CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-560/S014

Trade Name: Fosamax Tablets

Generic Name: alendronate sodium

Sponsor: Merck Research Laboratories

Approval Date: March 19, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560/S014

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560/S014

APPROVAL LETTER

NDA 20-560/S-011, S-014

MAR 19 1999

Merck Research Laboratories
Attention: Michelle Kloss, Ph.D.
Director, Regulatory Affairs
P.O. Box 4, BLA-20
West Point, PA 19486-0004

Dear Dr. Kloss:

Please refer to your supplemental new drug applications dated September 17, 1997, received September 18, 1997 (S-011), and July 23, 1998, received July 24, 1998 (S-014), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) Tablets.

We also acknowledge the receipt of your October 8, 1998, submission containing final printed labeling in response to our May 12, 1998 letter approving your supplemental new drug application (S-011).

We have reviewed the labeling (7957010) for supplement-011 for the prescribing information (PI) that you submitted in accordance with our May 12, 1998, letter, and we find it acceptable.

We note that supplement 014 was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c). Your submission stated November 1, 1998 as the implementation date for the changes.

This supplemental new drug application (Supplement - 014) provides for revisions to the WARNINGS and ADVERSE REACTIONS sections of the package insert and to the patient package insert (PPI) as follows:

1. Addition of "and rarely followed by esophageal stricture" to types of esophageal adverse experiences in the WARNINGS section.

2. Addition of "rarely, esophageal stricture" and "Skin: rash (occasionally with photosensitivity)" to the ADVERSE REACTIONS, *Post-Marketing experience* section.

3. In the "What are the possible side effects of FOSAMAX?" section of the Patient Package Insert, addition of a trademark footnote (page 1), an editorial revision to the first paragraph (replacing "and" with "or"), and addition of "(occasionally made worse by sunlight)" after rash

We have completed the review of this supplemental application (S-014) and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert [7957009]and patient package insert [7969405]submitted July 23, 1998). Accordingly, the supplemental application is approved effective on the date of this letter.

We note that the final printed labeling (FPL) submitted for supplement 014 dated July 23, 1998, has been superseded by the final printed labeling (FPL) submitted October 8, 1998, for Supplement 011 and includes the PI (7957010) labeling changes in supplement 014.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Randy Hedin, R.Ph., Regulatory Management Officer, at (301) 827-6430.

Sincerely,

3/19/99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RH 3/18/99

cc:
Archival NDA 20-560
HFD-510/Div. Files
HFD-510/R.Hedin
HF-2/MedWatch (with labeling)(with CSO labeling review)

HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: RH/December 3, 1998
Initialed by:
final:
filename: N20560AP.L11

APPROVAL (AP) S-014
ACK & RETAIN (ar) S-011

The Patient Package Insert (7969405) in S-014 and the Package Insert (7957010) in S-011 (10-8-98) are the most current approved labels.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-261/S014

LABELING

MAR 19 1999

APPROVED

MERCK & CO., INC.
West Point, PA 19486, USA

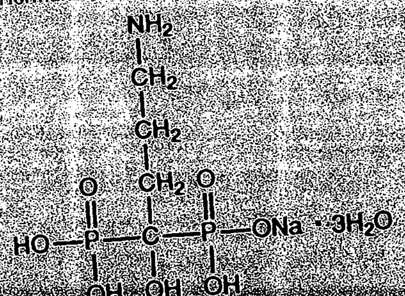
FOSAMAX®
(ALENDRONATE SODIUM TABLETS)

DESCRIPTION

FOSAMAX® (alendronate sodium) is an aminobisphosphonate 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 $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ 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 or 52.21 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5.0, 10.0 and 40.0 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate.

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 activ-

trations 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

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 (≥65 years of age) 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.**

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; no other specific drug interaction studies were performed.

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. 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 0.7% for doses ranging from 5 to 40 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 (0.78%) when administered after an overnight fast and 2 hours before breakfast.

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. Concen-

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; no other specific drug interaction studies were performed.

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

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)
Renal Clearance (mL/min) (n=6)	71	(64, 78)

Pharmacodynamics

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.

Alendronate is an aminobisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of

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(Alendronate Sodium Tablets)

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. Alendronate thus reduces the elevated rate of bone turnover observed in postmenopausal women to approximate more closely that in premenopausal women. Alendronate is not an estrogen and does not have the benefits and risks of estrogen replacement therapy.

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.

In long-term (two- or three-year) osteoporosis treatment studies, FOSAMAX 10 mg/day reduced urinary excretion of markers of bone resorption, including deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50-60% 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 total serum alkaline phosphatase, by approximately 50% and 25-30%, respectively, to reach a plateau after 6 to 12 months. In osteoporosis prevention studies, FOSAMAX 5 mg/day decreased these markers by approximately 40% and 15%, respectively. 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, but no further decreases were observed for the three-year duration of the studies. Similar reductions were observed with FOSAMAX 5 mg/day. 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.

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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 highly 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.

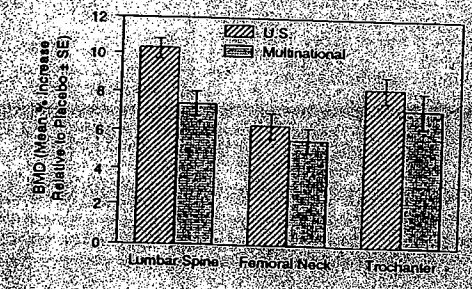
Clinical Studies

Treatment of osteoporosis in 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.

Increase in BMD
FOSAMAX 10 mg/day in Two Studies at Three Years



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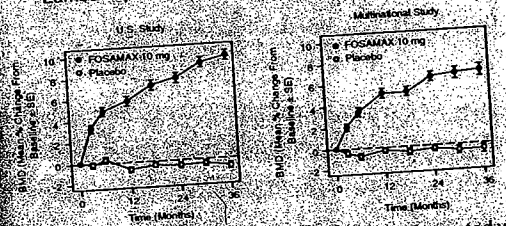
Highly significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur 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.) Thus, FOSAMAX appears to reverse the progression of osteoporosis. 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).

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 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 continuous, daily treatment with FOSAMAX is required to maintain the effect of the drug.

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 significant 48% 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 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 statistically significant smaller loss in stature than those who received placebo (-3.0 mm vs. -4.6 mm). Furthermore, of patients who

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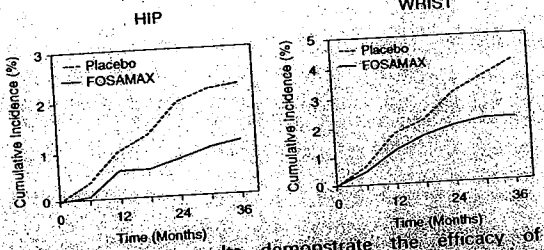
ately similar reductions of hip and wrist fractures were seen in pooled earlier osteoporosis treatment studies.

Cumulative Incidence of Patients with Hip and Wrist Fractures

FIT
(Vertebral Fracture Study)



Overall, these results demonstrate the efficacy of FOSAMAX to reduce the incidence of fractures at the spine, hip and wrist, which are the three most common sites of osteoporotic fracture.

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.

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 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.

vs. 1.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a statistically significant smaller loss in stature than those who received placebo (–3.0 mm vs. –4.6 mm). 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.

The Vertebral Fracture Study of the Fracture Intervention Trial (FIT) included results from 2027 patients who had at least one baseline vertebral (compression) fracture. The results of this study demonstrated the reduction in fracture incidence due to FOSAMAX. In this three-year, randomized, double-blind, placebo-controlled study, 1022 patients received FOSAMAX and 1005 patients received placebo. Treatment with FOSAMAX resulted in statistically significant and clinically meaningful reductions in the proportion of patients experiencing fractures as shown in the table below.

Effect of FOSAMAX on Fracture Incidence Over Three Years in the Vertebral Fracture Study of FIT

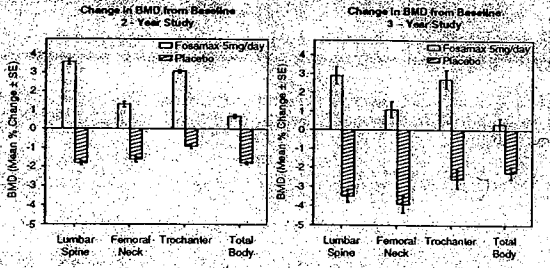
	% of Patients		
	FOSAMAX	Placebo	Reduction (%) in Fracture Incidence
Patients with:			
≥1 new vertebral fracture	8.0	15.0	47
≥2 new vertebral fractures	0.5	4.9	90
≥1 painful vertebral fracture	2.3	5.0	55
Hip fractures	1.1	2.2	51
Wrist/forearm fractures	2.2	4.1	49

Furthermore, treatment with FOSAMAX significantly reduced the incidence of total hospitalizations (24.9% vs. 30.4%).

The reduction in the incidence of vertebral fractures (FOSAMAX versus placebo) in the Vertebral Fracture Study of FIT (in which all women had at least one baseline vertebral fracture) was consistent with that in the combined U.S. and Multinational (U.S./Multi) treatment studies (see above), in which 80% of the women did not have a vertebral fracture at baseline. During these three-year studies, treatment with FOSAMAX reduced the proportion of women experiencing at least one new vertebral fracture in both study populations by approximately 50% (FIT: 47% reduction, $p<0.001$; U.S./Multi: 48% reduction, $p = 0.034$). Similarly, FOSAMAX reduced the proportion of women experiencing multiple (two or more) new vertebral fractures by approximately 90% in both studies ($p<0.001$). Thus, FOSAMAX reduces the incidence of fractures whether or not patients have experienced a previous vertebral fracture.

The two figures below display the cumulative incidence of patients with hip and wrist fractures over 3 years in the Vertebral Fracture Study of FIT. In both figures, the cumulative incidence of patients with these types of fracture is lower with FOSAMAX compared with placebo at all time points. FOSAMAX reduced the proportion of women experiencing hip fracture by 51% and wrist fracture by 48%. Proportion

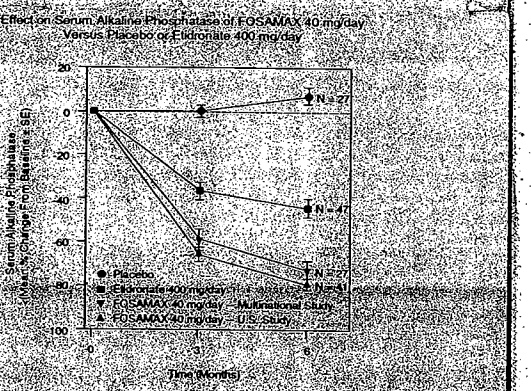
day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.



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

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.

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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, 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 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, wrist, 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.

- FOSAMAX is indicated for the treatment of Paget's disease of bone.

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although no increased risk was observed in pre-marketing clinical trials.

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

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

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disturbances of mineral metabolism (such as vitamin D deficiency) should also be effectively treated. 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. Adequate calcium and vitamin D intake should be ensured to provide for these enhanced needs.

Information for Patients

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when each tablet is swallowed 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 FOSAMAX with a full glass of water (6-8 oz) and 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 and consult their physician.

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 excessive cigarette smoking, and/or alcohol consumption, if these factors exist.

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.

Drug Interactions (also see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drug Interactions*)

Estrogen

The safety and effectiveness of the concomitant use of hormone replacement therapy and FOSAMAX in postmenopausal women has not been established.

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 drug.

bone mass (for example, postmenopausal estrogen deficiency), thin 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.

FOSAMAX is indicated for the treatment of Paget's disease of bone.

- 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
- 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, 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 or retrosternal pain.

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 a full glass (6-8 oz) 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).

PRECAUTIONS

General

There have been rare (post marketing) reports of gastric and duodenal ulcers, some severe and with complications.

Estrogen

The safety and effectiveness of the concomitant use of hormone replacement therapy and FOSAMAX in postmenopausal women has not been established.

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 drug.

Aspirin

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

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 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 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.

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 vivo* 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 was weakly positive at concentrations ≥ 5 mM in the presence of cytotoxicity.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (four times the 10 mg human dose based on surface area).

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 1 times (1 mg/kg) to 9 times

(10 mg/kg) the 10 mg human dose based on surface area, mg/m². No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (50 times the 10 mg human dose based on surface area, mg/m²).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (13 times the 10 mg human dose based on surface area) 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 (0.5 times the recommended human dose) 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.

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 Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

Of the patients receiving FOSAMAX in the two large osteoporosis treatment studies and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45% 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.

Use in Men

Safety and effectiveness in male osteoporosis have not been established.

ADVERSE REACTIONS

Clinical Studies

In clinical studies, adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 3900 postmenopausal women in clinical studies.

Treatment of Osteoporosis

In two large, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational), 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 reported 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

	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.

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.

In the Vertebral Fracture Study of the Fracture Intervention Trial, discontinuation of therapy due to any clinical adverse experience occurred in 7.6% of 1022 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for the third year and 9.4% of 1005 patients treated with placebo. Simi-

larly, discontinuations due to upper gastrointestinal adverse experiences were comparable: FOSAMAX, 2.6%; placebo, 2.6%. The overall adverse experience profile was similar to that seen in other studies with FOSAMAX 5 or 10 mg/day.

Prevention of osteoporosis

The safety of FOSAMAX 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. The 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

	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.

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 pain, 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 3% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Laboratory findings

In the double-blind, multicenter, controlled studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18% and 3% respectively of patients taking FOSAMAX versus approximately 12% and 1% of those taking placebo. However, the

FOSAMAX®
(Alendronate Sodium Tablets)

utes 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).

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 10 mg once a day.

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

The recommended dosage is 5 mg once a day.

Safety of treatment or prevention of osteoporosis with FOSAMAX for longer than four years has not been studied; extension studies are ongoing.

Paget's disease of bone

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. 3600 — Tablets FOSAMAX 10 mg, are white, round, uncoated tablets with a bone image and code MRK 936 on one side and a bone image and FOSAMAX on the other. They are supplied as follows:

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

(6505-01-424-1105 10 mg 30's)

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

NDC 0006-0936-28 unit-dose packages of 100

(6505-01-424-1113 10 mg 100's)

NDC 0006-0936-82 bottles of 1000

NDC 0006-0936-72 carton of 25 UNIBLISTER™ cards of 31 tablets each

No. 3592 — Tablets FOSAMAX 40 mg, are white, triangular, shaped, uncoated tablets with code MRK 242 on one side and FOSAMAX on the other. They are supplied as follows:

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

(6505-01-424-1111 40 mg 30's)

Storage

Store in a well-closed container at room temperature

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.

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

Skin: rash (occasionally with photosensitivity).

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m²) and 966 mg/kg (2898 mg/m²), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m²).

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.

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, FOSAMAX should only be swallowed upon arising for the day with a full glass of water (6-8 oz) and patients should not lie down for at least 30 min-

15-30°C (59-86°F).

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FOSAMAX®
(ALENDRONATE SODIUM TABLETS)

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APPR

FOSAMAX® (Alendronate Sodium Tablets)
Patient Information about
FOSAMAX® (FOSS-ah-max) for Osteoporosis
Generic name: alendronate sodium (a-LEN-dro-nate)

7969405

Please read this information before you start taking FOSAMAX*. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss FOSAMAX when you start taking your medication and at regular checkups.

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, swallow your FOSAMAX tablet with a full glass (6-8 oz) of plain water only.**
   Not mineral water
   Not coffee or tea
   Not juice
2. **After swallowing your FOSAMAX tablet do not lie down - stay fully upright (sitting or standing) for at least 30 minutes and until after your first food of the day. Do not chew or suck on a tablet of FOSAMAX.** This will help the FOSAMAX tablet reach your stomach quickly and help avoid irritation of your esophagus (the tube that connects your mouth with your stomach).
3. **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.
4. **Do not take FOSAMAX at bedtime or before getting up for the day.**

You will find more information about osteoporosis at the end of this leaflet.

How does FOSAMAX work?

FOSAMAX works by:

- Reducing the activity of the cells that cause bone loss
- Decreasing the faster rate of bone loss that occurs after menopause
- Increasing the amount of bone in most patients

These effects are seen as soon as three months after therapy with FOSAMAX has begun. These effects continue as long as you keep taking FOSAMAX. The density of bone is maintained or increased and the bone is less likely to fracture. Thus, FOSAMAX prevents or reverses the progression of osteoporosis.

Who should not take FOSAMAX?

Patients with:

- Certain disorders of the esophagus (the tube that connects your mouth with your stomach)
- Inability to stand or sit upright for at least 30 minutes
- Low levels of calcium in their blood
- Severe kidney disease
- Allergy to FOSAMAX

Patients who are:

- Pregnant or Nursing
  FOSAMAX is for use by women after menopause. If you are pregnant or nursing, you should not be taking FOSAMAX. Talk to your doctor.

What other medical problems should I discuss with my doctor?

other medication of the day, including antacids, calcium supplements and vitamins. FOSAMAX is effective only if taken when your stomach is empty.

4. **Do not take FOSAMAX at bedtime or before getting up for the day.**
5. **If you have difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking FOSAMAX and call your doctor.**
6. Take FOSAMAX once a day, every day.
7. It is important that you continue taking FOSAMAX for as long as your doctor prescribes it. FOSAMAX can treat your osteoporosis or help you from getting osteoporosis only if you continue to take it.
8. If you miss a dose do not take it later in the day. Continue your usual schedule of 1 tablet once a day the next morning.

What is FOSAMAX?

FOSAMAX is for the treatment or prevention of osteoporosis (thinning of bone) in women after menopause. It reduces the chance of having a hip, wrist or spinal fracture.

FOSAMAX is for use by women after menopause. If you are pregnant or nursing, you should not be taking FOSAMAX. Talk to your doctor.

What other medical problems should I discuss with my doctor?

Talk to your doctor about any:

- Problems with swallowing
- Stomach or digestive problems
- Other medical problems you have or have had in the past

What are the possible side effects of FOSAMAX?

Some patients may develop severe digestive reactions including irritation, inflammation or ulceration (occasionally with bleeding) of the esophagus (the tube that connects your mouth with your stomach). These reactions can cause chest pain, heartburn or difficulty or pain upon swallowing. This 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.

Like all prescription drugs, FOSAMAX may cause side effects. Side effects usually have been mild. They generally have not caused

patients to stop taking FOSAMAX. Some patients treated with FOSAMAX experienced abdominal (stomach) pain. This is the most commonly reported side effect. Less frequently reported side effects are:

Nausea, heartburn, irritation or pain of the esophagus (the tube that connects your mouth with your stomach), vomiting, difficulty swallowing, a full or bloated feeling in the stomach, constipation, diarrhea and gas.

Rarely stomach or other peptic ulcers (some severe) have occurred.

Bone, muscle or joint pain, headache, or an altered sense of taste were also experienced by some patients. Rarely, a rash (occasionally made worse by sunlight) has occurred. Allergic reactions such as hives or rarely swelling of the face, lips, tongue and/or throat which may cause difficulty in breathing or swallowing have also been reported. Mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.

Anytime you have a medical problem you think may be related to FOSAMAX, talk to your doctor.

What should I know about osteoporosis?

Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause. Menopause happens when the ovaries stop producing the female hormone, estrogen, or are removed (which may occur

bone to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of mobility.

How can osteoporosis in postmenopausal women be treated or prevented?

- **Medication.**
  Your doctor has prescribed FOSAMAX. FOSAMAX acts specifically on your bones. FOSAMAX is not a hormone and does not have the benefits and risks of estrogen (hormone replacement therapy) elsewhere in your body. Either FOSAMAX or estrogen may be used to treat or prevent osteoporosis. You may want to talk to your doctor about these options.
- **Lifestyle changes.**
  In addition to FOSAMAX, your doctor may recommend one or more of the following lifestyle changes:
  - **Stop smoking.** Smoking appears to increase the risk of osteoporosis.
  - **Reduce the use of alcohol.** Too much alcohol appears to increase the risk of osteoporosis and injuries that may cause fractures.
  - **Exercise regularly.** Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries including fractures. You should consult your doctor before you begin any exercise program.
  - **Eat a balanced diet.** Adequate dietary calcium is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements such as calcium or vitamin D.

the bones. It is common in women after menopause. Menopause happens when the ovaries stop producing the female hormone, estrogen, or are removed (which may occur, for example, at the time of a hysterectomy). After menopause, bone is removed faster than it is formed, so bone loss occurs and bones become weaker. Therefore, maintaining bone mass is important to keep your bones healthy.

At the start osteoporosis usually has no symptoms, but it can result in fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they cause height loss. Eventually the spine becomes curved and the body becomes bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause

advise you whether you need to change your diet or take any dietary supplements such as calcium or vitamin D.

This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others. Keep FOSAMAX and all medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, drink a full glass of milk and contact your local poison control center or emergency room immediately. Do not induce vomiting. Do not lie down.

This leaflet provides a summary of information about FOSAMAX. If you have any questions or concerns about either FOSAMAX or osteoporosis, talk to your doctor. In addition, talk to your pharmacist or other health care provider.

Issued March 1998

MERCK & CO., INC.
West Point, PA 19486, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560/S014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-014

AUG 12 1998

Merck Research Laboratories
Sumneytown Pike P.O. Box 4
BLA-20
West Point, PA 19486

Attention: Michelle W. Kloss, Ph.D.
Director Regulatory Affairs

Dear Dr. Kloss:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Fosamax (Alendronate Sodium Tablets)
NDA Number:	20-560
Supplement Number:	S-014
Date of Supplement:	July 23, 1998
Date of Receipt:	July 24, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 22, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-560/S-014
HFD-510/Div. Files
HFD-510/CSO/R. Hedin

filename: C:\DATA\WPFILES\20560ACK

SUPPLEMENT ACKNOWLEDGEMENT

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

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APPROVED
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SRM
10-28-98

ORIGINAL

NDA NO. 20-560 REF. NO. 14
NDA SUPPL FOR SE

July 23, 1998

MERCK
Research Laboratories

Solomon Sobel, M D., Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 24 1998
HFD-510

NDA 20-560: FOSAMAX™
(Alendronate Sodium Tablets)

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED

NC
RW Steigerwalt
10/27/98

Dear Dr. Sobel:

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70 (c), we submit a supplement to NDA 20-560.

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in the Labeling of the approved New Drug Application for FOSAMAX™.

This supplemental application provides for labeling revisions to the **WARNINGS** and **ADVERSE REACTIONS**, *Post-Marketing Experience* sections of the Physicians Package Circular, and also provides for revisions under **"What are the possible side effects of FOSAMAX?"** in the Patient Package Insert. Specifically, the text "and rarely followed by esophageal stricture" has been added to the **WARNINGS** section, and the text "rarely, esophageal stricture" and "Skin: rash (occasionally with photosensitivity)" have been added to the **ADVERSE REACTIONS**, *Post-Marketing Experience* section of the Package Circular. In the Patient Package Insert, the text "(occasionally made worse by sunlight)" has been added after "rash", along with an editorial revision, to the first paragraph. In addition, a trademark footnote has been added to the Patient Package Insert for consistency with the Package Circular.

Attached for submission are the following:

- Summary of Revisions
- Printed Package Circular #7957009 (15 mounted copies)
- Printed Patient Package Insert #7969405 (15 mounted copies)
- Annotated Package Circular (1 copy)
- Annotated Patient Package Insert (1 copy)

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS 3/19/99 DATE

The changes will become effective on or about November 1, 1998 and will apply to all packages of FOSAMAX™ distributed from the company's manufacturing facilities at West Point, PA.

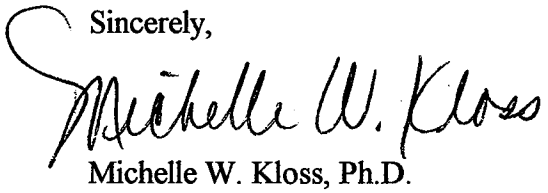
In accordance with the Food and Drug Administration Modernization Act of 1997, as indicated in the attached Form 3397, no user fee is required for this supplemental application.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or (b) of the Act.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be addressed to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Larry P. Bell, M.D. (610/397-2310).

Sincerely,



Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Attachment
q/carnal\mk217\cbe7_98.doc

Federal Express #1

Desk copy: Mr. Randy Hedin, CSO, HFD-510, Room 14B-19
Federal. Express #1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004

ATTN: Bonnie J. Goldmann, M.D.
Vice President
Regulatory Affairs

3. TELEPHONE NUMBER *(Include Area Code)*
(610) 397-2383

4. PRODUCT NAME
Alendronate Sodium TAblets; FOSAMAX

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

7. LICENSE NUMBER/NDA NUMBER

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☐ NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Vice President Regulatory Affairs	7/23/98

FORM FDA 3397 (12/93)

ORIGINAL

USER FEE DATA ENTRY/VALIDATION FORM

NDA # 20560 DOCUMENT ID/LETTER DATE SLR-019 July 23, 1998

APPLICANT NAME Merck Research Labs

PRODUCT NAME Fosmax (Alendronat Sodium) Tablet

FORM MUST BE COMPLETED ASAP

1. (YES) User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS

2. YES (NO) CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE *CROSS REFERENCED* IN ANOTHER SUBMISSION?

3. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION	FEE	NO FEE
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

4. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

5. P (S) PRIORITY OR STANDARD?

6. CSO SIGNATURE/DATE

SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5