CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-560 /S041
21-575/S004

Trade Name:	Fosamax Tablets Fosamax Oral Solution
Generic Name:	alendronate sodium
Sponsor:	Merck & Company, Inc.
Approval Date:	April 16, 2004

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APPLICATION NUMBER:

20-560 /S041

21-575/S004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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21-575/S004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-041
NDA 21-575/S-004

Merck & Co., Inc.
Attention: Michele Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 2000,
Mail Drop: RY 33-200
Rahway, NJ 07065

Dear Dr. Flicker:

Please refer to your supplemental new drug application (NDA) dated June 18, 2003, received June 19, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) Tablets (NDA 20-560), and your supplemental NDA dated April 9, 2004, received April 12, 2004, also submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) Oral Solution (NDA 21-575).

We acknowledge receipt of your submission dated April 9, 2004 to NDA 20-560.

These supplemental new drug applications propose new once-weekly dosing in men text for the package insert. The sections of the label that are modified are the CLINICAL PHARMACOLOGY, *men* section, the DOSAGE AND ADMINISTRATION section, the CLINICAL PHARMACOLOGY, *Osteoporosis in men* section, and the ADVERSE REACTIONS, *men* section of the package insert.

We have completed the review of these applications. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted April 9, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplements NDA 20-560/S-041 and NDA 21-575/S-004." Approval of these submissions by FDA is not required before the labeling is used.

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, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
4/16/04 03:20:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560/S041

21-575/S004

LABELING

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

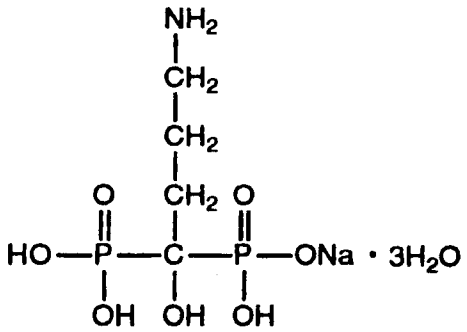
FOSAMAX®
(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

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 $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ 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, 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

* Registered trademark of MERCK & CO., Inc.

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: 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

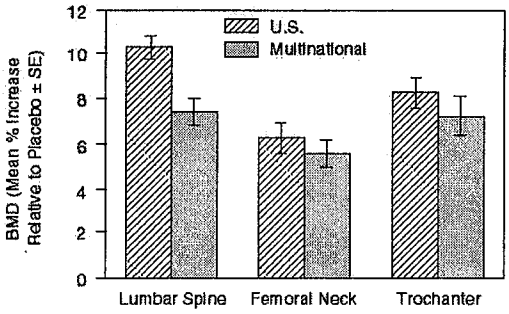
Postmenopausal women

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

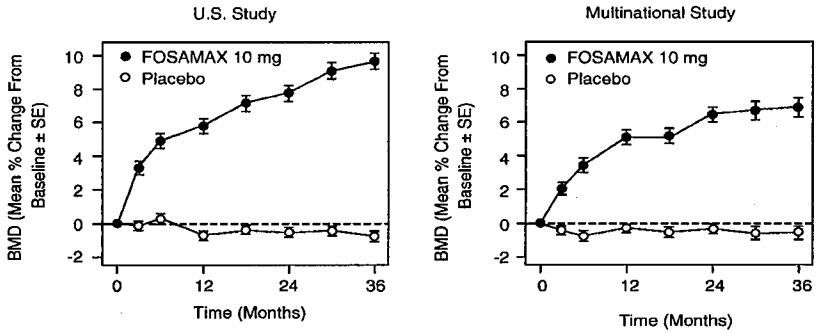
Increase in BMD
FOSAMAX 10 mg/day at Three Years



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)

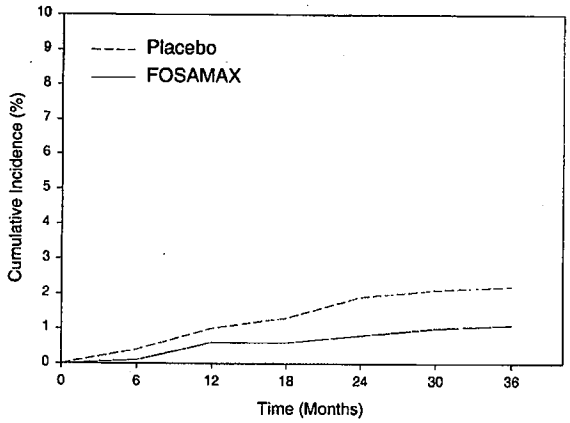
	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)†				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47***
≥ 2 new vertebral fractures	0.5	4.9	4.4	90***
Clinical (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).

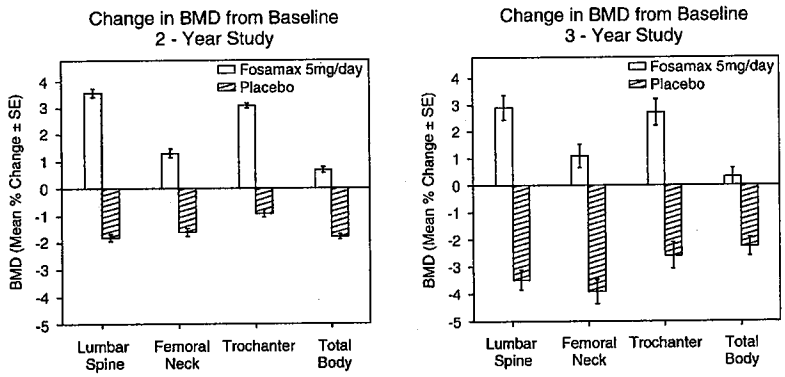
A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD T-score ≤-2 at the lumbar 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.

Osteoporosis Prevention Studies in Postmenopausal Women



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%).

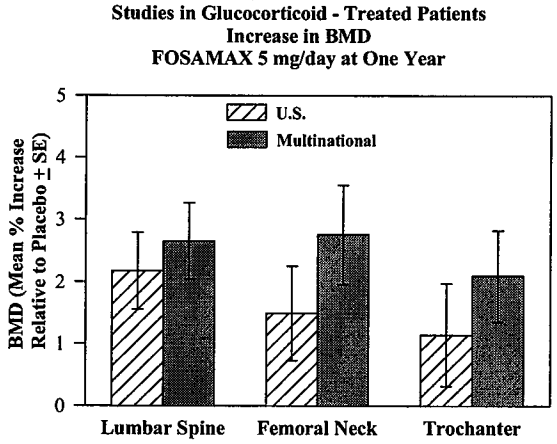
The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of FOSAMAX 10 mg once daily to HRT produced, at one year, significantly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

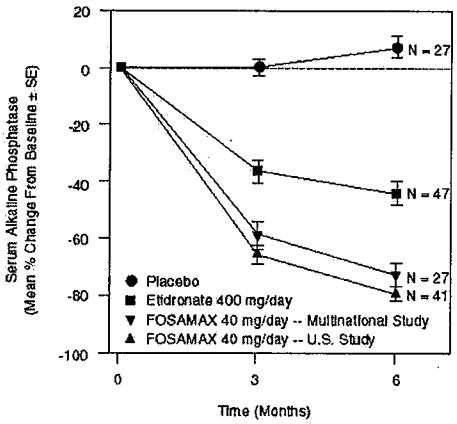
Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with FOSAMAX 5 and 10 mg/day, respectively. 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.

Studies in Paget's Disease of Bone
Effect on Serum Alkaline Phosphatase of FOSAMAX 40 mg/day
Versus Placebo or Etidronate 400 mg/day



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥60%) occurred in approximately 85% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. FOSAMAX was similarly effective 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 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 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 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 Study 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 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, 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.

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

Issued ~~February 2004~~
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560/S041

21-575/S004

SUMMARY REVIEW

TEAM LEADER MEMORANDUM

NDA: 20-560/s-041

DRUG: Alendronate

INDICATION: Treatment of male osteoporosis with once-weekly 70 mg alendronate

COMPANY: Merck

DATE SUBMITTED: June 18, 2003

PRIMARY REVIEWER: Theresa Kehoe, MD

PRIMARY REVIEWER'S REGULATORY RECOMMENDATION: Approve

DATE OF MEMO: March 29, 2004

Background

On September 29, 2000, the Division approved 10 mg once-daily alendronate for the treatment of male osteoporosis. On January 31, 2001 (supplement 025), the Division approved the addition of 70 mg once-weekly alendronate as an alternative dosing option for men with osteoporosis. This approval was based on indirect evidence; that is, evidence that 10 mg once-daily alendronate is effective in increasing BMD in women and men with osteoporosis; and 70 mg once-weekly alendronate is non-inferior in terms of BMD to 10 mg once-daily alendronate in women with osteoporosis. From these findings, safety data for the 70 mg once-weekly dose in men, and a phase 4 commitment from Merck to complete a one-year controlled trial of once-weekly alendronate in men with osteoporosis, the Division reasoned that it would be acceptable to include a 70 mg once-weekly alendronate dose as an alternative (to 10 mg once-daily) in the Dosage and Administration section of the labeling for male osteoporosis.

The subject of this supplemental NDA submission (041) is the final results of the above mentioned phase 4 study - protocol 165, A randomized, double-blind, multicenter, placebo-controlled 12-month study to evaluate the safety and efficacy of weekly dosed oral alendronate for the treatment of osteoporosis in men.

Synopsis of Protocol 165

This was a randomized, double-blind, multicenter, placebo-controlled 12-month study to evaluate the safety and efficacy of weekly dosed oral alendronate for the treatment of osteoporosis in men. The primary objective was to assess the treatment effect of oral alendronate 70 mg once-weekly vs. placebo on the change in BMD of the lumbar spine (LS) when administered for up to 12 months. Secondary objectives included assessing the effect of once-weekly alendronate on changes in BMD at the hip and total body; assessing the effect of active-drug treatment of biochemical makers of bone turnover; and to assess the effect of alendronate on height.

Patients were stratified by gonadal status prior to randomization in order to maintain an equal balance of hypo- and eugonadal men in each treatment group. Subjects were randomized (2:1) to received either 70 mg once-weekly alendronate or placebo. All subjects were instructed to take 1000 mg of elemental calcium and 400 IU of vitamin D per day.

In the interest of patient safety, the sponsor monitored all post-treatment BMD measurements and notified the sites and Merck of patients who lost 5% or more in bone mass from baseline. These patients, and those who experienced an osteoporotic clinical fracture, were discontinued early from the study.

DEXA scans were obtained at baseline and Months 6 and 12. Markers of bone turnover were measured at baseline and Months 3, 6, and 12.

Men aged 25 to 90 years with hypogonadal or idiopathic osteoporosis were eligible for the trial. The subjects had to have at least one of the following:

- Femoral neck BMD at least 2 SD below the mean for healthy young Caucasian males and a LS BMD at least 1 SD below the mean for young healthy Caucasian males, with no prior osteoporotic fracture;

or

- Lumbar spine BMD at least 2 SD below the mean for young normal White males and a femoral neck BMD at least 1 SD below the mean for young normal White males, with no prior osteoporotic fracture;

or

- Documented osteoporotic fracture and femoral neck BMD at least 1 SD below the mean for young normal White males.

Exclusion criteria included a history of recent (within 1 year prior to screening) major upper GI disease, including, but not limited to, peptic ulcer, malabsorption, esophageal disease or active GI bleeding or had ever had surgery of the upper GI tract other than pyloroplasty. Subjects with abnormalities of the esophagus which delayed esophageal emptying such as stricture or achalasia were also excluded.

A total of 167 patients were randomized to therapy: 109 to alendronate and 58 to placebo. Ninety-seven alendronate and 46 placebo subjects completed the 12-month study. Eight alendronate and 4 placebo discontinued because of a clinical adverse experience.

The two groups were well-matched at baseline. The average age was 66 years, 98% of the men were Caucasian, 41% were hypogonadal, and 59% eugonadal. Sixty-three percent of the men had a prevalent vertebral fracture and the baseline LS BMD T-score was –1.8.

The mean percent change from baseline to Month 12 in LS BMD was 4.28% in the alendronate group and 1.45% in the placebo group ($p<0.001$). The mean percent change from baseline to Month 12 in total hip BMD was 1.7% in the alendronate group and –0.17% in the placebo group ($p<0.001$). Total body BMD increased by 1.4% and by 0.20% in the alendronate and placebo groups, respectively ($p=0.018$).

For point of reference, in the once-daily alendronate study in male subjects with osteoporosis, the placebo-subtracted increase in LS BMD at one year was approximately 3.5%.

The levels of urinary NTX decreased by 51% in the alendronate group at Month 12 and decreased by 4.5% in the placebo group ($p<0.001$).

Two patients, both assigned to alendronate, died during conduct of the study; an additional subjects, also receiving alendronate, died during the post-study phase. These deaths were from a CVA, unknown cause, and lung cancer, respectively. Seventy-one percent of alendronate and 81% of placebo subjects had one or more adverse experiences. The incidence of serious AEs was about 13% for both treatment groups.

Sixteen percent of alendronate and 10% of placebo subjects had at least one GI-related AE. The largest difference in incidence rates between groups was for dyspepsia (4.6%, 1.7%) and GERD (2.8%, 0%).

Eight alendronate (7.5%) and 4 placebo(7.3%) subjects had at least one incident morphometric vertebral fracture as assessed at Month 12.

Proposed Labeling

CLINICAL PHARMACOLOGY

Pharmacodynamics, Osteoporosis in Men
A sentence stating that reduction in biochemical markers with once weekly 70 mg were similar to those with 10 mg/day have been added in support of the once weekly 70 mg dosing regimen.

Clinical Studies, Treatment of osteoporosis, Men
The first sentence has been revised to accommodate addition of the once weekly 70 mg study.

A paragraph has been added which provides study results that demonstrate the efficacy of once weekly 70 mg in men with osteoporosis. These data support the revised dosage recommendation in DOSAGE AND ADMINISTRATION.

The sentence "The safety and efficacy of once weekly FOSAMAX 70 mg in men with osteoporosis are currently being studied, but data are not yet available." has been deleted as a study (protocol 165) demonstrating safety and efficacy has been completed and is provided in this sNDA.

PREACUTIONS

Geriatric Use
The text sentence concerning patients over 65 years of age has been revised to incorporate information from the male once weekly 70 mg study.

ADVERSE REACTIONS

Clinical Studies, Treatment of osteoporosis, Men
The existing text and table have been revised to incorporate information from the male once weekly 70 mg study. The once weekly 70 mg safety data support the revised dosage recommendation in DOSAGE AND ADMINISTRATION and deletion of the sentence "The safety and . . . not yet available." in CLINICAL PHARMACOLOGY.

DOSAGE AND ADMINISTRATION

Treatment to increase bone mass in men with osteoporosis
The existing recommendation for 70 mg has been revised to the recommended dosage of 70 mg once weekly or 10 mg daily.

Comment

The proposed labeling changes are, in general, acceptable. See Dr. Kehoe's review of the labeling for her proposed modifications.

Conclusion and Recommendation

The results of this study confirm the assumption made by the Division when we allowed the alendronate labeling to include the 70 mg once weekly dose as an alternative to the 10 mg once daily dose prior to having controlled data: that is, 70 mg once weekly is an efficacious dosing regimen in men with idiopathic or hypogonadal osteoporosis. The placebo-subtracted increases in LS BMD were very similar in men treated with 10 mg once daily and 70 mg once weekly. No new or significant safety issues emerged from the review of this supplement. Pending agreement with the company on some minor labeling modifications, I recommend that this supplemental NDA be approved.

_____

Eric Colman, MD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
4/2/04 12:08:33 PM
MEDICAL OFFICER

David Orloff
4/2/04 12:19:39 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560/S041

21-575/S004

MEDICAL REVIEW(S)

CLINICAL REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)	
Application #: 20-560, S-041	**Application Type:** sNDA
Sponsor: Merck	**Proprietary Name:** FOSAMAX
Pharmaceutical Category: Bisphosphonate	**Route of Administration:** Oral
Indication: Treatment of Osteoporosis in Men	**Dosage:** 70mg once weekly
Reviewer: Theresa Kehoe, MD	**Date Review Completed:** March 31, 2004
Chemistry Reviewer: N/A	
Pharmacology Reviewer: N/A.	
Biopharmaceutics Reviewer: N/A	
Statistical Reviewer: Cynthia Liu, M.A.	
REVIEW SUMMARY: See Executive Summary	
OUTSTANDING ISSUE:	
RECOMMENDED REGULATORY ACTION:	N drive location:
New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**	
NDA, Efficacy/Label supplement: _____ **Approvable** _____ **Not Approvable**	
XX Approve	

SIGNATURES:

Medical Reviewer: Theresa Kehoe, M.D. **Date:** _____.

Medical Team Leader: Eric Colman, M.D. **Date:** _____.

Table of Contents

Clinical Review for NDA 21-688

Executive Summary

I. Recommendations

A. Recommendation on Approvability:
APPROVE

B. Recommendation on Phase 4 Studies and/or Risk Management Steps
None

II. Summary of Clinical Findings

A. **Brief Overview of Clinical Program:** This application is submitted as a supplemental new drug application requesting labeling changes to include alendronate 70-mg once weekly for the treatment of osteoporosis in men. The study submitted (Protocol 165) fulfills the postmarketing commitment agreed to at the time alendronate 10-mg daily for treatment of men with osteoporosis was approved. Alendronate 10-mg daily and 70-mg weekly are also currently approved for the treatment of postmenopausal osteoporosis.

B. **Efficacy:** This study, Protocol 165, demonstrates that in men with osteoporosis, treatment with alendronate 70-mg weekly for 1 year significantly increases lumbar spine, hip, and total body BMD. At one year, lumbar spine BMD increased 4.28% with alendronate therapy compared to 1.45% with placebo ($p < 0.0001$). The mean difference in percent change from baseline between the treatment groups was 2.82%. These results are similar to BMD increases observed in studies evaluating the efficacy of alendronate 10-mg daily in men with osteoporosis (protocol 096). In that study, at one year, treatment with alendronate resulted in a 4.85% increase in lumbar spine BMD, with a mean difference between treatment groups of 3.30%. The BMD increases seen in protocol 165 were accompanied by reductions in markers of bone turnover (NTx and BSAP). Subgroup analyses of baseline demographics did not reveal any clinically meaningful correlations with increases in lumbar spine BMD.

C. **Safety** There were no unexpected safety findings uncovered during the review of this supplemental NDA. There was an imbalance between the alendronate and placebo groups in the number of patients who died during and immediately following this study (3 vs 0). The causes of death in the alendronate group, stroke, lung cancer, and presumed sudden death, were not unusual given the mean age of the patient population. Furthermore, there was no evidence that the deaths were drug-related. The percentage of patients who experienced at least one serious adverse event was similar between the two treatment groups. The rates of premature

withdrawal due to adverse events were slightly higher in the placebo group than the alendronate group: 9% vs. 6%.. The overall incidence of clinical adverse events was generally similar across both treatment groups. A higher percentage of upper GI events occurred in the alendronate-treated group (16% vs. 10% in the placebo group), which was not unexpected. The incidence of clinical vertebral fractures was balanced between the two treatment groups. However, an imbalance between the alendronate and placebo groups in the number of patients who sustained nonvertebral fractures was noted (6% in the alendronate-treated group vs. 3% in the placebo-treated group). This imbalance may in part be due to traumatic fracture events. Overall, alendronate 70-mg once-weekly tablets were generally well tolerated in this study population of men with osteoporosis.

D. Dosing: The current dosing guidelines for the alendronate 70-mg once weekly tablet were followed in this study and should be maintained as is.

E. Special Populations: Alendronate 10-mg daily is currently approved for therapy in both men and postmenopausal women with osteoporosis. Alendronate 70-mg once weekly is currently approved for therapy in postmenopausal women. The age range of study participants was 26 – 96 years. Age analyses have previously been conducted for alendronate under NDA 20-560. The racial composition of this study population is almost entirely Caucasian. No racial analyses have been done, given the lack of available data.

Clinical Review

I. Introduction and Background

I.A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups: Merck Research Laboratories, Inc. has submitted this supplemental new drug application for alendronate sodium [(4-amino-1- hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate] 70-mg once weekly tablet, trade name Fosamax. Alendronate is a member of the bisphosphonate class of medications. This once weekly formulation is currently available for the treatment of osteoporosis in postmenopausal women and is labeled as an alternative dosing option to increase bone mass in men with osteoporosis. This application is submitted to fulfill a postmarketing commitment to study the effects of 70-mg once weekly alendronate on BMD in men with hypogonadal or idiopathic osteoporosis.

I.B. State of Armamentarium for Indication(s): In addition to the 10-mg once daily dose of alendronate, teriparatide 20-mg once daily is approved to increase bone mass in men with osteoporosis.

I.C. Important Milestones in Product Development: Alendronate sodium 10-mg daily was initially approved for the treatment of postmenopausal osteoporosis in September, 1995. Other indications subsequently approved include the prevention of osteoporosis in postmenopausal women (5-mg daily dose) in April 1997, the treatment of glucocorticoid-induced osteoporosis in women (5-mg daily or 10mg daily for postmenopausal women not on estrogen) and men (5-mg daily) receiving glucocorticoids in June 1999. A once weekly tablet formulation (35-mg for prevention of postmenopausal osteoporosis and 70-mg for treatment of postmenopausal osteoporosis) was approved in October 2000. Alendronate 10-mg daily was approved to increase bone mass in men with osteoporosis in September of 2000. Upon submission of a protocol investigating the 12-month safety and efficacy of weekly alendronate dosing in men (protocol 165), alendronate 70-mg once weekly was approved to increase bone mass in men with osteoporosis, with a post approval commitment to complete the protocol in progress.

I.D. Important Issues with Pharmacologically Related Agents: Bisphosphonates are used in the prevention and treatment of postmenopausal and corticosteroid-induced osteoporosis, Paget's disease, hypercalcemia of malignancy, and bony metastases. Safety concerns with oral bisphosphonates include esophageal and gastric irritation and ulceration.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Alendronate 70mg once weekly tablets have been previously approved for treatment of osteoporosis in postmenopausal women. No new chemistry or nonclinical pharmacology or toxicology data have been submitted with this supplemental NDA. A discussion of the pertinent findings has been incorporated into the appropriate sections of the efficacy review.

III. Human Pharmacokinetics and Pharmacodynamics

No new pharmacokinetic or pharmacodynamic data have been submitted with this supplemental NDA.

IV. Description of Clinical Data and Sources

IV.A. Overall Data: The focus of this application is protocol 165: A Randomized, Double-Blind, Multicenter, Placebo-Controlled, 12-Month Study to Evaluate the Safety and Efficacy of Weekly Dosed Oral Alendronate Sodium for the Treatment of Osteoporosis in Men.

IV.B. Postmarketing Experience: Alendronate has been marketed in more than 90 countries and it is estimated that as of June 2002, the cumulative patient-years of experience exceeded [redacted] million.

IV.C. Literature Review: A MEDLINE review was conducted for alendronate treatment in men. The sponsor has provided all relevant articles.

V. Clinical Review Methods

V.A. How the Review was Conducted: This review concentrates on Protocol 165, evaluating the safety and efficacy of alendronate 70mg once weekly in men with osteoporosis.

V.B. Overview of Materials Consulted in Review: The information reviewed was provided in an electronic format.

V.C. Overview of Methods Used to Evaluate Data Quality and Integrity: The Division of Scientific Investigation (DSI) was not consulted for this NDA.

VD. Were Trials Conducted in Accordance with Accepted Ethical Standards: All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

V.E. Evaluation of Financial Disclosure: Financial disclosure information was provided by the sponsor and reviewed by this reviewer. A total of 100 investigators and subinvestigators at 13 sites in the U.S. participated in Protocol 165. Three investigators were no longer at the site of record and no information was obtained. Eight investigators reported significant payments of other sorts. No investigator received payments based on the outcome of the study. Of the eight investigators with significant payments of other sorts, one investigator reported an extraordinarily large financial interest. However, the study results did not differ substantially when the data from this investigator were excluded. Demographic subgroup analyses showed consistent treatment effects on % change in lumbar spine BMD across all study sites.

VI. Review of Efficacy

VI.A. Brief Statement of Conclusions: This study demonstrates that in men with osteoporosis, treatment with alendronate 70-mg weekly for 1 year significantly increases lumbar spine, hip, and total body BMD. Increases in lumbar spine BMD were observed as early as 6 months after initiating treatment. These BMD increases were accompanied by reductions in markers of bone turnover (NTx and BSAP). The increases in BMD and the reduction in biochemical markers seen in osteoporotic men treated with alendronate 70-mg weekly were consistent with those observed in osteoporotic men treated with alendronate 10-mg daily.

VI.B. General Approach to Review of the Efficacy of the Drug: A detailed review of Protocol 165 results was performed to evaluate the efficacy of alendronate 70-mg once weekly in men with osteoporosis.

VI.C. Detailed Review of Protocol 165: A Randomized, Double-Blind, Multicenter, Placebo-Controlled, 12–Month Study to Evaluate the Safety and Efficacy of Weekly Dosed Oral Alendronate Sodium for the Treatment of Osteoporosis in Men

VI.C.1. Objectives

VI.C.1.a. Primary: To assess the treatment effect of oral alendronate 70-mg once weekly versus placebo on the change in BMD of the spine when administered for up to 12 months in men with osteoporosis.

VI.C.1.b. Secondary: In men with osteoporosis:

i. To assess the treatment effect of oral alendronate 70-mg once weekly versus placebo on the change in hip (femoral neck, trochanter, and total) and total body BMD when administered for 12 months.

ii. To examine the effects of oral alendronate 70-mg once weekly on biochemical markers of bone turnover (urinary NTx and BSAP) when administered for 12 months.

iii. To examine the relationship between the changes in bone mass at the spine and baseline BMD, biochemical markers of bone turnover, gonadal status, age, height, weight, and body mass index (BMI)

iiii. To describe the safety/tolerability profile of oral alendronate 70-mg once weekly when administered for up to 12 months.

VI.C.2. Study Design: Protocol 165 is a 12-month, double-blind, randomized, placebo-controlled study, to compare the safety and efficacy of once-weekly dosed oral alendronate for the treatment of osteoporosis in men. There were 167 patients randomized to receive either oral alendronate 70-mg or matching placebo, 2:1 ratio, once a week for 1 year.

COMMENT: This study is similar to the randomized, double-blind, placebo-controlled trial of daily oral alendronate for the treatment of osteoporosis in men, except that the study of daily oral alendronate (10-mg) was a 2-year study, while the current study was a 1-year study of weekly alendronate (70-mg). The purpose of the current study was to

demonstrate that the weekly 70-mg dose of alendronate is similarly well tolerated and effective for the treatment of osteoporosis in men. The sponsor feels that the absorption, distribution, and treatment effect of alendronate is similar in men and women. Alendronate 70-mg was compared to 10-mg daily in postmenopausal women and was found to be effective. Therefore, the company chose a placebo control for this trial because it was believed there would not be an adequate number of men to enroll in an equivalence trial of daily versus weekly alendronate. Because of ethical concerns, they limited this trial to one year.

VI.C.2.a. Population: Men between ages 25 and 90 who had confirmed osteoporosis were enrolled into the trial. Subjects were stratified at randomization by their gonadal status.

VI.C.2.a.i. Inclusion Criteria

- The patient was a man between the ages of 25 and 90 years.
- The patient had idiopathic osteoporosis or osteoporosis due to hypogonadism, and fulfilled one of the following 3 criteria:
    - Femoral neck BMD at least 2 SD below the mean for young normal White males (≤0.658 g/cm2 [redacted], ≤0.867 [redacted]) and a lumbar spine BMD at least 1 SD below the mean for young normal White males (≤1.005 g/cm2 [redacted], ≤1.135 [redacted] with no prior osteoporotic fracture, **or**
    - Lumbar spine BMD at least 2 SD below the mean for young normal White males (≤0.895 g/cm2 [redacted], ≤ 1.015 [redacted] and a femoral neck BMD at least 1 SD below the mean for young normal White males (≤0.794 g/cm2 [redacted] ≤0.987 [redacted], with no prior osteoporotic fracture, **or**
    - Documented osteoporotic fracture and femoral neck BMD at least 1 SD below the mean for young normal White males (≤ 0.794 g/cm2 [redacted] ≤0.987 [redacted] There were no spine BMD requirements if the patient had experienced an osteoporotic fracture.

Note: The absolute BMD values in g/cm^2 provided in the protocol and repeated above corresponded to BMD SDs below the mean for young normal White males and were, therefore, erroneous, for both the femoral neck and lumbar spine sites for the [redacted] densitometers and for the femoral neck site for [redacted] densitometers. These erroneous values resulted in the enrollment of 10 patients with higher than intended baseline BMD values. However, all patients who received at least one dose of study drug were included in the modified intention-to-treat (MITT) analysis.

The BMD cutoffs corresponding to BMD that is 1 SD below the mean for young normal White males was 0.794 g/cm2 [redacted] and 0.940 g/cm2 [redacted] for the femoral neck and 0.981 g/cm2 [redacted], 1.100 g/cm2 [redacted] for the lumbar spine. The BMD cutoffs corresponding to BMD that is 2 SD below the mean for young normal White males was 0.658 g/cm2 [redacted] and 0.810 g/cm2 [redacted] for femoral neck and 0.871 g/cm2 [redacted], 0.980 g/cm2 [redacted] for lumbar spine.

- The patient had a lumbar spine anatomy suitable for accurate measurement by dual-energy x-ray absorptiometry (DXA), with at least 3 evaluable vertebrae from L1 to L4.
- The patient was generally in good health.
- All screening laboratories were within or close to the laboratory-defined normal range.
    - Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) was within 2 times the upper limit of normal (ULN).
    - Serum free testosterone was below the age-specific normal range in patients designated as hypogonadal for stratification purposes.
    - Serum 25-hydroxyvitamin D was ≥11 ng/dL and not more than 20% above the ULN.
    - Blood glucose was <126 if fasting and <200 if nonfasting.
    - Either the red blood cell count (RBC), hemoglobin, or hematocrit was within 10% of the normal range.
    - Out-of-range white blood cell (WBC) differentials were allowable, as long as the investigator confirmed the values were not clinically significant, and the white cell count was normal.
    - All other laboratory values were within 10% of the normal range. Patients with screening laboratory values outside of these ranges could only be randomized with documented prior approval from the Merck clinical monitor and confirmation from the Investigator that the values were not clinically significant.
- The patient understood the procedures required for the study, was mentally and legally competent to give informed consent, and voluntarily agreed to participate, having been informed that he could have freely elected no treatment.

VI.C.2.a.ii. Exclusion Criteria

- The patient had a history of, or evidence for, metabolic bone disease, other than osteoporosis due to hypogonadism or idiopathic osteoporosis, including, but not limited to, glucocorticoid-induced osteoporosis, hyper- or hypoparathyroidism, Paget's disease of bone, osteomalacia, osteogenesis imperfecta, vitamin D deficiency (based on prestudy measurements of 25-hydroxyvitamin D levels) or active thyroid disease (including abnormalities in serum thyroid stimulating hormone [TSH] or free thyroxine).
- The patient had significant scoliosis, bony trauma, or sequelae of orthopedic procedures, which resulted in an anatomy unsuitable for accurate bone densitometry.
- The patient had hypogonadism due to causes, which affect multiple organs and systems (such as chronic renal failure, liver disease, celiac disease, hemochromatosis, cystic fibrosis, chronic infection).
- The patient had osteoporosis secondary to hypogonadism diagnosed during the screening visit (Visit 1) and desired to initiate testosterone replacement therapy prior to or during the study.
- The patient was currently on testosterone replacement therapy or had been on testosterone replacement therapy within 1 year of study entry.
- The patient had rheumatoid arthritis.
- The patient was receiving any medication that could have potentially altered bone or calcium metabolism, including anabolic steroids, vitamin A in excess of 10,000 IU/day,

vitamin D in excess of 1000 IU/day, metabolites of vitamin D (calcitriol or alfacalcidol), cyclosporin, or anticonvulsants.

- The patient was currently receiving or had used systemic or topical glucocorticoids within the previous year (except intermittent treatment with inhaled glucocorticoids for a total duration of less than 2 weeks during the previous year for acute exacerbation of asthma or chronic obstructive pulmonary disease [COPD]).
- The patient was unwilling to take calcium supplements during the study.
- The patient previously used any bisphosphonate therapy.
- The patient used calcitonin within the 6 months prior to screening.
- The patient used fluoride (>1 mg/day for >1 month) within the 24 months prior to screening.
- The patient had a current or recent (within the 5 years prior to screening) history of alcohol abuse or drug dependence.
- The patient had a history of myocardial infarction within 6 months prior to study start.
- The patient had a history of, or evidence for, any illness or had significant abnormalities on prestudy clinical or laboratory evaluations which, in the opinion of the investigator, might have complicated the interpretation of the study data.
- The patient had a history of recent (within 1 year prior to screening) major upper GI disease, including, but not limited to, peptic ulcer, malabsorption, esophageal disease or active GI bleeding or had ever had surgery of the upper GI tract other than pyloroplasty.
- The patient had abnormalities of the esophagus which delayed esophageal emptying such as stricture or achalasia.
- The patient had a previous or existing diagnosis of any cancer or other malignancy, unless it had been curatively treated for ≥10 years without evidence of recurrence. Prostate cancer must have been ruled out within the year prior to screening by a normal digital rectal examination by the patient's personal physician and normal levels of prostatic-specific antigen (PSA) at baseline. Patients with basal cell or epidermal skin cancer cured by appropriate treatment at any time before study entry were included. time of diagnosis, treatment history, or duration of remission.
- The patient had received hormonal therapy for prostate cancer within 3 years of study entry.
- The patient was unable to stand or sit upright for at least 30 minutes.
- The patient was not ambulatory or weighed over 250 lbs.
- The patient was either mentally or legally incompetent to give informed consent.
- The patient planned to move within 12 months to a location which would have made continued follow-up difficult.
- The patient had received any investigational drug within 30 days of study entry.

VI.C.2.b. Study Medications: Patients self-administered one alendronate 70-mg or placebo tablet once per week for 12 months. Concomitant therapy included [redacted] 500+D tablets (1 tablet taken with lunch and 1 tablet taken with dinner). Each [redacted] tablet contained 500 mg of elemental calcium plus 200 IU of vitamin D. Patients were instructed to take 1 tablet of study medication once per week, preferably on the same day each week, with a full glass (6 to 8 oz.) of plain water, at least 30 minutes before any other medication, food, or drink of the day,

and not to lie down until 30 minutes after dosing. Missed weekly doses were taken up to 1 day before the next scheduled weekly dose. No more than 1 dose was taken in a single day.

VI.C.2.c. Efficacy Measures: The primary efficacy response parameter was the percent change from baseline at Month 12 in BMD of the lumbar spine (L1 through L4). This site was chosen over other skeletal sites due to its higher proportion of trabecular bone. Since turnover is higher in trabecular bone, relative to cortical bone, it was expected there would be greater power to detect a treatment difference at this site, relative to the hip or total body.

Secondary efficacy response parameters included (a) the percent change from baseline at Month 6 in lumbar spine BMD; (b) the percent change from baseline at Months 6 and 12 in hip (femoral neck, trochanter, total) and total body BMD; (c) the percent change from baseline at Months 3, 6, and 12 in biochemical markers of bone turnover (NTx and BSAP).

VI.C.2.d. Safety Measures: The primary safety response parameter was the overall incidence of clinical and laboratory adverse experiences, since these are the most easily detectable and readily reported changes in the condition of the patient. Particular attention was given to the incidence of upper GI adverse experiences since these have been previously associated with the use of bisphosphonates. Other important safety parameters included the incidence of vertebral and nonvertebral fracture adverse experiences, proportion of patients exceeding predefined limits of change in laboratory values over time, and the mean change from baseline at Month 12 in BP, heart rate (HR), oral temperature, height, and weight.

VI.C.2.e. Study Methods:

VI.C.2.e.i. Bone Mineral Density: BMD was performed locally by DXA, using [redacted] densitometers. [redacted] was used as the central quality assurance center to advise the sites on standard procedures for obtaining and submitting BMD scans, equipment maintenance, and quality control procedures. Each site provided its own long-term quality control data using a hydroxyapatite phantom and performed daily scans of a standard [redacted] spine phantom each day DXA measurements were obtained. Baseline spine and hip BMD scans were analyzed locally, then sent to [redacted] for confirmation of eligibility. All subsequent BMD scans were analyzed centrally. Investigators were not provided the results until the end of the study, after all data were reconciled and treatment assignments were unblinded.

VI.C.2.e.ii. Biochemical Markers of Bone Turnover: Samples for urinary NTx [redacted] and serum BSAP were collected locally and analyzed centrally by [redacted] Urinary NTx was adjusted for creatinine levels. Investigators were not provided the results until the end of the trial, after all data were reconciled and treatment assignments were unblinded.

VI.C.2.e.iii. Fracture Assessment: Symptomatic vertebral and nonvertebral fractures, which occurred during the study, were confirmed radiographically and reported as clinical adverse experiences by the investigator.

Lateral spine radiographs were obtained locally at baseline and Month 12 or at the time of early discontinuation. Morphometric assessment of individual vertebral heights was performed by the central radiologist according to established procedures. An incident (new or worsening) vertebral fracture was defined as a decrease of greater than or equal to 20% and greater than or equal to 4 mm in any vertebral height between the baseline and subsequent radiograph. Vertebral heights were reported by the central radiologist in [illegible] In order to identify vertebral fractures, these results were converted to [illegible]

VI.C.2.e.iiii. Height: Height (without shoes) was measured using a [illegible] stadiometer. Three measurements were taken and, if any of these differed by 4 mm or more, a fourth and fifth measurement was obtained. The average of all measurements obtained at a particular visit was used as the value for that time point.

VI.C.2.f. Withdrawal Criteria: Men found to have lost 5% or more of bone mass from baseline or who experienced an osteoporotic fracture during the study were withdrawn from the study.

VI.C.2.g. Statistical Analyses: Sample size estimation was based on between-treatment estimates obtained from the results of the alendronate daily dosing in male osteoporosis. All power computations were made under the assumption of a two-sided test of hypotheses performed at α=0.05. Based on the results from prior studies (Protocol 096), a difference of 3% (SD=4%) in lumbar spine BMD percent change from baseline was anticipated between the alendronate and placebo groups at Month 12. A sample size of 80 patients in the alendronate group and 40 patients in the placebo group was planned to detect a difference of 3% between the 2 treatment groups with a power of 97%.

The MITT analysis was considered the primary analysis for all efficacy variables except biochemical markers. The MITT analysis set included all patients randomized in the study who had a baseline and at least one treatment-period measurement after at least one dose of double-blind therapy. The patients were analyzed according to the treatment group to which they were randomized (placebo or alendronate 70 mg). In the MITT analysis, missing values were imputed using the last-observation-carried forward technique.

VI.C.2.h. Protocol Amendments: The original protocol was amended 4 times.

Amendment #1 (24-Jul-2000): Dosing instructions were clarified to indicate that missed doses of weekly medication could be taken up to 6 days after the missed dose. Prohibited topical steroids were more clearly defined as "prescription strength." Breast and chest examinations were not required as part of the physical examination.

Amendment #2 (28-Nov-2000): Inclusion criteria e. was rewritten to more specifically define acceptable screening laboratory values for SGOT, SGPT, serum 25- hydroxyvitamin D, blood glucose, and hematology. Early stage (A, B) prostate cancer patients were allowed to participate provided they did not receive hormonal therapy within 3 years of study entry.

Amendment #3 (23-Mar-2001): Inclusion criteria 1.b. was revised to include patients with prior osteoporotic fractures in the definition of patients with more severe osteoporosis. Given concerns of a placebo-controlled study with the commercial availability of marketed

alendronate (both alendronate 10 mg daily and alendronate 70 mg weekly) for the treatment of osteoporosis in men, the protocol was amended to check for (and discontinue) high-risk patients, i.e., those with more than 5% bone loss from baseline or those who experienced an osteoporotic fracture during the study.

Amendment #4 (14-Jan-2002): A secondary hypothesis and efficacy endpoint was added to assess the effect of alendronate on the percent change in lumbar spine BMD at Month 6.

VI.C.3. Results

VI.C.3.a. Patient Disposition: A total of 579 subjects were screened with 167 subjects enrolled in the study. Of those enrolled, 143 (86%) completed the study.

Protocol 165: Patient Disposition		
	Placebo	**Alendronate**
Enrolled	58	109
Withdrew - Total	12 (21)	12 (11)
Withdrew - AE	8	4
Withdrew - Other	4	8
Completed Study	46 (79)	97 (89)

VI.C.3.b. Protocol Violations: One subject was excluded from the MITT analyses because of protocol deviations. A total of 30 subjects did not have adequate baseline lumbar spine BMD and were excluded from this analysis. A total of 26 subjects reportedly did not have Month 12 data to allow inclusion in the MITT analysis. Overall, 31 subjects (23 in the alendronate group and 8 in the placebo group) were excluded from MITT analysis because of protocol deviations.

COMMENT: Subjects were excluded from MITT analyses primarily due to lack of adequate baseline BMD data. This would not be expected to affect the overall efficacy and safety outcomes of the study.

VI.C.3.c. Demographics: Baseline subject demographics were well balanced across the treatment groups (see table below). Ninety-eight percent of enrolled subjects were White. Approximately 57% of enrolled subjects were ≥ 65 years of age. A total of 41% of subjects were hypogonadal. Baseline vertebral fractures, as determined by the investigator from the baseline spine radiographs, were reported in 63% (62% in the alendronate group and 66% in the placebo group) of subjects. Prior osteoporotic fractures were reported by 62% of the subjects, with a higher proportion in the placebo group (59% in the alendronate group compared to 67% in the placebo group).

Protocol 165: Demographics		
	Placebo	**Alendronate**
N	58 (%)	109 (%)
Age (yrs.)	66.7 ± 12.4	65.8 ± 10.7
≥ 65 years	30 (52)	65 (60)
Weight (kg)	79.1 ± 13.0	78.7 ± 11.7
Height (mm)	1713.7 ± 62.4	1743.7 ± 67.8
BMI (kg/m^2)	26.9 ± 4.5	25.8 ± 3.5

Protocol 165: Demographics		
	Placebo	Alendronate
Race		
Caucasian	57 (98)	106 (97)
Black		1
Other	1	3
Gonadal Status		
Hypogonadal	24 (41)	45 (41)
Eugonadal	34 (59)	64 (59)
Prevalent Vertebral Fracture		
Yes	38 (66)	67 (62)
No	19 (33)	38 (35)
Unknown	1 (2)	4 (4)
Prior Osteoporotic Fracture		
Yes	39 (67)	60 (59)
No	19 (33)	45 (41)
BMD T scores		
Lumbar Spine	-1.63 ± 1.50	-1.89 ± 1.24
Femoral Neck	-2.00 ± 0.61	-2.14 ± 0.50
Total Hip	-1.41 ± 0.71	-1.57 ± 0.64
Total Body	-0.21 ± 0.77	-0.17 ± 0.53

VI.C.3.d. Primary Efficacy Outcomes: The primary efficacy response parameter was the percent change from baseline at Month 12 in BMD of the lumbar spine (L1 through L4). As outlined in the table below, at one year, treatment with alendronate 70-mg once weekly resulted in a significantly larger increase in lumbar spine BMD (4.28%) when compared to placebo (1.45%) ($p < 0.0001$). The mean difference in percent change from baseline between the treatment groups was 2.82%, with a 95% CI of (1.51, 4.13).

Protocol 165: Lumbar Spine BMD (MITT) at 12 Months					
	Placebo	Alendronate	Treatment Difference	p-value	(LCL, UCL)
N	46	82			
Raw mean lumbar spine BMD ± SD					
Baseline	0.93 ± 0.18	0.90 ± 0.15			
Month 12	0.95 ± 0.19	0.94 ± 0.16			
Least-squares mean % change from baseline ± SE					
Month 12	1.45 ± 0.54	4.28 ± 0.43	2.82	<0.0001	(1.51, 4.13)

COMMENT: These results are similar to BMD increases observed in studies evaluating the efficacy of alendronate 10-mg daily in men with osteoporosis (protocol 096). In that study, at one year, treatment with alendronate resulted in a 4.85% increase in lumbar spine BMD, with a mean difference between treatment groups of 3.30%.

Subgroup analyses: Change in lumbar spine BMD at Month 12 was evaluated for several prespecified subgroup analyses. The subgroups examined included baseline lumbar spine BMD (T-score ≤-2.5, >-2.5), baseline femoral neck BMD (T-score ≤-2.5, >-2.5), prior osteoporotic fractures (yes, no), prevalent vertebral fractures (yes, no), age (<65 and ≥65; <75 and ≥75), and gonadal stratum (hypogonadal, eugonadal). Baseline lumbar spine BMD, femoral neck BMD,

height, weight, and body mass index (BMI) were also evaluated by tertile. Because of the limited sample size (only 4 patients were classified as "non-White"), a meaningful subgroup analysis of lumbar spine BMD changes could not be performed for race.

There was a significant quantitative treatment-by-subgroup interaction (p=0.014) for baseline weight; the treatment difference in lumbar spine BMD at Month 12 was smaller for heavier patients with baseline weight above the second tertile (= 82.1 kg) than for patients with baseline weight $\leq$ 82.1 kg. For all other subgroups, no significant interactions were observed. However, in general, the patients with lower baseline BMD tended to have a slightly higher response to treatment than to those with higher baseline BMD (5.4% for patients with a baseline BMD T-score $\leq$-2.5; 4.0% in those with a baseline BMD T-score >-2.5).

VI.C.3.e: Secondary Efficacy Outcomes: Secondary efficacy outcomes included (i) the percent change from baseline at Month 6 in lumbar spine BMD; (ii) the percent change from baseline at Months 6 and 12 in hip (femoral neck, trochanter, total) and total body BMD; (iii) the percent change from baseline at Months 3, 6, and 12 in biochemical markers of bone turnover (NTx and BSAP).

VI.C.3.e.i: Percent change from baseline at Month 6 in lumbar spine BMD: As outlined in the table below, at 6 months, treatment with alendronate 70-mg once weekly resulted in a significant increase in lumbar spine BMD (3.37%) when compared to placebo (1.135%) (p = 0.0002).

Protocol 165: Lumbar Spine BMD (MITT) at 6 Months					
	Placebo	Alendronate	Treatment Difference	p-value	(LCL, UCL)
N	46	82			
Raw mean lumbar spine BMD ± SD					
Baseline	0.9325 ± 0.1814	0.8982 ± 0.1532			
Month 6	0.9434 ± 0.1865	0.9240 ± 0.1552			
Least-squares mean % change from baseline ± SE					
Month 6	1.1306 ± 0.476	3.3660 ± 0.3739	2.2354	0.0002	(1.0879, 3.3829)

VI.C.3.e.ii: Percent change from baseline at Months 6 and 12 in hip (femoral neck, trochanter, total) and total body BMD: At one year, treatment with alendronate 70-mg once weekly resulted in significant increases in BMD at the hip when compared to placebo (see table below).

Protocol 165: Hip BMD and Total Body (MITT) at 6 and 12 Months						
	Placebo		Alendronate			
	BMD ± SD (gm/cm^2)	LSM % Change ± SE	BMD ± SD (gm/cm^2)	LSM % Change ± SE	Treatment Difference	p value
Femoral Neck						
Baseline	0.68 ± 0.10		0.67 ± 0.09			
Month 6	0.68 ± 0.10	0.15 ± 0.54	0.68 ± 0.09	1.79 ± 0.42	1.64	0.0138
Month 12	0.68 ± 0.10	0.17 ± 0.58	0.68 ± 0.09	2.06 ± 0.45	1.89	0.0075

Protocol 165: Hip BMD and Total Body (MITT) at 6 and 12 Months						
	Placebo		Alendronate			
	BMD ± SD (gm/cm^2)	LSM % Change ± SE	BMD ± SD (gm/cm^2)	LSM % Change ± SE	Treatment Difference	p value
Trochanter						
Baseline	0.65 ± 0.10		0.64 ± 0.11			
Month 6	0.66 ± 0.10	0.50 ± 0.36	0.65 ± 0.11	1.35 ± 0.28	0.85	0.0547
Month 12	0.66 ± 0.11	0.34 ± 0.38	0.66 ± 0.11	2.35 ± 0.29	2.01	<0.0001
Total Hip						
Baseline	0.84 ± 0.10		0.81 ± 0.10			
Month 6	0.84 ± 0.10	0.45 ± 0.30	0.82 ± 0.10	1.09 ± 0.23	0.64	0.0785
Month 12	0.84 ± 0.10	-0.17 ± 0.30	0.83 ± 0.10	1.70 ± 0.24	1.86	<0.0001
Total Body						
Baseline	1.09 ± 0.08		1.08 ± 0.10			
Month 6	1.09 ± 0.09	0.27 ± 0.24	1.09 ± 0.10	0.87 ± 0.18	0.60	0.0451
Month 12	1.09 ± 0.09	0.20 ± 0.41	1.10 ± 0.09	1.40 ± 0.31	1.20	0.0177

Femoral Neck BMD: Treatment with alendronate 70-mg once weekly for 12 months significantly increased femoral neck BMD (2.06%) relative to placebo (0.17%) (p=0.007). The mean difference between the treatment groups was 1.89%.

Trochanter BMD: After 12 months of treatment, there was a significant increase from baseline in trochanter BMD of 2.35% in the alendronate group compared with 0.34% in the placebo group (p <0.0001). The mean difference between the treatment groups was 2.01%.

Total Hip BMD: Treatment with alendronate 70-mg once weekly for 12 months significantly increased total hip BMD (1.70%) relative to placebo (-0.17%) (p <0.0001). The mean difference between the treatment groups was 1.87%.

Total Body BMD: After 12 months of treatment, there was a significant increase from baseline in trochanter BMD of 1.40% in the alendronate group compared with 0.20% in the placebo group (p=0.018). The mean difference between the treatment groups was 1.20%.

VI.C.3.e.iii: Percent change from baseline at Months 3, 6, and 12 in biochemical markers of bone turnover (NTx and BSAP): Biochemical marker endpoints were assessed to provide information on the effect of alendronate on bone formation and resorption. Serum and second morning void urine samples were obtained for measurements of biochemical markers of bone turnover and were analyzed at a central reference laboratory. Urinary N-telopeptide of type II collagen (NTx) was measured as an index of overall bone resorption, while serum bone specific alkaline phosphatase was measured an index of bone formation.

NOTE: Slight numerical differences were found between the company's statistical review and the FDA reviewer's statistical analyses of the biochemical markers of bone turnover. The information presented here are from Ms. Liu's analyses of the data.

Urinary NTX: As outlined in the table below, treatment with alendronate 70-mg once weekly for 12 months significantly decreased NTx relative to placebo (p <0.0001). The geometric mean

percent changes from baseline to Month 12 were -49.34% and -0.53% in the alendronate and placebo groups, respectively.

Bone Specific Alkaline Phosphatase: Treatment with alendronate 70-mg once a week for 12 months also significantly decreased BSAP relative to placebo ($p < 0.0001$). The geometric mean percent changes from baseline to Month 12 were -33.11% and -9.87% in the alendronate and placebo groups, respectively.

Protocol 165: Biochemical Markers of Bone Turnover

	Placebo		Alendronate		Treatment Difference	p value
	Raw value ± SD	LSM % Change ± SE	Raw value ± SD	LSM % Change ± SE		
Urinary NTX (pmol BCE/umol)						
Baseline	33.13 ± 15.48		31.93 ± 12.50			
Month 12	31.00 ± 13.76	-0.53 ± 8.03	15.99 ± 7.05	-49.34 ± 3.06	-49.07	<0.0001
BSAP (ng/mL)						
Baseline	13.26 ± 4.87		13.76 ± 5.00			
Month 12	11.97 ± 4.37	-9.87 ± 3.77	9.02 ± 3.14	-33.11 ± 2.09	-25.78	<0.0001

VI.D. Efficacy Conclusions: This study demonstrates that in men with hypogonadal or idiopathic osteoporosis, treatment with alendronate 70-mg weekly for 1 year significantly increases lumbar spine, hip, and total body BMD. At one year, lumbar spine BMD increased 4.28% with alendronate therapy compared to 1.45% with placebo ($p < 0.0001$). The mean difference in percent change from baseline between the treatment groups was 2.82%. These results are similar to BMD increases observed in studies evaluating the efficacy of alendronate 10-mg daily in men with osteoporosis (protocol 096). In that study, at one year, treatment with alendronate resulted in a 4.85% increase in lumbar spine BMD, with a mean difference between treatment groups of 3.30%. The BMD increases seen in protocol 165 were accompanied by the expected reductions in markers of bone turnover (NTx and BSAP). Subgroup analyses did not reveal any clinically meaningful correlations with increases in lumbar spine BMD.

VII. Review of Safety

VII.A. Brief Statement of Conclusions: There were no unexpected safety findings uncovered during the review of this supplemental NDA. There was an imbalance between the alendronate and placebo groups in the number of patients who died during and immediately following this study (3 vs 0). The causes of death in the alendronate group, stroke, lung cancer, and presumed sudden death, were not unusual given the mean age of the patient population. Furthermore, there was no evidence that the deaths were drug-related. The percentage of patients who experienced at least one serious adverse event was similar between the two treatment groups. The rates of premature withdrawal due to adverse events were slightly higher in the placebo group than the alendronate group: 9% vs. 6%.. The overall incidence of clinical adverse events was generally similar across both treatment groups. A higher percentage of upper GI events occurred in the alendronate-treated group (16% vs. 10% in the placebo group), which was not unexpected. The incidence of clinical vertebral fractures was balanced between the two treatment groups. However, an imbalance between the alendronate and placebo groups in the number of patients

who sustained nonvertebral fractures was noted (6% in the alendronate-treated group vs. 3% in the placebo-treated group). This imbalance may in part be due to traumatic fracture events. Overall, alendronate 70-mg once-weekly tablets were generally well tolerated in this study population of men with osteoporosis.

VII.B. Description of Patient Exposure: All participants randomized to either alendronate 70-mg once weekly or placebo received at least one dose of study drug. One hundred nine subjects received alendronate and 58 subjects received placebo. The mean exposure to study therapy was 48.3 weeks for the alendronate-treated group and 44.8 weeks for the placebo-treated group (see Table below).

Protocol 165: Patient Exposure						
Months Patients Received Treatment	**≤ 1**	**>1 to 3**	**>3 to 6**	**>6 to 12+**	**Total**	**Mean Number of Weeks on Treatment**
Alendronate	3	3	0	103	109	48.3
Placebo	4	0	1	53	58	44.8

VII.C. Methods and Specific Findings of Safety Review

VII.C.1. Disposition: As outlined in the table below, a total of 124 subjects had at least 1 clinical adverse event during the study: 77 (71%) in the alendronate group and 47 (81%) in the placebo group. Overall, there were 3 patients who died in the alendronate group and no deaths in the placebo group. One death occurred in the post treatment phase (Day 32 off treatment) and is not listed in the table. Serious adverse events occurred in 14 subjects (13%) in the alendronate group and in 8 subjects (14%) in the placebo group. Seven patients (6%) in the alendronate group and 5 patients (8.6%) in the placebo group discontinued from the study due to an adverse event.

Protocol 165: Patient Disposition		
	Placebo	**Alendronate**
Enrolled	58	109
Completed Study	46 (79)	97 (89)
No Adverse events	11 (19)	32 (29)
One or More Adverse Events	47 (81)	77 (71)
Deaths	0 (0)	2 (2)
Serious Adverse Events	8 (14)	14 (13)
AE Leading to Withdrawal	5 (9)	7 (6)

VII.C.2. Deaths: A total of 3 subjects enrolled in the study died, all having received alendronate. Two of the deaths were during the treatment phase of the study: An 80-year-old man died following a cerebrovascular accident on study Day 344. A second subject, a 70-year-old man, died from unknown causes, reported as natural causes on study Day 297. The third subject died 32 days after discontinuation of study drug (due to a nonserious adverse event - confusion) as a result of a malignant lung neoplasm.

COMMENT: There was an imbalance between the alendronate and placebo groups in the number of patients who died during and immediately following this study. However, the

causes of death in the alendronate group were not unusual given the average age of the patient population. Because of concerns raised by studies of other bisphosphonates, an analysis was previously performed to compare lung cancer mortality rates between postmenopausal women randomized to alendronate and placebo in the Fracture Intervention Trial. This analysis showed no association between the use of alendronate and either lung cancer mortality or all-cause mortality. Most likely, this imbalance noted here is not related to the drug therapy.

VII.C.3. Serious Adverse Events: A serious adverse event was defined as any adverse event that resulted in death, was life-threatening, resulted in significant or persistent disability/incapacity, resulted in or prolonged inpatient hospitalization, or was a congenital anomaly/birth defect. The overall incidence of SAEs was 14% in the placebo group and 13% in the alendronate group. In the alendronate-treated group, in addition to the previously discussed subjects that died, 6 subjects had cardiovascular adverse events, 3 subjects sustained fractures and one subject each experienced urolithiasis, basal cell carcinoma and syncope. In the placebo treated group, 2 subjects each experienced prostate disorders and cerebrovascular disorders, while one subject each experienced wrist fracture, pancreatitis, wound infection and inguinal hernia.

VII.C.4. Adverse Events Leading to Withdrawal: Seven patients (6%) in the alendronate-treated group and 5 patients (9%) in the placebo-treated group withdrew from the study due to an adverse event. In the alendronate-treated group, two subjects withdrew due to GI adverse events, 2 subjects withdrew due to fracture, one subject withdrew due to back pain and 2 subjects died, as previously discussed. In the placebo-treated group, one subject each withdrew due to wrist fracture, epigastric pain, pancreatitis, cardiovascular disease and prostate cancer.

VII.C.5. Adverse Events: The overall incidence of clinical adverse events was generally similar across both treatment groups (see table below). The most common clinical adverse events in both the alendronate treated group (32%) and the placebo treated group (40%) occurred in the musculoskeletal system, followed by body as a whole (34% in the alendronate treated group and 28% in the placebo treated group). The most common specific clinical adverse events were upper respiratory infection (alendronate 10%, placebo 12%), back pain (alendronate 6%, placebo 9%), constipation (alendronate 7%, placebo 5%), and diarrhea (alendronate 6%, placebo 5%).

Protocol 165: Adverse Events, by body system		
	Placebo	70mg
Subjects Enrolled	58	109
Subjects with 1 or more AE	47 (81)	77 (71)
Events:		
Body as a whole	20 (34)	30 (28)
Cardiovascular	10 (17)	14 (13)
Digestive	13 (22)	29 (27)
Endocrine	2 (3)	2 (2)
Eyes, Ears, Nose, Throat	8 (14)	10 (9)
Heme and Lymphatic	0 (0)	2 (2)
Immune	0 (0)	1 (1)
Metabolism and Nutrition	1 (2)	4 (4)

Protocol 165: Adverse Events, by body system		
	Placebo	70mg
Musculoskeletal	23 (40)	35 (32)
Nervous	6 (10)	11 (10)
Psychiatric	1 (2)	4 (4)
Respiratory	0 (0)	7 (6)
Skin and Appendages	5 (9)	8 (7)
Urogenital	8 (14)	6 (6)

VII.C.6. Adverse Events of Special Interest

VII.C.6.a. Gastrointestinal Adverse Events: Overall, 23 patients reported an upper GI adverse event. A higher percentage of upper GI events occurred in the alendronate-treated group (16%) compared to the placebo-treated group (10%). None of the upper GI events was considered serious. A total of 3 subjects withdrew from the study due to upper GI adverse events (2 in the alendronate-treated group and one in the placebo-treated group). As outlined in the table below, dyspepsia (2.8% in the alendronate group vs 1.7% in the placebo group) and gastroesophageal reflux disease (3% in the alendronate vs 0% in the placebo group) were more common in the alendronate-treated group, whereas abdominal pain was more common in the placebo group (3% in the placebo group vs 1% in the alendronate group).

Protocol 165: Gastrointestinal Adverse Events		
	ALN 70-mg	Placebo
	(N=109)	(N=58)
	n (%)	n (%)
Patients with one or more GI AE	17 (16)	6 (10)
Patients without adverse experiences	92 (84)	52 (90)
Abdominal Distention	0 (0)	1 (2)
Abdominal Pain	3 (3)	3 (5)
Anorexia	1 (1)	0 (0)
Digestive Gas Symptoms	1 (1)	1 (2)
Dyspepsia	5 (5)	1 (2)
Epigastric Discomfort	1 (1)	1 (2)
Gastric Ulcer	1 (1)	0 (0)
Gastroesophageal Reflux Disease	3 (3)	0 (0)
Heartburn	4 (4)	2 (3)
Vomiting	2 (2)	0 (0)
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories. ALN = Alendronate.		

COMMENT: Subjects with a prior history of gastrointestinal diseases were not excluded from enrollment in this study. The proportion of subjects with a history of upper GI disease was similar between the treatment groups (24% of both treatment groups). A prior history of gastric and/or duodenal perforation, ulcers, or bleeds was reported by 5% and 3% of subjects in the alendronate and placebo groups, respectively. Concomitant use of anti-inflammatory medication was also not excluded in this study. A similar proportion of subjects in each treatment group used NSAID/aspirin-containing drugs during the study (69% in the alendronate group vs. 66% in the placebo group). While on NSAID/aspirin-

containing therapy, 12 of 75 subjects in the alendronate-treated group reported upper GI adverse events, as did 2 of 38 subjects in the placebo-treated group. The gastrointestinal adverse events seen in this study reflect findings from previous studies and are known complications of alendronate use.

VII.C.6.b. Vertebral Fractures Reported as Adverse Events: Overall, eight subjects had clinical vertebral fractures: 5 (5%) in the alendronate group and 3 (5%) in the placebo group. The odds ratio of vertebral fracture adverse experiences in alendronate patients compared with placebo patients was 0.88 (95% CI = [0.16, 5.89]). Of the 5 subjects experiencing vertebral fractures in the alendronate, 2 were reported as associated with excessive trauma. One of the 3 patients in the placebo group experienced a fracture that was due to excessive trauma.

VII.C.6.c. Nonvertebral Fractures Reported as Adverse Events: Overall, seven subjects had nonvertebral fractures reported: 6 (6%) in the alendronate group and 1 (2%) in the placebo group. The odds ratio of nonvertebral fracture adverse experiences in alendronate patients compared with placebo patients was 3.32 (95% CI = [0.39, 155.36]). Of the 6 subjects experiencing nonvertebral fractures in the alendronate group, 3 were associated with excessive trauma and 1 was considered osteoporotic. The patient in the placebo group fractured his wrist as a result of a fall, a fracture the investigator considered osteoporotic.

COMMENT: The incidence of clinical vertebral fractures was balanced between the two treatment groups. However, an imbalance between the alendronate and placebo groups in the number of patients who sustained nonvertebral fractures was noted (6% in the alendronate-treated group vs. 3% in the placebo-treated group). This imbalance may in part be due to traumatic fracture events or may simply reflect a chance finding. In any event, based on the totality of clinical and preclinical data, there is no reason to believe that once weekly alendronate increases the risk for nonvertebral fractures.

VII.C.6.d. Arthralgia and Myalgia: Postmarketing surveillance suggests that alendronate may be associated with increased musculoskeletal symptoms. In this small controlled study, no increase in myalgia, arthralgia or bone pain was noted with alendronate use.

VII.C.6.e. Ocular Symptoms: A recently published report reviewed the findings of ocular inflammation in patients on bisphosphonate therapy[1]. In this study, there were no reports of uveitis, scleritis or conjunctivitis.

VII.C.7. Laboratory: Laboratory data are summarized for the 161 patients who had base baseline values obtained. Laboratory adverse events were recorded for a total of 15 (9%) subjects. The proportion of subjects with a laboratory adverse event was similar across both treatment groups, occurring in 10 subjects (10%) in the alendronate group and 5 subjects (9%) in the placebo group. The most frequently reported laboratory abnormalities were decreased erythrocytes, hematocrit, and hemoglobin occurring in 3 patients (3%) in the alendronate treated group and 1 patient (2%) in the placebo group. Predefined limits of change (from baseline) were

[1] Fraunfelder FW. Bisphosphonates and ocular inflammation. *N Engl J Med.* 2003. 348 (12):1187.

established for all laboratory safety analyses. Overall, there were no significant differences between treatment groups for any laboratory parameter.

VII.C.8. Other Safety Tests

VII.C.8.a. Vital Signs and Weight: There were no clinically significant changes from baseline or differences between treatment groups for systolic and diastolic BP, pulse rate, weight, and oral temperature. No formal statistical comparisons were performed.

VII.C.8.b. Morphometric Vertebral Fractures: A total of 121 subjects (80 alendronate and 41 placebo) were included in the morphometric analysis of incident vertebral fractures. Overall, 9 subjects had at least 1 new vertebral fracture assessed by digital morphometry: 6 (8%) in the alendronate group and 3 (7%) in the placebo group. The odds ratio of incident vertebral fracture in alendronate-treated subjects compared with placebo-treated subjects was 1.03 (95% CI = [0.21, 6.69]).

VII.D. Adequacy of Safety Testing: The safety monitoring conducted during this study appears to have been adequate.

VII.E. Summary of Critical Safety Findings and Limitations of Data: There were no unexpected safety findings uncovered during the review of this supplemental NDA. There was an imbalance between the alendronate and placebo groups in the number of patients who died during and immediately following this study. The causes of death in the alendronate group were not unusual given the mean age of the patient population. The percentage of patients who experienced at least one serious adverse event was similar between the two treatment groups. The rates of premature withdrawal due to adverse events were slightly higher in the placebo-treated group (9% vs. 6% in the alendronate group). The overall incidence of clinical adverse events was generally similar across both treatment groups. A higher percentage of upper GI events occurred in the alendronate-treated group (16% vs. 10% in the placebo group), which was not unexpected. The incidence of clinical vertebral fractures was balanced between the two treatment groups. However, an imbalance between the alendronate and placebo groups in the number of patients who sustained nonvertebral fractures was noted (6% in the alendronate-treated group vs. 3% in the placebo-treated group). This imbalance may in part be due to traumatic fracture events. Overall, alendronate 70-mg once-weekly tablets were generally well tolerated in this study population of men with osteoporosis.

VIII. Dosing, Regimen, and Administration Issues

Alendronate 70-mg weekly is currently available in a tablet formulation. This current submission proposes the same dosing regimen as currently utilized. No significant safety issues were raised by the submitted data.

IX. Use in Special Populations

IX.A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation: Alendronate 10-mg daily is currently approved for therapy in both men and postmenopausal

women with osteoporosis. Alendronate 70-mg once weekly daily is currently approved for therapy in postmenopausal women. This study population is 100% male, evaluating the use of alendronate 70-mg once weekly in men with osteoporosis.

IX.B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy
Alendronate is currently approved for treatment and prevention of postmenopausal osteoporosis and to increase bone mass in men with osteoporosis. The age range of study participants is was 26 – 96 years. Age analyses have previously been conducted for alendronate under NDA 20-560. The racial composition of this study population is almost entirely Caucasian. No racial analyses have been done, given the lack of available data.

IX.C. Evaluation of Pediatric Program: Studies evaluating the safety and efficacy of the alendronate tablet formulation in the pediatric population are in progress.

X. Conclusions and Recommendations

X.A. Conclusions: Merck has submitted data showing that alendronate 70-mg once weekly tablet is efficacious in increasing BMD in men with osteoporosis. No significant safety issues were raised by the submitted data.

X.B. Recommendations: Based on efficacy and safety data evaluation, this reviewer recommends approval of this supplement, and the requested minor modifications to the labeling. Namely, the addition of weekly 70-mg oral alendronate tablet for treatment to increase bone mass in men with osteoporosis.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Theresa Kehoe
4/1/04 01:00:19 PM
MEDICAL OFFICER

Eric Colman
4/1/04 01:02:33 PM
MEDICAL OFFICER
Agree with Dr. Kehoe's recommendation

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560/S041

21-575/S004

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	20-560 (SE8-041)
Name of drug:	Fosamax® (Alendronate Sodium) Tablets
Applicant:	Merck Research Laboratories
Indication:	70-mg once weekly for treatment of osteoporosis in men
Documents reviewed:	\\Cdsesub1\n20560\S_041\2003-06-18\clinstat\studies\p165.pdf
Project manager:	Randy Hedin (HFD-510)
Clinical reviewer:	Theresa Kehoe, M.D. (HDF-510)
Dates:	Received 06/19/03; user fee (10 months) 04/19/04
Statistical reviewer:	Cynthia Liu, MA (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Biometrics division director:	Ed Nevius, Ph.D. (HFD-715)

Keywords: NDA review, clinical study, analysis of variance

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1. SUMMARY OF STATISTICAL REVIEW

Fosamax® (alendronate sodium) 70-mg once weekly dose (NDA 20-560/S-025) was approved on 1/31/01 for the indication "Treatment to increase bone mass in men with osteoporosis" based on the data from NDA 20-560/SE1-023, which was approved on 9/29/00 for 10-mg once daily dose in men with osteoporosis, and an agreement to conducting a post-approval study to provide additional efficacy and safety data in men with weekly dosing. Accordingly, the Phase V study results were submitted under NDA 20-560/SE8-041 to seek approval of the proposed changes to the Package Circular so that both 10-mg once daily and 70-mg once weekly doses be listed as recommended doses.

This is a 12-month, double-blind, randomized, multicenter (in USA), placebo-controlled trial to evaluate the safety and efficacy of once weekly oral alendronate for the treatment of osteoporosis in 167 men with idiopathic or hypogonadal osteoporosis. Bone mineral density (BMD) of lumbar spine (primary efficacy endpoint), proximal femur (femoral neck, trochanter, and total hip), and total body, determined by dual energy x-ray absorptiometry (DXA), were the clinical efficacy measures in this study as well as biochemical markers of bone turnover such as urine N-Telopeptides of Type I collagen (urinary NTx) and serum bone-specific alkaline phosphatase (serum BSAP).

The following points summarize the principal findings and conclusions:

- This reviewer's conclusions generally agree with the sponsor's conclusions, despite some numerical differences in the statistical results.

- Treatment with alendronate 70-mg once weekly for 12 months was highly effective, when compared with placebo, in increasing BMD of lumbar spine, regardless of age, race, height, gonadal status, baseline lumbar spine BMD, and baseline femoral neck BMD.

- Treatment with alendronate 70-mg once weekly for 12 months was highly effective, when compared with placebo, in increasing BMD of femoral neck, trochanter, total hip, and total body.

- Significant treatment effect on lumbar spine BMD was seen as early as 6 months.

- Treatment with alendronate 70-mg once weekly for 12 months was highly effective, when compared with placebo, in reducing the turnover rates of bone resorption and bone formation measured by urinary NTx and serum BSAP, respectively.

- Based on visual inspection, the response patterns in BMD and biochemical marker in the current study were similar to those seen at 1 year in men treated with 10-mg once daily study, with a small difference in magnitude of the treatment effect. Similarly, the response patterns in men were consistent with that in postmenopausal women for either 70-mg once weekly or 10-mg once daily dose, despite the difference in magnitude of the treatment effect.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

Alendronate has been studied by the sponsor for approximately 7 years and has been approved for the following indications:

- Treatment of osteoporosis in postmenopausal women (70 mg tablet once weekly or 10 mg tablet once daily)
- Treatment to increase bone mass in men with osteoporosis (10 mg tablet once daily)
- Prevention of osteoporosis in postmenopausal women (35 mg tablet once weekly or 5 mg tablet once daily)
- Treatment of glucocorticoid-induced osteoporosis in men and women (5 or 10 mg tablet once daily)
- Treatment of Paget's disease of bone in men and women (40 mg tablet once daily for 6 months)

This submission is a supplement to NDA 20-560 for Fosamax® (alendronate sodium) Tablets. The sponsor submitted the results of 1 Phase V controlled clinical trial (see the table below) conducted in men between age 25 and 90 years old, with idiopathic osteoporosis or osteoporosis due to hypogonadism, to seek approval of 70-mg once weekly dosing regimen for the treatment of osteoporosis in men.

Protocol No. Investigators	Study Design	Dose (mg)	Age/Gender/ Race	Primary Endpoint
165 12 investigators 12 centers (USA)	12-month, randomized, double-blind, placebo-controlled, multicenter, Phase V study to evaluate the safety and efficacy of weekly dosed oral alendronate sodium for the treatment of osteoporosis in men	Alendronate 70 mg (N = 109) Placebo (N = 58)	38 – 91 years (Mean = 66) M: 167 (100%) White: 163 (97.6%) Other: 4 (2.4%)	% change from baseline in bone mineral density of lumbar spine at Month 12

2.2 Data Analyzed and Sources

The electronic data files this reviewer used are located in \\Cdsesub1\n20560\S_041\2003-06-18\crt\datasets\stat\MK0217\Wamo\Prot165\data_analysis. In general, those data files (bmd_itt.xpt, bio_pp.xpt, and demog.xpt) were easy to work with, but a lot of redundant or unnecessary information was included in the data files.

2.3 Statistical Evaluation of Evidence on Efficacy

2.3.1 Sponsor's Results and Conclusions

This reviewer has verified the sponsor's analyses and found the results for BMD agreed with each other. There was a slight difference in the results of biochemical markers when the adjusted mean change from baseline in logarithm was back-transformed. This reviewer could not find the cause of the discrepancy. The formula this reviewer used is (exp(adjusted mean change from baseline in logarithm) – 1) × 100. Nevertheless, the conclusions for the biochemical marker parameters between the reviewer and sponsor's are the same.

The following points are the sponsor's conclusions regarding the efficacy of treatment with alendronate 70-mg once weekly for 12 months, when compared with placebo.

- Increases BMD of the lumbar spine.
- Increases BMD in the hip (femoral neck, trochanter, and total) and total body BMD.
- Reduces biochemical markers of bone turnover (urinary NTx and serum BSAP).
- Demonstrates increases in lumbar spine BMD as early as 6 months.
- Produces a consistent effect on lumbar spine BMD regardless of baseline BMD, biochemical markers of bone turnover, gonadal status, age, height, weight, and BMI.

In addition, the sponsor also claimed that the increases in BMD and the reductions in biochemical marker of bone turnover observed in the present study are consistent with those seen at one year in men treated with 10-mg once-daily study and in postmenopausal women treated with 10-mg once-daily or 70-mg once-weekly study.

This reviewer thinks that a clinical equivalence or non-inferiority study should have been conducted in order to compare the 70-mg once weekly dose with the 10-mg once daily dose. However, the sponsor noted that a placebo-controlled design was chosen because it was believed there would not be an adequate number of men to enroll in an equivalence trial of daily versus weekly alendronate (see the study report, p37).

2.3.2 Statistical Methodologies

Percentage change from baseline in BMD of lumbar spine, proximal femur (femoral neck, trochanter, and total hip), and total body were analyzed by this reviewer using an analysis of variance (ANOVA) model consisting of treatment, study center, and stratum main effects (the sponsor's model). Treatment-by-study center and treatment-by-stratum for lumbar spine BMD (primary efficacy endpoint) were tested initially and no significance was found suggesting similar response patterns across study centers as well as strata. The modified intention-to-treat (MITT) population with last-observation-carried-forward (LOCF)

techniques for missing values was the primary analysis data set for the BMD measures. Since the study centers 001, 010, 011, and 013 had a very small number of patients (<3) in the alendronate and/or placebo groups after excluding the patients without baseline values, this reviewer pooled them together, as the sponsor did, to avoid the sparseness problem.

Biochemical markers of bone turnover such as urinary NTx and serum BSAP were also analyzed using the same ANOVA model. Log-transformed fraction of baseline value (calculated as dividing the treatment period value by the baseline value and then applying the natural log) was the dependent variable. According to the sponsor, log transformation was used in order to normalize the distribution of the biochemical markers. Mean percentage change from baseline was obtained by back transforming the mean change from baseline in logarithm. The per-protocol (PP) population without any imputation for missing values was the primary analysis data set due to the fact that the changes in biochemical measurements were transient, despite continued treatment with alendronate; and therefore, they were best analyzed without carrying values forward (see the study report, p51).

The sponsor did not adjust for multiplicity because (1) % change from baseline in lumbar spine BMD at Month 12 was the solely primary efficacy endpoint; (2) Only 1 comparison (alendronate 70 mg versus placebo) was made for the primary endpoint; (3) Month 6 analysis on lumbar spine BMD to detect an early treatment effect was done only if there was a significant treatment difference at Month 12; and (4) Month 3 analysis on biochemical markers were performed for regulatory purposes to [redacted] and the results were not planned to affect the continuation of the study.

This reviewer also analyzed the data by adding baseline BMD to the model, but found no major discrepancy in the results. Therefore, in order to compare the current study (Protocol 165) with the previously approved studies in men (Protocol 096) and in postmenopausal women (Protocol 118), this reviewer decided to adopt the sponsor's analysis methods for this review.

2.3.3 Detailed Review of Protocol 165 (from 7/00 to 04/02)

Study Design and Objectives

Protocol 165 was a Phase V, 12-month, randomized, double-blind, placebo-controlled, 2-parallel-group, multicenter (in USA) trial, conducted in men between age 25 and 90 years old with idiopathic osteoporosis or osteoporosis due to hypogonadism.

Patients were stratified according to their gonadal status at baseline (hypogonadal or eugonadal) and then randomized in a 2:1 ratio to receive either alendronate (70 mg once weekly) or matching placebo. Allocation numbers were pre-assigned in blocks of 3 (2

alendronate and 1 placebo) to the study sites. Hypogonadal patients were assigned the lowest available allocation number, while eugonadal patients were assigned the highest available number. Scheduled visits were at Months 0, 3, 6, and 12.

The primary objective was to assess the treatment effect of oral alendronate 70-mg once weekly versus placebo on the change in BMD of the spine when administered for up to 12 months in men with osteoporosis. The associated primary efficacy variable was percentage change from baseline in lumbar spine BMD at Month 12. To detect an early treatment effect, Month 6 data were also evaluated, but contingent upon a significant finding at Month 12.

The stated secondary objectives of interest in this review were to assess the treatment effect on the changes in hip (fermoral neck, trochanter, and total) and total body BMD and biochemical markers of bone turnover. The associated variables were percentage change from baseline in hip and total body BMD at Months 6 and 12 and percentage change from baseline in urinary NTx and serum BSAP at Months 3, 6, and 12.

Subject Disposition

There were 167 subjects randomized: 58 and 109 for the placebo and alendronate groups, respectively. Of the 167 randomized, 143 (85.6%) completed the study and 24 (14.4%) discontinued from the study (Text Table 1). Although the withdrawal rate of the placebo group (20.7%) was greater than that of the alendronate group (11.0%), no meaningful pattern could be discerned from any of the specific reasons for discontinuation (Fisher-Freeman-Halton exact test p = 0.0994). In addition, the number of completers in each group was close to the sample size that the trial was powered on (40 and 80 for placebo and alendronate, respectively, for 97% power). Therefore, this reviewer feels that the ~15% overall withdrawal rate should not cause any major bias in the determination of treatment efficacy.

Text Table 1 – Subject Disposition (the sponsor's Table 5 modified)

	Placebo	Alendronate	Total
Number of randomized subjects	58	109	167
Number of completers	46 (79.3%)	97 (89.0%)	143 (85.6%)
Number of withdrawals	12 (20.7%)	12 (11.0%)	24 (14.4%)
Clinical adverse experience	4	8	12
Lost to follow-up	3	1	4
Patient discontinued for other	2	0	2!
Patient withdrew consent	1	2	3
Protocol deviation	2	1	3

! = Two patients met the criteria for excessive bone loss (i.e., a decrease in BMD ≥5%) at Month 6 and were discontinued from the study.

Demographic and Baseline Characteristics

No statistically significant differences in age, race, weight, BMI, and stratum were observed between the alendronate and placebo groups. The mean baseline height in the placebo group was significantly smaller than that of the alendronate group (p = 0.0074, Text Table 2). The sponsor, however, noted no clinically meaningful difference in height.

Text Table 2 – Demographic and Baseline Characteristics of All Available Randomized Subjects

Characteristic	Placebo	Alendronate	Total
Age (year):			
Mean ± SD	66.7 ± 12.4	65.8 ± 10.7	66.1 ± 11.3
Range	43 – 91	38 – 85	38 – 91
<65 (%)	28 (48.3)	44 (40.4)	72 (43.1)
≥65 (%)	30 (51.7)	65 (59.6)	95 (56.9)
Race:			
White (%)	57 (98.3)	106 (97.2)	163 (97.6)
Other (%) [a]	1 (1.7)	3 (2.8)	4 (2.4)
Weight (kg):			
Mean ± SD	79.1 ± 13.0	78.7 ± 11.7	78.9 ± 12.1
Range	52.2 – 109.3	55.8 – 111.6	52.2 – 111.6
Height (mm):			
Mean ± SD	1713.7 ± 62.4	1743.7 ± 67.8	1733.1 ± 67.3
Range	1560.0 – 1832.0	1547.3 – 1998.2	1547.3 – 1998.2
BMI (kg/m^2):			
Mean ± SD	26.9 ± 4.5	25.8 ± 3.5	26.2 ± 3.9
Range	20.1 – 40.3	17.9 – 35.8	17.9 – 40.3
Stratum:			
Hypogonadal (%)	24 (41.4)	45 (41.3)	69 (41.3)
Eugonadal (%)	34 (58.6)	64 (58.7)	98 (58.7)

The sponsor's Tables 13 and 14 modified

[a]Other included 1 Black, 1 Asian, 1 Indian, and 1 Native American

Efficacy Results and Discussion

Based on this reviewer's analyses, the baseline BMD for each of the 5 skeletal sites and the baseline biochemical markers were comparable between the 2 study groups.

In the following text tables, treatment difference in positive and negative directions for BMD and biochemical marker, respectively, favor alendronate. LCL = 95% lower confidence limit and UCL = 95% upper confidence limit.

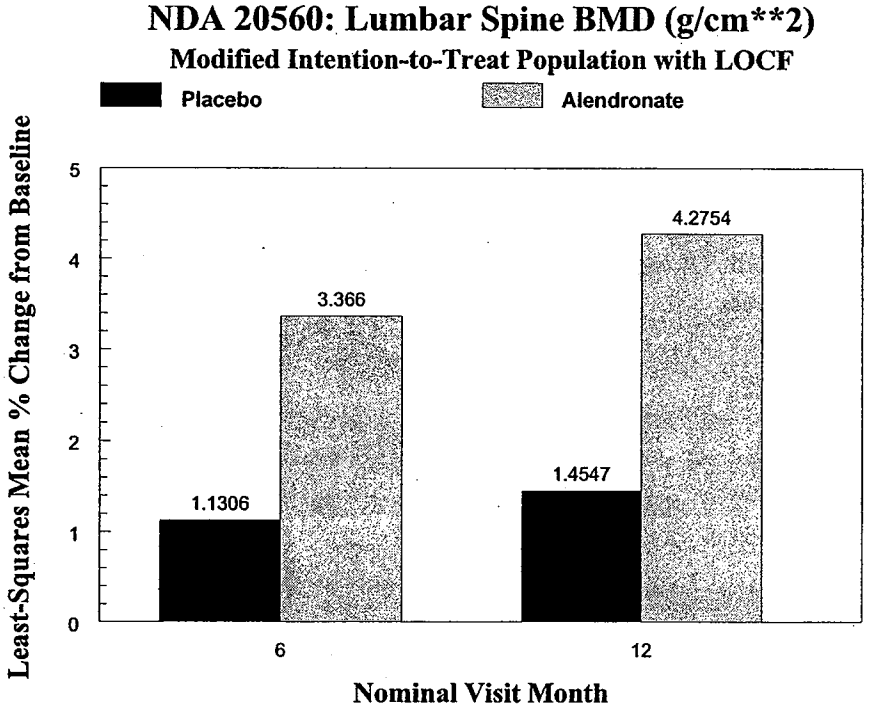
BMD of Lumbar Spine (L1-L4). Both alendronate and placebo groups showed an increased mean lumbar spine BMD over baseline at Months 6 and 12 using the MITT approach with

LOCF techniques (Text Table 3). The mean % change from baseline at Month 12 in the alendronate group was significantly larger than that of the placebo group (4.28% and 1.45%, respectively, $p < 0.0001$, Text Figure 1). The observed treatment difference, 2.82%, was smaller than, but close to the expected difference, 3%, used for the power and sample size calculation in the study. Significant treatment effect of alendronate was also observed at Month 6 when compared to that of the placebo ($p = 0.0002$).

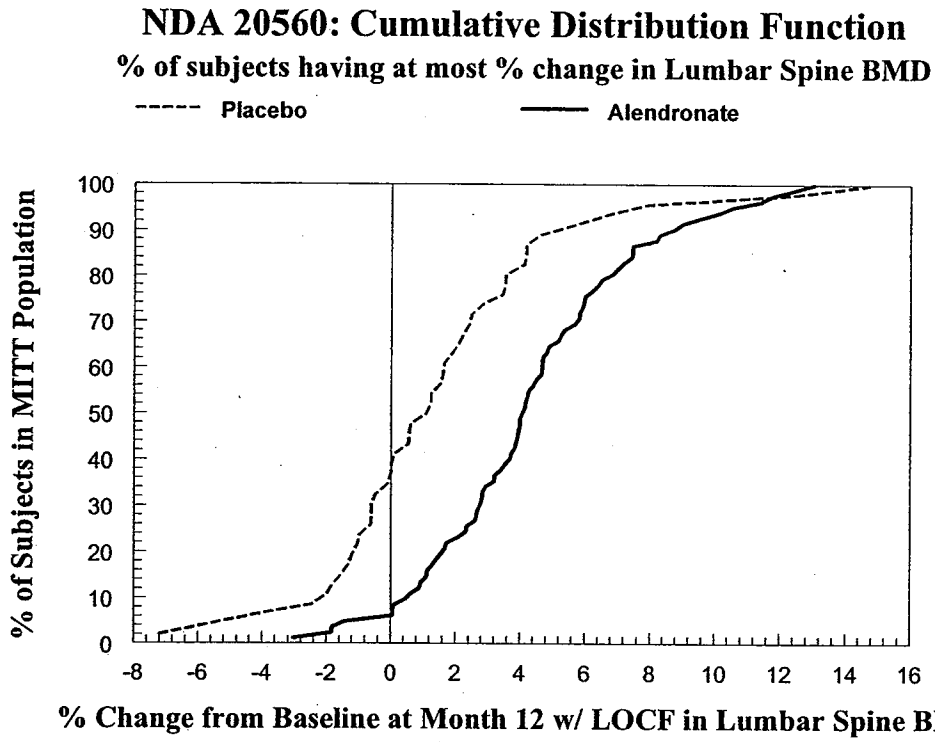
Text Table 3 – Results for Lumbar Spine BMD Using MITT Approach with LOCF

	Placebo once weekly	Alendronate 70 mg once weekly	Treatment Difference	p-value	(LCL, UCL)
Raw mean lumbar spine BMD ± standard deviation (sample size)					
Baseline	0.9325 ± 0.1814 (46)	0.8982 ± 0.1532 (82)			
Month 6	0.9434 ± 0.1865 (46)	0.9240 ± 0.1552 (81)			
Month 12	0.9465 ± 0.1868 (46)	0.9365 ± 0.1555 (82)			
Least-squares mean % change from baseline ± standard error (sample size)					
Month 6	1.1306 ± 0.4769 (46)	3.3660 ± 0.3739 (81)	2.2354	0.0002	(1.0879, 3.3829)
Month 12	1.4547 ± 0.5454 (46)	4.2754 ± 0.4268 (82)	2.8207	<0.0001	(1.5107, 4.1307)

Text Figure 1



Text Figure 2



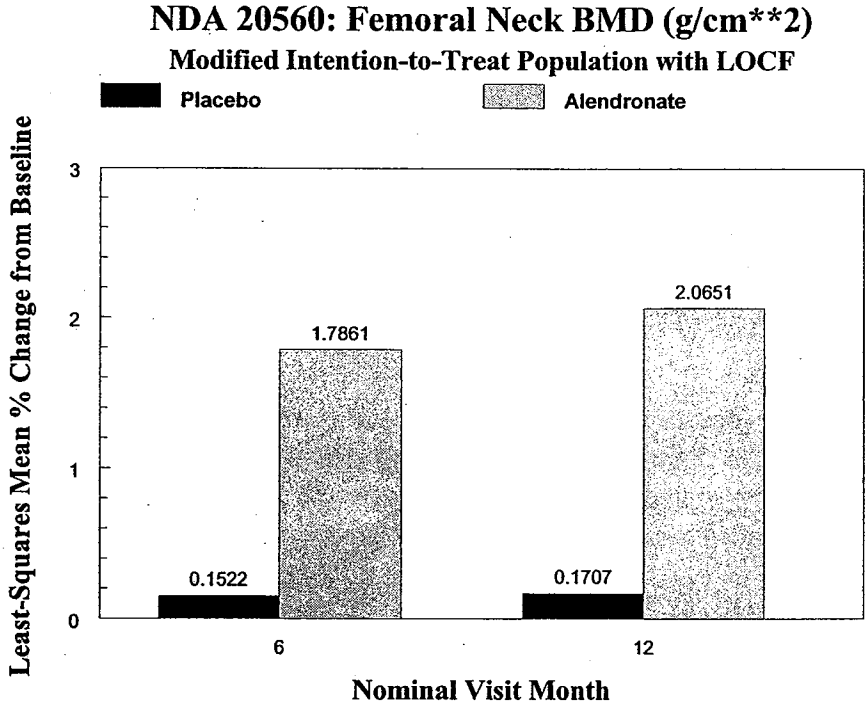
Based on Text Figure 2, one can see that the placebo group had more subjects (37%) showing decreased lumbar spine BMD from baseline at Month 12 when compared with the alendronate group (5%). Also, for the same percentage of subjects, greater % changes from baseline in lumbar spine BMD at Month 12 were observed in the alendronate group compared to the placebo group.

BMD of Femoral Neck. Both alendronate and placebo groups showed an increased mean femoral neck BMD over baseline at Months 6 and 12 using the MITT approach with LOCF techniques (Text Table 4). The mean % change from baseline at Month 12 in the alendronate group was significantly larger than that of the placebo group (2.07% and 0.17%, respectively, $p = 0.0075$, Text Figure 3). Significant treatment effect of alendronate was also observed at Month 6 when compared to that of the placebo ($p = 0.0138$).

Text Table 4 – Results for Femoral Neck BMD Using MITT Approach with LOCF

	Placebo once weekly	Alendronate 70 mg once weekly	Treatment Difference	p-value	(LCL, UCL)
Raw mean femoral neck BMD ± standard deviation (sample size)					
Baseline	0.6784 ± 0.0963 (46)	0.6666 ± 0.0872 (84)			
Month 6	0.6803 ± 0.1022 (46)	0.6782 ± 0.0894 (84)			
Month 12	0.6800 ± 0.0985 (46)	0.6802 ± 0.0892 (84)			
Least-squares mean % change from baseline ± standard error (sample size)					
Month 6	0.1522 ± 0.5412 (46)	1.7861 ± 0.4197 (84)	1.6338	0.0138	(0.3392, 2.9285)
Month 12	0.1707 ± 0.5761 (46)	2.0651 ± 0.4467 (84)	1.8944	0.0075	(0.5163, 3.2725)

Text Figure 3

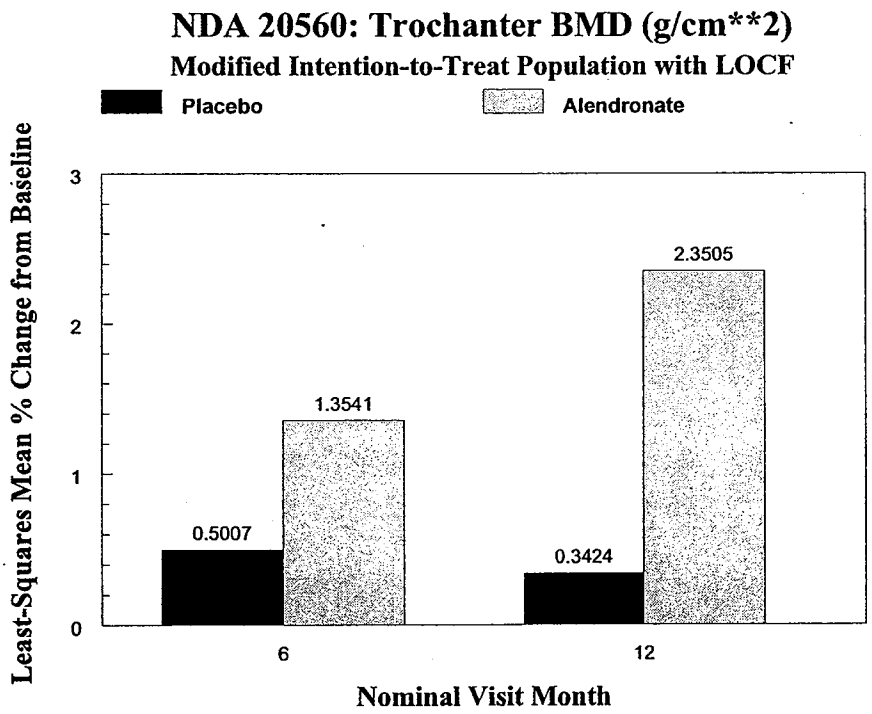


BMD of Trochanter. Both alendronate and placebo groups showed an increased mean trochanter BMD over baseline at Months 6 and 12 using the MITT approach with LOCF techniques (Text Table 5). The mean % change from baseline at Month 12 in the alendronate group was significantly larger than that of the placebo group (2.35% and 0.34%, respectively, $p < 0.0001$, Text Figure 4). In contrast to lumbar spine and femoral neck, treatment effect of alendronate at Month 6 was not significantly better than that of the placebo ($p = 0.0547$).

Text Table 5 – Results for Trochanter BMD Using MITT Approach with LOCF

	Placebo once weekly	Alendronate 70 mg once weekly	Treatment Difference	p-value	(LCL, UCL)
Raw mean trochanter BMD ± standard deviation (sample size)					
Baseline	0.6534 ± 0.1032 (45)	0.6439 ± 0.1129 (84)			
Month 6	0.6562 ± 0.1045 (45)	0.6518 ± 0.1130 (84)			
Month 12	0.6557 ± 0.1065 (45)	0.6587 ± 0.1147 (84)			
Least-squares mean % change from baseline ± standard error (sample size)					
Month 6	0.5007 ± 0.3641 (45)	1.3541 ± 0.2800 (84)	0.8534	0.0547	(0.0176, 1.7245)
Month 12	0.3424 ± 0.3834 (45)	2.3505 ± 0.2949 (84)	2.0081	<0.0001	(1.0910, 2.9252)

Text Figure 4

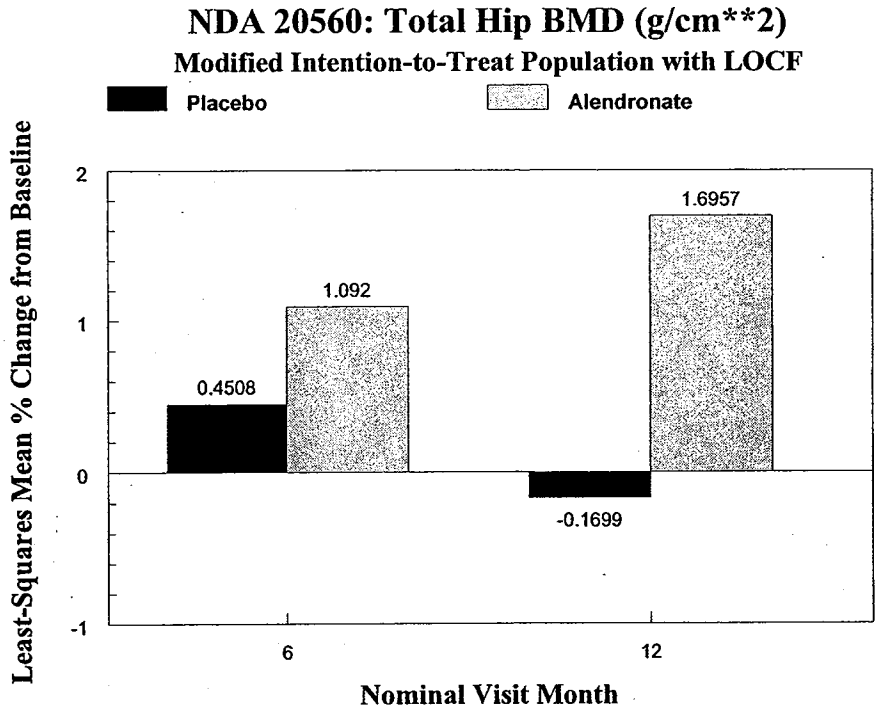


BMD of Total Hip. Both Months 6 and 12 mean total hip BMD were increased over baseline in the alendronate-treated group, but not in the placebo-treated group (Text Table 6). Based on the MITT approach with LOCF techniques, the mean % change from baseline at Month 12 in the alendronate group was significantly larger than that of the placebo group (1.70% and –0.17%, respectively, $p < 0.0001$, Text Figure 5). As in the case of trochanter, treatment effect of alendronate at Month 6 was not significantly better than that of the placebo ($p = 0.0785$).

Text Table 6 – Results for Total Hip BMD Using MITT Approach with LOCF

	Placebo once weekly	Alendronate 70 mg once weekly	Treatment Difference	p-value	(LCL, UCL)
Raw mean total hip BMD ± standard deviation (sample size)					
Baseline	0.8383 ± 0.1003 (46)	0.8148 ± 0.0984 (84)			
Month 6	0.8423 ± 0.1041 (46)	0.8235 ± 0.0988 (84)			
Month 12	0.8374 ± 0.1041 (46)	0.8285 ± 0.0992 (84)			
Least-squares mean % change from baseline ± standard error (sample size)					
Month 6	0.4508 ± 0.2990 (46)	1.0920 ± 0.2319 (84)	0.6412	0.0785	(-0.0741, 1.3565)
Month 12	-0.1699 ± 0.3053 (46)	1.6957 ± 0.2367 (84)	1.8656	<0.0001	(1.1353, 2.5959)

Text Figure 5

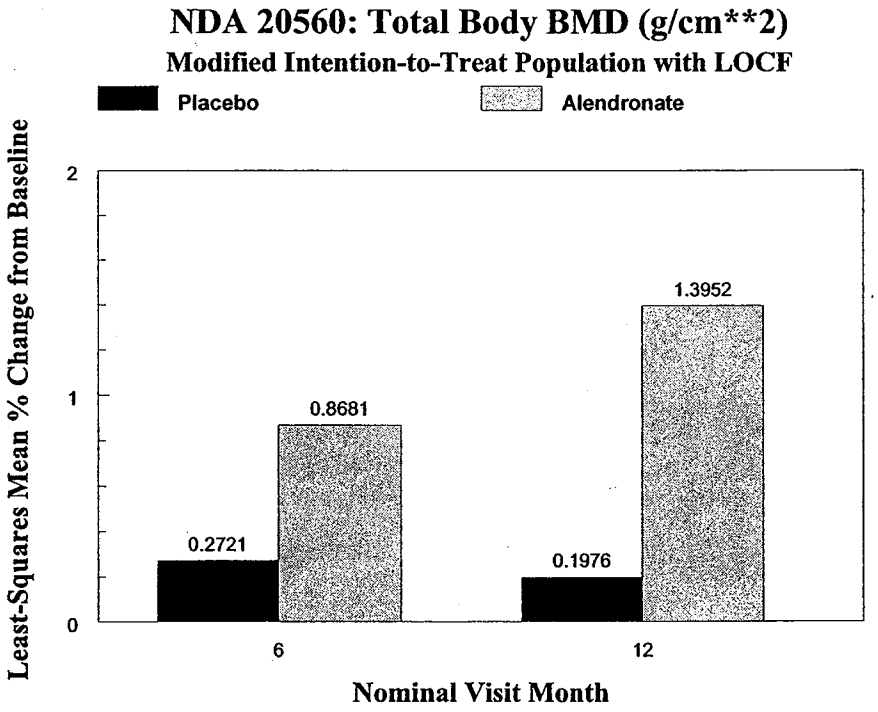


BMD of Total Body. Both alendronate and placebo groups showed an increased mean total body BMD over baseline at Months 6 and 12 using the MITT approach with LOCF techniques (Text Table 7). The mean % change from baseline at Month 12 in the alendronate group was significantly larger than that of the placebo group (1.40% and 0.20%, respectively, p = 0.0177, Text Figure 6). Significant treatment effect of alendronate was also observed at Month 6 when compared to that of the placebo (p = 0.0451).

Text Table 7 – Results for Total Body BMD Using MITT Approach with LOCF

	Placebo once weekly	Alendronate 70 mg once weekly	Treatment Difference	p-value	(LCL, UCL)
Raw mean total body BMD ± standard deviation (sample size)					
Baseline	1.0888 ± 0.0871 (48)	1.0809 ± 0.0991 (90)			
Month 6	1.0921 ± 0.0897 (47)	1.0895 ± 0.0963 (90)			
Month 12	1.0933 ± 0.0908 (48)	1.0964 ± 0.0923 (90)			
Least-squares mean % change from baseline ± standard error (sample size)					
Month 6	0.2721 ± 0.2455 (47)	0.8681 ± 0.1837 (90)	0.5960	0.0451	(0.0132, 1.1789)
Month 12	0.1976 ± 0.4148 (48)	1.3952 ± 0.3130 (90)	1.1976	0.0177	(0.2111, 2.1840)

Text Figure 6



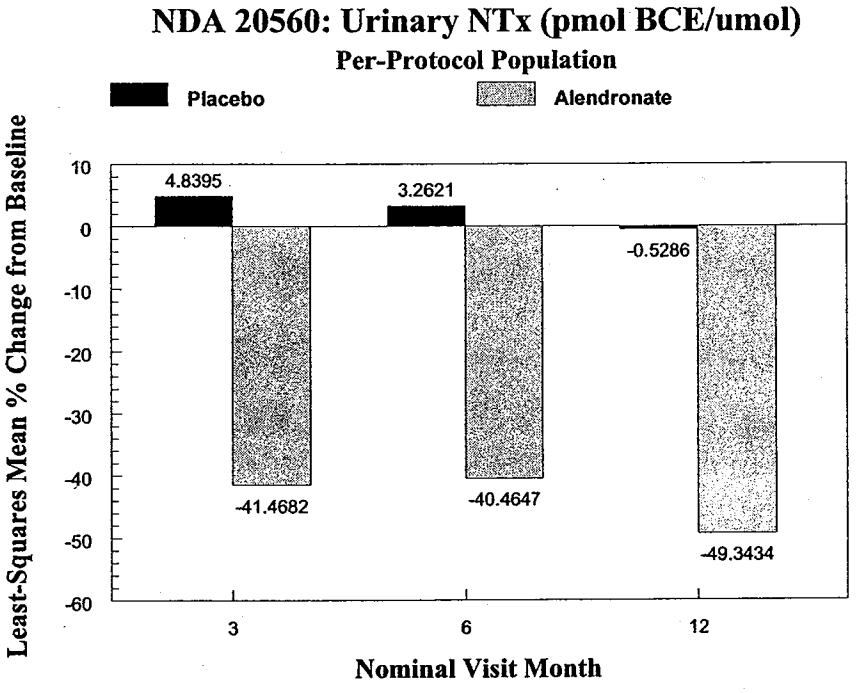
The BMD measurements were obtained from 2 different machine types - [redacted] ; and [redacted] The former type generally showed smaller BMD values than the latter one (see the sponsor's Table 16, p77). Since [redacted] densitometer was used for the majority of subjects, this reviewer also performed the above analyses for this particular group and found the results were consistent with that of the whole population.

Urine N-Telopeptides of Type I Collagen (Urinary NTx). Both alendronate and placebo groups showed a decreased mean urinary NTx over baseline at Month 12 using the PP approach (Text Table 8). The mean % change from baseline at Month 12 in the alendronate group was significantly larger than that of the placebo group (-49.34% and –0.53%, respectively, $p < 0.0001$). Significant treatment effect of alendronate was also observed at Months 3 and 6 when compared to that of the placebo ($p < 0.0001$, Text Figure 7).

Text Table 8 – Results for Urinary NTx Using PP Approach

	Placebo once weekly	Alendronate 70 mg once weekly	Treatment Difference	p-value	(LCL, UCL)
Raw mean Urinary NTx ± standard deviation (sample size)					
Baseline	33.1333 ± 15.4752 (45)	31.9333 ± 12.4988 (90)			
Month 12	31.0000 ± 13.7593 (45)	15.9889 ± 7.0512 (90)			
Least-squares mean % change from baseline ± standard error (sample size)					
Month 12	-0.5286 ± 8.0313 (45)	-49.3434 ± 3.0576 (90)	-49.0742	<0.0001	(-57.79, -38.57)

Text Figure 7



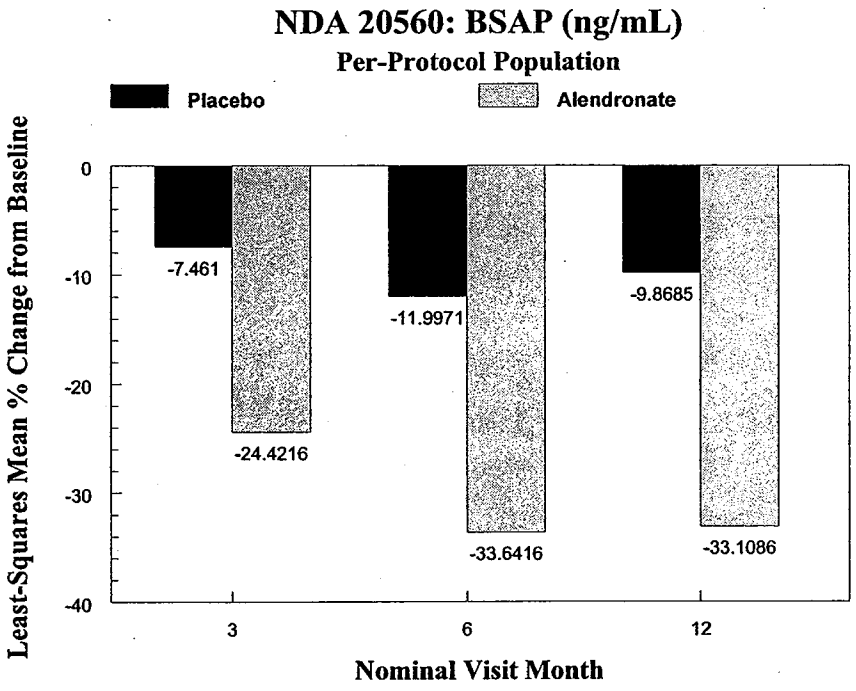
Note that the % changes from baseline at Month 12 obtained using back-transformation by the sponsor were –4.45% and –51.09% for the placebo and alendronate groups, respectively.

Serum Bone-Specific Alkaline Phosphatase (Serum BSAP). Both alendronate and placebo groups showed a decreased mean serum BSAP over baseline at Month 12 using the PP approach (Text Table 9). The mean % change from baseline at Month 12 in the alendronate group was significantly larger than that of the placebo group (-33.11% and –9.87%, respectively, $p < 0.0001$). Significant treatment effect of alendronate was also observed at Months 3 and 6 when compared to that of the placebo ($p < 0.0001$, Text Figure 8).

Text Table 9 – Results for Serum BSAP Using PP Approach

	Placebo once weekly	Alendronate 70 mg once weekly	Treatment Difference	p-value	(LCL, UCL)
Raw mean serum BSAP ± standard deviation (sample size)					
Baseline	13.2640 ± 4.8663 (45)	13.7552 ± 4.9988 (90)			
Month 12	11.9698 ± 4.3715 (45)	9.0179 ± 3.1454 (90)			
Least-squares mean % change from baseline ± standard error (sample size)					
Month 12	-9.8685 ± 3.7702 (45)	-33.1086 ± 2.0924 (90)	-25.7847	<0.0001	(-32.67, -18.21)

Text Figure 8



Note that the % changes from baseline at Month 12 obtained using back-transformation by the sponsor were –9.93% and –34.25% for the placebo and alendronate groups, respectively.

Since baseline heights were significantly different between the 2 study groups (see Demographic and Baseline Characteristics section), this reviewer also included height in the model as a continuous covariate and found the results were consistent with the original findings for both BMD and biochemical marker measures.

2.4 Findings in Special/Subgroup Populations

Subgroup analysis was performed for the primary efficacy endpoint, % change from baseline in lumbar spine BMD at Month 12, based on the MITT approach with LOCF techniques.

A significant treatment-by-subgroup interaction was observed for the baseline weight ($p = 0.014$), and consequently, the body mass index ($p = 0.097$), that were evaluated by tertile (<33.3%, between 33.3% and 66.6%, >66.6%). The inconsistent treatment effect occurred for the heavier subjects whose mean % change from baseline in lumbar spine BMD at Month 12 was slightly larger in the placebo group than in the alendronate group, while an opposite finding was seen for the majority of the subjects (Text Table 10). Clinical input is needed to determine the significance of this qualitative interaction.

Text Table 10 – Least-squares Mean % Change from Baseline for Subgroups of Body Weight at Baseline

Lumbar Spine BMD	<33.3%	33.3% - 66.6%	66.6%
Placebo once weekly	2.04 (N = 15)	-0.48 (N = 19)	3.70 (N = 12)
Alendronate 70 mg once weekly	4.86 (N = 24)	4.30 (N = 33)	3.61 (N = 25)

Treatment effects on % change in lumbar spine BMD were consistent across the pre-specified subgroups of age (<65 or ≥65), height (by tertile), study center, stratum (hypogonadal or eugonadal), prevalent fractures (yes or no), prior osteoporotic fracture (yes or no), baseline lumbar spine BMD (by tertile and T-scores ≤-2.5, >-2.5), and baseline femoral neck BMD (by tertile and T-scores ≤-2.5, >-2.5) (all interaction $p \geq 0.10$, see the sponsor's Table 44 for summary descriptive statistics). In general, across those subgroups, higher mean % changes from baseline in lumbar spine BMD at Month 12 were observed in the alendronate groups compared to the placebo groups.

No subgroup analyses for race and gender were performed since the majority of the subjects were White (almost 98%) and all the study subjects were males.

2.5 Statistical and Technical Issues

No major statistical or technical issues were observed in the study.

2.6 Statistical Evaluation of Collective Evidence

The efficacy of alendronate in BMD across the 5 skeletal sites (Text Figure 9) and in biochemical marker of bone turnover (Text Figure 10) is tabulated below (Text Table 11). It shows that at Month 12, the alendronate 70-mg once weekly dose was significantly better than the placebo in increasing bone mineral density across lumbar spine, hip, and total body skeletal sites and in reducing the turnover rates of bone resorption and formation.

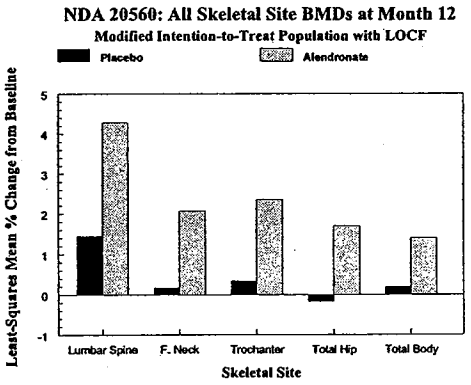
Text Table 11 – Summary of Efficacy in BMD and Biochemical Marker at Month 12

Least-squares Mean % Change from Baseline ± Standard Error (Sample Size)

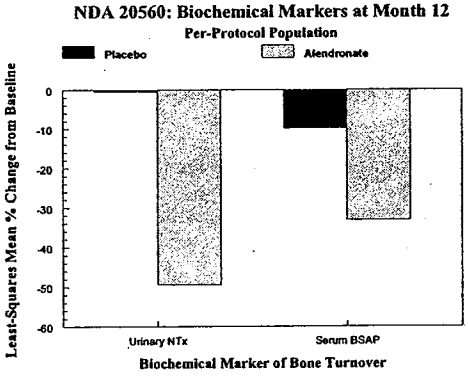
Protocol 165	Placebo once weekly	Alendronate 70 mg once weekly	Treatment Difference	p-value	(LCL, UCL)
Lumbar Spine	1.4547 ± 0.5454 (46)	4.2754 ± 0.4268 (82)	2.8207	<0.0001	(1.5107, 4.1307)
Femoral Neck	0.1707 ± 0.5761 (46)	2.0651 ± 0.4467 (84)	1.8944	0.0075	(0.5163, 3.2725)
Trochanter	0.3424 ± 0.3834 (45)	2.3505 ± 0.2949 (84)	2.0081	<0.0001	(1.0910, 2.9252)
Total Hip	-0.1699 ± 0.3053 (46)	1.6957 ± 0.2367 (84)	1.8656	<0.0001	(1.1353, 2.5959)
Total Body	0.1976 ± 0.4148 (48)	1.3952 ± 0.3130 (90)	1.1976	0.0177	(0.2111, 2.1840)
Urinary NTx	-0.5286 ± 8.0313 (45)	-49.3434 ± 3.0576 (90)	-49.0742	<0.0001	(-57.79, -38.57)
Serum BSAP	-9.8685 ± 3.7702 (45)	-33.1086 ± 2.0924 (90)	-25.7847	<0.0001	(-32.67, -18.21)

Positive and negative treatment differences in BMD and biochemical marker, respectively, favor Alendronate.
LCL = 95% lower confidence limit; UCL = 95% upper confidence limit

Text Figure 9



Text Figure 10



This reviewer also retrieved the sponsor's clinical study reports for Protocol 096, submitted on 3/31/00 (NDA 20560/SE1-023), and Protocol 118, submitted on 12/22/99 (NDA 20560/SE2-021), from electronic document room (EDR) to compare the efficacy of alendronate with that of the present study (Text Table 12). Based on visual inspection, in

both men and women's studies, the alendronate 70-mg once weekly dose generally showed slightly smaller changes in BMD and biochemical marker compared to the 10-mg once daily dose. In addition, the changes in men were generally smaller than that in postmenopausal women for either dose.

Text Table 12 – Fosamax (alendronate) % Change from Baseline at Month 12 among the Osteoporosis Studies

	Men				Postmenopausal Women	
	Protocol 165 70 mg once weekly		Protocol 096[a] 10 mg once daily		Protocol 118[b] 70 mg once weekly	Protocol 118[b] 10 mg once daily
Lumbar Spine BMD	4.28	2.82	4.85	3.30	5.08	5.39
Femoral Neck BMD	2.07	1.89	2.41	2.36	2.29	2.85
Trochanter BMD	2.35	2.01	2.95	2.35	3.92	4.37
Total Hip BMD	1.70	1.87	2.25	2.14	2.89	3.14
Total Body BMD	1.40	1.20	1.66	0.87	1.03	1.02
Urinary NTx	-49.34	-49.07	-58.38	-55.51[c]	-56	-64
Serum BSAP	-33.11	-25.78	-38.13	-32.29[c]	-41	-45

[a]Protocol 096 was a 2-year study, but the numbers shown here were the results of Month 12.
[b]Protocol 118 had no placebo-controlled group.
[c]The reviewer's calculation based on (exp(adjusted mean change from baseline in logarithm) - 1) *100.
Grayed columns show the observed treatment difference between the alendronate and placebo groups.

2.7 Conclusions and Recommendations

Despite the numerical difference in the statistical results of biochemical markers of bone turnover between the reviewer and the sponsor's, our conclusions are in general consensus.

In summary, after 12 months of treatment in men with idiopathic osteoporosis or osteoporosis due to hypogonadism, the alendronate 70-mg once weekly dose showed nominal statistical superiority over placebo based on the BMD measurements of lumbar spine, femoral neck, trochanter, total hip, and total body. Alendronate also reduced the rate of bone turnover as assessed by biochemical markers such as urine N-Telopeptides of Type I collagen and serum bone-specific alkaline phosphatase. In addition, a significant positive treatment effect on lumbar spine BMD was seen as early as 6 months. Except for body weight at baseline and BMI, similar response patterns for lumbar spine BMD at Month 12 were observed across the subgroups of age, height, gonadal status, baseline lumbar spine BMD, and baseline femoral neck BMD. Note that the sponsor also concluded consistent treatment effects for the subgroups of baseline weight and BMI as well (see Sponsor's Results and Conclusions section).

Treatment effects seen in BMD and biochemical marker at 1 year were consistent between the alendronate 70-mg once weekly dose (Protocol 165) and 10-mg once daily dose (Protocol 096) in men, even though the 70-mg dose generally showed numerically smaller efficacy than the 10-mg dose did. Likewise, the response patterns in men were consistent with that in postmenopausal women for either dose (Protocol 118), but numerically smaller in magnitude.

2.8 Labeling Comments

This reviewer found that the results from the 1-year data of Protocol 165 support the proposed changes by the sponsor to the Package Circular with regard to efficacy.

Prepared by: Cynthia Liu, MA, Statistical Reviewer

Concurred by: Todd Sahlroot, Ph.D., Statistics Team Leader

CC: HFD-510/RHedin, EColman, TKehoe
HFD-715/ENevius, TSahlroot, CLiu
HFD-700/CAnello

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Cynthia Liu
1/12/04 05:17:45 PM
BIOMETRICS

Todd Sahlroot
1/13/04 10:23:34 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560/S041

21-575/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # NDA 20-560/S-041

Trade Name Fosamax Tablets Generic Name Alendronate Sodium

Applicant Name Merck & Co. Inc. HFD-510

Approval Date April 16, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      The study is a bioavailability study comparing the oral solution to the 70 mg weekly tablet.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /__/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X__/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X__/ NO /___/

If yes, NDA # 20-560 Drug Name Fosamax Tablets

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # #165

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #165

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 32,033 YES /X/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Randy Hedin
6/14/04 09:44:02 AM

David Orloff
6/14/04 05:05:51 PM

EXCLUSIVITY SUMMARY for NDA # NDA 21-575/S-004

Trade Name Fosamax Oral Solution Generic Name Alendronate Sodium

Applicant Name Merck & Co. Inc. HFD-510

Approval Date April 16, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      The study is a bioavailability study comparing the oral solution to the 70 mg weekly tablet.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /__/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X__/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X__/ NO /___/

If yes, NDA # 20-560 Drug Name Fosamax Tablets

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
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Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

David Orloff
4/19/04 04:52:37 PM

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-560/S-041
NDA 21-575/S-004

Name of Drug: Fosamax (alendronate sodium) Tablets
Fosamax (alendronate sodium) Oral Solution

Sponsor: Merck Research Laboratories

Material Reviewed

Submission Dates:

- April 9, 2004 submission containing revised draft labeling for the package insert (PI) for the tablet (NDA 20-560), and solution (NDA-21-575) formulations.

Background and Summary Description:

- The supplement proposes new once-weekly dosing in men text for the package insert. The sections of the label that are changed to reflect the new data are the CLINICAL PHARMACOLOGY, *men,* section, the DOSAGE AND ADMINISTRATION section, the CLINICAL PHARMACOLOGY, *Osteoporosis in men* section, and the ADVERSE REACTIONS, *men* section of the package insert

Review

Package Insert

The draft PI submitted April 9, 2004, was compared to the FPL submitted October 6, 2003 (Identifier # 7957023, revision date September 2003), and they are identical except for the following:

- The sentence, "Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly FOSAMAX 70 mg." is added to the first paragraph of the *Osteoporosis in men* subsection of the **CLINICAL PHARMACOLOGY** section.

- In the *Men* subsection of the *Clinical Studies* section the first sentence is changed from, "The efficacy of FOSAMAX 10 mg once daily in men with osteoporosis was demonstrated in a two year, double-blind, placebo-controlled, multicenter study, which enrolled a total of 241 men between the ages of 31 and 87 (mean, 63)" to, "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)."

- In the *Men* subsection of the *Clinical Studies* section, the second paragraph, "The safety and efficacy of once weekly FOSAMAX 70 mg in men with osteoporosis are currently being studied but data are not yet available." is deleted and replaced with, "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 $\leq$ -2 at the femoral neck and $\leq$ -1 at the lumbar spine, 2) a BMD T-score $\leq$ -2 at the lumbar spine and $\leq$ -1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score $\leq$ -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 ($\geq$ 65 hears vs. < 65 years), gonadal function (baseline testosterone < 9 ng/dL vs. $\geq$ 9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score $\leq$ vs. > -2.5)."

- In the *Geriatric Use* subsection of **PRECAUTIONS** section, the phrase, "the osteoporosis study in men," is changed to this, "osteoporosis studies in men." In the same subsection, "50%" is changed to "54%."

- In the *Men* subsection of the **ADVERSE REACTIONS** section the first sentence is changed from, "In a two-year, placebo-controlled, double-blind, multicenter study, discontinuation of therapy due to any clinical adverse experience occurred in 2.7% of men treated with FOSAMAX 10 mg/day and 10.5% of men treated with placebo." to, "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. 6.6% for placebo."

  Also, in the *Men* subsection of the **ADVERSE REACTIONS** section, the Osteoporosis Study in Men table is changed to add the data from the one

year study.

- The following paragraph is added to the *Pregnancy Category C:* subsection of the **PRECAUTIONS** section, ""Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporation 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, predominately 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 this risk has not been studied." This statement was approved in supplement 042, and is acceptable.

- In the *Treatment to increase bone mass in men with osteoporosis* subsection of the **DOSAGE AND ADMINISTRATION** section, the text, "The recommended dosage is one 10 mg tablet once daily. Alternatively, one 70 mg tablet or one bottle of 70 mg oral solution once weekly may be considered." is changed to, "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"

Conclusions

The only changes to the label are noted above. An approval letter should be issued.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

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/s/

Randy Hedin
4/15/04 10:46:54 AM
CSO

Memorandum to File

To: NDA 20-560 file
From: E. Chikhale, Ph.D. – Chemistry Reviewer
Subject: NDA 20-560/S-041, Environmental Assessment
Date: 4-13-04

The supplement provides for a labeling revision, based on submitted clinical data from Protocol 165 ("*A Randomized, Double-Blind, Multicenter, Placebo-controlled, 12 month Study to evaluate the Safety and Efficacy of Weekly Dosed Oral Alendronate Sodium for the treatment of Osteoporosis in Men*"). This study is part of the fulfillment of a Phase IV commitment.

The applicant proposes to remove the sentence: "The safety and efficacy of once weekly FOSAMAX 70 mg in men with osteoporosis are currently being studied, but data are not yet available" from the CLINICAL PHARMACOLOGY, *Men*, section. The applicant proposes to replace this sentence with clinical data from Protocol 165.

The applicant is requesting a categorical exclusion from the requirement to prepare an Environmental Assessment under 21 CFR 25.31 (a), because the change will not increase the use of the active moiety. Based on discussion with the medical team leader, Eric Coleman, MD, the use of Fosamax in men with osteoporosis was already part of the labeling and dosing, and the proposed change did not increase the use or population of the drug substance. Therefore, the request for a categorical exclusion is acceptable.

CC:
HFD-510/Division File
HFD-510/D. Orloff (Div. Dir.)
HFD-510/E. Galliers (Supv. CSO)
HFD-510/S/ R. Hedin (CSO)
HFD-510/M. Gautam-Basak (Team Leader)
HFD-510/E. Chikhale (Chem. Reviewer)

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/s/

Elsbeth Chikhale
4/15/04 04:24:55 PM
CHEMIST

Mamta Gautam-Basak
4/16/04 08:39:53 AM
CHEMIST
Concur

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-560/S-041

Merck & Company, Inc.
Attn: Michele R. Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 2000, Mail Drop: RY 33-200
Rahway, NJ 07065

Dear Dr. Flicker:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	FOSAMAX® (alendronate sodium) Tablets
NDA Number:	20-560
Supplement number:	S-041
Review Priority Class:	Standard (S)
Date of supplement:	June 18, 2003
Date of receipt:	June 19, 2003

This supplemental application proposes among other minor changes to the Men subsection of the CLINICAL PHARMACOLOGY section and changes the *Treatment to increase bone mass in men with osteoporosis* subsection of the DOSAGE AND ADMINISTRATION section to read.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 18, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 19, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
7/3/03 02:49:27 PM

MEMO OF FILING MEETING

Date August 14, 2003 Time: 3:00 to 3:15 PM Location: 14B-45

NDA 20-560/S-041 Fosamax (alendronate sodium) Tablets

Type of Meeting: Filing Meeting

External participant: None

Meeting Chair: Mr. Randy Hedin

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Division of Metabolic and Endocrine Drug Products:
Theresa Kehoe, M.D., Clinical Reviewer
Eric Colman, M.D., Clinical Team Leader
Randy Hedin, R.Ph., Senior Regulatory Management Officer

Division of Biometrics II
Todd Sahlroot, Ph.D., Team Leader
Cynthia Liu, M.A., Reviewer

External participant Attendees and titles:

None

Meeting Objectives:

To determine if NDA 20-560/S-041 will be filed, and discuss plans for the review of the supplemental NDA.

Discussion Points:

- Chemistry: An environmental assessment is the only issue and the chemistry team leader stated, before the meeting, that the supplement will be assigned to Elsbeth Chikhale.
- Statistics: The application is fileable. No review issues are apparent at this time.
- Clinical: The application is fileable. No review issues are apparent at this time.

Decisions (agreements) reached:

- The application will be filed.
- The review will be done as a standard review. The goal to finish the reviews, with team leader signoff, is March 19, 2004. The action package should start circulating on March 26, 2004. The user fee goal date is April 19, 2004.
- The application will not be discussed at an Advisory Committee Meeting.
- Division of Scientific Investigations (DSI) audits may be requested. The decision to request audits will be made after review of the financial disclosure data.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Schedule status meetings as appropriate.

{See appended electronic signature page}

Randy Hedin, Senior Regulatory Management Officer, HFD-510

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/s/

Randy Hedin
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