronate 70 mg once weekly and placebo.

In an additional one-year study in men and women (n **=** 335; mean age: 50) the overall safety and tolerability profiles of alendronate 70 mg once weekly were similar to that of placebo and no difference was seen between men and women.

Prevention of Osteoporosis in Postmenopausal Women:
The safety of alendronate 5 mg/day in postmenopausal women 40 to60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1400 patients randomized to receive alendronate for either two or three years. In these studies the overall safety profiles of alendronate 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with alendronate 5 mg/day and 5.7% of 648 patients treated with placebo. Adverse experiences reported by the investigators as possibly, probably or definitely drug-related in ≥ 1 % of patients treated with either alendronate 5 mg/day or placebo are presented in the following table:

Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients Treated for Osteoporosis		
	Alendronate 5 mg/day % (n = 642)	**Placebo % (n = 648)**
Gastrointestinal		
Abdominal pain	1.7	3.4
Acid regurgitation	1.4	2.5
Diarrhea	1.1	1.7
Dyspepsia	1.9	1.7
Nausea	1.4	1.4

* Considered possibly, probably, or definitely drug-related as assessed by the investigators.

Concomitant Use with Estrogen/Hormone Replacement Therapy:
In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with alendronate 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis:
In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of alendronate 5 or 10 mg/day were generally similar to that of placebo. Adverse experiences reported by the investigators as possibly, probably or definitely drug-related in ≥ 1 % of patients treated with either alendronate 5 or 10 mg/day or placebo are presented in the following table:

Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients Treatment and Prevention of Glucocorticoid-Induced Osteoporosis			
	Alendronate 10 mg/day % (n = 157)	**Alendronate 5 mg/day % (n = 161)**	**Placebo % (n = 159)**
Gastrointestinal			
Abdominal pain	3.2	1.9	0.0
Acid regurgitation	2.5	1.9	1.3
Constipation	1.3	0.6	0.0
Melena	1.3	0.0	0.0
Nausea	0.6	1.2	0.6
Diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
Headache	0.6	0.0	1.3

* Considered possibly, probably, or definitely drug-related as assessed by the investigators.

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies was consistent with that observed in the first year.

Paget 's disease of Bone
In clinical studies (Paget's disease and osteoporosis), adverse experiences reported in 175 patients taking alendronate 40 mg/day for 3 to12 months were similar to those in postmenopausal women treated with alendronate 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking alendronate 40 mg/day (17.7% alendronate vs 10.2% placebo). Isolated cases of esophagitis and gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal pain (bone, muscle or joint), which has been described in patients with Paget's disease treated with other bisphosphonates, was reported by the investigators as possibly, probably, or definitely drug-related in approximately 6% of patients treated with alendronate 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with alendronate 40 mg/day and 2.4% of patients treated with placebo.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Skin: rash and erythema

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory Tests
In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronate versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg P[5]/dL(0.65 mM) were similar in both treatment groups.

In a small, open-label study, at higher doses (80 mg/day) some patients had elevated transaminases. However, this was not observed at 40 mg/day. No clinically significant toxicity was associated with these laboratory abnormalities.

Rare cases of leukemia have been reported following therapy with other bisphosphonates. Any causal relationship to either the treatment or to the patients' underlying disease has not been established.

Post-Market Adverse Drug Reactions
The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and angioedema; transient symptoms of myalgia, malaise, asthenia and fever have been reported with APO-ALENDRONATE typically in association with initiation of treatment; symptomatic hypocalcemia both in association with predisposing conditions and in patients without known predisposing conditions; peripheral edema

Dental: localized osteonecrosis of the jaw (ONJ) generally associated with local infection (including osteomyelitis) and/or tooth extraction with delayed healing (see WARNINGS AND PRECAUTIONS, General)

[5] P: Elemental phosphorus

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, esophageal stricture or perforation, and oropharyngeal ulceration; gastric or duodenal ulcers, some severe and with complications (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION)

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe and/or incapacitating; joint swelling; low-energy femoral shaft fracture
(see WARNINGS AND PRECAUTIONS).

Nervous System: dizziness, vertigo, dysgeusia.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis

Special Senses: uveitis, scleritis or episcleritis; osteonecrosis of the external auditory canal(cholesteatoma)

DRUG INTERACTIONS[6]

Overview

Animal studies have demonstrated that alendronate is highly concentrated in bone and is retained only minimally in soft tissue. No metabolites have been detected. Although alendronate is bound approximately 78% to plasma protein in humans, its plasma concentration is so low after oral dosing that only a small fraction of plasma-binding sites is occupied, resulting in a minimal potential for interference with the binding of other drugs. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other drugs by those systems in humans. In summary, APO-ALENDRONATE is not expected to interact with other drugs based on effects on protein binding, renal excretion, or metabolism of other drugs.

Drug-Drug Interactions

If taken at the same time it is likely that calcium supplements, antacids, other multivalent cations and other oral medications will interfere with absorption of APO-ALENDRONATE. Therefore, patients must wait at least one-half hour after taking APO-ALENDRONATE before taking any other oral medication.

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown; no other specific drug interaction studies were performed.

[6] PrFOSOMAX® Product Monograph dated May 26, 2017, page 13-15.

Concomitant use of hormone replacement therapy (HRT [estrogen ± progestin]) and alendronate was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of alendronate and HRT resulted in greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments (see ADVERSE REACTIONS, Clinical Studies, Concomitant Use with Estrogen/Hormone Replacement Therapy). The studies were too small to detect antifracture efficacy, and no significant differences in fracture incidence among the treatment groups were found.

Specific interaction studies were not performed. Alendronate was used in osteoporosis studies in men, postmenopausal women, and glucocorticoid users, with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions.

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving daily therapy with dosages of alendronate greater than 10 mg and acetylsalicylic acid-containing products. This was not observed in a study with alendronate 70 mg once weekly.

Alendronate may be administered to patients taking nonsteroidal anti-inflammatory drugs (NSAIDs). In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking alendronate 5 or 10 mg/day compared to those taking placebo.

However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with APO-ALENDRONATE.

Drug-Food Interactions

Food and beverages other than plain water may markedly reduce the absorption and effectiveness of alendronate. APO-ALENDRONATE must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only (see DOSAGE AND ADMINISTRATION, Administration).

Drug-Herb Interactions

Herbal products may interfere with the absorption of alendronate. APO-ALENDRONATE must be taken at least one-half hour before any herbal products.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with alendronate (e.g., dizziness, vertigo, visual disturbances, and severe bone, muscle or joint pain) may affect some patients' ability to drive or operate machinery. Individual responses to alendronate may vary.

DOSAGE AND ADMINISTRATION[7]

Recommended Dose

Treatment of Osteoporosis in Postmenopausal Women and in Men

The recommended dosage is:

- one 70 mg tablet once weekly

  or

- one 10 mg tablet once daily.

Prevention of Osteoporosis in Postmenopausal Women

The recommended dosage is 5 mg once a day.

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis in Men and Women

The recommended dosage is 5 mg once a day, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is 10 mg once a day.

Paget's Disease of Bone in Men and Women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's Disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with alendronate. Specific retreatment data are not available, although responses to alendronate were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with APO-ALENDRONATE may be considered, following a six-month post-treatment evaluation period, in patients who have relapsed based on increases in serum alkaline phosphatase (which should be measured periodically). Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

The optimal duration of bisphosphonate 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 APO-ALENDRONATE on an individual patient basis.

Dosage Adjustment

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 0.58 to 1 mL/s [35 to 60 mL/min]). APO-ALENDRONATE is not recommended for patients with more severe renal insufficiency (creatinine clearance <0.58 mL/s [< 35 mL/min]) due to lack of experience.

Missed Dose

Patients should be instructed that if they miss a dose of APO-ALENDRONATE 70 mg once weekly, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

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[7] PrFOSOMAX® Product Monograph dated May 26, 2017, page 15-16.

Administration

APO-ALENDRONATE must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only. Other beverages (including mineral water), food, and some medications are known to reduce the absorption of APO-ALENDRONATE (see DRUG INTERACTIONS). Waiting less than 30 minutes will lessen the effect of APO-ALENDRONATE by decreasing its absorption into the body.

APO-ALENDRONATE should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, an APO-ALENDRONATE tablet should be swallowed with a full glass of water (200 to 250 mL). Patients should not lie down for at least 30 minutes and until after their first food of the day. APO-ALENDRONATE should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS AND PRECAUTIONS).

All patients must receive supplemental calcium and Vitamin D, if dietary intake is inadequate. Although no specific studies have been conducted on the effects of switching patients on another therapy for osteoporosis or Paget's disease to APO-ALENDRONATE, there are no known or theoretical safety concerns related to APO-ALENDRONATE in patients who previously received any other antiosteoporotic or antipagetic therapy.

OVERDOSAGE[8]

No specific information is available on the treatment of overdosage with APO-ALENDRONATE (alendronate sodium). Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY[9]

Mechanism of Action

APO-ALENDRONATE is a bisphosphonate that acts as a potent, specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

[8] 8 PrFOSOMAX® Product Monograph dated May 26, 2017, page 16.
[9] PrFOSOMAX® Product Monograph datedMay 26, 2017, page 16-20.

Osteoporosis in Postmenopausal Women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on xray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with alendronate 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and crosslinked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received alendronate 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with alendronate. In osteoporosis treatment studies, alendronate 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase, by approximately 25 to 30%, to reach a plateau after 6 to 12 months. In osteoporosis prevention studies, alendronate 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during a one-year study with alendronate 70 mg once weekly for the treatment of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with alendronate. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of alendronate 10 mg. No further decreases in serum calcium were observed for the five year duration of treatment, however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with alendronate 5 mg/day. In a one-year study with alendronate 70 mg once weekly, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to alendronate but also a decrease in renal phosphate reabsorption.

Osteoporosis in Men

Even though osteoporosis is less prevalent in men than in postmenopausal women, a significant proportion of osteoporotic fractures occur in men. The prevalence of vertebral deformities appears to be similar in men and women. Treatment of men with osteoporosis with alendronate 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving alendronate 70 mg once weekly.

Glucocorticoid-Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, alendronate 5 and 10 mg/day reduced cross-linked N-telopeptides of type 1 collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, alendronate 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's Disease of Bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

Alendronate decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, alendronate 40 mg once daily for six months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, alendronate induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Pharmacokinetics

Summary of Pharmacokinetic Parameters in the Normal Population		
	Mean	90% Confidence Interval
Absolute bioavailability of 5 mg tablet, taken 2 hours before first meal of the day	0.63% (females)	(0.48, 0.83)
Absolute bioavailability of 10 mg tablet, taken 2 hours before first meal of the day	0.78% (females)	(0.61, 1.04)

	0.59% (males)	(0.43, 0.81)
Absolute bioavailability of 40 mg tablet, taken 2 hours before first meal of the day	0.60% (females)	(0.46, 0.78)
Absolute bioavailability of 70 mg tablet, taken 2 hours before first meal of the day	0.57% (females)	(0.44, 0.73)
Renal Clearance mL/s (mL/min) (n=6)	1.18 (71)	(1.07, 1.3) (64, 78)

Absorption:
Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men was 0.59%.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Distribution:
Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

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

Excretion:
Following a single IV dose of [^{14}C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with alendronate (10 mg daily), the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations and Conditions

Pediatrics (<18 years of age):

The oral bioavailability in children (4 to 16 years of age) with osteogenesis imperfecta (OI) was similar to that observed in adults; however, alendronate is not indicated for use in children (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Geriatrics (≥65 years of age):

Bioavailability and disposition (urinary excretion) were similar in elderly (≥ 65 years of age) and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Gender:

Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Race:

Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency:

As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Renal Insufficiency:

Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 0.58 to 1 mL/s [35 to 60 mL/min]). APO-ALENDRONATE is not recommended for patients with more severe renal insufficiency (creatinine clearance **<** 0.58 mL/s [<35 mL/min]) due to lack of experience.

STORAGE AND STABILITY

Store at room temperature (15°C to 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each tablet of APO-ALENDRONATE contains 6.53, 13.05, 52.20 or 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 5, 10 and 40 mg and 70 mg, respectively, of alendronate and the following non-medicinal ingredients: magnesium stearate, mannitol and microcrystalline cellulose.

AVAILABILITY OF DOSAGE FORMS:

APO-ALENDRONATE 5 mg: each white, round, flat-faced, bevelled edged tablet, engraved “A” on one side and “5” on the other, contains alendronate sodium equivalent to 5 mg alendronate. Available in bottles of 100 and 500, and in unit dose packages of 30.

APO-ALENDRONATE 10 mg: each white, round, biconvex tablet, engraved “APO” on one side and “10” on the other, contains alendronate sodium equivalent to 10 mg alendronate. Available in bottles of 100 and 500, and in unit dose packages of 30.

APO-ALENDRONATE 40 mg: each white, triangular, biconvex tablet, engraved “APO” over “40” on one side and plain on the other, contains alendronate sodium equivalent to 40 mg alendronate. Available in bottles of 100, and in unit dose packages of 30.

APO-ALENDRONATE 70 mg: each white, oval, biconvex tablet, engraved “APO” on one side and “ALE70” on one side, contains alendronate sodium equivalent to 70 mg alendronate. Available in bottles of 100, and in unit dose packages of 4 and 30.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

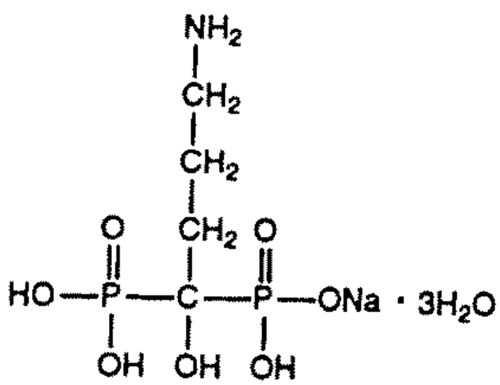
Proper Name: Alendronate sodium

Chemical Names: Phosphonic acid, (4-amino-1-hydroxybutylidene) bis-, monosodium salt, trihydrate

Sodium trihydrogen (4-amino-1-hydroxybutylidene) diphosphonate, trihydrate

Molecular formula and molecular weight: $C_4H_{12}NNaO_7P_2 \bullet 3H_2O$
325.12 g/mol

Structural Formula:



Physicochemical properties:

Description: Alendronate Sodium is a white, crystalline, non hygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

CLINICAL TRIALS[10]

Comparative Bioavailability Studies

A comparative bioavailability study was performed using healthy human volunteers. The urinary excretion of alendronate was measured and compared following oral administration of 1 x 40 mg of either Apo-Alendronate 40 mg tablets or Fosamax 40 mg tablets. The results from measured data are summarized below:

Summary Table of the Comparative Bioavailability Data Alendronate (Dose: 1 x 40 mg) From Measured Data – Under Fasting Conditions Based on Alendronate				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence interval (%) **
	Apo-Alendronate	Fosamax®†		
X^U_{0-T} (ng)	154810 190252 (68)	164919 211422 (83)	92.7	82.6 – 104.1
$X^U_{0-\infty}$ (ng)	162855 196760 (65)	176125 222964 (81)	91.0	80.9 – 102.4
R^U_{max} (ng/hr)	40583 50933 (77)	45597 59397 (90)	88.2	77.6 – 100.2
T_{max} (hr)*	1.67 (36)	1.77 (30)		
$t_{1/2}$ (hr)*	32.7 (63)	33.0 (58)		

Note: X^U_{0-T} and $X^U_{0-\infty}$ are the amount of the drug excreted unchanged in the urine from time 0 to the time of the last measurable amount excreted and infinity, respectively. R^U_{max} is the maximum urinary excretion rate of the drug.

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Fosamax® is marketed by Merck Frosst Canada Ltd.

Treatment of Osteoporosis

Postmenopausal Women
Effect on Bone Mineral Density

The efficacy of alendronate 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years duration. These included two large three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in bone mineral density (BMD) of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate 10 mg/day relative to placebo-treated patients at three years for each of these studies.

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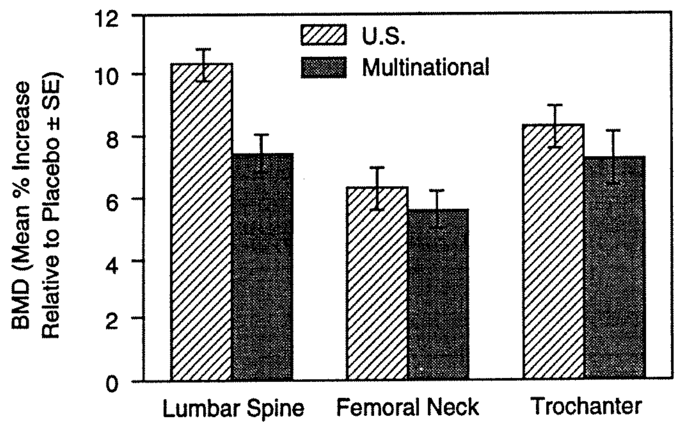
[10] PrFOSOMAX® Product Monograph dated December 23, 2015, page 23-32.

Osteoporosis Treatment Studies in Postmenopausal Women

Increase in BMD
Alendronate 10 mg/day at Three Years

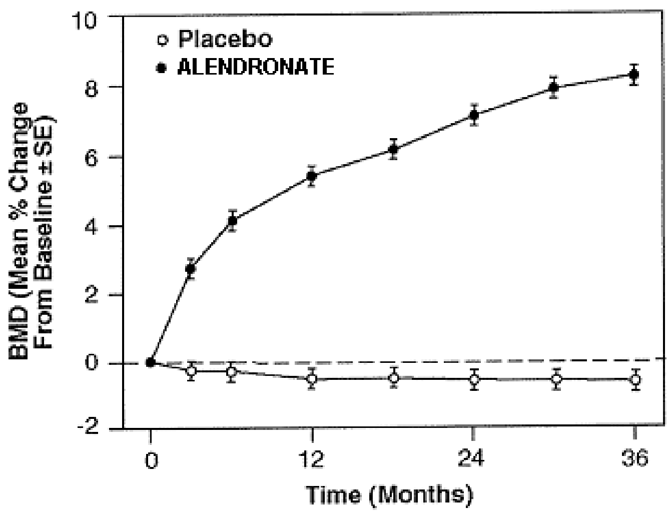


In the combined studies, after three years, BMD of the lumbar spine, femoral neck and trochanter in placebo-treated patients decreased significantly by between 0.65 and 1.16%. Highly significant increases, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received alendronate 10 mg/day. Total body BMD also increased significantly in both studies, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the entire three years of treatment (see following figure for lumbar spine results). In the two-year extension of these studies, treatment with alendronate 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years three and five: lumbar spine, 0.94%; trochanter, 0.88%).

BMD at the femoral neck, forearm and total body were maintained. Thus, alendronate reverses the progression of osteoporosis. Alendronate was similarly effective regardless of age, race, baseline rate of bone turnover, renal function and use with a wide range of common medications.

Osteoporosis Treatment Studies in Postmenopausal Women

Time Course of Effect of Alendronate 10 mg/day Versus Placebo: Lumbar Spine BMD Percent Change From Baseline



In a separate study, alendronate 10 mg/day for two years induced highly significant increases in BMD of the spine, femoral neck, trochanter, and total body relative to either intranasal salmon calcitonin 100 IU/day or placebo.

The therapeutic equivalence of alendronate 70 mg once weekly (n = 519) and alendronate 10 mg daily (n = 370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70 mg once weekly group and 5.4% (5.0, 5.8%; 95% CI) in the 10mg daily group. The two treatment groups were also similar with regard to BMD increases at other skeletal sites. In trials with alendronate changes in BMD of this magnitude were associated with a decrease in fracture incidence (see below).

Effects of Withdrawal

In patients with postmenopausal osteoporosis treated with alendronate 10 mg/day for one or two years the effects of treatment withdrawal were assessed. Following discontinuation, bone turnover gradually returned toward pretreatment levels, and BMD no longer increased although accelerated bone loss was not observed. These data indicate that treatment with alendronate must be continuous to produce progressive increases in bone mass.

Effect on Fracture Incidence

To assess the effects of alendronate on vertebral fracture incidence, the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of alendronate (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year).

There was a statistically significant 48% reduction in the proportion of patients treated with alendronate experiencing one or more vertebral fractures relative to those treated with placebo (3.2% vs 6.2%). An even greater reduction in the total number of vertebral fractures (4.2 vs 11.3 per 100 patients) was also observed. Furthermore, of patients who sustained any vertebral fracture, those treated with alendronate experienced less height loss (5.9 mm vs 23.3 mm) due to a reduction in both the number and severity of fractures.

Additionally, analysis of the data pooled across doses of ≥ 2.5 mg from five placebo-controlled studies of two or three years' duration including the U.S. and Multinational studies (alendronate: n**=** 1012, placebo: n **=** 590) revealed a significant 29% reduction in non-vertebral fracture incidence (alendronate**,** 9.0% vs placebo, 12.6%). Like the effect on vertebral fracture incidence, these results of alendronate treatment are consistent with the observed increases in bone mass.

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline vertebral (compression) fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline vertebral fracture)
This randomized, double-blind, placebo-controlled 2027-patient study (alendronate n=1022; placebo, n=1005) demonstrated that treatment with alendronate resulted in statistically significant and clinically meaningful reductions in fracture incidence at three years as shown in the following table.

Effect of Alendronate on Fracture Incidence In the Three-Years Study of FIT (Patients with Vertebral Fracture at Baseline)

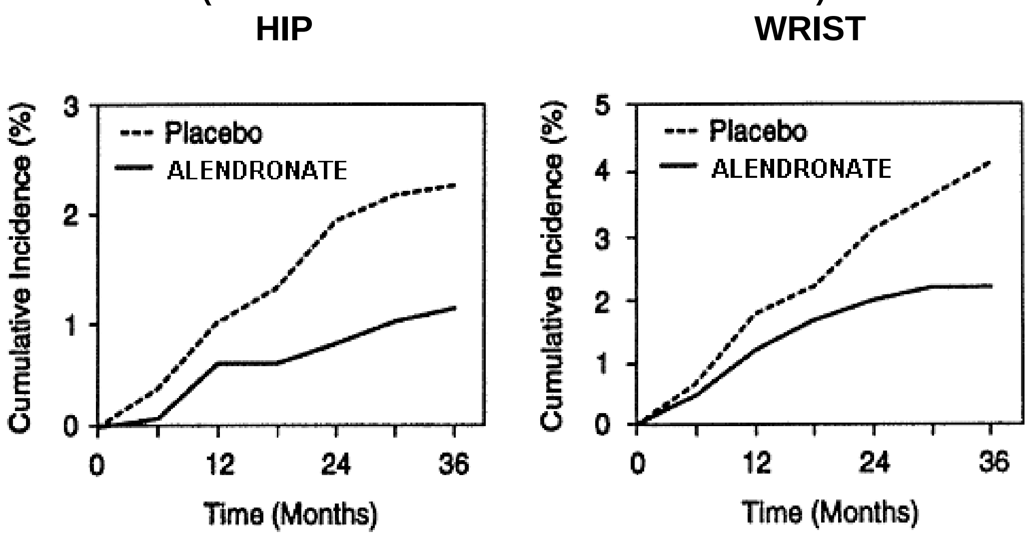
	% of Patients		
Patients with:	**Alendronate (n = 1022)**	**Placebo (n = 1005)**	**Reduction (%) in Fracture Incidence**
Vertebral fractures (diagnosed by X-ray)†			
≥ 1 new vertebral fracture	7.9	15.0	47***
≥ 2 new vertebral fractures	0.5	4.9	90***
Painful (clinical) fractures			
≥ 1 painful vertebral fracture	2.3	5.0	54**
Any painful fracture	13.8	18.1	26**
Hip fracture	1.1	2.2	51*
Wrist (forearm) fracture	2.2	4.1	48*

† Number evaluable for vertebral fracture: alendronate, n=984; placebo, n=966
* p<0.05, ** p<0.01, *** p<0.001

Furthermore, in this population of patients with baseline vertebral fracture, treatment with alendronate significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

The following two figures display the cumulative incidence of hip and wrist fractures in the Three-Year Study of FIT. In both figures, the cumulative incidence of these types of fracture is lower with alendronate compared with placebo at all time points. Alendronate reduced the incidence of hip fracture by 51 % and wrist fracture by 48%. Proportionately similar reductions of hip and wrist fractures were seen in pooled earlier osteoporosis treatment studies.

Cumulative Incidence of Hip and Wrist Fractures in the Three-Year Study of FIT (Patients with Vertebral Fracture at Baseline)



Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline vertebral fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (alendronate n=2214; placebo, n=2218) further demonstrated the reduction in fracture incidence due to alendronate. The intent of the study was to recruit women with osteoporosis, i.e. with a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the following table for the patients with osteoporosis.

Effect of Alendronate on Fracture Incidence in Osteoporotic† Patients In the Four-Year Study of FIT (Patients with Vertebral Fracture at Baseline)			
	% of Patients		
Patients with:	**Alendronate (n = 1545)**	**Placebo (n = 1521)**	**Reduction (%) in Fracture Incidence**
≥ 1 painful fracture	12.9	16.2	22**
≥ 1 vertebral fracture††	2.5	4.8	48***
≥ 1 painful vertebral fracture	1.0	1.6	41†††
Hip fracture	1.0	1.4	29†††
Wrist (forearm) fracture	3.9	3.8	none

† Baseline femoral neck BMD at least 2 SD below the mean for young adult women

†† Number evaluable for vertebral fracture: alendronate, n=1426; placebo, n=1428

††† Not significant

** p = 0.01, *** p<0.001

In all patients (including those without osteoporosis), the reductions in fracture incidence were: ≥1 painful fracture, 14% (p = 0.072); ≥1 vertebral fracture, 44% (p = 0.001); ≥1 painful vertebral fracture, 34% (p = 0.178), and hip fracture, 21% (p = 0.44). The incidence of wrist fracture in all patients was alendronate, 3.7%; placebo, 3.2% (not significant).

Combined FIT Studies

The reductions in fracture incidence for the combined Three- and Four-Year Studies of FIT are shown in the following table.

Effect of Alendronate on Fracture Incidence in the Combined (Three- and Four-Year) Studies of FIT		
	Reduction (%) in Fracture Incidence Alendronate vs. Placebo	
Patients with:	**Osteoporotic Patients† (n = 5093)**	**All patients (n = 6459)**
Vertebral fractures (diagnosed by (X-ray) ††		
≥ 1 vertebral fracture	48***	46***
≥ 2 vertebral fractures	88***	84***
Painful (clinical) fractures		
Any painful fracture	24***	18**
Painful vertebral fracture	50***	47***
Hip fracture	40*	36‡‡
Wrist (forearm) fracture†††	18‡	6‡

† Includes all patients in the Three-Year Study plus osteoporotic patients (baseline femoral neck BMD at least 2 SD below the mean for young adult women) in the Four-Year Study

†† Number evaluable for vertebral fractures: osteoporotic patients, n=4804; all patients, n=6084

††† Significant reduction in wrist fracture incidence was observed in the Three-Year Study (patients with baseline vertebral fracture) but not in the Four-Year Study (patients without baseline vertebral fracture)

‡ Not significant

** p<0.05, ** p<0.0l, *** p<0.00l, ‡‡ p=0.059

Consistency of Fracture Results

The reductions in the incidence of vertebral fractures (alendronate vs. placebo) in the Three- and Four-Year Studies of FIT were consistent with that in the combined U.S. and Multinational *(U.S./Mult)* treatment studies (see above), in which 80% of the women did not have a vertebral fracture at baseline. During these studies, treatment with alendronate reduced the proportion of women experiencing at least one new vertebral fracture by approximately 50% (Three-Year FIT: 47% reduction, p **<** 0.001; Four-Year FIT: 44% reduction, p **=** 0.001; U.S./Mult: 48% reduction, p **=** 0.034). In addition, alendronate reduced the proportion of women experiencing multiple (two or more) new vertebral fractures by approximately 90% in the U.S./Mult. and Three-Year FIT Studies (p **<** 0.001). Thus, alendronate reduces the incidence of vertebral fractures whether or not patients have experienced a previous vertebral fracture.

Overall, these results demonstrate the consistent efficacy of alendronate to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with the greatest morbidity.

Bone Histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with alendronate at doses ranging from 1 to 20 mg/day for one, two or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, indicate that bone formed during therapy with alendronate is of normal quality.

Men
The efficacy of alendronate in men with osteoporosis was demonstrated in two clinical studies.

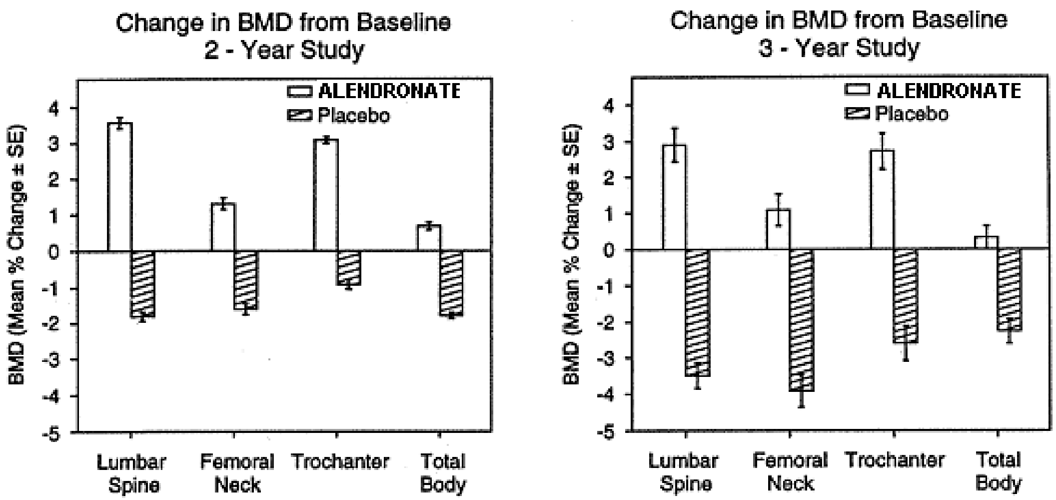
A two-year, double-blind, placebo-controlled, multicenter study of alendronate 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). At two years, the mean increases relative to placebo in BMD in men receiving alendronate 10mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6% (all $p \leq 0.001$). Consistent with much larger studies in postmenopausal women, in these men, alendronate 10 mg/day reduced the incidence of new vertebral fracture (assessed by quantitative radiography) relative to placebo (0.8% vs. 7.1%, respectively; p=0.017) and, correspondingly, also reduced height loss (-0.6 vs. -2.4 mm; respectively; p=0.022).

A one-year, double-blind, placebo-controlled, multicenter study of alendronate 70 mg once weekly enrolled a total of 167 men between the ages of 38 and 91 (mean 66). At one year, the mean increases in BMD relative to placebo were significant at the following sites: lumbar spine, 2.8% ($p \leq 0.001$); femoral neck, 1.9% (p=0.007); trochanter, 2.0% ($p \leq 0.001$); and total body, 1.2% (p=0.018). These increases in BMD were similar to those seen at one year in the 10 mg once-daily study. The trial was not powered to detect a clinical difference in fracture incidence between the alendronate and placebo groups. However, other studies with daily or weekly alendronate administrations have consistently demonstrated a relationship between increases in BMD (a surrogate marker) and decreases in fracture rate (clinical endpoint). Therefore, it can be assumed that this relationship is also true in men given a weekly administration of alendronate (see REFERENCES).

In both studies alendronate was effective regardless of age, gonadal function or baseline BMD (femoral neck and lumbar spine).

Prevention of Osteoporosis in Postmenopausal Women
Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40-60 years of age. One thousand six hundred nine patients (alendronate 5 mg/day: n = 498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (alendronate 5 mg/day: n = 88), who were between six months and three years postmenopausal, were treated for up to three years. As expected, in the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, alendronate 5 mg/day effectively prevented bone loss, and induced highly significant increases in bone mass at each of these sites (see following figures). In addition, alendronate 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. Alendronate 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

Osteoporosis Prevention Studies in Postmenopausal Women



Bone Histology

Bone histology was normal in the 28 patients biopsied at the end of three years who received alendronate at doses of up to 10 mg/day.

Concomitant Use with Estrogen/Hormone Replacement Therapy (HRT)

The effects on BMD of treatment with alendronate 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or alendronate alone (both 6.0%).

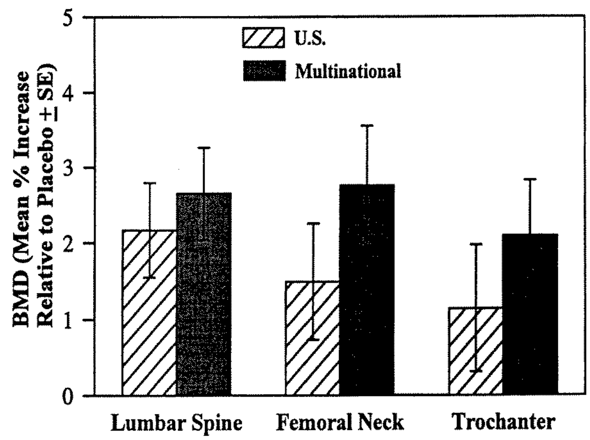
The effects on BMD when alendronate was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n= 428). The addition of alendronate 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD. The studies were too small to detect antifracture efficacy, and no significant differences in fracture incidence among the treatment groups were found.

Glucocorticoid-Induced Osteoporosis

The efficacy of alendronate 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design (United States and Multinational [which also included alendronate 2.5 mg/day]). These studies enrolled a total of 560 patients between the ages of 17 and 83. Patients received supplemental calcium and Vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate 5 mg/day for each study.

Studies in Glucocorticoid-Treated Patients
Increase in BMD
Alendronate 5 mg/day at One Year



After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received alendronate 5 or 10 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with alendronate 5 or 10 mg/day. The increases in BMD (relative to placebo) with alendronate 10 mg/day were greater than those with alendronate 5 mg/day only in postmenopausal women not receiving estrogen therapy, at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. Alendronate was effective regardless of dose or duration of glucocorticoid use. In addition, alendronate was similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone Histology
Bone histology was normal in the 49 patients biopsied at the end of one year who received alendronate at doses of up to 10 mg/day.

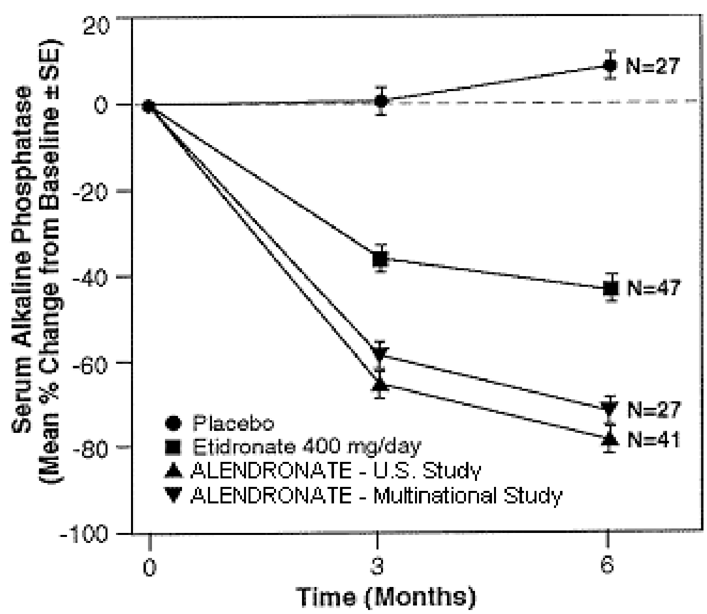
Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with alendronate 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with alendronate 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with alendronate (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (alendronate 0.7% vs. placebo 6.8%).

Paget's Disease of Bone
The efficacy of alendronate 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.

Studies in Paget's Disease of Bone

Effect on Serum Alkaline Phosphatase of Alendronate 40 mg/day versus Placebo or Etidronate 400 mg/day



At six months the suppression in alkaline phosphatase in patients treated with alendronate was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline $\geq$ 60%) occurred in approximately 85% of patients treated with alendronate in the combined studies vs 30% in the etidronate group and 0% in the placebo group. Alendronate was similarly effective irrespective of age, gender, race, renal function, use with a wide range of common medications, prior use of other bisphosphonates, or baseline alkaline phosphatase.

Bone Histology

Bone histology was evaluated in 33 patients with Paget's disease treated with alendronate 40 mg/day for 6 months. As in patients treated for osteoporosis (see CLINICAL TRIALS, Treatment of Osteoporosis, Postmenopausal Women, Bone Histology) alendronate did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with alendronate, even where preexisting bone was woven and disorganized. Overall, bone histology data confirm that bone formed during treatment with alendronate is of normal quality.

DETAILED PHARMACOLOGY[11]

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H] alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H] alendronate administration, in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix, where it is no longer pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Animal Pharmacology

The ability of alendronate to prevent or reverse the bone loss associated with estrogen deficiency was tested *in vivo* in baboons and rats.

[11] [Pr]FOSOMAX® Product Monograph dated May 26, 2017, page 32-34.

Ovariectomized adult baboons undergo bone changes similar to those caused by estrogen deficiency in women. In both, these are reflected early on by increases in biochemical markers of bone resorption (such as urinary deoxypyridinoline) and bone formation (such as serum alkaline phosphatase and osteocalcin). Alendronate, administered for 24 months intravenously every two weeks at 0.05 mg/kg or 0.25 mg/kg (equivalent to human oral doses* of approximately 25 and 125 mg/day), maintained or slightly reduced the levels of biochemical markers in a dose-dependent manner. Importantly, continuous treatment did not cause progressive suppression of bone turnover during this 24-month study. Histomorphometric analysis of trabecular bone after 24 months of treatment showed that alendronate, in a dose-dependent manner, prevented the increase in bone turnover caused by ovariectomy and significantly increased the vertebral bone volume. Alendronate also decreased bone turnover in the cortical bone of the radius and prevented an increase in cortical bone porosity. Both in trabecular and cortical bone, there was a positive bone balance at the level of individual remodeling sites (basic multicellular units, BMUs). Bone histology at all sites examined was normal. Furthermore, alendronate significantly increased the BMD of the lumbar spine and the mechanical strength of vertebral trabecular bone. A highly significant positive correlation was found between lumbar spine BMD and bone strength. In summary, these studies indicate that even at doses equivalent to a human oral dose* of approximately 125 mg/day alendronate maintains normal bone quality while increasing both bone mass and bone strength.

Also, alendronate increased bone mass and vertebral strength in ovariectomized rats. Three-month old rats were ovariectomized and four months later were treated with alendronate 0, 0.28, 2.8, or 28 mcg/kg subcutaneously twice weekly (equivalent to human oral doses* of 0, 0.57, 5.7, and 57 mg/day for six months). Measurements of the mechanical properties of the lumbar vertebrae showed that ovariectomy caused a significant reduction in stiffness and ultimate strength. In alendronate-treated rats, the strength and trabecular bone mass of vertebral bone showed a dose-dependent increase relative to control animals.

In a second study, 6.5-month-old rats were ovariectomized; alendronate treatment was started six months later and was continued for one year. Alendronate was given subcutaneously twice weekly at 1.8 and 18 mcg/kg (equivalent to human oral doses* of 3.7 and 37 mg/day). Alendronate treatment dose-dependently reduced bone turnover and increased bone mass, both in trabecular and cortical bone. The observed increases in bone mass correlated with increased vertebral strength, both of which were significant relative to the control group at the higher dose. In the alendronate-treated rats, the histology of bone was normal, rates of mineralization were normal, and there were no signs of osteomalacia.

In a study of prevention of bone loss due to estrogen deficiency, 4-month-old rats were ovariectomized and, beginning the next day, alendronate 0.1 or 0.5 mg/kg/day was administered daily by oral gavage for one year. Alendronate treatment at 0.5 mg/kg/day prevented the ovariectomy-induced bone loss and loss of bone strength observed in untreated ovariectomized controls. Alendronate treatment also maintained the histomorphometric parameters at the levels seen in untreated non-ovariectomized controls.

Two-year treatment (starting from the age of six weeks) of normal growing rats of both sexes with doses up to 3.75 mg/kg/day also produced similar findings, including increased bone mass, increased bone strength, and normal bone histology.

* Based on a patient weight of 50 kg

The resorbability of bone produced during alendronate treatment was also studied in rats in a model of rapid bone formation following bone marrow injury. Bone formed during daily treatment with 1 mcg/kg subcutaneously (equivalent to a 7.1 mg/day human oral dose[*]) was completely resorbed at a rate indistinguishable from controls. Bone formed at 2 mcg/kg/day subcutaneously was completely resorbed 24 days after cessation of treatment versus 14 days in controls. Bone formed at 8 and 40 mcg/kg/day subcutaneously was also resorbed, albeit at slower rates, indicating that even at doses equivalent to a human oral dose* of 285 mg/day bone resorption is not completely inhibited by alendronate treatment.

In a three-year study with alendronate in normal mature dogs at doses up to 1 mg/kg/day given orally (equivalent to a human oral dose* of 50 mg/day), there was no evidence of osteomalacia or spontaneous fractures. Histomorphometric evaluation of static and dynamic variables of bone remodeling in the lumbar vertebrae showed: (1) no effect on the cortical and trabecular bone mass or trabecular bone architecture; (2) the expected slight decrease in the rate of bone turnover; and (3) no effect on osteoid maturation time, which is a measure of the time between bone matrix deposition and mineralization. Biomechanical testing showed no deleterious effect on bone strength. The amount of alendronate in bone after three years of treatment at human oral doses* equivalent to 50 mg/day was insignificant (12 ppm) in relation to the total amount of mineral in bone.

Oral treatment with alendronate at 2 mg/kg/day (equivalent to a human oral dose* of 100 mg/day) for 9 weeks before and/or for 16 weeks after an experimental fracture had no deleterious effects on fracture healing in dogs. However, there was a delay in callus remodelling.

Ancillary pharmacology studies evaluating the effects of alendronate on different organ systems showed no important changes in cardiovascular, renal, gastric, and respiratory function in dogs or in central nervous system function in mice.

Four hours after IV administration to mice, [^{3}H] alendronate localization on osteoclast surfaces was about 10-fold higher than on osteoblast surfaces over a wide range of doses, showing selectivity of alendronate for resorption surfaces.

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization was 6000-fold the antiresorptive dose, suggesting a safety margin for drug-induced osteomalacia. The relevance of these findings to humans is unknown.

[*] Based on a patient weight of 50 kg

TOXICOLOGY[12]

Acute Toxicity

The oral LD_{50} values of alendronate in female rats and mice were 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2) (equivalent to human oral doses* of 27,600 and 48,300 mg), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2 (equivalent to a human oral dose* of 10,000 mg).

Chronic Toxicity

Alendronate-related changes in the repeated dose-toxicity studies of up to one year in rats and three years in dogs consisted of retention of primary spongiosa of bone in areas of endochondral bone formation, sustained reduction of alkaline phosphatase activities, and transient reduction in serum calcium and phosphate concentrations. These are related to the desired pharmacologic activity of alendronate. The species most sensitive to nephrotoxicity (dogs) required a dose* equivalent to at least 100 mg in humans to manifest nephrotoxicity. Rats also showed evidence of this effect at higher doses. Gastrointestinal toxicity was seen in rodents only. This appears to be due to a direct effect on the mucosa and occurred only at doses greater than 2.5 mg/kg/day.

Carcinogenicity

No evidence of carcinogenic effect was observed in a 105-week study in rats receiving oral doses up to 3.75 mg/kg/day and in a 92-week study in mice receiving oral doses up to 10 mg/kg/day.

Harderian gland (a retroorbital gland not present in humans) adenomas were increased in high-dose female mice (p **=** 0.003) in a 92-week carcinogenicity study at doses of alendronate of 1, 3 and 10 mg/kg/day (males) or 1, 2 and 5 mg/kg/day (females). These doses are equivalent to 0.5 to 4 times the 10 mg human dose based on surface area, mg/m^2.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p **=** 0.003) in a 2-year carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 1 and 3 times the 10 mg human dose based on surface area.

Mutagenesis

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation. Similarly, no evidence of mutagenicity was observed in an *in vitro* mammalian cell mutagenesis assay, an *in vitro* alkaline elution assay in rat hepatocytes, and an *in vivo* chromosomal aberration assay in mice at IV doses up to 25 mg/kg/day (75 mg/m^2). In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate was weakly positive at concentrations $\geq$ 5 mM in the presence of cytotoxicity. This is of no relevance to safety in humans since similar concentrations are not achievable *in vivo* at therapeutic doses. Furthermore, clear negative results in four of five genotoxicity studies, including the most relevant studies for human carcinogenic potential (the *in vivo* chromosomal aberration assay and the microbial mutagenesis assay), and negative carcinogenicity studies in rats and mice lead to the conclusion that there is no evidence of genotoxic or carcinogenic risks from alendronate in humans.

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[12] [12] [Pr]FOSOMAX® Product Monograph dated December 23, 2015, page 34-35.

* Based on a patient weight of 50 kg

Reproduction
Alendronate had no effect on fertility or reproductive performance (male or female) in rats at oral doses up to 5 mg/kg/day. The only drug-related effect seen in these studies was difficulty in parturition in rats, which is directly related to pharmacologically mediated hypocalcemia. This effect can be prevented in rats by calcium supplementation. Furthermore, a clear no-effect level of 1.25 mg/kg/day was established.

Development
In developmental toxicity studies, there were no adverse effects at doses up to 25 mg/kg/day in rats and 35 mg/kg/day in rabbits.