

Cervical Polyps Called Less Risky Post Menopause

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NASHVILLE, TENN. — Cervical polyps in postmenopausal women might pose lower risk of malignancy, dysplasia, and atypia than those found in premenopausal women, according to a study presented at the annual meeting of the North American Menopause Society.

Dr. Peter F. Schnatz of the University of Connecticut, Farmington, and his col-

leagues searched a pathology database for cases of endocervical polyp excision recorded over a 5-year period. A total of 1,993 polyps were found. Mean patient age was 48 years (range 16-95 years), and most came from private ob.gyn. practices.

For women younger than 50 years, the investigators found an incidence for malignancy, dysplasia, and atypia of 0.18%, 0.70%, and 2.1%, respectively. For women at least 50 years old, the incidence rates were 0.12%, 0.24%, and 1.2%. Although

the differences between the two age groups for each individual prevalence did not reach statistical significance, the overall difference in the prevalence of any of the three abnormalities (3% for younger women vs. 1.5% in the older group) did reach significance ($P = .03$). There were two malignancies reported, with one in each age group.

Dr. Schnatz said that the findings of low prevalence of abnormalities for cervical polyps should reassure patients. Moreover,

“routine removal is reasonable, given the high likelihood of symptoms, the small possibility of malignancy or transformation to malignancy, and the potential marker for uterine or extrauterine disease, as well as the ease of removal,” he said.

He noted that polyps are the most common benign neoplastic growth in the cervix; are found in roughly 5% of women, most commonly in multiparous women older than 20 years; and are rare before menarche. ■

FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol) Tablets BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, General)

WARNINGS

FOSAMAX PLUS D, 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, occasionally with bleeding and 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 D 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 D 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 supervision. 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.

PRECAUTIONS

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid 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. Presumably due to the effects of alendronate on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur. *Cholecalciferol*: FOSAMAX PLUS D alone should not be used to treat vitamin D deficiency (commonly defined as 25-hydroxyvitamin D level below 9 ng/mL). 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. Vitamin D₃ supplementation may worsen hypercalcemia and/or hypercalciuria when administered to patients with diseases associated with unregulated over-production 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 sodium). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months 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 bisphosphonate. In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups. *Dental*: Osteonecrosis 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. *General*: 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 renewed. 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 patients 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 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™ (alendronate sodium/cholecalciferol) 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® (alendronate sodium) was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, Clinical Studies, Concomitant use with estrogen/hormone replacement therapy (HRT) and ADVERSE REACTIONS, Clinical Studies, Concomitant use with estrogen/hormone replacement therapy). *Calcium Supplements/Antacids*. It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate. Therefore, patients must wait at least one-half hour after taking FOSAMAX PLUS D before taking any other oral medications. *Aspirin*. In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products. *Nonsteroidal Anti-inflammatory Drugs (NSAIDs)*. FOSAMAX 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 gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX 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 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/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 1 times a 40 mg human daily dose based on surface area, mg/m². The relevance of this finding to humans is unknown. Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results. Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m²). *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, 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 in vertebral (cervical, thoracic, and lumbar), skull, and sternal 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 area, mg/m²). 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 parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/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 in delivery; calcium supplementation IV prevented maternal, but not fetal deaths. Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied. *Cholecalciferol—*No data are available for cholecalciferol (vitamin D₃). Administration of high doses (≥10,000 IU/every other day) of ergocalciferol (vitamin D₂) to pregnant rabbits, resulted in abortions and an increased incidence of fetal aortic stenosis. Administration of vitamin D₃ (40,000 IU/day) to pregnant rats resulted in neonatal death, decreased fetal weight, and impaired osteogene-

sis of long bones postnatally. There are no studies in pregnant women. FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol) should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers. 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.

Pediatric Use. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use. Of the patients receiving FOSAMAX® (alendronate sodium) in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, 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. *Treatment of osteoporosis—Postmenopausal women.* In two identically designed, 2-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX (10 mg/day for 3 years, n=196) or placebo (n=397) for the United States/Multinational Studies were *Gastrointestinal*: abdominal pain 6.8% and 4.8%, nausea 3.6% and 4.0%, dyspepsia 3.6% and 3.5%, constipation 3.1% and 1.8%, diarrhea 3.1% and 1.8%, flatulence 2.6% and 0.5%, acid regurgitation 2.0% and 4.3%, esophageal ulcer 1.5% and 0.0%, vomiting 1.0% and 1.5%, dysphagia 1.0% and 0.0%, abdominal distention 1.0% and 0.8%, gastritis 0.5% and 1.3%. *Musculoskeletal*: musculoskeletal (bone, muscle, joint) pain 4.1% and 2.5%, muscle cramp 0.0% and 0.1%. *Nervous System/Psychiatric*: headache 2.6% and 1.5%, dizziness 0.0% and 0.1%, and *Special Senses*: taste perversion 0.5% and 1.0%, respectively. For the Fracture Intervention Trial, with either FOSAMAX (5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years, n=3236) or placebo (n=3223), corresponding values were *Gastrointestinal*: abdominal pain 1.5% and 1.5%, nausea 1.1% and 1.5%, dyspepsia 1.1% and 1.2%, constipation 0.0% and 0.2%, diarrhea 0.6% and 0.3%, flatulence 0.2% and 0.3%, acid regurgitation 1.1% and 0.9%, esophageal ulcer 0.1% and 0.1%, vomiting 0.2% and 0.3%, dysphagia 0.1% and 0.1%, abdominal distention 0.0% and 0.0%, gastritis 0.6% and 0.7%. *Musculoskeletal*: musculoskeletal (bone, muscle, joint) pain 0.4% and 0.3%, muscle cramp 0.2% and 0.1%. *Nervous System/Psychiatric*: headache 0.2% and 0.2%, dizziness 0.0% and 0.1%; and *Special Senses*: taste perversion 0.1% and 0.0%, respectively. Rarely, rash and erythema have occurred. One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered. The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study. In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group were *Gastrointestinal*: abdominal pain 3.7% and 3.0%, dyspepsia 2.7% and 2.5%, acid regurgitation 1.9% and 2.4%, nausea 1.9% and 2.4%, abdominal distention 1.0% and 1.4%, constipation 0.8% and 1.6%, flatulence 0.4% and 1.6%, gastritis 0.2% and 1.1%, gastric ulcer 0.0% and 3.2%; and *Musculoskeletal*: musculoskeletal (bone, muscle, joint) pain 2.9% and 3.2%, and muscle cramp 0.2% and 1.1%, respectively. *Men*. In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day (n=146) vs. 10.5% for placebo (n=95), and 6.4% for once weekly FOSAMAX 70 mg (n=109) vs. 8.6% for placebo (n=58). The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo for the two-year study were *Gastrointestinal*: acid regurgitation 4.1% and 3.2%, flatulence 4.1% and 1.1%, gastroesophageal reflux disease 0.7% and 3.2%, dyspepsia 3.4% and 0.0%, diarrhea 1.4% and 1.1%, abdominal pain 2.1% and 1.1%, and nausea 2.1% and 0.0%, respectively; for the one-year study, the adverse experiences were *Gastrointestinal*: acid regurgitation 0.0% and 0.0%, flatulence 0.0% and 0.0%, gastroesophageal reflux disease 2.8% and 0.0%, dyspepsia 2.8% and 1.7%, diarrhea 2.8% and 0.0%, abdominal pain 0.9% and 3.4%, and nausea 0.0% and 0.0%, respectively. *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. *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, placebo-controlled studies involving over 1,200 patients randomized to receive

FOSAMAX® (alendronate sodium) for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day (n=642) and placebo (n=648) 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 (n=362) and FOSAMAX 5 mg daily (n=361) were similar. The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with FOSAMAX 5 mg/day or placebo for the two- or three-year studies were *Gastrointestinal*: dyspepsia 1.9% and 1.4%, abdominal pain 1.7% and 3.4%, acid regurgitation 1.4% and 2.5%, nausea 1.4% and 1.4%, diarrhea 1.1% and 1.7%, constipation 0.9% and 0.5%, abdominal distention 0.2% and 0.3%; and *Musculoskeletal*: musculoskeletal (bone, muscle or joint) pain 0.8% and 0.9%, respectively. For the one-year study with FOSAMAX 5 mg/day and once weekly FOSAMAX 35 mg, corresponding values were *Gastrointestinal*: dyspepsia 2.2% and 1.7%, abdominal pain 4.2% and 2.2%, acid regurgitation 4.2% and 4.7%, nausea 2.5% and 1.4%, diarrhea 1.1% and 0.6%, constipation 1.7% and 0.3%, abdominal distention 1.4% and 1.1%; and *Musculoskeletal*: musculoskeletal (bone, muscle or joint) pain 1.9% and 2.2%, respectively. *Treatment of glucocorticoid-induced osteoporosis.* In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 mg/day (n=161) or FOSAMAX 10 mg/day (n=157) or placebo (n=159) were *Gastrointestinal*: abdominal pain 1.9%, 3.2%, and 0.0%; acid regurgitation 1.9%, 2.5%, and 1.3%; constipation 0.6%, 1.3%, and 0.0%; melena 0.0%, 1.3%, and 0.0%; nausea 1.2%, 0.6%, and 0.6%; diarrhea 0.0%, 0.0%, and 1.3%; and *Nervous System/Psychiatric*: headache 0.0%, 0.6%, and 1.3%, respectively. The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year. *Paget's disease of bone.* In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment. Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo. *Laboratory Test Findings—*In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups. *FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol)*: In a fifteen week double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of FOSAMAX PLUS D was similar to that of FOSAMAX once weekly 70 mg.

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. Transient symptoms of 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*: 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). Localized osteonecrosis of 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); joint swelling. *Nervous system*: dizziness and vertigo. *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.

For more detailed information, please read the Prescribing Information.

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