MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

7957025

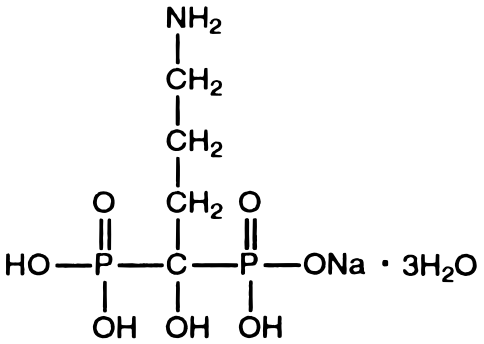
FOSAMAX®
(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

DESCRIPTION

FOSAMAX* (alendronate sodium) is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \bullet 3H_2O$ and its formula weight is 325.12. The structural formula is:



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

Tablets FOSAMAX for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

CLINICAL 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

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administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not 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.

Pharmacokinetics

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 (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

FOSAMAX 70 mg oral solution and FOSAMAX 70 mg tablet are equally bioavailable.

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%.

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 (64, 78; 90% confidence interval [CI]), 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

Pediatric Info

Pediatric: Alendronate pharmacokinetics have not been investigated in patients <18 years of age.

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

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

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 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal**

insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.

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.

Drug Interactions (also see PRECAUTIONS, *Drug Interactions*)

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.

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%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

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 (spinal) 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 one-year studies with once weekly FOSAMAX 70 mg for the treatment of osteoporosis and once weekly FOSAMAX 35 mg for the prevention 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 one-year studies with once weekly FOSAMAX 35 and 70 mg, 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

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 once weekly FOSAMAX 70 mg.

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 I 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.

Clinical Studies

Treatment of osteoporosis

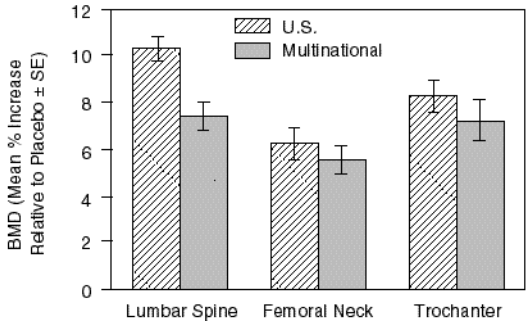
Postmenopausal women

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 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

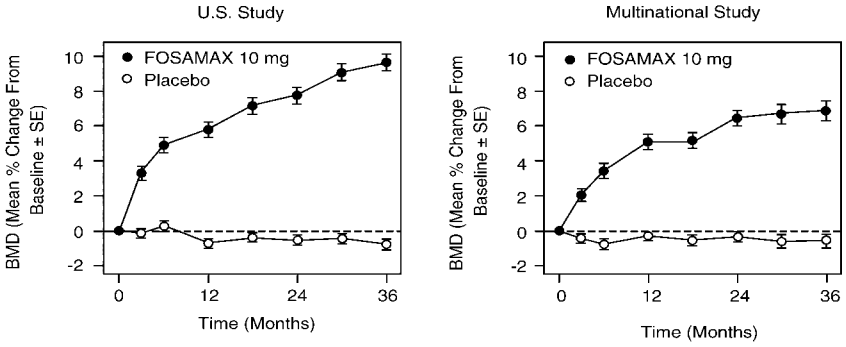
Increase in BMD
FOSAMAX 10 mg/day at Three Years



At three years significant increases in BMD, 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 each study, 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 three years of treatment. (See figures below for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with FOSAMAX 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean). Thus, overall FOSAMAX reverses the loss of bone mineral density, a central factor in the progression of osteoporosis.

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 patients with postmenopausal osteoporosis treated with FOSAMAX 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups. These data indicate that continued treatment with FOSAMAX is required to maintain the effect of the drug.

The therapeutic equivalence of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, 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 (n=440) and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of FOSAMAX on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third of these were clinically symptomatic), 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 reduction in the proportion of patients treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic 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 reductions in fracture incidence at three years as shown in the table below.

Effect of FOSAMAX on Fracture Incidence in the Three-Year Study of FIT
(patients with vertebral fracture at baseline)

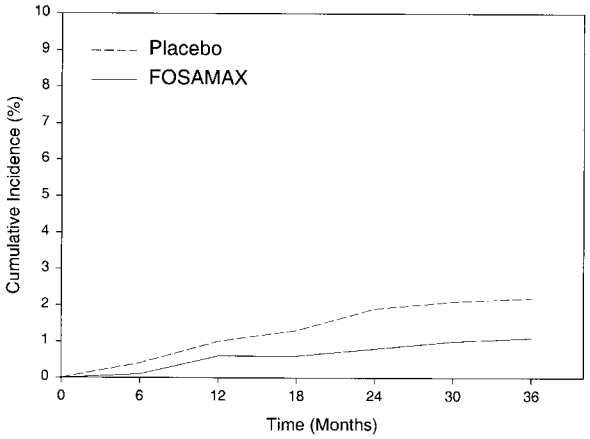
	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)[†]				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47***
≥ 2 new vertebral fractures	0.5	4.9	4.4	90***
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26[‡]
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54**
Hip fracture	1.1	2.2	1.1	51*
Wrist (forearm) fracture	2.2	4.1	1.9	48*

[†]Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966
*p<0.05, **p<0.01, ***p<0.001, [‡]p=0.007

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

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX, p=0.047. The figure below displays the cumulative incidence of hip fractures in this study.

Cumulative Incidence of Hip Fractures in the
Three-Year Study of FIT
(patients with radiographic vertebral fracture at baseline)



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

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study was to recruit women with osteoporosis, defined as 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 table below 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)

	Percent of Patients			
	FOSAMAX (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)††				
≥ 1 new vertebral fracture	2.5	4.8	2.3	48***
≥ 2 new vertebral fractures	0.1	0.6	0.5	78*
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22**
≥ 1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)†††
Hip fracture	1.0	1.4	0.4	29 (NS)†††
Wrist (forearm) fracture	3.9	3.8	-0.1	NS†††

†Baseline femoral neck BMD at least 2 SD below the mean for young adult women
††Number evaluable for vertebral fractures: FOSAMAX, n=1426; placebo, n=1428
†††Not significant. This study was not powered to detect differences at these sites.
*p=0.035, ** p=0.01, ***p<0.001

Fracture results across studies

In the Three-Year Study of FIT, FOSAMAX reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p<0.001); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, p=0.001); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, p=0.034).

FOSAMAX reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, p<0.001) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, p<0.001) in the Three-Year Study of FIT. In the Four-Year Study of FIT, FOSAMAX reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, p=0.035).

Thus, FOSAMAX reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

FOSAMAX, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

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, support the conclusion that bone formed during therapy with FOSAMAX is of normal quality.

Men

The efficacy of FOSAMAX in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

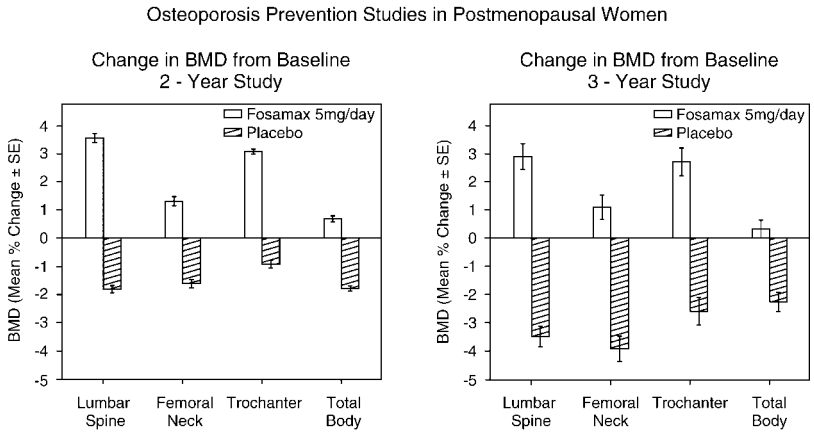
A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with FOSAMAX also reduced height loss (FOSAMAX, -0.6 mm vs. placebo, -2.4 mm).

A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD T-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dL vs. ≥9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2.5 vs. >-2.5).

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 postmenopause, were treated for up to three years. 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 prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). 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.



The therapeutic equivalence of once weekly FOSAMAX 35 mg (n=362) and FOSAMAX 5 mg daily (n=361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35-mg once-weekly group (n=307) and 3.2% (2.9, 3.5%; 95% CI) in the 5-mg daily group (n=298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

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%).

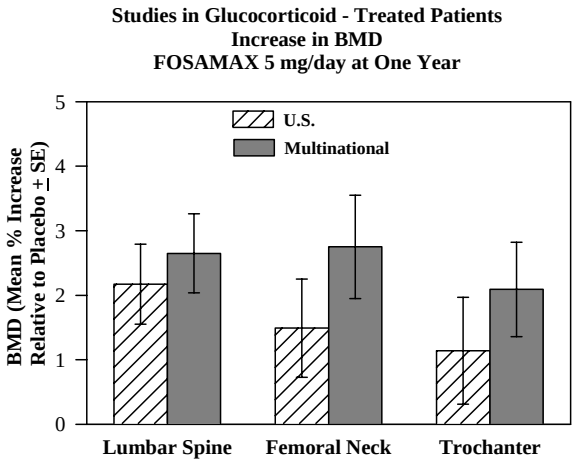
The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of FOSAMAX 10 mg once daily to HRT produced, at one year, significantly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

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied.

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, one performed in the United States and the other in 15 different countries (Multinational [which also included FOSAMAX 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. 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 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 mg/day. The increases in BMD with FOSAMAX 10 mg/day were similar to those with FOSAMAX 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with FOSAMAX 10 mg/day were greater than those with FOSAMAX 5 mg/day 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.

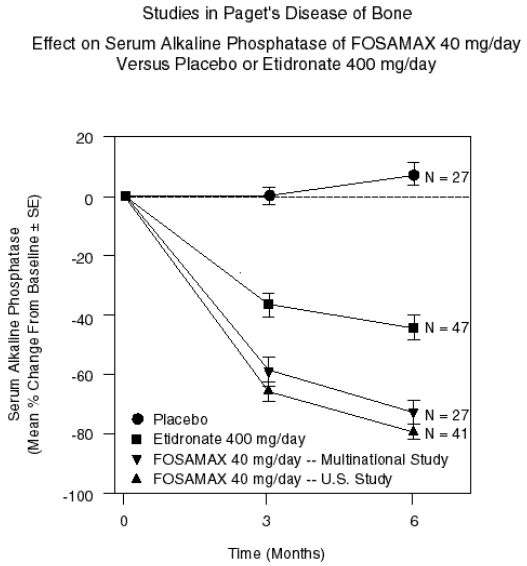
Bone histology was normal in the 49 patients biopsied at the end of one year who received FOSAMAX at doses of up to 10 mg/day.

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.



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 regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

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 Studies, Treatment of osteoporosis in 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 support the conclusion that bone formed during treatment with FOSAMAX is of normal quality.

ANIMAL PHARMACOLOGY

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 (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

FOSAMAX is indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
  - For the treatment of osteoporosis, FOSAMAX increases bone mass and reduces the incidence of 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 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*.)
  - 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 (for example, at least 1 standard deviation below the mean for healthy young adult women); 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.

- Treatment to increase bone mass in men with osteoporosis
- Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.
- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone having 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.

CONTRAINDICATIONS

- 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.
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and 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 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). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

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, gastritis, duodenitis, or ulcers).

There have been post-marketing reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

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

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency)

should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on 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.

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocorticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the patient package insert before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

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 (6-8 oz). To facilitate gastric emptying patients should drink at least 2 oz (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 <u>and</u> 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 and consult their physician.

Patients should be instructed that if they miss a dose of once weekly FOSAMAX, 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.

Drug Interactions (also see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drug Interactions*)
Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies*, *Concomitant use with estrogen/hormone replacement therapy (HRT)* and ADVERSE REACTIONS, *Clinical Studies*, *Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some 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 medications.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral 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 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early,

middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Info

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), 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. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 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%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	FOSAMAX* % (n=196)	Placebo % (n=397)	FOSAMAX** % (n=3236)	Placebo % (n=3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

* 10 mg/day for three years
** 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

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

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

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

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients		
	Once Weekly FOSAMAX 70 mg % (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

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo are presented in the following table.

Osteoporosis Studies in Men Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients				
	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly FOSAMAX 70 mg % (n=109)	Placebo % (n=58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

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.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

Osteoporosis Prevention Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or
Definitely Drug Related by the Investigators and
Reported in ≥1% of Patients

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	FOSAMAX 5 mg/day % (n=361)	Once Weekly FOSAMAX 35 mg % (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

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 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 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered 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.

One-Year Studies in Glucocorticoid-Treated Patients
Adverse Experiences Considered Possibly, Probably, or
Definitely Drug Related by the Investigators and
Reported in ≥1% of Patients

	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

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), 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). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered 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.

Laboratory Test Findings

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

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. Transient symptoms of myalgia, malaise and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

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

Special Senses: rarely uveitis, rarely scleritis.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), 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).

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.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, *Drug Interactions*). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications 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 (6-8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes <u>and</u> 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, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

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

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

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

Treatment to increase bone mass in men with osteoporosis

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 (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly

  or
- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

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.

HOW SUPPLIED

No. 3759 — Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other. They are supplied as follows:

NDC 0006-0925-31 unit-of-use bottles of 30

NDC 0006-0925-58 unit-of-use bottles of 100.

No. 3797 — Tablets FOSAMAX, 10 mg, are white, oval, wax-polished tablets with code MRK on one side and 936 on the other. They are supplied as follows:

NDC 0006-0936-31 unit-of-use bottles of 30

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100

NDC 0006-0936-82 bottles of 1,000.

No. 3813 — Tablets FOSAMAX, 35 mg, are white, oval, uncoated tablets with code 77 on one side and a bone image on the other. They are supplied as follows:

NDC 0006-0077-44 unit-of-use blister package of 4

NDC 0006-0077-21 unit dose packages of 20.

No. 3592 — Tablets FOSAMAX, 40 mg, are white, triangular-shaped, uncoated tablets with code MRK 212 on one side and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0212-31 unit-of-use bottles of 30.

No. 3814 — Tablets FOSAMAX, 70 mg, are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other. They are supplied as follows:

NDC 0006-0031-44 unit-of-use blister package of 4

NDC 0006-0031-21 unit dose packages of 20.

No. 3833 — Oral Solution FOSAMAX, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows:

NDC 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 mL each.

Storage

FOSAMAX Tablets:

Store in a well-closed container at room temperature, 15-30°C (59-86°F).

FOSAMAX Oral Solution:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Do not freeze.

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