PRODUCT CIRCULAR

Tablets
FOSAMAX®† Once Weekly 70 mg
(alendronate sodium, MSD)

I. THERAPEUTIC CLASS

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

II. INDICATIONS

- FOSAMAX is indicated in postmenopausal women for the treatment of osteoporosis to prevent fractures, including those of the hip and spine (vertebral compression fractures).
- FOSAMAX is indicated for the treatment of osteoporosis in men to prevent fractures.

III. DOSAGE AND ADMINISTRATION

Treatment of osteoporosis in postmenopausal women and in men,

The recommended dosage is one 70 mg tablet once weekly.

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.

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IV. 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)

V. 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. Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection) and smoking. Patients who develop ONJ should receive appropriate care by an oral surgeon and discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment. Dental surgery may exacerbate the condition.

For patients requiring invasive dental surgery (e.g., tooth extraction, dental implants), clinical judgment of the treating physician and/or oral surgeon should guide the management plan, including bisphosphonate treatment, of each patient based on individual benefit/risk assessment..

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 have been reported in a small number of long-term (usually longer than three years) bisphosphonate-treated patients. Some were stress fractures (some of which were reported as insufficiency fractures) occurring in the absence of apparent trauma. 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 these 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.

VI. PREGNANCY

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

VII. NURSING MOTHERS

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

VIII. PEDIATRIC USE

FOSAMAX is not indicated for use in children.

IX. USE IN THE ELDERLY

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

X. 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).

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.

XI. 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 $\geq$ 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 $\geq$ 1% of patients treated with FOSAMAX 10 mg/day and at a greater incidence than in patients treated with placebo: musculoskeletal (bone, muscle or joint) pain (FOSAMAX, 4.1% vs. placebo, 2.5%), constipation (3.1%, 1.8%), diarrhea (3.1%, 1.8%), flatulence (2.6%, 0.5%), and headache (2.6%, 1.5%).

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

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of FOSAMAX once weekly 70 mg (n = 519) and FOSAMAX 10 mg daily (n = 370) were similar. The following adverse experiences were reported by the investigators as possibly, probably, or definitely drug related in $\geq$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 10mg/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 femoral shaft fracture (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.

XIa. 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.

XII. 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.

XIII. AVAILABILITY

Fosamax® (alendronate sodium, MSD) once weekly 70mg tablets are supplied in 4 tablets pack. Each tablet contains alendronate sodium equivalent to 70 mg alendronic acid.