Who should not take FOSAMAX PLUS D?

Have certain problems with your esophagus, the tube

ingredients. A list of ingredients is at the end of this

If you are pregnant or nursing, talk to your doctor about

whether taking FOSAMAX PLUS D is right for you based

Other medical problems you have or had in the past

including prescription and non-prescription medicines,

Know the medicines you take. Keep a list of them and

See "What is the most important information I should

make sure it works for you. In addition, follow these

Take 1 dose of FOSAMAX PLUS D once a week.

information about how to take the medicine and to help

Choose the day of the week that best fits your schedule

After getting up for the day and before taking your

first food, drink, or other medicine, swallow your

FOSAMAX PLUS D tablet with a full glass (6-8 oz) of

• It is important that you keep taking FOSAMAX PLUS D

FOSAMAX PLUS D to continue to work, you need to

If you miss a dose, take only 1 FOSAMAX PLUS D

tablet on the morning after you remember. Do not

take 2 tablets on the same day. Continue your usual

schedule of 1 FOSAMAX PLUS D tablet once a week

If you think you took more than the prescribed dose of

contact your local poison control center or emergency

room right away. Do not try to vomit. Do not lie down.

FOSAMAX PLUS D, drink a full glass of milk and

What should I avoid while taking FOSAMAX PLUS D?

supplements before taking FOSAMAX PLUS D.

FOSAMAX PLUS D to eat, drink, or take other

Do not lie down for at least 30 minutes after taking

What are the possible side effects of FOSAMAX PLUS D?

Some patients may get severe digestive reactions from

information I should know about FOSAMAX PLUS D?")

These reactions include irritation, inflammation, or ulcers

of the esophagus, which may sometimes bleed. This may

water with FOSAMAX PLUS D or if they lie down in less

Esophagus reactions may get worse if patients continue

to take FOSAMAX PLUS D after developing symptoms of

FOSAMAX PLUS D. (See "What is the most important

occur especially if patients do not drink a full glass of

than 30 minutes or before their first food of the day.

FOSAMAX PLUS D. Do not lie down until after your

Do not eat, drink, or take other medicines or

Wait for at least 30 minutes after taking

medicines or supplements.

first food of the day.

an irritated esophagus.

for as long as your doctor says to take it. For

on your chosen day.

Every week take 1 tablet of FOSAMAX PLUS D on your

know about FOSAMAX PLUS D?" for important

show it to your doctor and pharmacist each time you see

Also tell your doctor about all medicines you take,

that connects your mouth with your stomach

Are allergic to FOSAMAX PLUS D or any of its

Have low levels of calcium in your blood

Cannot stand or sit upright for at least 30 minutes

Do not take FOSAMAX PLUS D if you:

on possible risk to you and your child.

Stomach or digestive problems

vitamins, and herbal supplements.

your doctor or get a new medicine.

How should I take FOSAMAX PLUS D?

Sarcoidosis, leukemia, lymphoma

Problems with swallowing

Talk to your doctor if you have or have had:

Have severe kidney disease

Read the patient information before you start taking FOSAMAX PLUS D*. Also, read the leaflet each time you refill your prescription, just in case anything has changed This leaflet does not take the place of discussions with your doctor about your medical condition or treatment. You and your doctor should discuss FOSAMAX PLUS D when you start taking your medicine and at regular checkups.

What is the most important information I should know about FOSAMAX PLUS D?

- You must take FOSAMAX PLUS D exactly as directed to help make sure it works and to help lower the chance of harmful
- Choose the day of the week that best fits your schedule. Every week, take 1 FOSAMAX PLUS D tablet on your chosen day
- After getting up for the day and before taking your first food, drink, or other medicine, swallow your FOSAMAX PLUS D tablet with a full glass (6-8 oz) of plain

Do not take FOSAMAX PLUS D with: Mineral water Coffee or tea

- . Do not chew or suck on a tablet of **FOSAMAX PLUS D.**
- After swallowing your FOSAMAX PLUS D tablet, do not lie down — stay fully upright (sitting, standing, or walking) for at least 30 minutes. Do not lie down until after your first food of the day. This will help the FOSAMAX PLUS D tablet reach your stomach quickly and help reduce the chance that FOSAMAX PLUS D might irritate your esophagus, the tube that connects your mouth with your stomach
- After swallowing your FOSAMAX PLUS D tablet, wait at least 30 minutes before taking your first food, drink, or other medicine of the day, including antacids, calcium, and other supplements and vitamins. FOSAMAX PLUS D is effective only if it is taken when your stomach is
- Do not take FOSAMAX PLUS D at bedtime or before getting up for the day.
- If you have chest pain, new or worsening heartburn, or have trouble or pain when you swallow, stop taking FOSAMAX PLUS D and call your doctor

Some patients may need more vitamin D than is in FOSAMAX PLUS D. Your doctor may recommend additional vitamin D supplementation.

What is FOSAMAX PLUS D?

FOSAMAX PLUS D is a prescription medicine that contains alendronate sodium and vitamin D₂ (cholecalciferol) as the active ingredients. FOSAMAX PLUŠ D provides a week's worth of vitamin D₃ (2800 IU). The Daily Value is 400 IU.

FOSAMAX PLUS D is used for:

- The treatment of osteoporosis (thinning of bone) in women after menopause. It reduces the chance of having a hip or spinal fracture (break).
- Treatment to increase bone mass in men with osteoporosis.

Improvement in bone density may be seen as early as 3 months after you start taking FOSAMAX PLUS D. For FOSAMAX PLUS D to continue to work, you need to

FOSAMAX PLUS D is not a hormone.

There is more information about osteoporosis and vitamin D at the end of this leaflet.

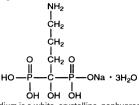
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MERCK & CO., INC. Whitehouse Station, NJ 08889, USA

FOSAMAX PLUS D™ (ALENDRONATE SODIUM/CHOLECALCIFEROL) TABLETS

FOSAMAX PLUS D* contains alendronate sodium, a bisphosphonate, and cholecalciferol (vitamin D₂). 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 hydroxy-

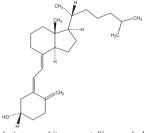
apatite found in bone. Alendronate sodium is chemically described as (4-amino-1hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate. The empirical formula of alendronate sodium is C₄H₁₂NNaO₇P₂•3H₂O and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic pow It is soluble in water, very slightly soluble in alcohol, and practically

Cholecalciferol (vitamin D₃) is a secosterol that is the natural precursor of the calcium-regulating hormone calcitriol (1,25 dihydroxy-

The chemical name of cholecalciferol is $(3\beta,5Z,7E)-9,10$ secocholesta-5.7.10(19)-trien-3-ol. The empirical formula of cholecalciferol is C27H44O and its molecular weight is 384.6. The structural formula is:



Cholecalciferol is a white, crystalline, odorless powder Cholecalciferol is practically insoluble in water, freely soluble in usual

organic solvents, and slightly soluble in vegetable oils. FOSAMAX PLUS D for oral administration contains 91.37 mg of alendronate monosodium salt tribydrate, the molar equivalent of 70 mg of free acid, and 70 mcg of cholecalciferol equivalent to 2800 International Units (IU) vitamin D. Each tablet contains the ollowing inactive ingredients: microcrystalline cellulose, lactose anhydrous, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hydroxytoluene, modified food starch, and sodium aluminum silicate.

CLINICAL PHARMACOLOGY

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 [3H]alendronate in bone showed about 10-fold higher uptake on steoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [3H]alendronate administration in rats and mice, espectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While acorporated 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.

Vitamin $\mathbf{D_3}$ is produced in the skin by photochemical conversion of 7-dehydrocholesterol to previtamin $\mathbf{D_3}$ by ultraviolet light. This is followed by non-enzymatic isomerization to vitamin D₂. In the absence of adequate sunlight exposure, vitamin D3 is an essential dietary nutrient. Vitamin ${\bf D_3}$ in skin and dietary vitamin ${\bf D_3}$ (absorbed into chylomicrons) is converted to 25-hydroxyvitamin ${\bf D_3}$ 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, bone formation and bone resorption.

Vitamin D 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, increased parathyroid hormone levels, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in more severe hyperparathyroidism, hypophosphatemia proximal muscle weakness, bone pain and osteomalacia.

Pharmacokinetics Absorption

Alendronate Sodium

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging 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.

The alendronate in the FOSAMAX PLUS D tablet and the FOSAMAX®** (alendronate sodium) 70 mg tablet is equally A study examining the effect of timing of a meal on the bio-

availability 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%. Cholecalciferol

Following administration of FOSAMAX PLUS D after an overnight fast and two hours before a standard meal, the baseline adjusted mean area under the serum-concentration-time curve (AUC_{0.120 bro} for vitamin D_3 was 120.7 ng-hr/mL. The baseline adjusted mean maximal serum concentration (C_{max}) of vitamin D_3 was 4.0 ng/mL, and the baseline adjusted mean time to maximal serum concentration (T_{max}) was 10.6 hrs. The bioavailability of the 2800 IU vitamin D_3 in FOSAMAX PLUS D is similar to 2800 IU vitamin D₃ administered alone.

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FOSAMAX PLUS D™

Alendronate Sodium 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%.

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 tissue and stored as vitamin D₃ at these sites for later release into the circulation Circulating vitamin D₂ is bound to vitamin D-binding protein.

There is no evidence that alendronate is metabolized in animals or

orm. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D₃ undergoes glucuronidation prior to

Alendronate Sodium

Following a single IV dose of [14C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or o 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. Cholecalciferol

When radioactive vitamin D₃ was intravenously administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4% of the administered dose, and the mean fecal excretion of radioactivity after 48 hours was 4.9% of the administered dose. In both cases, the excreted radioactivity was almost exclusively as metabolites of the parent. The mean half-life of baseline adjusted vitamin D_3 in the serum following an oral dose of FOSAMAX PLUS D is approximately 14 hours. Special Populations

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

Gender: Bioavailability and the fraction of an IV dose of alendronate

Alendronate Sodium

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

Dietary requirements of vitamin D_3 are increased in the elderly. Race: Pharmacokinetic differences due to race have not been

Renal Insufficiency:

Alendronate Sodiun

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

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

Patients with renal insufficiency will have decreased ability to form the active 1,25-dihydroxyvitamin $\mathring{\mathsf{D}}_3$ metabolite

ndronate Sodiur As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with

Vitamin D₂ may not be adequately absorbed in patients who have nalabsorption due to inadequate bile production

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 H₂-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 bio availability 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.

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

Pharmacodynamics 1 4 1

Cholecalciferol

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of oster cells. Alendronate reduces bone resorption with no direct effect or bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass that leads to an ncreased 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 oone 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 ostmenonausal 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

FOSAMAX PLUS D™

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone esorption, deoxypyridinoline and cross-linked N-telopeptides of type collagen, by approximately 50% and 70%, respectively, to reach evels 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 turnove were observed in postmenopausal women during one-vear studies with once weekly FOSAMAX 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 three through five. In one-year studies with once weekly FOSAMAX 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

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.

. Cholecalciferol Vitamin D is required for normal bone formation. Vitamin D insufficiency associated with negative calcium balance, leading to increased parathyroid hormone levels and worsening of bone loss associated with associated with a reduction in serum calcium concentrations and ncreased parathyroid hormone levels. In a 15-week trial 717 postmenopausal women and men, mean age 67 years, with orosis (lumbar spine bone mineral density [BMD] of at least 2.5 standard deviations below the premenopausal mean) were randomized to receive either weekly FOSAMAX PLUS D 70 mg/2800 IU vitamin D or weekly FOSAMAX 70 mg alone with no vitamin D supplementation. Patients who were vitamin D deficient (25-hydroxyvitamin D <9 ng/mL) at baseline were excluded. Treatment with FOSAMAX PLUS D 70 mg/2800 IU resulted in a smaller reduction i serum calcium levels (-0.9%) when compared to FOSAMAX 70 mg alone -1.4%). As well, treatment with FOSAMAX PLUS D 70 mg/2800 IU res in a significantly smaller increase in parathyroid hormone levels when

compared to FOSAMAX 70 mg alone (14% and 24%, respectively). The sufficiency of patients' vitamin D status is best assessed by measuring 25-hydroxyvitamin D levels. In the 15-week trial mentioned above, baseline 25-hydroxyvitamin D levels were 22.2 ng/mL in the FOSAMAX PLUS D group and 22.1 ng/mL in the FOSAMAX only group. After 15 weeks of treatment, the mean levels were 23.1 ng/mL and 18.4 ng/mL in the FOSAMAX PLUS D and FOSAMAX only groups, respectively. The final levels of 25-hydroxyvitamin D at week 15 are summarized in the table below

25-hydroxyvitamin D Levels after Treatment with FOSAMAX PLUS D and FOSAMAX 70 mg at Week 15*

5-hydroxyvitamin D Ranges ng / mL)	< 9	9-14	15-19	20-24	25-29	30-62	Fu
OSAMAX PLUS D	4 (1.1)	37 (10.4)	87 (24.4)	84 (23.5)	82	63 (17.7)	frac incid
N=357) OSAMAX 70 mg	46 (13.1)	66 (18.8)	108	58 (16.5)	(23.0) 37	36 (10.3)	In
N=351)			(30.8)		(10.5)		22 (2

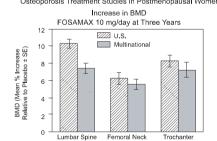
* Patients who were vitamin D deficient (25-hydroxyvitamin D <9 ng/mL) at baseline were

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.

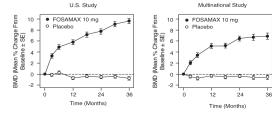
Osteoporosis Treatment Studies in Postmenopausal Wo



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 BMI 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 eviden early as three months and continued throughout the three years treatment. (See figures below for lumbar spine results.) In the tw year extension of these studies, treatment of 147 patients v FOSAMAX 10 mg/day resulted in continued increases in BMD at th lumbar spine and trochanter (absolute additional increases betwee years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. FOSAMA was similarly effective regardless of age, race, baseline rate of bon turnover, and baseline BMD in the range studied (at least 2 standar deviations below the premenopausal mean). Thus, overall FOSAMA reverses the loss of bone mineral density, a central factor in th 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 U.S. Study



patients with postmenopausal osteoporosis treated with FOSAMAX 10 mg/day for one or two years, the effects of treatment

further increases in bone mass and the rates of bone loss were simila to those of the placebo groups. These data indicate that continued reatment 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 othe skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third studies were combined in an analysis that compared placebo to the ooled dosage groups of FOSAMÁX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a tically 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% relativ 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 postmenopausal women: the Three-Year Study of patients who had at east one baseline radiographic vertebral fracture and the Four-Yea Study of patients with low bone mass but without a baseline vertebral acture. 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

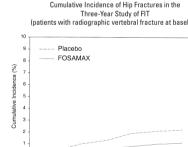
one baseline radiographic vertebral fracture) This randomized, double-blind, placebo-controlled, 2027-patient

study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that nent with FOSAMAX resulted in statistically significant reductions in fracture incidence at three years as shown in the table Effect of FOSAMAX on Fracture Incidence in the Three-Year Study of FIT

	Percent of Patients				
	FOSAMAX Plan (n=1022) (n=		Absolute Reduction in Fracture Incidence	Rela Redu in Fra Ris	
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 ²	
≥ 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	

Furthermore, in this population of patients with baseline vertebral acture, treatment with FOSAMAX significantly reduced the

the Three-Year Study of FIT, fractures of the hip occurred in (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.



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

the table below for the patients with osteoporosis.

(patients without vertebral fracture at baseline)

	Pero	ent of Pati	ents	
	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	1.0	1.6	0.6	41 (NS)†††
fracture				
Hip fracture	1.0	1.4	0.4	29 (NS)†††
Wrist (forearm) fracture	3.9	3.8	-0.1	NS†††

111 Not significant. This study was not powered to detect differences at these sites. *p=0.035, **p=0.01, ***p<0.001

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).

(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, n<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).

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 iring therapy with FOSAMAX is of normal quality.

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:) a BMD T-score \leq -2 at the femoral neck and \leq -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 eight 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 fore \leq -2 at the femoral neck and \leq -1 at the lumbar spine, 2) a BMD [-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a line osteoporotic fracture and a BMD T-score ≤-1 at the femora 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 lumba spine T-score \leq -2.5 vs. >-2.5).

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 rolled study of hysterectomized postmenopausal oste women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) thar 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

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 nip, femoral neck, and trochanter. No significant effect was seen for

a one-year, double-blind, placebo-controlled study in postmenopausa

osteoporotic women (n=428). The addition of FOSAMAX 10 mg once

total body BMD. showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by minerali 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.

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 corres ponding 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 PLUS D is indicated for:

Treatment of osteoporosis in postmenopausal wo For the treatment of osteoporosis, FOSAMAX PLUS D increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compressio 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 o

history of osteoporotic fracture. (See CLINICAL PHARMA-COLOGY, Pharmacodynamics.)

. Treatment to increase bone mass in men with osteoporosis

CONTRAINDICATIONS Abnormalities of the esophagus which delay esophageal emptying

such as stricture or achalasia Inability to stand or sit upright for at least 30 minutes

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

FOSAMAX PLUS D, like other bisphosphonate-containing products,

y cause local irritation of the upper gastrointestinal mucosa Esophageal adverse experiences, such as esophagitis, esophagea llcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been orted in patients receiving treatment with alendronate. In some cases these have been severe and required hospitalization hysicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be icted to discontinue FOSAMAX PLUS D and seek medica attention if they develop dysphagia, odynophagia, retrosternal pain or

The risk of severe esophageal adverse experiences appears to be and/or who fail to swallow it with a full glass (6-8 oz) of water, and/or who continue to take FOSAMAX PLUS D 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 PLUS D should be used under appropriate 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 D 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 with alendronate, some severe and with complications although no increased risk was observed in controlled clinical trials.

Causes of osteoporosis other than estrogen deficiency, aging, and alucocorticoid use should be considered Alendronate Sodium Hypocalcemia must be corrected before initiating therapy with

FOSAMAX PLUS D (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 D.

mineral, small, asymptomatic decreases in serum calcium and phosphate may occur.

Cholecalciferol Following absorption, vitamin ${\rm D_3}$ enters the blood as part of

Metabolism

Alendronate Sodiun

Vitamin D₃ is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D_3 , and subsequently metabolized in the kidney to 1.25-dihydroxyvitamin D₂, which represents the biologically active

Excretion

excreted in urine were similar in men and women

Preclinical studies show that, in rats with kidney failure, increasing mounts 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

with impaired renal function. No dosage adjustment is necessary for patients with mild-torenal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX PLUS D is not recommended for patients with more severe

Hepatic Insufficiency.

nepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions (also see PRECAUTIONS, Drug Interactions Alendronate Sodium

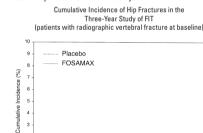
Alendronate Sodium

therapy with alendronate and did not differ from placebo after

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 ithout 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.

Fracture Intervention Trial: Three-Year Study (patients with at least

dence of hospitalizations (25.0% vs. 30.7%).



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

Effect of FOSAMAX on Fracture Incidence in Osteoporotic[†] Patients in the Four-Year Study of FIT

	Per			
	FOSAMAX (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)	Ħ.			
≥ 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 ^{†††}

Fracture results across studies
In the Three-Year Study of FIT, FOSAMAX reduced the percentage

FOSAMAX reduced the percentage of women experiencing multiple

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

Presumably due to the effects of alendronate on increasing bone

keep taking it.

* Trademark of Merck & Co., Inc.

supplementation and measurement of 25-hydroxyvitamin D should be

hypercalciuria when administered to natients with diseases associated with unregulated overproduction of 1,25 dihydroxyvitamin D (e.g., leukemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients. Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs includes FOSAMAX (alendronate). Most of the patients were postmenopausa women. The time to onset of symptoms varied from one day to several onths after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when

rechallenged with the same drug or another bisp In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., pre-existing dental disease, anemia, coagulopathy, infection) Patients who develop osteonecrosis of the jaw

(ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment Renal insufficiency
FOSAMAX PLUS D is not recommended for

patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Information for Patients

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

Patients should be instructed to take supplemental calcium if intake is inadequate. Patients at increased risk for Vitamin D insufficiency (e.g., those who are nursing home bound, chronically ill, over the age of 70 years) should be instructed to take additional vitamin D. Patients with gastrointestinal malabsorption syndromes should be informed that they may require additional vitamin D supplementation. 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 PLUS D 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 alendronate (see CLINICAL PHARMACOLOGY.

Pharmacokinetics Absorption To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation natients should be instructed to swallow each tablet of FOSAMAX PLUS D with a full glass of water (6-8 oz) and not to lie down for at least 30 minutes and until after their first food

of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX PLUS D 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 D and consult their physician.

Patients should be instructed that if they miss a dose of FOSAMAX PLUS D, 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.

Drug Interactions (also see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions) Alendronate Sodium 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 ong-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY therapy (HRT) and ADVERSE REACTIONS. Clinical Studies. Concomitant use with estrogen/hormone replacement therapy).

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate. Therefore patients must wait at least one-half hour after taking FOSAMAX PLUS D

before taking any other oral medications 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

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) FOSAMAX PLUS D 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 strointestinal 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 gastrointestina irritation, caution should be used during concomitant use with FOSAMAX PLUS D Cholecalciferol

Drugs that may impair the absorption of cholecalciferol Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g., cholestyramine, colestipol) may impair the absorption of vitamin D.

Drugs that may increase the catabolism of cholecalciferol Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D.

Carcinogenesis, Mutagenesis, Impairment of Fertility The following data are based on findings for the individual components of FOSAMAX PLUS D.

Alendronate Sodium Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a

FOSAMAX PLUS D™

-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/m². 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 times a 40 mg human daily dose based on surface area, mg/m². The elevance 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 henatocytes 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

Cholecalciferol

The carcinogenic potential of cholecalciferol (vitamin D₃) has not been studied in rodents. Calcitriol, the hormonal metabolite of cholecalciferol, was not genotoxic in the Ames microbial mutagenesis assay with or without metabolic activation, and in an in vivo micronucleus assay in mice. Ergocalciferol (vitamin D₂) at high doses (150,000 to

200,000 IU/kg/day) administered prior to mating resulted in altered estrous cycle and inhibition of pregnancy in rats. The potential effect of cholecalciferol on male fertility is unknown in rats.

Pregnancy Category C:

Alendronate Sodium

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 n 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/m2. 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

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/m²) resulting in delays and failures of delivery. Protracted arturition 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/m²) 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 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 pnate 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. Cholecalciferol

No data are available for cholecalciferol (vitamin D₂). Administration of high doses (≥10,000 IU/every other day) of ergocalciferol (vitamin D_2) to pregnant rabbits, resulted in abortions and an increased incidence of fetal aortic stenosis. Administration of vitamin D_2 (40,000 IU/day) to pregnant rats resulted in neonatal death, decreased fetal weight, and impaired osteogenesis of long bones

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

Cholecalciferol and some of its active metabolites pass into breast milk. 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 PLUS D is administered to nursing women.

Safety and effectiveness in pediatric patients have not been 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 trea and osteoporosis studies in men (see CLINICAL PHARMACOLOGY. Clinical Studies), 45% and 54%, 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. Dietary requirements of vitamin D₃ are increased in the elderly.

ADVERSE REACTIONS

Clinical Studies

FOSAMAX 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.

In two identically designed, three-year, placebo-controlled, doubleblind, multicenter studies (United States and Multinational; n=994). discontinuation of therapy due to any clinical adverse experience rred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture ntervention 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 placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Wome Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related

т, по по во по							
ı	Jnited States/Mult	inational Studies	Fracture Intervention Trial				
_	F0SAMAX*	Placebo	FOSAMAX**	Placebo			
	%	%	%	%			
_	(n=196)	(n=397)	(n=3236)	(n=3223)			
strointestinal							
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			
sculoskeletal							
musculoskeletal (bon							
muscle or joint) pai		2.5	0.4	0.3			
muscle cramp	0.0	1.0	0.2	0.1			
vous System/Psychia							
headache	2.6	1.5	0.2	0.2			
dizziness	0.0	1.0	0.0	0.1			
cial Senses							
taste perversion	0.5	1.0	0.1	0.0			
0 mg/day for three yea	irs						

*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 ncomitant aspirin developed an anastomotic ulcer with mild emorrhage, 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 rience 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

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

10 mg daily were similar. The adverse experiences considered by the

gators as possibly, probably, or definitely drug related in $\geq 1\%$ of

	Once Weekly FOSAMAX	FOSAMAX
	70 mg	10 mg/day
	%	%
	(n=519)	(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,	2.9	3.2
joint) pain		
muscle cramp	0.2	1.1

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

Osteoporosis Studies in Me Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related

by the investigators and Reported in ≥2% of Patients						
Two-year	Study	One-year Study				
		Once Weekly				
FOSAMAX	Placebo	FOSAMAX 70 mg	Placebo			
10 mg/day	%	%	%			
%	(n=95)	(n=109)	(n=58)			
(n=146)						
				•		
4.1	3.2	0.0	0.0			
4.1	1.1	0.0	0.0			
0.7	3.2	2.8	0.0			
3.4	0.0	2.8	1.7			
1.4	1.1	2.8	0.0			
2.1	1.1	0.9	3.4			
2.1	0.0	0.0	0.0			
	Two-year FOSAMAX 10 mg/day % (n=146) 4.1 4.1 0.7 3.4 1.4 2.1	FOSAMAX Placebo 10 mg/day % (n=95) (n=146) 4.1 3.2 4.1 1.1 0.7 3.2 3.4 0.0 1.4 1.1 2.1 1.1	Two-year Study FOSAMAX Placebo 10 mg/day %	Two-year Study		

Concomitant use with estrogen/hormone replacement

In two studies (of one and two years' duration) of postmenopausa 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.

Other studies with FOSAMAX

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, placeboontrolled 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 ma daily were similar

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

osis Prevention Studies in Postmenopausal Wome periences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

Two/Three-Year Studies		┨	One-Ye	ear Study
FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)		FOSAMAX 5 mg/day % (n=361)	Once Weekly FOSAMAX 35 mg % (n=362)
1.9	1.4	Ш	2.2	1.7
1.7	3.4		4.2	2.2
1.4	2.5	Ш	4.2	4.7
1.4	1.4		2.5	1.4
1.1	1.7		1.1	0.6
0.9	0.5	Ш	1.7	0.3
0.2	0.3		1.4	1.1
, 0.8	0.9		1.9	2.2
	FOSAMAX 5 mg/day % (n=642) 1.9 1.7 1.4 1.4 1.1 0.9 0.2	FOSAMAX 5 mg/day % (n=642)	FOSAMAX 5 mg/day % (n=642) (n=648) 1.9 1.4 1.7 3.4 1.4 2.5 1.4 1.4 1.1 1.7 0.9 0.5 0.2 0.3	FOSAMAX 5 mg/day % 5 mg/day % (n=642) (n=648) (n=361) 1.9 1.4 2.2 1.7 3.4 4.2 1.4 2.5 4.2 1.4 1.4 2.5 1.1 1.7 1.1 0.9 0.5 1.7 0.2 0.3 1.4 , 0.8 0.9 1.9

Treatment of glucocorticoid-induced osteoporosis In two, one-year, placebo-controlled, double-blind, multicente 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.

FOSAMAX PLUS D™

5 mg/day 10 mg/day (n=157)(n=161)(n=159) acid regurd

One-Year Studies in Glucocorticoid-Treated Patient

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

Additionally, musculoskeletal (bone, muscle or joint) pain, which as been described in patients with Paget's disease treated with other hisphosphonates, 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 disconti therapy. Discontinuation of therapy due to any clinical adverse ence 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 ved in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking cebo. However, the incidences of decreases in serum calciun < 8.0 mg/dL (2.0 mM) and serum phosphate to $\leq 2.0 \text{ mg/dL} (0.65 \text{ mM})$ were similar in both treatment groups. FOSAMAX PLUS D

In a fifteen week double-blind, multinational study in osteoporotic nopausal women (n=682) and men (n=35), the safety profile of FOSAMAX PLUS D was similar to that of FOSAMAX once weekly 70 mg. The following adverse reactions have been reported in post-

marketing use with alendronate: Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise and rarely, fever have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with pre-

disposing 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). the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain). Skin: rash (occasionally with photosensitivity), pruritus, rarely

severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

Alendronate Sodium

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

with alendronate. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartb 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

Dialysis would not be beneficial.

Cholecalciferol

Significant lethality occurred in mice treated with a single high oral dose of calcitriol (4 mg/kg), the hormonal metabolite of cholecalciferol.

There is limited information regarding doses of cholecalciferol associated with acute toxicity, although intermittent (yearly or twice arly) single doses of ergocalciferol (vitamin D_2) as high as 600,000 IU have been given without reports of toxicity. Signs and symptoms of vitamin D toxicity include hypercalcemia, hypercalciuria anorexia, nausea, vomiting, polyuria, polydipsia, weakness, and patients with suspected vitamin D toxicity. Standard therapy includes restriction of dietary calcium, hydration, and systemic glucocorticoids in patients with severe hypercalcemia.

Dialysis to remove vitamin D would not be beneficial

DOSAGE AND ADMINISTRATION

FOSAMAX PLUS D 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 alendronate (see PRECAUTIONS, *Drug* Interactions). Waiting less than 30 minutes, or taking FOSAMAX PLUS D will lessen the effect of alendronate by decreasing its absorption into

To facilitate delivery to the stomach and thus reduce the notential for esophageal irritation, FOSAMAX PLUS D should only be swallowed upon arising for the day with a full glass of water (6-8 oz) and patients should not lie down for at least 30 minutes <u>and</u> until after their first food of the day. FOSAMAX PLUS D 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 if dietary intake is inadequate (see PRECAUTIONS, *General*). Patients at increased risk for Vitamin D insufficiency (e.g., those who are nursing home bound, chronically ill, over the age of 70 years) should receive vitamin D supplementation in addition to that provided in FOSAMAX PLUS D. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered.

The recommended intake of vitamin D is 400 IU-800 IU daily. FOSAMAX PLUS D is intended to provide seven days' worth of 400 IU daily vitamin D in a single, once-weekly dose. No dosage adjustment is necessary for the elderly or for patients

(see INDICATIONS AND USAGE)

with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX PLUS D 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

The recommended dosage is one 70 mg/2800 IU tablet once weekly.

Treatment to increase bone mass in men with osteoporosis
The recommended dosage is one 70 mg/2800 IU tablet once weekly.

FOSAMAX PLUS D™

No. 3870 — Tablets FOSAMAX PLUS D 70 mg/2800 IU are white to off-white, modified capsule-shaped tablets with code 710 on one side

and an outline of a bone image on the other. They are supplied as NDC 0006-0710-44 unit of use blister packages of 4 NDC 0006-0710-21 unit dose packages of 20

Store at 20-25°C (68-77°F), excursions between 15-30°C (59-86°F) are allowed. [See USP Controlled Room Temperature.] Protect from moisture and light. Store tablets in the original blister package until

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

MSD FROSST IBERICA, S.A.

Manufactured for:

Madrid, Spain

Issued July 2005

9655601

FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol) Tablets

Stop taking FOSAMAX PLUS D and call your doctor right away if you get any of these signs of possible serious

Chest pain

Heartburn Trouble or pain when swallowing

Side effects in patients taking FOSAMAX PLUS D usually have been mild. They generally have not caused patients to stop taking FOSAMAX PLUS D.

The most common side effect is abdominal (stomach area) pain. Less common side effects are nausea. vomiting, a full or bloated feeling in the stomach, constipation, diarrhea, black or bloody stools (bowel movements), gas, headache, a changed sense of taste, and bone, muscle, or joint pain.

Severe bone, joint, and/or muscle pain has been reported in patients taking, by mouth, bisphosphonate drugs that are used to treat osteoporosis (thin bones). However, such reports have been rare. This group of drugs includes FOSAMAX PLUS D. Most of the patients were postmenopausal women (women who had stopped having periods). Patients developed pain within one day to several months after starting the drug. Most patients experienced relief after stopping the drug. Patients who develop severe bone, joint, and/or muscle pain after starting FOSAMAX PLUS D should contact their

Transient flu-like symptoms (rarely with fever), typically at the start of treatment, have occurred.

In rare cases, patients taking FOSAMAX PLUS D may get itching or eye pain, or a rash that may be made worse by sunlight. Rarely, severe skin reactions may occur. Patients may get allergic reactions, such as hives or, in rare cases, swelling that can be of their face, lips, tongue, or throat, which may cause trouble in breathing or swallowing. Mouth ulcers (sores) may occur if the FOSAMAX PLUS D tablet is chewed or dissolved in the mouth.

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

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

What should I know about osteoporosis?

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

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause, and may also occur in men. In osteoporosis, bone is removed faster than it is formed, so overall bone mass is lost and bones become weaker. Therefore, keeping bone mass is important to keep your bones healthy. In both men and women, osteoporosis may also be caused by certain medicines called corticosteroids

At first, osteoporosis usually has no symptoms, but it can cause fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they can make you shorter. Eventually, your spine can curve and your body can become bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause bones to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of ability to move around

Who is at risk for osteoporosis?

Many things put people at risk of osteoporosis. The following people have a higher chance of getting osteoporosis:

- Women who are going through or who are past
- menopause Men who are elderly

- Are white (Caucasian) or oriental (Asian)
- Do not get enough calcium or vitamin D
- Take bone thinning medicines (like prednisone or other corticosteroids) for a long time

What should I know about vitamin D?

Vitamin D is an essential nutrient, required for calcium absorption and healthy bones. The main source is through exposure to summer sunlight, which makes vitamin D in our skin. Winter sunlight in most of the United States is too weak to produce vitamin D. Even in the summer, clothing or sun block can prevent enough sunlight from getting through. In addition, as people age, their skin becomes less able to make vitamin D. Very few foods are natural sources of vitamin D. Some foods, such as milk, some brands of orange juice and breakfast cereals are fortified with vitamin D.

FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol) Tablets

Too little vitamin D leads to low calcium absorption and low phosphate. These are minerals that make bones strong. Even if you are eating a diet rich in calcium or taking a calcium supplement, your body cannot absorb calcium properly unless you have enough vitamin D. Too little vitamin D may lead to bone loss and osteoporosis. Severe vitamin D deficiency may cause muscle weakness which can lead to falls, and greater risk of fracture.

What can I do to help treat osteoporosis?

that can cause fractures.

In addition to FOSAMAX PLUS D, your doctor may suggest one or more of the following lifestyle changes:

- Stop smoking. Smoking may increase your chance of getting osteoporosis.
- Reduce the use of alcohol. Too much alcohol may increase the chance of osteoporosis and injuries
- Exercise regularly. Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries, including fractures. Talk with your doctor before you begin
- any exercise program. • Eat a balanced diet. Having enough calcium in your diet is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements, such as calcium or additional vitamin D.

What are the ingredients in FOSAMAX PLUS D?

Active ingredients: alendronate sodium and cholecalciferol (vitamin D₃). FOSAMAX PLUS D provides a week's worth of vitamin D₃ (2800 IU). The Daily Value is 400 IU.

Inactive ingredients: cellulose, lactose, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hvdroxytoluene, modified food starch, and sodium aluminum silicate.

How do I store FOSAMAX PLUS D?

the reach of children.

to others.

- Store FOSAMAX PLUS D at 68 to 77°F (20 to 25°C) Protect from moisture and light. Store tablets in the
- original blister package or bottle and carton until time of use. • Safely discard FOSAMAX PLUS D that is out-of-date
- or no longer needed Keep all FOSAMAX PLUS D and all medicines out of

General information about using FOSAMAX PLUS D safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. This medicine was prescribed for your particular condition. Alendronate in FOSAMAX PLUS D acts specifically on your bones. Do not use it for another condition or give it

This leaflet is a summary of information about FOSAMAX PLUS D. If you have any questions or concerns about FOSAMAX PLUS D or osteoporosis, talk to your doctor, pharmacist, or other health care provider. You can ask your doctor or pharmacist for information about FOSAMAX PLUS D written for health care providers. For more information, call 1-877-408-4699 (toll-free) or visit the following website: www.fosamaxplusd.com.

Manufactured for:

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(mobility).

Do not exercise Smoke Drink alcohol often

Are thin • Have family member with osteoporosis

Rx only

Madrid, Spain