

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

 **FOSAMAX[®]**

alendronate sodium

Tablet, 70 mg, Oral

Bone Metabolism Regulator

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RECENT MAJOR LABEL CHANGES

| | |
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| 1 INDICATIONS | 07/2021 |
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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FOSAMAX® (alendronate sodium) is indicated for:

- The treatment of osteoporosis in postmenopausal women.
 - For the treatment of osteoporosis in postmenopausal women, FOSAMAX® increases bone mass and prevents fractures, including those of the hip and spine (vertebral compression fractures).
- The treatment of osteoporosis in men.
 - For the treatment of osteoporosis in men, FOSAMAX® increases bone mass and reduces the incidence of fractures.
- The prevention of osteoporosis in postmenopausal women¹
 - For the prevention of osteoporosis, alendronate sodium 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.
- The treatment and prevention of glucocorticoid-induced osteoporosis in men and women.¹
 - Alendronate sodium is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density.

¹ Although alendronate tablets 5 mg, 10 mg, and 40 mg are available in the marketplace, FOSAMAX is no longer marketed in the 5 mg, 10 mg, 35 mg, and 40 mg strengths. It may be necessary to use alternate alendronate sodium products to achieve the appropriate dose.

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](#)).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

- FOSAMAX® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- 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](#)).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Although alendronate tablets 5mg, 10mg, and 40mg may be available in the marketplace, FOSAMAX® is no longer marketed in the 5mg, 10mg, and 40mg strengths. It may be necessary to use alternate alendronate sodium products to achieve the appropriate dose.

Although an oral solution of alendronate may be available in the marketplace, FOSAMAX® oral solution is no longer marketed.

4.2 Recommended Dose and Dosage Adjustment

- **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. The use of alternate alendronate sodium product is necessary to achieve this dose.

- **Prevention of Osteoporosis in Postmenopausal Women**

The recommended dosage is 5 mg once a day. The use of alternate alendronate sodium product is necessary to achieve this dose.

- **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. The use of alternate alendronate sodium product is necessary to achieve this dose.

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 FOSAMAX® 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]). FOSAMAX® is not recommended for patients with more severe renal insufficiency (creatinine clearance < 0.58 mL/s [< 35 mL/min]) due to lack of experience.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

FOSAMAX® 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 FOSAMAX® (see DRUG INTERACTIONS). Waiting less than 30 minutes will lessen the effect of FOSAMAX® by decreasing its absorption into the body.

FOSAMAX® should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX® tablet should be swallowed with a full glass of water (200–250 mL). Patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX® 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 to FOSAMAX® there are no known or theoretical safety concerns related to FOSAMAX® in patients who previously received any other antiosteoporotic therapy.

4.5 Missed Dose

Patients should be instructed that if they miss a dose of FOSAMAX® 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.

5 OVERDOSAGE

No specific information is available on the treatment of overdose with FOSAMAX®. 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|-------------------------|--|--|
| Oral | Tablet/ 70 mg/ Each tablet contains 91.37 mg of alendronate monosodium salt trihydrate, which is equivalent to 70 mg of free acid. | Anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose. |

FOSAMAX®70 mg tablets, a white, oval uncoated tablet with an outline of a bone image on one side and 31 on the other.

FOSAMAX®70 mg tablets are available in blister packages of 4 tablets.

FOSAMAX® tablets are gluten free.

7 WARNINGS AND PRECAUTIONS

General

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, patients should be instructed to swallow each tablet of FOSAMAX® 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 FOSAMAX® 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 FOSAMAX®

immediately and consult their physician.

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

Endocrine and Metabolism

Hypocalcemia must be corrected before initiating therapy with FOSAMAX® (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 FOSAMAX®. 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 FOSAMAX® for predisposing conditions.

Due to the positive effects of FOSAMAX® in increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, in whom the pre-treatment 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 receiving glucocorticoids.

Gastrointestinal

FOSAMAX®, 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 FOSAMAX®. 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 FOSAMAX® 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 FOSAMAX® and/or who fail to swallow it with the recommended amount of water, and/or who continue to take FOSAMAX® 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 FOSAMAX® on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX® 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.

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 FOSAMAX[®]. 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 FOSAMAX[®], the percentages of patients with these symptoms were similar in the FOSAMAX[®] 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.

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.

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 FOSAMAX®.

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.

Reproductive Health: Female and Male Potential Fertility

The effect of FOSAMAX® on human fertility has not been evaluated. Animal study data is included in Section 16. [NON-CLINICAL TOXICOLOGY](#)

7.1 Special Populations

7.1.1 Pregnant Women

FOSAMAX[®] has not been studied in pregnant women and should not be given to them. The extent of exposure in pregnancy during clinical trials: No experience.

7.1.2 Breast-feeding

It is unknown whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. FOSAMAX[®] should not be used during breast-feeding.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

In clinical studies, there was no age-related difference in the efficacy or safety profiles of FOSAMAX[®].

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In clinical studies, FOSAMAX[®] 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.

FOSAMAX[®] has been evaluated for safety in clinical studies in approximately 7200 postmenopausal women.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 FOSAMAX[®] 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 FOSAMAX[®] 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 $\geq 1\%$ of patients treated with either FOSAMAX[®] 10 mg/day or placebo are presented in the following table.

Table 1 - Drug-Related* Adverse Experiences Reported in $\geq 1\%$ of Patients Treated for Osteoporosis

| | FOSAMAX[®] 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 | 0.5 | 1.0 |

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

One patient treated with FOSAMAX[®] (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 FOSAMAX[®] 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 FOSAMAX[®] 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued FOSAMAX[®] 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 FOSAMAX® 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: FOSAMAX®, 3.2%; placebo, 2.7%. The overall adverse experience profile was similar to that seen in other studies with FOSAMAX® 5 or 10 mg/day.

In a one-year, double-blind multicenter study, the overall safety and tolerability profiles of FOSAMAX® 70 mg once weekly and FOSAMAX® 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:

Table 2 - Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients Treated for Osteoporosis

| | FOSAMAX® 70 mg once weekly n = 519 (%) | FOSAMAX® 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 distention | 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 FOSAMAX® 10 mg/day [n=146] and a one-year study of FOSAMAX® 70 mg once weekly [n=109]), the safety profile of FOSAMAX® 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 FOSAMAX® mg/day vs. 10.5% for placebo, and 6.4% for FOSAMAX® 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 FOSAMAX® 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 FOSAMAX® 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 FOSAMAX® 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX® for either two or three years. In these studies, the overall safety profiles of FOSAMAX® 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 FOSAMAX® 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 FOSAMAX® 5 mg/day or placebo are presented in the following table:

Table 3 - Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients. Prevention of Osteoporosis

| | FOSAMAX® 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 |

| | FOSAMAX® 5 mg / day n = 642 (%) | Placebo n = 648 (%) |
|---|--|------------------------------------|
| Musculoskeletal | | |
| musculoskeletal (bone, muscle or joint) | 2.9 | 3.2 |
| pain | 0.2 | 1.1 |
| muscle cramp | | |

* 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 FOSAMAX® 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 FOSAMAX® 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 FOSAMAX® 5 or 10 mg/day or placebo are presented in the following table:

Table 4 - Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients. Treatment and Prevention of Glucocorticoid-induced Osteoporosis

| | FOSAMAX® 10 mg / day n = 157 (%) | FOSAMAX® 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.

8.3 Less Common Clinical Trial Adverse Reactions

Skin: rash and erythema

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

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 FOSAMAX[®] 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 P¹/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.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported in post-marketing use of FOSAMAX[®]:

Body as a Whole: hypersensitivity reactions including urticaria and angioedema; transient symptoms of myalgia, malaise, asthenia and fever have been reported with FOSAMAX[®] 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](#))

¹ 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)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Animal studies have demonstrated that FOSAMAX[®] 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, FOSAMAX[®] is not expected to interact with other drugs based on effects on protein binding, renal excretion, or metabolism of other drugs.

9.3 Drug-Behavioural 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 FOSAMAX[®] (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 FOSAMAX[®] may vary.

9.4 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 FOSAMAX[®]. Therefore, patients must wait at least one-half hour after taking FOSAMAX[®] 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 H₂-antagonists is unknown; no other specific drug interaction studies were

performed.

Concomitant use of hormone replacement therapy (HRT [estrogen ± progestin]) and FOSAMAX[®] was assessed in two clinical studies of one- or two-years' duration in postmenopausal osteoporotic women. Combined use of FOSAMAX[®] 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 Trial Adverse Drug Reactions, 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. FOSAMAX[®] 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 FOSAMAX[®] greater than 10 mg and acetylsalicylic acid-containing products. This was not observed in a study with FOSAMAX[®] 70 mg once weekly.

FOSAMAX[®] may be administered to patients taking nonsteroidal anti-inflammatory drugs (NSAIDs). In a three-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 FOSAMAX[®] 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 FOSAMAX[®]

9.5 Drug-Food Interactions

Food and beverages other than plain water may markedly reduce the absorption and effectiveness of alendronate. FOSAMAX[®] 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](#)).

9.6 Drug-Herb Interactions

Herbal products may interfere with the absorption of alendronate. FOSAMAX[®] must be taken at least one-half hour before any herbal products.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

FOSAMAX® 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.

10.2 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.

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 x-ray, 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 FOSAMAX® 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked 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 FOSAMAX® 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 FOSAMAX®. In osteoporosis treatment studies, FOSAMAX® 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, FOSAMAX® 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 FOSAMAX® 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 FOSAMAX®. 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 FOSAMAX® 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 FOSAMAX® 5 mg/day. In a one-year study with FOSAMAX® 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 FOSAMAX® 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 FOSAMAX® 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 FOSAMAX® 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, FOSAMAX® 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, FOSAMAX® 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

10.3 Pharmacokinetics

Table 5 - Summary of alendronate sodium 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.

Elimination

Following a single IV dose of [¹⁴C] 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 FOSAMAX[®] (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:** The oral bioavailability in children (4 to 16 years of age) with osteogenesis imperfecta (OI) was similar to that observed in adults; however, FOSAMAX[®] is not indicated for use in children (see [WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics](#)).
- **Geriatrics:** 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](#)).

- **Sex:** Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.
- **Ethnic Origin:** 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]). FOSAMAX® is not recommended for patients with more severe renal insufficiency (creatinine clearance < 0.58 mL/s [< 35 mL/min]) due to lack of experience.

11 STORAGE, STABILITY AND DISPOSAL

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

Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

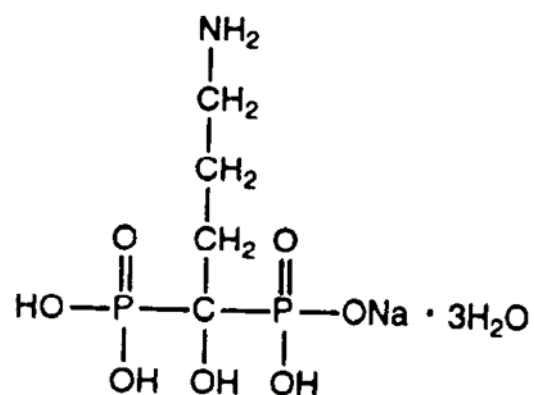
Drug Substance

Proper name: alendronate sodium

Chemical name: FOSAMAX® contains alendronate sodium, which is described chemically as: (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

Molecular formula and molecular mass: $C_4 H_{12} NNaO_7 P_2 \cdot 3H_2O$ and 325.12

Structural formula:



Physicochemical properties: Alendronate is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of osteoporosis in postmenopausal women

Table 6 - Summary of patient demographics for clinical trials (treatment of osteoporosis in postmenopausal women)

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---------|---|---|--------------------|------------------|-------|
| PN035 | Double -blind, randomized, placebo-controlled, parallel group multicenter extension study | PBO FOS 5mg FOS 10mg FOS 20/5mg ORAL 3 years | 478 | 45-82 | Women |
| PN037 | Double -blind, randomized, placebo-controlled, parallel group multicenter extension study | PBO FOS 5mg FOS 10mg FOS 20/5mg ORAL 3 years | 516 | 44 to 84 | Women |
| PN041 | Double-blind, randomized, parallel-group study | PBO FOS 10mg FOS 20mg sCT ORAL 2 years | 286 | 48-76 | Women |
| PN118 | Randomized, Double-blind, multicenter study | FOS 10mg FOS 35mg (twice a week) FOS 70mg (once a week) ORAL 1 year | 1258 | 42-95 | Women |

| | | | | | |
|-------|--|---|------|-------|-------|
| PN026 | Double-blind, randomized, placebo controlled-parallel group, multicenter study | PBO FOS 5mg FOS 10mg FOS 20mg/PBO FOS 40mg/PBO FOS 40mg/2.5mg ORAL 2 (+1*year) | 188 | 42-75 | Women |
| PN054 | Double-blind, randomized, placebo controlled, parallel-group study | PBO FOS 1mg FOS 2.5mg FOS 5mg ORAL 2 years | 359 | 59-85 | Women |
| FIT 1 | Randomized, placebo-controlled | PBO FOS 10mg ORAL 3 years | 2027 | 55-81 | Women |
| FIT 2 | Randomized, placebo-controlled | PBO FOS 10mg ORAL 4 years | 4432 | 55-80 | Women |

| | | | | | |
|-------|---|--|-----|-------|-------|
| PN072 | Double-blind, randomized, placebo-controlled, multicenter study | FOS 10mg + conjugated estrogens (0.625 mg) OR conjugated estrogens (0.625 mg) OR PBO OR FOS 10mg ORAL 2 years | 425 | 42-82 | Women |
| PN097 | Triple-blind, randomized, placebo-controlled, parallel-group, multicenter study | FOS 10 mg/day + HRT (estrogen + progestin) OR PBO/HRT ORAL 1 year | 428 | 40-84 | Women |

PBO= Placebo; FOS=alendronate (mg/day); sCT=Intranasal salmon calcitonin 100 IU/day; FOS 20/PBO, FOS 40/PBP= alendronate 20 or 40mg for 1 year followed by placebo for 1 year; FOS 40/2.5= alendronate 40mg for 3 months followed by 2.5 for 21 months; FOS 20/5=alendronate 20mg for 2 years followed by 5mg for 1 year

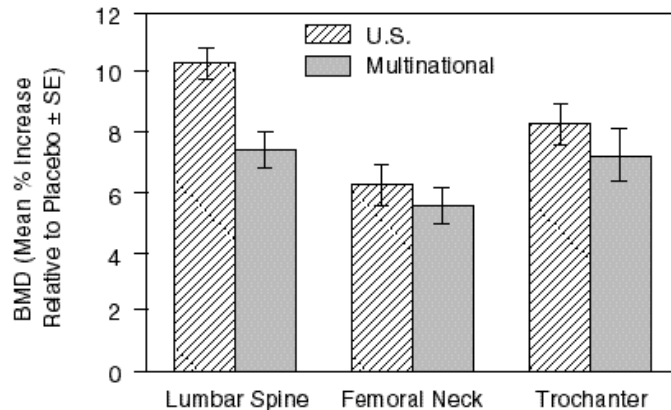
*Following 2 years of treatment, patients were followed for a further year off treatment

Effect on Bone Mineral Density

The efficacy of FOSAMAX® 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 BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX® 10 mg/day relative to placebo-treated patients at three years for each of these studies.

Osteoporosis Treatment Studies in Postmenopausal Women

Increase in BMD FOSAMAX 10 mg/day at Three Years

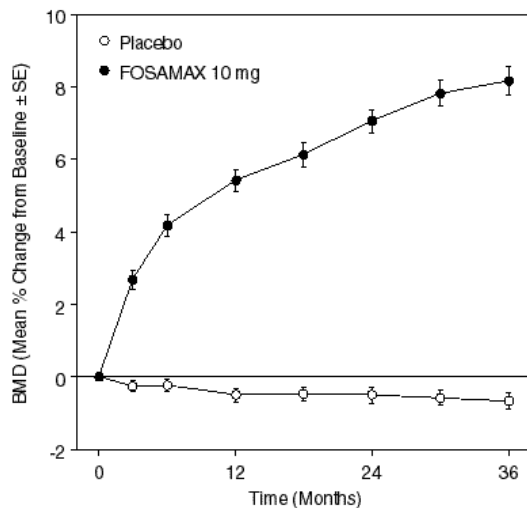


In the combined studies, after three years, BMD of the lumbar spine, femoral neck and trochanter in placebo-treated patients decreased significantly by between 0.65 and 1.16%. Highly significant increases, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX[®] 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 FOSAMAX[®] 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, FOSAMAX[®] reverses the progression of osteoporosis. FOSAMAX[®] 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 FOSAMAX 10 mg/day Versus Placebo:
Lumbar Spine BMD Percent Change from Baseline



In a separate study, FOSAMAX[®] 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 FOSAMAX[®] 70 mg once weekly (n=519) and FOSAMAX[®] 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 10-mg daily group. The two treatment groups were also similar with regard to BMD increases at other skeletal sites. In trials with FOSAMAX[®] 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 FOSAMAX[®] 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 FOSAMAX[®] must be continuous to produce progressive increases in bone mass.

Effect on Fracture Incidence

To assess the effects of FOSAMAX[®] on vertebral fracture incidence, the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of FOSAMAX[®] (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 FOSAMAX[®] 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 FOSAMAX[®] 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 (FOSAMAX[®] n=1012, placebo: n=590) revealed a significant 29% reduction in non-vertebral fracture incidence (FOSAMAX[®] 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 (FOSAMAX[®] n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX[®] resulted in statistically significant and clinically meaningful reductions in fracture incidence at three years as shown in the following table.

Table 7 - Effect of FOSAMAX[®] on Fracture Incidence in the Three-Year Study of FIT (Patients with Vertebral Fracture at Baseline)

| Patients with: | % of Patients | | Reduction (%) in Fracture Incidence |
|--|-------------------------------|------------------|-------------------------------------|
| | FOSAMAX [®] (n=1022) | Placebo (n=1005) | |
| 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* |

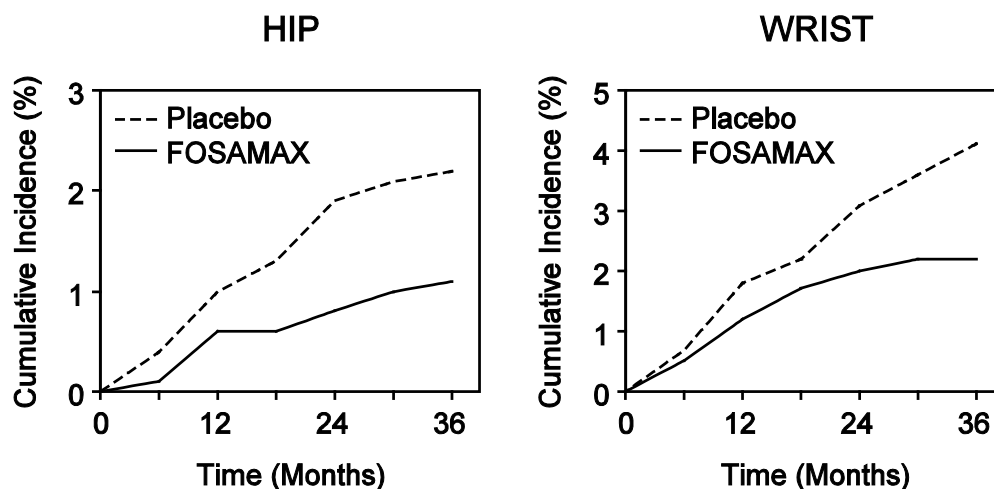
†Number evaluable for vertebral fracture: FOSAMAX[®], n=984; placebo, n=966

- * p < 0.05
- ** p < 0.01
- *** p < 0.001

Furthermore, in this population of patients with baseline vertebral fracture, treatment with FOSAMAX® 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 FOSAMAX® compared with placebo at all time points. FOSAMAX® 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 (FOSAMAX® n=2214; placebo, n=2218) further demonstrated the reduction in fracture incidence due to FOSAMAX®. 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.

Table 8 - Effect of FOSAMAX® on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT (Patients without Vertebral Fracture at Baseline)

| Patients with: | % of Patients | | Reduction (%) in Fracture Incidence |
|--------------------------------|----------------------|----------------------|-------------------------------------|
| | FOSAMAX® (n=1545) | Placebo (n= 1521) | |
| ≥ 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: FOSAMAX®, 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 FOSAMAX®, 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.

Table 9 - Effect of FOSAMAX® on Fracture Incidence in the Combined (Three- and Four-Year) Studies of FIT

| Patients with: | Reduction (%) in Fracture Incidence FOSAMAX® vs. Placebo | |
|---|---|--------------------------|
| | 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 ² | 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=0.059

*p < 0.05

**p < 0.01

***p < 0.001

Consistency of Fracture Results

The reductions in the incidence of vertebral fractures (FOSAMAX[®] 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 FOSAMAX[®] 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, FOSAMAX[®] 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, FOSAMAX[®] reduces the incidence of vertebral fractures whether or not patients have experienced a previous vertebral fracture.

Overall, these results demonstrate the consistent efficacy of FOSAMAX[®] 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 FOSAMAX[®] 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 FOSAMAX[®] is of normal quality.

Treatment of osteoporosis in men

Table 10 - Summary of patient demographics for clinical trials (treatment of osteoporosis in men)

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---------|--|--|--------------------|------------------|-----|
| PN096 | Double-blind randomized placebo-controlled, multicenter, multinational study | PBO FOS 10mg Calcium (500 mg) and Vitamin D (400 IU) supplement daily ORAL 2 years | 241 | 31-87 | Men |
| PN165 | Double-blind, placebo-controlled, multicenter study | PBO FOS 70mg (once weekly) ORAL 1 year | 167 | 38-91 | Men |

PBO= Placebo; FOS=alendronate (mg/day)

The efficacy of FOSAMAX® in men with osteoporosis was demonstrated in two clinical studies.

A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX® 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 FOSAMAX® 10 mg/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, FOSAMAX® 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 FOSAMAX® 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.

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

Prevention of osteoporosis in postmenopausal women

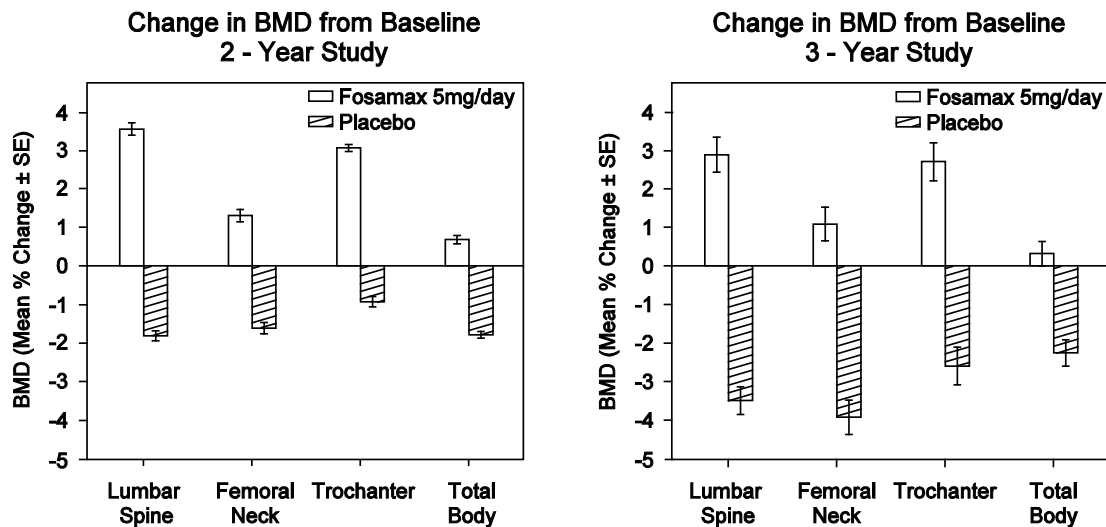
Table 11 - Summary of patient demographics for clinical trials (prevention of osteoporosis in postmenopausal women)

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---------|---|--|--------------------|------------------|-------|
| PN055 | Double-blind, placebo-controlled | PBO FOS 2.5mg FOS 5mg Estrogen/progestin ORAL 2 years | 1609 | 44-60 | Women |
| PN029 | Double-blind, placebo-controlled, parallel-group, multicenter study | PBO FOS 1mg FOS 5mg FOS 10mg FOS 20mg/PBO ORAL 3 years | 447 | 40-60 | Women |

PBO= Placebo; FOS=alendronate (mg/day)

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 (FOSAMAX® 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 (FOSAMAX® 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, FOSAMAX® 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, FOSAMAX® 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX® 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 FOSAMAX® at doses of up to 10 mg/day.

Concomitant Use with Estrogen/Hormone Replacement Therapy (HRT)

The effects on BMD of treatment with FOSAMAX® 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 FOSAMAX® alone (both 6.0%).

The effects on BMD when FOSAMAX® 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 FOSAMAX® 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.

Treatment and prevention of glucocorticoid-induced osteoporosis in men and women

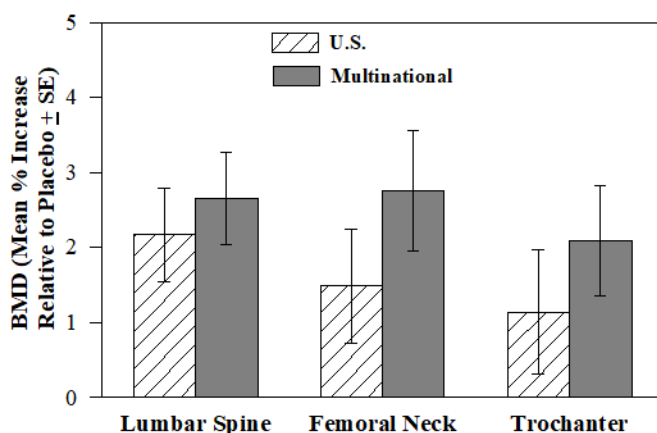
Table 12 - Summary of patient demographics for clinical trials (treatment and prevention of glucocorticoid-induced osteoporosis in men and women)

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---------|---|---|--------------------|------------------|--------------|
| PN082 | Randomized, double-blind placebo-controlled, dose ranging | PBO FOS 2.5 mg FOS 5 mg FOS 10mg 7.5 mg/day prednisone or equivalent ORAL 48 weeks | 328 | 17-79 | Men Women |
| PN083 | Randomized, double-blind placebo-controlled, dose ranging | PBO FOS 5mg FOS 10mg 7.5 mg/day prednisone or equivalent ORAL 48 weeks | 232 | 19-83 | Men Women |

PBO= Placebo; FOS=alendronate (mg/day)

The efficacy of FOSAMAX® 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 FOSAMAX® 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 FOSAMAX® 5 mg/day for each study.

**Studies in Glucocorticoid - Treated Patients
Increase in BMD
FOSAMAX 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 FOSAMAX[®] 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 FOSAMAX[®] 5 or 10 mg/day. The increases in BMD (relative to placebo) with FOSAMAX[®] 10 mg/day were greater than those with FOSAMAX[®] 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. FOSAMAX[®] was effective regardless of dose or duration of glucocorticoid use. In addition, FOSAMAX[®] 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 FOSAMAX[®] 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 FOSAMAX[®] 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 FOSAMAX[®] 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 FOSAMAX[®] (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 (FOSAMAX[®] 0.7% vs. placebo 6.8%).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

The oral LD50 values of alendronate in female rats and mice were 552 mg/kg (3256 mg/m²) and 966 mg/kg (2898 mg/m²) (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/m²) (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/m².

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.

Genotoxicity: 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/m²). In an in vitro chromosomal aberration assay in Chinese hamster ovary cells, however,

alendronate was weakly positive at concentrations ≥ 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.

Reproductive and Developmental Toxicology: 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.

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FOSAMAX®

alendronate sodium tablets

Read this carefully before you start taking **FOSAMAX®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FOSAMAX®**.

What is FOSAMAX® used for?

FOSAMAX is used in adults to treat osteoporosis in men and postmenopausal women. Osteoporosis is a thinning and weakening of the bones. FOSAMAX® helps to rebuild bone and makes bone less likely to fracture.

FOSAMAX is not for use in children under 18 years of age.

How does FOSAMAX® work?

FOSAMAX contains a medicinal ingredient called alendronate sodium. Alendronate sodium belongs to a class of non-hormonal drugs called bisphosphonates. The bisphosphonates are similar to a molecule naturally made in your body that will break down bone tissue. Alendronate binds to the receptors in your body to prevent the bone from breaking down. This process also helps rebuild bone.

What are the ingredients in FOSAMAX®?

Medicinal ingredients: alendronate sodium.

Non-medicinal ingredients: Anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

FOSAMAX® comes in the following dosage forms:

Tablet 70 mg.

Do not use FOSAMAX® if you:

- Have certain disorders of the esophagus (the tube that connects your mouth with your stomach)
- Are unable to stand or sit upright for at least 30 minutes.
- Are allergic to alendronate sodium any other ingredients in FOSAMAX. If you are not sure about this, talk to your healthcare professional before taking FOSAMAX.
- Have low blood calcium.

- Have SEVERE kidney disease. If you have any doubts if this applies to you, speak to your physician.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FOSAMAX®. Talk about any health conditions or problems you may have, including if you:

- have low blood calcium or a condition that affects your ability to absorb minerals (i.e. Vitamin D deficiency). This condition must be treated before you begin treatment with FOSAMAX. Your doctor will monitor your condition during your treatment. You should consume a sufficient amount of calcium and Vitamin D if you are already receiving glucocorticoids medicines. Speak to your doctor if you experience muscle spasms or nerve problems (i.e. abnormal tingling or prickling sensations).
- have digestive problems. These may include difficulty swallowing, esophagus diseases, ulcers, inflammation of the first part of the small intestines, and inflammation of the lining of the stomach.
- may be at risk of developing osteonecrosis (bone damage in the jaw). Speak to your doctor if have a planned dental extraction. Your doctor may request a dental check-up before starting FOSAMAX. You may also be at risk of causing bone damage to your jaw if you:
 - o have cancer
 - o have or had poor dental health, gum or teeth disease
 - o have poor oral hygiene, dentures that do not fit well.
 - o have anemia (low red blood cell count)
 - o have infection
 - o have a blood disorder where your blood cannot form clots in the normal way
 - o have diabetes (high blood sugar).
 - o get chemotherapy, or radiotherapy.
 - o take corticosteroids, or immunosuppressive drugs.
 - o take angiogenesis inhibitors; they are drugs that slow down the growth of new blood vessels and are used mostly to treat cancer (e.g. bevacizumab).
 - o are or have been a smoker.
 - o are a heavy alcohol user.
- have or have had any medical problems including known kidney disease.
- have any allergies.

Other warnings you should know about:

Gastrointestinal Problems

Taking FOSAMAX incorrectly may cause you to experience problems with your esophagus. Stop taking FOSAMAX and speak to your doctor if you experience difficulty or pain upon

swallowing, chest/breastbone pain or new or worsening heartburn. To avoid problems with your esophagus and allow the drug to reach the stomach, consider the following instructions:

- swallow each tablet of FOSAMAX with a full glass of water.
- do NOT chew or suck the tablet.
- do NOT lie down for at least 30 minutes and until your first meal of the day.
- do NOT take FOSAMAX at bedtime or before starting your day.

Muscle and skeletal problems

Drugs such as FOSAMAX may cause serious bone, joint or muscle pain. You may experience relief from these symptoms after you end your treatment. Long term treatment with FOSAMAX may cause stress fractures (repetitive trauma) or low energy fractures (falls from standing). Your doctor will:

- evaluate your condition if they suspect you have developed a fracture.
- will examine the cause of the stress fracture and provide appropriate care
- pause your treatment depending on your condition.

Eye problems

Drugs such as FOSAMAX may cause vision problems. Different parts of your eye may experience inflammation or you may develop an eye infection. Your doctor may end your treatment if they identify symptoms of inflammation.

Bone damage in ear

Treatment with FOSAMX may cause bone damage in your ear. Talk to your doctor if you have ear pain and/or discharge from the ear while taking FOSAMAX®

Use in pregnancy and breast-feeding

Do not take Fosamax if you are pregnant or breast feeding.

Lifestyle changes:

Consult with your doctor about lifestyle changes when taking FOSOMAX. These may include changes to your diet, use of dietary supplements, exercising and stop smoking.

Driving and using machines:

Before you do tasks that may require special attention, wait until you know how you respond to FOSAMAX. There have been side effects reported with FOSAMAX that may affect your ability to drive or operate machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FOSAMAX®:

- Calcium supplements, antacids, and other oral medications will interfere with the absorption of FOSAMAX® if they are taken at the same time. You must wait at least half an hour after taking FOSAMAX® before taking any other oral medication.
- Intravenous ranitidine
- herbal products, food and beverages other than plain water may impact your ability to absorb FOSAMAX. Wait at least half an hour after taking FOSAMAX before you take any herbal products, food or beverages.

How to take FOSAMAX®:

- Always take FOSAMAX exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
- It is important that you continue taking FOSAMAX® for as long as your doctor prescribes it.
- Your doctor may ask you to take calcium and vitamin D while you are on FOSAMAX® therapy.

Usual dose:

Take one FOSAMAX tablet once a week.

Follow these instructions carefully:

1. Choose the day of the week that best fits your schedule. Every week, take one tablet of FOSAMAX® on your chosen day.
2. After getting up for the day and before taking your first food, beverage, or other medication, swallow your FOSAMAX® tablet only with plain water (200 to 250 mL). **Do NOT chew or suck on the tablet.** To make sure FOSAMAX is absorbed by your body, do **NOT** take FOSAMAX with:
 - mineral water
 - coffee or tea
 - juice

If your normal drinking water is classified as “hard water”, you should consider taking this medication with distilled water (i.e., not mineral water).

3. After taking your FOSAMAX®, do not lie down - stay fully upright (sitting, standing or walking) for at least 30 minutes and do not lie down until after your first food of the day.
4. Do NOT take FOSAMAX® at bedtime or before getting up for the day. This will help FOSAMAX:
 - reach your stomach quickly and;

- reduce the potential for irritation of your esophagus (the tube that connects your mouth with your stomach).
5. After taking your FOSAMAX[®], wait at least 30 minutes before taking your first food, beverage, or other medication of the day. This includes antacids, calcium supplements and vitamins. FOSAMAX[®] is effective only if taken when your stomach is empty.
6. If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking FOSAMAX[®] immediately and call your doctor.

Overdose:

If you take too much FOSAMAX, drink a full glass of milk and contact your physician immediately. Do not make yourself vomit. Do not lie down.

If you think you, or a person you are caring for, have taken too much FOSAMAX[®], contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, just take one dose of FOSAMAX[®] on the morning after you remember. Do NOT take two doses on the same day. Return to taking one dose once a week, as originally scheduled on your chosen day.

What are possible side effects from using FOSAMAX[®]?

These are not all the possible side effects you may have when taking FOSAMAX[®]. If you experience any side effects not listed here, tell your healthcare professional.

- digestive problems
 - Acid reflux
 - Bloating feeling in stomach
 - Constipation
 - Diarrhea
 - Excessive gas
 - Nausea
 - Stomach pain
 - Vomiting
- dizziness, spinning sensation or a changed sense of taste.
- flu-like symptoms (rarely with fever) and/or generally feeling unwell.
- joint swelling or swelling in their hands or legs.
- lack or loss of strength
- mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.
- muscle cramps and/or aches
- skin problems

- Rash that may be made worse by sunlight
- Hair loss
- Itchy skin

| Serious side effects and what to do about them | | | |
|---|---|---------------------|--|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| UNCOMMON | | | |
| Allergic reactions such as: - hives - swelling of the face, lips, tongue and/or throat - difficulty in breathing or swallowing | | | √ |
| Severe bone, joint, and/or muscle pain | | √ | |
| New or unusual pain in the hip or thigh | | √ | |
| Esophageal inflammation or ulcers causing: - chest pain - heartburn - difficulty or pain upon swallowing | | | √ |
| Stomach inflammation, stomach or other peptic ulcers occasionally associated with black and/or bloody stools | | | √ |
| Jaw problems associated with delayed healing and infection, often following tooth extraction | | | √ |
| Eye inflammation associated with eye pain; eye redness; sensitivity to light, decreased vision | | | √ |
| Stevens-Johnson syndrome and/or toxic epidermal necrolysis (Severe skin | | | √ |

| Serious side effects and what to do about them | | | |
|--|--------------------------------------|--------------|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| reactions): redness, blistering and/or peeling of large areas of the skin | | | |
| Low blood calcium: - numbness or tingling around the mouth or in the hands or feet - muscle spasms in the face, hands, or feet | | | √ |
| RARE | | | |
| Persistent ear pain | | √ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health

Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Do not use this medicine after the month and year written after EXP (expiry date) on the container.

Keep out of reach and sight of children.

If you want more information about FOSAMAX®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>; the Organon Canada website www.organon.ca, or by calling 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.

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