PRODUCT MONOGRAPH

PrFOSAMAX®

alendronate sodium tablets
40 mg and 70 mg alendronate

alendronate sodium oral solution
70 mg/75 mL alendronate

Bone Metabolism Regulator

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Date of Revision:
February 20, 2013

Submission Control No: 160679

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FOSAMAX®

alendronate sodium

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 40 mg, 70 mg	Lactose anhydrous. *For a complete listing see Dosage Forms, Composition and Packaging section.*
Oral	Oral Solution 70 mg/75 mL	

INDICATIONS AND CLINICAL USE

FOSAMAX® (alendronate sodium) is indicated for:

- The treatment and prevention of osteoporosis in postmenopausal women.

    - For the treatment of osteoporosis, FOSAMAX® 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, FOSAMAX® 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 FOSAMAX® 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.

    - 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.

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

- 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.
- Patients at increased risk of aspiration should not receive FOSAMAX® oral solution.
- Hypocalcemia (see WARNINGS AND PRECAUTIONS).
- Renal insufficiency with creatinine clearance < 0.58 mL/s [< 35 mL/min] (see DOSAGE AND ADMINISTRATION).

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. To facilitate gastric emptying, patients should drink at least 60 mL (a quarter of a cup) of water after taking FOSAMAX® oral solution. 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.

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer 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, 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.

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.

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.

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, 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

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.

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:
FOSAMAX® has not been studied in pregnant women and should not be given to them.

Nursing Women:
FOSAMAX® has not been studied in nursing mothers and should not be given to them.

Pediatrics (< 18 years of age):
FOSAMAX® is not indicated for use in children.

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

Monitoring and Laboratory Tests:
Not Applicable.

ADVERSE REACTIONS

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, 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.

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 ≥ 1% of patients treated with either FOSAMAX® 10 mg/day or placebo are presented in the following table.

Drug-Related* Adverse Experiences Reported in ≥ 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		
taste perversion	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:

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, 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® 10mg/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:

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

* 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:

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.

Paget's Disease of Bone

In clinical studies (Paget's disease and osteoporosis), adverse experiences reported in 175 patients taking FOSAMAX® 40 mg/day for 3 - 12 months were similar to those in postmenopausal women treated with FOSAMAX® 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX® 40 mg/day (17.7% FOSAMAX® 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 FOSAMAX® 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 FOSAMAX® 40 mg/day and 2.4% of patients treated with placebo.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Skin: Rarely, rash and erythema have occurred.

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 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 P*/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

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: Hypersensitivity reactions including urticaria and rarely angioedema. As with other bisphosphonates, transient symptoms as in an acute-phase response (myalgia, malaise, asthenia and rarely, fever) have been reported with FOSAMAX®, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, both in association with predisposing conditions and in patients without known predisposing conditions. Rarely, peripheral edema.

Dental: Localized osteonecrosis of the jaw (ONJ) has been reported rarely with oral bisphosphonate treatment. ONJ is generally associated with local infection (including osteomyelitis), tooth extraction with delayed healing (see WARNINGS AND PRECAUTIONS, General).

Gastrointestinal: Esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Some of these have been serious and required hospitalization. Rarely, gastric or duodenal ulcers, some severe and with complications (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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

Nervous System: Dizziness, vertigo, dysgeusia.

Skin: Rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.
Special Senses: Rarely uveitis, scleritis or episcleritis.

* P: Elemental phosphorus

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.

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 H_2-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®.

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).

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.

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 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.

DOSAGE AND ADMINISTRATION

Recommended Dose

Treatment of Osteoporosis in Postmenopausal Women and in Men
The recommended dosage is:
- one 70 mg tablet once weekly
  or
- one bottle of 70 mg oral solution 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 FOSAMAX®. Specific retreatment data are not available, although responses to FOSAMAX® were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX® 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 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.

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.

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). To facilitate gastric emptying, FOSAMAX® oral solution should be followed by at least 60 mL (a quarter of a cup) of water. 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 or Paget's disease to FOSAMAX®, there are no known or theoretical safety concerns related to FOSAMAX® in patients who previously received any other antiosteoporotic or antipagetic therapy.

OVERDOSAGE

No specific information is available on the treatment of overdosage 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.

ACTION AND CLINICAL PHARMACOLOGY

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.

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%).

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.

FOSAMAX® decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, FOSAMAX® 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, FOSAMAX® 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 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).

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]). 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.

STORAGE AND STABILITY

Tablets:
Store at room temperature (15°C - 30°C).

Oral Solution:
Store at 25°C, excursions permitted to 15°C - 30°C. Do not freeze.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms
FOSAMAX® 40 mg tablets, a white, triangle-shaped uncoated tablet with FOSAMAX on one side and MSD 212 on the other. Available in blister packages of 28 tablets.

FOSAMAX® 70 mg tablets, a white, oval uncoated tablet with an outline of a bone image on one side and 31 on the other. Available in blister packages of 4 tablets.

FOSAMAX® 70 mg/75 mL oral solution, is a clear, colorless solution with a raspberry flavor. Available in unit-of-use cartons of 4 single-dose bottles.

Composition
Each tablet of FOSAMAX® contains 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 40 and 70 mg, respectively, of free acid and the following non-medicinal ingredients: anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

FOSAMAX® tablets are gluten free.

Each bottle of FOSAMAX® oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid and the following non-medicinal ingredients: artificial raspberry flavor, citric acid anhydrous, purified water, sodium citrate dihydrate and sodium saccharin. Added as preservatives are sodium propylparaben and sodium butylparaben.

FOSAMAX® oral solution is gluten free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

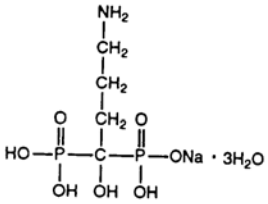
Proper name: alendronate sodium

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

Molecular formula: $C_4H_{12}NNaO_7P_2 \bullet 3H_2O$

Molecular mass: 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.

CLINICAL TRIALS

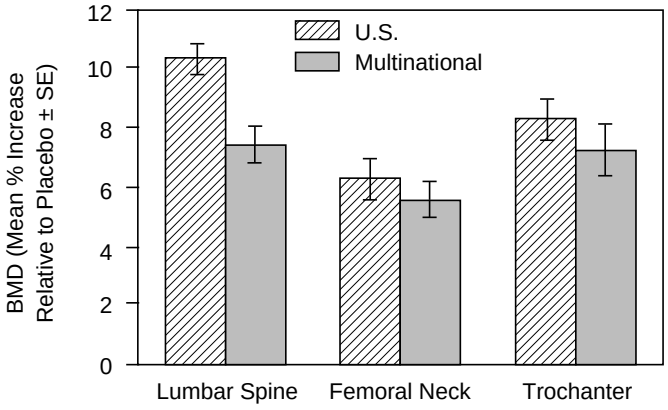
Treatment of Osteoporosis

Postmenopausal Women

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

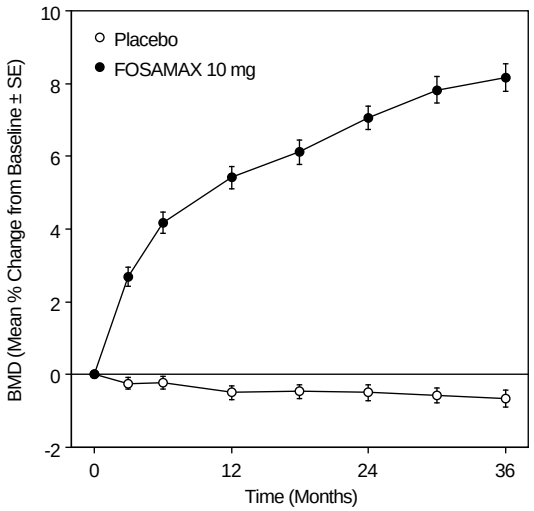


In the combined studies, after three years, BMD of the lumbar spine, femoral neck and trochanter in placebo-treated patients decreased significantly by between 0.65 and 1.16%. Highly significant increases, relative both to baseline and placebo, were seen at each measurement site in each study in patients 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.

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

Patients with:	% of Patients FOSAMAX® (n = 1022)	% of Patients 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*

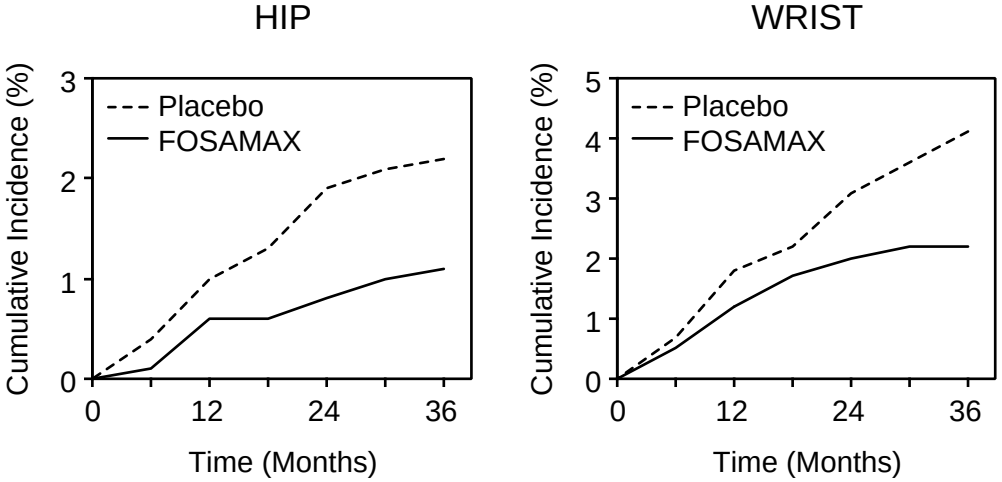
† Number evaluable for vertebral fracture: FOSAMAX®, n=984; placebo, n=966
* p<0.05, ** p<0.01, *** p<0.001

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.

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.

Effect of FOSAMAX® on Fracture Incidence in the Combined (Three- and Four-Year) Studies of FIT		
	Reduction (%) in Fracture Incidence FOSAMAX® 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†††	18ᵀ	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<0.01, *** p<0.001, ‡‡ p=0.059

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.

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

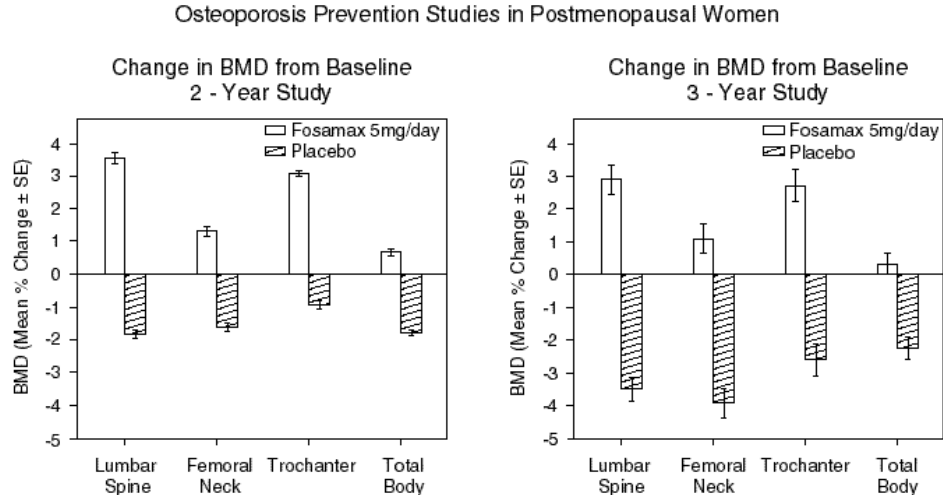
A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX® 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX® 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; 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 (see SELECTED BIBLIOGRAPHY).

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
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.



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.

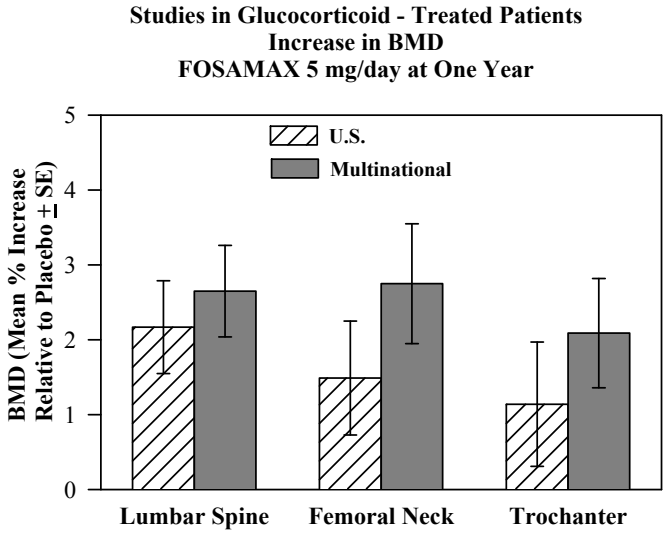
Concomitant Use with Estrogen/Hormone Replacement Therapy (HRT)
The effects on BMD of treatment with FOSAMAX® 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic 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.

Glucocorticoid-Induced Osteoporosis

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.



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.

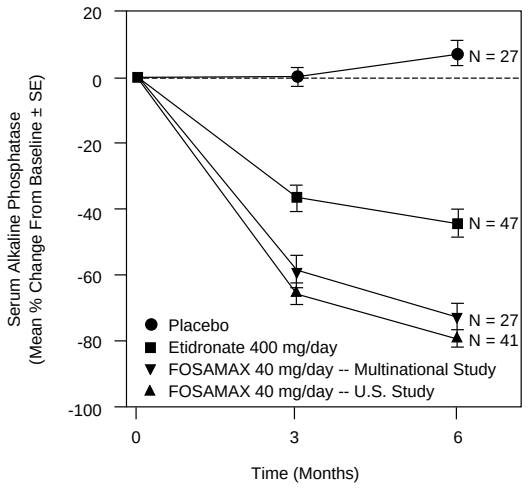
After one year, 2.3% of patients treated with FOSAMAX® 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with FOSAMAX® (pooled dosage groups: 5 or 10 mg for two years or 2.5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

Paget's Disease of Bone

The efficacy of FOSAMAX® 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 FOSAMAX 40 mg/day
Versus Placebo or Etidronate 400 mg/day



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX® 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 ≥ 60%) occurred in approximately 85% of patients treated with FOSAMAX® in the combined studies vs 30% in the etidronate group and 0% in the placebo group. FOSAMAX® 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 FOSAMAX® 40 mg/day for 6 months. As in patients treated for osteoporosis (see CLINICAL TRIALS, Treatment of Osteoporosis, Postmenopausal Women, Bone Histology) FOSAMAX® did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX®, even where preexisting bone was woven and disorganized. Overall, bone histology data confirm that bone formed during treatment with FOSAMAX® is of normal quality.

DETAILED PHARMACOLOGY

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.

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

*Based on a patient weight of 50 kg

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 μg/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 μg/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.

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 μg/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 μg/kg/day subcutaneously was completely resorbed 24 days after cessation of treatment versus 14 days in

* Based on a patient weight of 50 kg

controls. Bone formed at 8 and 40 µg/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.

TOXICOLOGY

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 ≥ 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.

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* Based on a patient weight of 50 kg

*Based on a patient weight of 50 kg

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.

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.

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PART III: CONSUMER INFORMATION

℞FOSAMAX®
alendronate sodium tablets and oral solution
70 mg alendronate once weekly dosage

This leaflet is part III of a three-part "Product Monograph" published when FOSAMAX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FOSAMAX®. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this insert carefully before starting FOSAMAX® once weekly and every time your prescription is renewed.

ABOUT THIS MEDICATION

What the medication is used for:
FOSAMAX® is the brand name for the substance alendronate sodium available **only on prescription** from your physician. Alendronate sodium is a member of a class of non-hormonal drugs called bisphosphonates.

Your physician has prescribed FOSAMAX® because you have a disease known as osteoporosis. FOSAMAX® helps to rebuild bone. This will help prevent you from developing fractures.

Since it is not known how long FOSAMAX® should be continued for osteoporosis, you should discuss the need to stay on this medication with your doctor regularly to determine if FOSAMAX® is still right for you

What it does:
How is normal bone maintained?
Bone undergoes a normal process of rebuilding that occurs continuously throughout your skeleton. First, old bone is removed (resorbed), then new bone is laid down (formed). This balanced process of resorbing and forming bone keeps your skeleton healthy and strong.

What is osteoporosis and why should it be treated or prevented?
Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause and may also occur in men.

Osteoporosis often occurs in women several years after the menopause, which occurs when the ovaries stop producing the female hormone, estrogen, or are removed (which may occur, for example, at the time of a hysterectomy). The earlier a woman reaches the menopause, the greater the risk of osteoporosis. Osteoporosis can also occur in men due to several causes, including aging and/or a low level of the male hormone, testosterone. In all instances, bone is removed faster than it is formed, so bone loss occurs and bones become weaker. Therefore, maintaining bone mass and preventing further bone loss are important to keep your skeleton healthy. Early on, osteoporosis usually has no symptoms. If left untreated, however, it can result in fractures (broken bones). Although fractures usually cause pain, fractures of the bones of the spine may go unnoticed until they cause height loss. Fractures may occur during normal, everyday activity, such as lifting, or from minor injury that would not ordinarily fracture normal bone. Fractures usually occur at the hip, spine, or wrist and can lead not only to pain, but also to considerable deformity and disability (such as stooped posture from curvature of the spine, and loss of mobility).

How can osteoporosis be treated?
Your physician has prescribed FOSAMAX® to treat your osteoporosis. FOSAMAX® not only prevents the loss of bone but actually helps to rebuild bone you may have lost and makes bone less likely to fracture. Thus, FOSAMAX® reverses the progression of osteoporosis.

In addition, your physician may recommend one or more of the following lifestyle changes:

Stop smoking. Smoking appears to increase the rate at which you lose bone and, therefore, may increase your risk of fracture.

Exercise. Like muscles, bones need exercise to stay strong and healthy. Consult your physician before you begin any exercise program.

Eat a balanced diet. Your physician can advise you whether to modify your diet or to take any dietary supplements.

When it should not be used:
Do not take 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.
- Have difficulty swallowing liquids. You should not take FOSAMAX® oral solution.
- Are allergic to any of its ingredients.
- Have low blood calcium.
- Have SEVERE kidney disease. If you have any doubts if this applies to you, speak to your physician.

What the medicinal ingredient is:
Tablets: Each 70 mg tablet of FOSAMAX® contains alendronate sodium.
Oral Solution: Each bottle of 70 mg oral solution of FOSAMAX® contains alendronate sodium.

What the nonmedicinal ingredients are:
Tablets: anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

Oral Solution: artificial raspberry flavor, citric acid anhydrous, purified water, sodium citrate dihydrate and sodium saccharin. Added as preservatives are sodium propylparaben and sodium butylparaben.

What dosage forms it comes in:
FOSAMAX® once weekly is available as a white, oval 70 mg tablet and as a clear, colorless, oral solution 70 mg/75 mL.

WARNINGS AND PRECAUTIONS

Before you use FOSAMAX® talk to your doctor or pharmacist:

- If you have cancer, gum disease, poor oral hygiene, or diabetes. If you are receiving chemotherapy, radiotherapy, corticosteroids, or immunosuppressive drugs. If you are or have been a smoker, or are a heavy alcohol user. If you have any of these conditions you should consider having a dental examination before starting FOSAMAX®.
- About any medical problems you have or have had, including known kidney disease.
- About any dental problems you have or have had.
- About any allergies.
- If you have any swallowing or digestive problems.

You should always tell your physician about all drugs you are taking or plan to take, including those obtained without a prescription.

Use in pregnancy and breast-feeding
Do not take FOSAMAX® if you are pregnant or breast-feeding.

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

Use in elderly
FOSAMAX® works equally well in, and is equally well tolerated by, patients older and younger than 65 years of age.

Can I drive or operate machinery while using FOSAMAX®?
There have been side effects reported with FOSAMAX® that may affect your ability to drive or operate machinery. Individual responses to FOSAMAX® may vary (See SIDE EFFECTS AND WHAT TO DO ABOUT THEM).

INTERACTIONS WITH THIS MEDICATION

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 one-half hour after taking FOSAMAX® before taking any other oral medication.

PROPER USE OF THIS MEDICATION

Usual dose:
How should I take FOSAMAX® once weekly?
Your doctor has prescribed FOSAMAX® once weekly either as tablets, or bottles of oral solution.

These are the important things you must do to help make sure you will benefit from FOSAMAX®:

1. Choose the day of the week that best fits your schedule. Every week, take one dose of FOSAMAX® (one tablet or one entire bottle of solution) on your chosen day.

2. After getting up for the day and before taking your first food, beverage, or other medication, take your FOSAMAX® with plain water only as follows:

- **Tablets:** Swallow one tablet with a full glass (200 to 250 mL) of plain water.
- **Oral Solution:** Drink one entire bottle of solution followed by at least 60 mL (a quarter of a cup) of plain water.

Do **not** take FOSAMAX® with:
- mineral water
- coffee or tea
- juice

Although it has not been tested, because of high mineral content, "hard water" may decrease absorption of FOSAMAX®. If your normal drinking water is classified as “hard water”, you should consider taking this medication with distilled water (i.e., not mineral water).

Do not chew or suck on a tablet of FOSAMAX®.

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.

The above actions will help FOSAMAX® reach your stomach quickly and help 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, including 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.

7. 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.

8. It is important that you continue taking FOSAMAX® for as long as your doctor prescribes it. FOSAMAX® can treat your osteoporosis only if you continue to take it.

Calcium and vitamin D are also important for strong bones. Your doctor may ask you to take calcium and vitamin D while you are on FOSAMAX® therapy.

Why is it important to continue to take FOSAMAX®?
It is important to take FOSAMAX® over the long-term to

continue to help rebuild bone you may have lost. It is, therefore, important to follow your physician's instructions for taking FOSAMAX® without skipping doses or varying from your prescribed treatment schedule. It is also important to continue to follow your physician's advice on lifestyle changes.

Overdose:
If you take too many doses, drink a full glass of milk and contact your physician immediately. Do not induce vomiting. Do not lie down.

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

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most patients do not have side effects from FOSAMAX®; however, as with any medicine, FOSAMAX® may have unintended or undesirable effects. Side effects usually have been mild. Some patients may experience digestive disturbances such as nausea, vomiting or black and/or bloody stools. Some digestive disturbances may be severe including irritation or ulceration of the esophagus (the tube that connects your mouth with your stomach) which can cause chest pain, heartburn or difficulty or pain upon swallowing. These reactions may occur especially if patients do not drink the recommended amount of water with FOSAMAX® and/or if they lie down in less than 30 minutes or before their first food of the day. Esophageal reactions may worsen if patients continue to take FOSAMAX® after developing symptoms suggesting irritation of the esophagus.

Some patients may experience bone, muscle and/or joint pain which is rarely severe. Patients who develop severe bone, joint, and/or muscle pain should contact their physician. Most patients experienced relief after stopping the drug. Rarely, patients may also experience joint swelling or swelling in their hands or legs. Transient flu-like symptoms (rarely with fever), typically at the start of treatment, have occurred. In rare cases, patients taking FOSAMAX® may get itching or eye pain, or a rash that may be made worse by sunlight. Hair loss has been reported. Rarely, severe skin reactions may occur. Allergic reactions such as hives or, rarely, swelling of the face, lips, tongue and/or throat, which may cause difficulty in breathing or swallowing, may occur. Patients may experience dizziness, vertigo (spinning sensation) or a changed sense of taste. Rarely, symptoms of low blood calcium may occur (for example, numbness or tingling around the mouth or in the hands or feet; muscle spasms in the face, hands, or feet). Rarely, stomach or other peptic ulcers (some severe) have occurred. Mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.

Rarely, patients have had jaw problems associated with delayed healing and infection, often following tooth extraction.

Rarely, patients have experienced fracture in a specific part of the thigh bone. If you develop new or unusual pain in the hip or thigh, contact your doctor.

Anytime you have a medical problem you think may be from taking FOSAMAX®, even if it is not listed above, talk to your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / effects		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		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			√
	Bone, joint, and/or muscle pain		√	
	New or unusual pain in the hip or thigh		√	
	Digestive disturbances causing: - chest pain - heartburn - difficulty or pain upon swallowing - black and/or bloody stools			√
	Esophageal, stomach or other peptic ulcers			√
	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			√
	Severe skin reactions			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / effects		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Symptoms of low blood calcium: - numbness or tingling around the mouth or in the hands or feet - muscle spasms in the face, hands, or feet			√

This is not a complete list of side effects. For any unexpected effects while taking FOSAMAX®, contact your doctor or pharmacist.

HOW TO STORE IT

Tablets: Store at room temperature (15°C - 30°C).
Oral Solution: Store at room temperature (15°C - 30°C). Do not freeze.

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

Remember to keep FOSAMAX® and all medications safely away from children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

How can I learn more about FOSAMAX® and osteoporosis?
You may obtain further information from your physician or pharmacist, who has more detailed information about FOSAMAX® and osteoporosis.

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.merck.ca

or by contacting the sponsor, Merck Canada Inc.:

By toll-free telephone: 1-800-567-2594
By toll-free fax: 1-800-369-3090

By regular mail:
Merck Canada Inc.
Pharmacovigilance
P.O. Box 1005
Pointe-Claire - Dorval, QC H9R 4P8

This leaflet was prepared by Merck Canada Inc.

Last revised: February 20, 2013

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PART III: CONSUMER INFORMATION

℞FOSAMAX®
alendronate sodium tablets
40 mg alendronate daily dosage

This leaflet is part III of a three-part "Product Monograph" published when FOSAMAX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FOSAMAX®. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this insert carefully before starting FOSAMAX® and every time your prescription is renewed.

ABOUT THIS MEDICATION

What the medication is used for:
FOSAMAX® is the brand name for the substance alendronate sodium available **only on prescription** from your physician. Alendronate sodium is a member of a class of non-hormonal drugs called bisphosphonates.

Your physician has prescribed FOSAMAX® because you have a disease known as Paget's disease of bone.

What it does:
How is normal bone maintained?
Bone undergoes a normal process of rebuilding that occurs continuously throughout your skeleton. First, old bone is removed (resorbed), then new bone is laid down (formed). This balanced process of resorbing and forming bone keeps your skeleton healthy and strong.

What is Paget's disease of bone?
In Paget's disease, bone resorption and formation are abnormally increased resulting in weakened bone. This may lead to pain, deformity, and/or fracture.

How can Paget's disease of bone be treated?
Your physician has prescribed FOSAMAX® to treat this disease. FOSAMAX® slows down bone resorption, which allows the bone-forming cells time to rebuild normal bone.

When it should not be used:
Do not take 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 any of its ingredients.
- Have low blood calcium.
- Have SEVERE kidney disease. If you have any doubts if this applies to you, speak to your physician.

What the medicinal ingredient is:
Each 40 mg tablet of FOSAMAX® contains alendronate sodium.

What the nonmedicinal ingredients are:
anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

What dosage forms it comes in:
FOSAMAX® is available as a white, triangular-shaped 40 mg tablet.

WARNINGS AND PRECAUTIONS

Before you use FOSAMAX® talk to your doctor or pharmacist:

- If you have cancer, gum disease, poor oral hygiene, or diabetes. If you are receiving chemotherapy, radiotherapy, corticosteroids, or immunosuppressive drugs. If you are or have been a smoker, or are a heavy alcohol user. If you have any of these conditions you should consider having a dental examination before starting FOSAMAX®.
- About any medical problems you have or have had, including known kidney disease.
- About any dental problems you have or have had.
- About any allergies.
- If you have any swallowing or digestive problems.

You should always tell your physician about all drugs you are taking or plan to take, including those obtained without a prescription.

Use in pregnancy and breast-feeding
Do not take FOSAMAX® if you are pregnant or breast-feeding.

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

Use in elderly
FOSAMAX® works equally well in, and is equally well tolerated by, patients older and younger than 65 years of age.

Can I drive or operate machinery while using FOSAMAX®?
There have been side effects reported with FOSAMAX® that may affect your ability to drive or operate machinery. Individual responses to FOSAMAX® may vary (See SIDE EFFECTS AND WHAT TO DO ABOUT THEM).

INTERACTIONS WITH THIS MEDICATION

The use of acetylsalicylic acid (ASA) with 40 mg of FOSAMAX® may increase the chance of stomach upset. You should speak to your physician if you take ASA.

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 one-half hour after taking FOSAMAX® before taking any other oral medication.

PROPER USE OF THIS MEDICATION

Usual dose:
How should I take FOSAMAX®?

These are the important things you must do to help make sure you will benefit from FOSAMAX®:

1. After getting up for the day and before taking your first food, beverage, or other medication, swallow your FOSAMAX® tablet with a full glass (200 to 250 mL) of plain water only.

- Not mineral water
- Not coffee or tea
- Not juice

Although it has not been tested, because of high mineral content, "hard water" may decrease absorption of FOSAMAX®. If your normal drinking water is classified as "hard water", you should consider taking this medication with distilled water (i.e., not mineral water).

Do not chew or suck on a tablet of FOSAMAX®.

2. After swallowing your FOSAMAX® tablet 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.

3. Do not take FOSAMAX® at bedtime or before getting up for the day.

The above actions will help the FOSAMAX® tablet reach your stomach quickly and help reduce the potential for irritation of your esophagus (the tube that connects your mouth with your stomach).

4. After swallowing your FOSAMAX® tablet, wait at least 30 minutes before taking your first food, beverage, or other medication of the day, including antacids, calcium supplements and vitamins. FOSAMAX® is effective only if taken when your stomach is empty.

5. If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking FOSAMAX® immediately and call your doctor.

6. Take one FOSAMAX® tablet once a day, every day.

7. It is important that you continue taking FOSAMAX® for as long as your doctor prescribes it.

Calcium and vitamin D are also important for strong bones. Your doctor may ask you to take calcium and vitamin D while you are on FOSAMAX® therapy.

Overdose:
If you take too many tablets, drink a full glass of milk and contact your physician immediately. Do not induce vomiting. Do not lie down.

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

Missed dose:
Take FOSAMAX® once daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule of one tablet once a day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most patients do not have side effects from FOSAMAX®; however, as with any medicine, FOSAMAX® may have unintended or undesirable effects. Side effects usually have been mild. Some patients may experience digestive disturbances such as nausea, vomiting or black and/or bloody stools. Some digestive disturbances may be severe including irritation or ulceration of the esophagus (the tube that connects your mouth with your stomach) which can cause chest pain, heartburn or difficulty or pain upon swallowing. These reactions may occur especially if patients do not drink a full glass of water with FOSAMAX® and/or if they lie down in less than 30 minutes or before their first food of the day. Esophageal reactions may worsen if patients continue to take FOSAMAX® after developing symptoms suggesting irritation of the esophagus.

Some patients may experience bone, muscle and/or joint pain which is rarely severe. Patients who develop severe bone, joint, and/or muscle pain should contact their physician. Most patients experienced relief after stopping the drug. Rarely, patients may also experience joint swelling or swelling in their hands or legs. Transient flu-like symptoms (rarely with fever), typically at the start of treatment, have occurred. In rare cases, patients taking FOSAMAX® may get itching or eye pain, or a rash that may be made worse by sunlight. Hair loss has been reported. Rarely, severe skin reactions may occur. Allergic reactions such as hives or, rarely, swelling of the face, lips, tongue and/or throat, which may cause difficulty in breathing or swallowing, may occur. Patients may experience dizziness, vertigo (spinning sensation) or a changed sense of taste. Rarely, symptoms of low blood calcium may occur (for example, numbness or tingling around the mouth or in the hands or feet; muscle spasms in the face, hands, or feet). Rarely, stomach or other peptic ulcers (some severe) have occurred. Mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.

Rarely, patients have had jaw problems associated with delayed healing and infection, often following tooth extraction.

Rarely, patients have experienced fracture in a specific part of the thigh bone. If you develop new or unusual pain in the hip or thigh, contact your doctor.

Anytime you have a medical problem you think may be from taking FOSAMAX®, even if it is not listed above, talk to your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptoms / effects		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		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			√
	Bone, joint, and/or muscle pain		√	
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	Digestive disturbances causing: - chest pain - heartburn - difficulty or pain upon swallowing - black and/or bloody stools			√
	Esophageal, stomach or other peptic ulcers			√
	Jaw problems associated with delayed healing and infection, often following tooth extraction			√
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This is not a complete list of side effects. For any unexpected effects while taking FOSAMAX®, contact your doctor or pharmacist.

HOW TO STORE IT

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  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

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NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

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