SG-OG0217-MF-012023

PRODUCT CIRCULAR

Tablets
FOSAMAX®
(alendronate sodium)

I. THERAPEUTIC CLASS

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

II. INDICATIONS

FOSAMAX is indicated for the treatment of osteoporosis in postmenopausal women.

For the treatment of osteoporosis, FOSAMAX reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures).

FOSAMAX is indicated for the treatment of osteoporosis in men.

The optimal duration of use of bisphosphonates for the treatment of osteoporosis has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

III. DOSAGE AND ADMINISTRATION

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

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, FOSAMAX should only be swallowed upon arising for the day with a full glass of water and patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see PRECAUTIONS).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women and in men
The recommended dosage is one 70 mg tablet once weekly.

IV. CLINICAL PHARMACOLOGY

Pharmacokinetic properties

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability in men (0.6%) was similar to that in women. Bioavailability was decreased similarly (by

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

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

The oral bioavailability in children was similar to that observed in adults (see PEDIATRIC USE).

Distribution

Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low for analytical detection (< 5 ng/mL). Protein binding in human plasma is approximately 78%.

Biotransformation

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

Elimination

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other drugs by those systems in humans.

Characteristics in patients

Preclinical studies show that the drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative IV doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Pharmacodynamic properties

Alendronate is an aminobisphosphonate that, in animal studies, localizes preferentially to sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation. Since bone formation and bone resorption are coupled, bone formation is also reduced, but less so than resorption, leading to progressive gains in bone mass. During exposure to alendronate, normal bone is formed that incorporates alendronate into its matrix where it is pharmacologically inactive.

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in growing rats. The lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data indicate that, unlike etidronate, alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass and a consequent increased risk of fracture, usually of the spine, hip, and wrist. It occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation, leading to loss of bone mass.

Daily oral doses of alendronate in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as hydroxyproline, deoxypyridinoline, and cross-linked N-telopeptides of type I collagen). These biochemical changes returned toward baseline values as early as three weeks following the discontinuation of alendronate despite the long retention of alendronate in the skeleton.

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received FOSAMAX 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies, FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30%, to reach a plateau after 6 to 12 months. In osteoporosis prevention studies, FOSAMAX 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with FOSAMAX once weekly 70 mg for the treatment of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

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

studies with FOSAMAX once weekly 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX but also a decrease in renal phosphate reabsorption.

Osteoporosis in men

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

Treatment of osteoporosis

Postmenopausal women

Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postmenopausal women with osteoporosis was demonstrated in four clinical studies of two or three years' duration. In patients receiving FOSAMAX 10 mg/day, the mean increases in bone mineral density (BMD) of the lumbar spine, femoral neck, and trochanter at three years for the pooled data from the two largest studies of virtually identical design were 8.82%, 5.90%, and 7.81%, respectively, relative to placebo.

These increases were highly significant relative both to baseline and placebo at each measurement site in each study. Total body BMD also increased significantly in both studies, indicating that the increases in bone mass of the lumbar spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the entire three years of treatment. In the two-year extension of these studies, treatment with FOSAMAX 10 mg/day resulted in continued

increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. Thus, FOSAMAX reverses the progression of osteoporosis. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, renal function and use with a wide range of common medications.

In patients with postmenopausal osteoporosis treated with FOSAMAX 10 mg/day for one or two years the effects of treatment withdrawal were assessed. Following discontinuation, bone turnover gradually returned toward pretreatment levels, and BMD no longer increased although accelerated bone loss was not observed. These data indicate that treatment with FOSAMAX must be continuous to produce progressive increases in bone mass.

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

Effect on fracture incidence

Analysis of the data pooled across doses at three years from the two large studies of postmenopausal women with osteoporosis revealed a statistically significant and clinically meaningful 48% reduction in the proportion of patients treated with FOSAMAX experiencing one or more vertebral fractures (3.2%) relative to those treated with placebo (6.2%). Furthermore, of patients who sustained any vertebral fracture, those treated with FOSAMAX experienced less height loss (5.9 mm vs. 23.3 mm) due to a reduction in both the number and severity of fractures.

Additionally, analysis of the data pooled across doses of ≥ 2.5 mg from five studies of two or three years' duration including the two large studies revealed a significant 29% reduction in non-vertebral fracture incidence (FOSAMAX 9.0% vs. placebo 12.6%).

The Fracture Intervention Trial (FIT) consisted of two placebo-controlled studies in postmenopausal women: the Three-Year Study of 2027 patients who had at least one baseline vertebral (compression) fracture and the Four-Year Study of 4432 patients with low bone mass but without a baseline vertebral fracture, 69% of whom had osteoporosis as defined by a baseline femoral neck BMD at least 2 standard deviations below the mean for young adult women.

Combined results of patients with osteoporosis from both studies demonstrated statistically significant and clinically meaningful reductions in the incidence of: ≥ 1 vertebral fracture (FOSAMAX 4.7% vs. placebo 8.9%; a 48% reduction), ≥ 2 vertebral fractures (0.3% vs. 2.3%; an 88% reduction), ≥ 1 painful vertebral fracture (1.5% vs. 3.0%; a 50% reduction), any painful fracture (13.2% vs. 16.9%; a 24% reduction), and hip fracture (1.1% vs. 1.7%; a 40% reduction). A non-significant 18% reduction was seen in wrist (forearm) fracture. In all FIT patients, including those without osteoporosis, the reductions in the incidence of the following fractures were: ≥ 1 vertebral, 46%; ≥ 2 vertebral, 84%; painful vertebral, 47%; any painful, 18%; hip, 36%; and wrist (forearm), 6%.

The Three-Year Study demonstrated statistically significant reductions in the incidence of: ≥ 1 new vertebral fracture (FOSAMAX 7.9% vs. placebo 15.0%; a 47% reduction), ≥ 2 new vertebral fractures (0.5% vs. 4.9%; a 90% reduction), ≥ 1 painful vertebral fracture (2.3% vs. 5.0%; a 54% reduction), hip fracture (1.1% vs. 2.2%; a 51% reduction), and wrist (forearm) fracture (2.2% vs. 4.1%; a 48% reduction). Furthermore, in this population of patients with baseline vertebral fracture treatment with FOSAMAX significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Four-Year Study, analysis of the osteoporotic women revealed statistically significant reductions in the incidence of **≥** 1 painful fracture (FOSAMAX 12.9% vs. placebo 16.2%; a 22% reduction) and **≥** 1 vertebral fracture (2.5% vs. 4.8%; a 48% reduction). The 29% reduction in the incidence of hip fracture (FOSAMAX 1.0% vs. placebo 1.4%) did not reach statistical significance in this study. In all patients (including those without osteoporosis), the incidence of **≥** 1 painful fracture was reduced by 14% and ≥ 1 vertebral fracture by 44%. The incidence of wrist fracture was similar in osteoporotic patients treated with FOSAMAX

(3.9%) or placebo (3.8%); the incidence of wrist fracture was also similar in all patients treated with FOSAMAX (3.7%) or placebo (3.2%).

Overall, these results demonstrate the consistent efficacy of FOSAMAX to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with the greatest morbidity.

Bone histology

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

Men

The efficacy of FOSAMAX 10 mg once daily in men (ages 31 to 87; mean, 63) with osteoporosis was demonstrated in a two-year study. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6% (all $p \leq 0.001$). FOSAMAX was effective regardless of age, race, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with much larger studies in postmenopausal women, in these men, FOSAMAX 10 mg/day reduced the incidence of new vertebral fracture (assessed by quantitative radiography) relative to placebo (0.8% vs. 7.1%, respectively; p=0.017) and, correspondingly, also reduced height loss (– 0.6 vs. – 2.4 mm; respectively; p=0.022).

Concomitant use with estrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with FOSAMAX 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year study of

hysterectomized postmenopausal osteoporotic women. At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or FOSAMAX alone (both 6.0%).

The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year study in postmenopausal osteoporotic women. The addition of FOSAMAX 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

V. 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)

VI. PRECAUTIONS

FOSAMAX, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking FOSAMAX and/or who fail to swallow it with a full glass of water, and/or who continue to take FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION).

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

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

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow FOSAMAX with a full glass of water and not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

Localized osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported rarely with oral bisphosphonates (see SIDE EFFECTS, *Post-Marketing Experience*). Most reported cases of bisphosphonate-associated ONJ have been in cancer patients treated with intravenous bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors), poor

oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection) and smoking. Patients who develop ONJ should receive appropriate care by an oral surgeon and discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment. Dental surgery may exacerbate the condition.

For patients requiring dental procedures (e.g., tooth extraction, dental implants), there are no data available to suggest whether discontinuation of biphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan, including bisphosphonate treatment, of each patient based on individual benefit/risk assessment.

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

Low-energy fractures of the subtrochanteric and proximal femoral shaft and other bones have been reported in a small number of long-term (time to onset in the majority of cases ranged from 18 months to 10 years) bisphosphonate-treated patients. Some were stress fractures (some of which were reported as insufficiency fractures) occurring in the absence of apparent trauma or induced by mild external force. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. Approximately one third of the reported femur fractures were bilateral; therefore, the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. Stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of

bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

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

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

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

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other 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.

VII. PREGNANCY

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

VIII. NURSING MOTHERS

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

IX. PEDIATRIC USE

FOSAMAX is not indicated for use in children.

X. USE IN THE ELDERLY

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

XI. DRUG INTERACTIONS

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

No other drug interactions of clinical significance are anticipated.

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of FOSAMAX and HRT resulted in greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments (see SIDE EFFECTS, *Clinical Studies*, *Concomitant use with estrogen/hormone replacement therapy*).

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

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

XII. SIDE EFFECTS

Clinical Studies

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

Treatment of osteoporosis

Postmenopausal women

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

Rarely, rash and erythema have occurred.

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

In the two-year extension (treatment years 4 and 5) of the above studies, the overall safety profile of FOSAMAX 10 mg/day was similar to that observed during the three-year placebo-controlled period. Of the 151 patients who received continued treatment 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 FOSAMAX once weekly 70 mg (n = 519) and FOSAMAX 10 mg daily (n = 370) were similar. The following adverse experiences were reported by the investigators as possibly, probably, or definitely drug related in ≥ 1% of patients in either treatment group: abdominal pain (FOSAMAX once weekly 70 mg, 3.7%; FOSAMAX 10 mg daily, 3.0%), musculoskeletal

(bone, muscle or joint) pain (2.9%, 3.2%), dyspepsia (2.7%, 2.2%), acid regurgitation (1.9%, 2.4%), nausea (1.9%, 2.4%), abdominal distension (1.0%, 1.4%), constipation (0.8%, 1.6%), flatulence (0.4%, 1.6%), muscle cramp (0.2%, 1.1%), gastritis (0.2%, 1.1%), and gastric ulcer (0.0%, 1.1%).

Men

In two, placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day [n = 146] and a one-year study of FOSAMAX once weekly 70 mg [n = 109]), the safety profile of FOSAMAX was generally similar to that seen in postmenopausal women.

Other studies in men and women

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

In an additional one-year study in men and women (n = 335; mean age: 50) the overall safety and tolerability profiles of FOSAMAX once weekly 70 mg were similar to that of placebo and no difference was seen between men and women.

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.

Post-Marketing Experience

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

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

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

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

Nervous system: dizziness, vertigo, dysgeusia.

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

Special senses: rarely uveitis, scleritis, or episcleritis. Cholesteatoma of the external auditory canal (focal osteonecrosis) has been reported rarely.

XIIa. Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking FOSAMAX versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg P/dL (0.65 mM) were similar in both treatment groups.

XIII. OVERDOSAGE

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage.

Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

XIV. AVAILABILITY

FOSAMAX 70 mg tablets each containing 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid, is supplied in packs of 4 tablets.

XV. STORAGE

Store FOSAMAX below 30ºC.

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ORGANON