(alendronate sodium/cholecalciferol)

LOCAL PRODUCT CIRCULAR

FOSAMAX PLUS® 70/5600

(alendronate sodium 70 mg/cholecalciferol 5600 IU)

I. THERAPEUTIC CLASS

FOSAMAX PLUS contains alendronate sodium and cholecalciferol (vitamin D3).

Alendronate Sodium

Alendronate sodium is a bisphosphonate that acts as a potent, specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Cholecalciferol

Cholecalciferol (vitamin D3) is a secosterol that is the natural precursor of the calcium-regulatinghormone calcitriol (1,25-dihydroxyvitamin D3)

II. INDICATIONS

FOSAMAX PLUS is indicated

- For the treatment of osteoporosis in postmenopausal women to increase bone mass, prevent fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass or by the

presence or history of osteoporotic fracture.

- Treatment of osteoporosis in men to prevent fractures.

III. CLINICAL PHARMACOLOGY

IIIa. Mechanism of Action

Alendronate Sodium

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 boneshowed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bonesexamined 6 and 49 days after [^{3}H] alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix, where it is no longer pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry inbaboons 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.

Cholecalciferol

Vitamin D3 is produced in the skin by photochemical conversion of 7-dehydrocholesterol to previtamin D3 by ultraviolet light. This is followed by non-enzymatic isomerization to vitamin D3. In the absence of adequate sunlight exposure, vitamin D3 is an essential dietary nutrient. Vitamin D3 in skin and dietary vitamin D3 (absorbed into chylomicrons) is converted to 25-hydroxyvitamin D3 in the liver. Conversion to the active calcium-mobilizing hormone 1,25-

dihydroxyvitamin D3 (calcitriol) in the kidney is stimulated by both parathyroid hormone and hypophosphatemia. The principal action of 1,25-dihydroxyvitamin D3 is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, boneformation and bone resorption.

Vitamin D3 is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in secondary hyperparathyroidism, hypophosphatemia, proximal muscle weakness and osteomalacia, further increasing the risk of falls and fractures in osteoporotic individuals. Supplemental vitamin D reduces these risks and their consequences.

IIIb. Pharmacokinetics

IIIb-1. Absorption

Alendronate Sodium

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 in men (0.6%) was similar tothat in women.

The alendronate in the FOSAMAX PLUS (70 mg/5600 IU) tablet and the FOSAMAX 70 mg tablet is bioequivalent.

Bioavailability was decreased similarly (by approximately 40%) whether alendronate was administered one or one-half hour before a standardized breakfast. In osteoporosis studies, FOSAMAX was effective when administered at least 30 minutes before the first food or beverageof the day.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Cholecalciferol

Following administration of FOSAMAX PLUS (70 mg/5600 IU) after an overnight fast and two hours before a meal, the mean area under the serum- concentration-time curve ($AUC_{0\text{-}80\ hrs}$) for vitamin D3 (unadjusted for endogenous vitamin D3 levels) was 490.2 ng hr/ml. The mean maximal serum concentration (C_{max}) of vitamin D3 was 12.2 ng/ml and the median time to maximal serum concentration (T_{max}) was 10.6 hours. The bioavailability of the vitamin D3 in FOSAMAX PLUS (70 mg/5600 IU) is similar to an equal dose of vitamin D3 administered alone.

IIIb-2. Distribution

Alendronate Sodium

Studies in 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 for analytical detection (less than 5 ng/mL). Protein binding in human plasma is approximately 78%.

Cholecalciferol

Following absorption, vitamin D3 enters the blood as part of chylomicrons. Vitamin D3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D3 at these sites for later release into the circulation. Circulating vitamin D3 is bound to vitamin D- binding protein.

IIIb-3. Metabolism

Alendronate Sodium

There is no evidence that alendronate is metabolized in animals or humans.

Cholecalciferol

Vitamin D3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D3 undergoes glucuronidation prior to elimination.

IIIb-4. Elimination

Alendronate Sodium

Following a single IV dose of [^{14}C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces.

Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min, and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, reflecting release of alendronate from the skeleton.

Cholecalciferol

When radioactive vitamin D3 was administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4%, and the mean fecal excretion of radioactivity after 4 days was 4.9%. In both cases, the excreted radioactivity was almost exclusively as metabolites of the parent. The mean half-life of vitamin D3 in the serum following an oral dose of FOSAMAX PLUS (70 mg/2800 IU) is approximately 24 hours.

IIIb-5. Characteristics in Patients

Preclinical studies show that the alendronate that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative IV doses up to 35 mg/kg in animals. 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 (see DOSAGE AND ADMINISTRATION).

IIIc. 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. It 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 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 hydroxyproline, deoxypyridinoline, and cross-linked N-telopeptides of type I collagen). These biochemical changes returned toward baseline values as early as three weeks following thediscontinuation of therapy with alendronate and did not differ from placebo after 7 months despite the long retention of alendronate in the skeleton.

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. 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. Similar reductions in the rate of bone turnover were observed in postmenopausal women during a one-year study with FOSAMAX once weekly 70 mg for the treatment of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX. In the long- term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment, however,serum phosphate returned toward prestudy levels during years 3 through 5. In one-year studies with FOSAMAX once weekly 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

Even though osteoporosis is less prevalent in men than in postmenopausal women, a significant proportion of osteoporotic fractures occur in men. The prevalence of vertebral deformities appears to be similar in men and women. Treatment of men with osteoporosis with FOSAMAX 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving FOSAMAX once weekly 70 mg.

IIId. Clinical Studies

Treatment of osteoporosis

FOSAMAX PLUS studies

The effect of FOSAMAX PLUS (alendronate 70 mg/vitamin D3 2800 IU) on vitamin D status was demonstrated in a 15-week, double-blind, multinational study of 717 osteoporotic postmenopausal women and men (serum 25-hydroxyvitamin D at baseline: mean, 22.2 ng/mL [56 nmol/L]; range, 9- 90 ng/mL [22.5-225 nmol/L]). Patients received FOSAMAX PLUS (70 mg/2800 IU) (n=350 women, 10 men) or FOSAMAX (alendronate) 70 mg (n=332 women, 25 men) once a week; additional vitamin D supplements were prohibited. The percentage of patients with serum 25-hydroxyvitamin D ≥ 15 ng/mL (37.5 nmol/L) was significantly higher with FOSAMAX PLUS (70 mg/2800 IU) vs. alendronate only (89% vs. 68%, respectively). The percentage of patients with serum 25- hydroxyvitamin D ≥ 9 ng/mL (22.5 nmol/L) was significantly higher with FOSAMAX PLUS (70 mg/2800 IU) vs. alendronate only (99% vs 87%, respectively). There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups.

The effect of FOSAMAX PLUS (alendronate 70 mg/vitamin D3 2800 IU) with an additional 2800 IU vitamin D3 for a total of 5600 IU once weekly was demonstrated in a 24-week, extension study that enrolled 652 osteoporotic post-menopausal women and men. Patients in the Vitamin D3 2800 group received FOSAMAX PLUS (70 mg/2800 IU) (n=305 women, 21 men) and those in the Vitamin D3 5600 group received FOSAMAX PLUS (70 mg/2800 IU) with an additional 2800 IU vitamin D3 (n=314 women, 12 men) once a week; additional vitamin D supplements were allowed. After 24-weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher

in the Vitamin D3 5600 group (27.9 ng/ml [70 nmol/l]) than in the Vitamin D3 2800 group (25.6 ng/ml [64 nmol/l]). The percentage of patients with serum 25-hydroxyvitamin D ≥ 15 ng/mL (37.5 nmol/L) was higher with the Vitamin D3 5600 group vs. the Vitamin D3 2800 group

(96.9% vs. 94.4%, respectively). The percentage of patients with serum 25-hydroxyvitamin D ≥ 9 ng/mL (22.5 nmol/L) was higher with the Vitamin D3 5600 group vs. the Vitamin D3 2800 group (100% vs. 99.7%, respectively) through the 24-week extension. There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups. The percentage of patients with hypercalciuria at the end of the 24-week extension was not statistically different between treatment groups.

FOSAMAX (alendronate sodium) studies

Postmenopausal women

Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postmenopausal women with osteoporosis was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two large three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following table shows the mean increases in bone mineral density (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

WomenIncrease in BMD

FOSAMAX 10 mg/day Relative to Placebo at Three Years

STUDY	LUMBAR SPINE Mean % (SE)	FEMORAL NECK Mean % (SE)	TROCHANTER Mean % (SE)
U.S.	10.34 (0.51)	6.26 (0.70)	8.32 (0.72)
Multinational	7.35 (0.43)	5.49 (0.72)	7.22 (0.89)
Combined	8.82 (0.43)	5.90 (0.50)	7.81 (0.56)

In the combined studies, after three years, BMD of the lumbar spine, femoral neck and trochanter in placebo-treated patients decreased significantly by between 0.65% and 1.16%. Highly significant

increases, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in both studies, indicating that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the entire three years of treatment. In the two-year extension of these studies, treatment with FOSAMAX 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. Thus, FOSAMAX reverses the progression of osteoporosis. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, renal function, and use with a wide rangeof common medications.

In a separate study, FOSAMAX 10 mg/day for two years induced highly significant increases in BMD of the spine, femoral neck, trochanter, and total body relative to either intranasal salmon calcitonin 100 IU/day or placebo.

In patients with postmenopausal osteoporosis treated with FOSAMAX 10mg/ day for one or

two years the effects of treatment withdrawal were assessed. Following discontinuation, bone turnover gradually returned toward pretreatment levels, and BMD no longer increased although accelerated bone loss was not observed. These data indicate that treatment with FOSAMAX must be continuous to produce progressive increases in bone mass.

The therapeutic equivalence of FOSAMAX once weekly 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. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70-mg once-weekly group and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group. The two treatment groups were also similar with regard to BMD increases at other skeletal sites. These data support the expectation that FOSAMAX once weekly 70 mg will have effects to reduce the incidence of fractures similar to those of daily treatment (see below).

Effect on fracture incidence

To assess the effects of FOSAMAX on vertebral fracture incidence, the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant and clinically meaningful 48% reduction in the proportion of patients treated with FOSAMAX experiencing one or more vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%). An even greater reduction in the total number of vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. Furthermore, of patients who sustained any vertebral fracture, those treated with FOSAMAX experienced less height loss (5.9 mm vs. 23.3 mm) due to a reduction in both the number and severity of fractures.

Additionally, analysis of the data pooled across doses of ≥ 2.5 mg from five placebo-controlled studies of two or three years' duration including the U.S. and Multinational studies (FOSAMAX, n = 1012; placebo, n = 590) revealed a significant 29% reduction in non-vertebral fracture incidence (FOSAMAX, 9.0% vs. placebo, 12.6%). Like the effect on vertebral fracture incidence, these results of alendronate treatment are consistent with the observed increases in bone mass.

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline vertebral (compression) fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027-patient study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in statistically significant and clinically meaningful reductions in fracture incidence at three years as shown in the table below. Proportionately similar reductions of hip and wrist fractures were seen in the five pooled osteoporosis treatment studies (see above).

Effect of FOSAMAX on Fracture Incidence in the Three-YearStudy of FIT (patients with vertebral fracture at baseline)		
Patients with:	% of Patients FOSAMAX Placeb	Reduction (%) inFracture Incidence

	o (n = 1022)	(n = 1005)	
Vertebral fractures (diagnosed byX-ray) †			
≥ 1 new vertebral fracture	7.9	15.0	47***
≥ 2 new vertebral fractures	0.5	4.9	90***
Painful (clinical) fractures			
≥ 1 painful vertebral fracture	2.3	5.0	54**
Any painful fracture	13.8	18.1	26**
Hip fracture	1.1	2.2	51*
Wrist (forearm) fracture	2.2	4.1	48*

† Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966

*p<0.05, **p<0.01, ***p<0.001

Furthermore, in this population of patients with baseline vertebral fracture, treatment with FOSAMAX significantly reduced the incidence of hospitalizations resulting from any cause (25.0% vs. 30.7%, a 20% reduction). This difference appears to be related, at least in part, to the reductionin fracture incidence.

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

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further demonstrated the reduction in fracture incidence were due to FOSAMAX. The intent of the study was to recruit women with osteoporosis, i.e. with a baseline femoral neck BMD at least two standard deviations below the mean for young adult women.

However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of FOSAMAX on Fracture Incidence in Osteoporotic † Patientsin the Four-Year Study of FIT (patients without vertebral fracture at baseline)

	% of Patients		
	FOSAMAX (n=1545)	Placebo (n=1521)	Reduction (%) in Fracture Incidence
Patients with:			
1 painful fracture	12.9	16.2	22**
1 vertebral fracture † †	2.5	4.8	48***
≥ 1 painful vertebral fracture	1.0	1.6	41 † † †
Hip fracture	1.0	1.4	29 † † †
Wrist (forearm) fracture	3.9	3.8	None

† Baseline femoral neck BMD at least 2 SD below the mean for young adult women

† † Number evaluable for vertebral fracture: FOSAMAX, n=1426; placebo, n=1428

† † † Not significant

**p = 0.01, ***p <0.001

In all patients (including those without osteoporosis), the reductions in fracture incidence

were: ≥ 1 painful fracture, 14% (p = 0.072); ≥ 1 vertebral fracture, 44% (p = 0.001); ≥ 1 painful vertebral fracture, 34% (p = 0.178), and hip fracture, 21% (p = 0.44). The incidence of wrist fracture in all patients was FOSAMAX, 3.7%; placebo, 3.2% (not significant).

Combined FIT Studies

The reductions in fracture incidence for the combined Three- and Four-Year Studies of FIT areshown below.

Effect of FOSAMAX on Fracture Incidence in the Combined(Three- and Four-Year) Studies of FIT		
	Reduction (%) in Fracture IncidenceFOSAMAX vs. Placebo	
	Osteoporoticpatients † (n = 5093)	All patients(n = 6459)
Vertebral fractures (diagnosedby X-ray) † †		
≥ 1 vertebral fracture	48***	46***
≥ 2 vertebral fractures	88***	84***
Painful (clinical) fractures		
Any painful fracture	24***	18**
Painful vertebral fracture	50***	47***
Hip fracture	40*	36 ‡ ‡

Wrist (forearm) fracture † † †	18 ‡	6 ‡

† Includes all patients in the Three-Year Study plus osteoporotic patients (baseline femoral neck BMD at least 2 SD below the mean for young adult women) in the Four-Year Study

† † Number evaluable for vertebral fractures: osteoporotic patients, n=4804; all patients, n=6084)

† † † Significant reduction in wrist fracture incidence was observed in the Three-Year Study (patients with baseline vertebral fracture) but not in the Four-Year Study (patients without baseline vertebral fracture)

‡ Not significant

*p<0.05, **p<0.01, ***p<0.001, ‡ ‡

p=0.059Consistency of fracture results

The reductions in the incidence of vertebral fractures (FOSAMAX versus placebo) in the Three- and Four-Year Studies of FIT were consistent with that in the combined U.S. and Multinational (U.S./Mult) treatment studies (see above), in which 80% of the women did not have a vertebral fracture at baseline. During these studies, treatment with FOSAMAX reduced the proportion of women experiencing at least one new vertebral fracture by approximately 50% (Three-Year FIT: 47% reduction, $p < 0.001$; Four-Year FIT: 44% reduction, $p = 0.001$; U.S./Mult: 48% reduction,$p = 0.034$). In addition, FOSAMAX reduced the proportion of women experiencing multiple (two or more) new vertebral fractures by approximately 90% in the U.S./Mult. and Three-Year FIT studies ($p<0.001$). Thus, FOSAMAX reduces the incidence of vertebral fractures whether or not patients have experienced a previous vertebral fracture.

Overall, these results demonstrate the consistent efficacy of FOSAMAX to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic

fracture associated with the greatest morbidity.

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging from 1 to 20 mg/day for one, two or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, indicate that bone formed during therapywith FOSAMAX is of normal quality.

Men

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

A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6% (all $p \leq 0.001$). Consistent with much larger studies in postmenopausal women, in these men, FOSAMAX 10 mg/day reduced the incidence of new vertebral fracture (assessed by quantitative radiography) relative to placebo (0.8% vs. 7.1%, respectively; $p=0.017$) and, correspondingly, also reduced height loss (-0.6 vs. -
2.4 mm, respectively; $p=0.022$).

A one-year, double-blind, placebo-controlled, multicenter study of FOSAMAX once weekly 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean 66). At one year, the mean increases in BMD relative to placebo were significant at the following sites: lumbar spine, 2.8% ($p \leq 0.001$); femoral neck, 1.9% ($p = 0.007$); trochanter, 2.0% ($p \leq 0.001$); and total body, 1.2% (p

= 0.018). These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

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

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.

IV. DOSAGE AND ADMINISTRATION

FOSAMAX PLUS must be taken at least half an hour before the first food, beverage, or medication of the day with plain water only. Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of alendronate (see DRUG

INTERACTIONS).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, FOSAMAX PLUS should only be swallowed upon arising for the day with a full glass of water and patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX PLUS 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 PRECAUTIONS).

The recommended dosage is one 70 mg/5600 IU tablet once weekly. For most osteoporotic patients the appropriate dose is 70 mg/5600 IU once weekly. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy reevaluated on a periodic basis. (see CLINICAL STUDIES)

Patients should receive supplemental calcium and/or vitamin D, if dietary intake is inadequate (see PRECAUTIONS). Physicians should consider the vitamin D intake from vitamins and dietarysupplements. FOSAMAX PLUS 70 mg/5600 IU is intended to provide seven days' worth of 800 IU daily vitamin D in a single, once-weekly dose, respectively.

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 PLUS is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience.

V. CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture orachalasia
- Inability to stand or sit upright for at least 30 minutes

- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS)

VI. PRECAUTIONS

Alendronate sodium

FOSAMAX PLUS, like other bisphosphonate-containing products, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate. 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 PLUS 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 PLUS and/or who fail to swallow it with a full glass of water, and/or who continue to take FOSAMAX PLUS 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).

While no increased risk was observed in extensive clinical trials with alendronate, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications.

Because of possible irritant effects of alendronate on the upper gastrointestinal mucosa and a

potential for worsening of the underlying disease, caution should be used when FOSAMAX PLUS is given to patients with active upper gastrointestinal problems, such as dysphagia, esophageal diseases (including known Barrett's esophagus), gastritis, duodenitis, or ulcers.

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow FOSAMAX PLUS with a full glass of water and not to lie down for

at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX PLUS 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 PLUS and consult their physician.

Localized osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported rarely with oral bisphosphonates (see SIDE EFFECTS, *Post-Marketing Experience*). Most reported cases of bisphosphonate-associated ONJ have been in cancer patients treated with intravenous bisphosphonates. Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, co- morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection) and smoking. Patients who develop ONJ should receive appropriate care by an oral surgeon and discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment. Dental surgery may exacerbate the condition.

For patients requiring invasive dental surgery (e.g. tooth extraction, dental implants), clinical

judgment of the treating physician and/or oral surgeon should guide the management plan, including bisphosphonate treatment, of each patient based on individual benefit/risk assessment.

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factor for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms such as pain or discharge, or chronic ear infections.

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see SIDE EFFECTS, *Post-Marketing Experience*). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Low-energy fractures of the subtrochanteric and proximal femoral shaft and other bones have been reported in a small number of long-term (usually longer than three years) bisphosphonate-treated patients. Some were stress fractures (some of which were reported as insufficiency fractures) occurring in the absence of apparent trauma or induced by mild external force. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. Approximately one third of the reported femur fractures were bilateral; therefore, the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. Stress fractures with similar clinical features also have

occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered,pending evaluation of the patient, based on individual benefit/risk assessment.

Patients should be instructed that if they miss a dose of FOSAMAX PLUS, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

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

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

Hypocalcemia must be corrected before initiating therapy with FOSAMAX PLUS (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 PLUS.

Due to the positive effects of alendronate in increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur. There have been rare reports of symptomatic hypocalcaemia, which have occasionally been severe and often occurred in patients with predisposing conditions (eg. Hypoparathyroidism, vitamin D deficiency and

calciummalabsorption).

Cholecalciferol

Vitamin D3 may increase the magnitude of hypercalcemia and/or hypercalciuria when administered to patients with diseases associated with unregulated overproduction of calcitriol (eg, leukemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.

Patients with malabsorption may not adequately absorb vitamin D3.

VII. PREGNANCY

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

VIII. NURSING MOTHERS

FOSAMAX PLUS has not been studied in breast-feeding women and should not be given to them.

IX. PEDIATRIC USE

FOSAMAX PLUS has not been studied in children and should not be given to them.

X. USE IN THE ELDERLY

In clinical studies, there was no age-related difference in the efficacy or safety profiles ofFOSAMAX PLUS.

XI. DRUG INTERACTIONS

Alendronate Sodium

If taken at the same time it is likely that calcium supplements, antacids, and other oral medications will interfere with absorption of alendronate. Therefore, patients must wait at least one-half hour after taking FOSAMAX PLUS before taking any other oral medication.

No other drug interactions of clinical significance are anticipated.

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX® was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of FOSAMAX and HRT resulted in greater increases in bone mass, together with greater decreases

in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments (see SIDE EFFECTS, *Clinical Studies*, *Concomitant use with estrogen/hormone replacement therapy*).

Specific interaction studies were not performed. FOSAMAX was used in osteoporosis studies in men and postmenopausal women, with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions.

Since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

Cholecalciferol

Olestra, mineral oils, orlistat and bile acid sequestrants (eg cholestyramine, colestipol) may impair the absorption of vitamin D. Anticonvulsants, cimetidine and thiazides may increase the metabolism of vitamin D.

XII. SIDE EFFECTS

Clinical Studies

FOSAMAX

In clinical studies FOSAMAX was generally well tolerated. In studies of up to five years in duration, side effects, which usually were mild, generally did not require discontinuation of therapy.

Treatment of osteoporosis

Postmenopausal women

In two three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational) of virtually identical design, the overall safety profiles of FOSAMAX 10 mg/day and placebo were similar. The following upper gastrointestinal adverse experiences were reported by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with FOSAMAX 10 mg/day and at a greater incidence than in patients treated with placebo: abdominal pain (FOSAMAX, 6.6% vs. placebo, 4.8%), dyspepsia (3.6%, 3.5%), esophageal ulcer (1.5%,
0.0%), dysphagia (1.0%, 0.0%), and abdominal distention (1.0%, 0.8%).

Rarely, rash and erythema have occurred.

Additionally, the following adverse experiences were reported by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients treated with FOSAMAX 10 mg/day and at a greater incidence than in patients treated with placebo: musculoskeletal (bone, muscle or joint) pain (FOSAMAX, 4.1% vs. placebo, 2.5%), constipation (3.1%, 1.8%), diarrhea (3.1%, 1.8%),
flatulence (2.6%, 0.5%), and headache (2.6%, 1.5%).

In the two-year extension (treatment years 4 and 5) of the above studies, the overall safety profile of FOSAMAX 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued FOSAMAX 10 mg/day due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of FOSAMAX once weekly 70 mg (n = 519) and FOSAMAX 10 mg daily (n = 370) were similar. The following adverse experiences were reported by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients in either treatment group: abdominal pain (FOSAMAX once weekly 70 mg, 3.7%; FOSAMAX 10 mg daily, 3.0%), musculoskeletal (bone, muscle or joint) pain (2.9%, 3.2%), dyspepsia (2.7%, 2.2%), acid regurgitation (1.9%, 2.4%), nausea (1.9%, 2.4%),
abdominal distension (1.0%, 1.4%), constipation (0.8%, 1.6%), flatulence (0.4%, 1.6%), muscle cramp (0.2%, 1.1%), gastritis (0.2%, 1.1%), and gastric ulcer (0.0%, 1.1%).

Men

In two, placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX10 mg/day [n=146] and a one-year study of FOSAMAX once weekly 70 mg [n=109]), the safety profile of FOSAMAX was generally similar to that seen in postmenopausal women.

Other studies in men and women

In a ten-week endoscopy study in men and women (n = 277; mean age: 55) no difference was seen in upper gastrointestinal tract lesions between FOSAMAX once weekly 70 mg and placebo.

In an additional one-year study in men and women (n = 335; mean age: 50) the overall safety

and tolerability profiles of FOSAMAX once weekly 70 mg were similar to that of placebo and no difference was seen between men and women.

In two one-year studies in men and women (n=477) receiving glucocorticoids, melena was reported in two patients treated with FOSAMAX 10 mg/day.

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.

FOSAMAX PLUS

In a 15-week, double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of once weekly FOSAMAX PLUS (alendronate 70 mg/vitamin D3 2800 IU) was similar to that of FOSAMAX once weekly 70 mg. In the 24-week double-blind extension study in women (n=619) and men (n=33), the safety profile of FOSAMAX PLUS (70 mg/2800 IU) administered with an additional 2800 IU vitamin D3 for a total of 5600 IU was similar to that of FOSAMAX PLUS (70 mg/2800 IU).

Post-Marketing Experience

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

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. As with other bisphosphonates, transient symptoms as in an acute-phase response (myalgia, malaise, asthenia and rarely, fever) have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: nausea, vomiting, esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration; rarely, gastric or duodenal ulcers, some severe and with complications (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), with delayed healing has been reported rarely (see PRECAUTIONS).

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (seePRECAUTIONS); joint swelling; low-energy fractures of the femoral shaft and other bones (see PRECAUTIONS).

Nervous System: dizziness, vertigo, dysgeusia.

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

Special Senses: rarely uveitis, scleritis or episcleritis.

Very rare, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

XIIa. 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 P/dL (0.65 mM) were similar in both treatment groups.

XIII. OVERDOSAGE

Alendronate Sodium

No specific information is available on the treatment of overdosage with alendronate. 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.

Cholecalciferol

Vitamin D toxicity has not been documented during chronic therapy in generally healthy adults at a dose less than 10 000 IU/day. In a clinical study of healthy adults, a 4000 IU daily dose of vitamin D_3 for up to five months was not associated with hypercalciuria or hypercalcemia.

XIV. AVAILABILITY

FOSAMAX PLUS 70mg/5600 IU

It is supplied in packs of 4’ s.

XV. APPEARANCE

FOSAMAX PLUS 70 mg/5600 IU: White to off-white, modified rectangular shaped tablet with "270"on one side and an outline of a bone shape on the other side.

XVI. STORAGE

Store below 30° C. Protect from moisture and light. Store tablets in the original blister package untiluse.

XVII. SHELF LIFE

Please refer to the expiry date on the carton.

XVIII. MANUFACTURER

Rovi Pharma Industrial Services,

S.AVia Complutense, 140

28805 Alcala de

HenaresMadrid, Spain

XIX. PRODUCT REGISTRATION HOLDER

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