SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

FOSAMAX® Once Weekly 70 mg Tablets

COMPOSITION

Each FOSAMAX Once Weekly 70 mg Tablet contains alendronate monosodium salt trihydrate (Merck Sharp & Dohme) equivalent to 70 mg of free acid.

PHARMACOLOGICAL CLASSIFICATION

A.3.2. Connective tissue medicines, non-hormonal preparations.

PHARMACOLOGICAL ACTION

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

MECHANISM OF ACTION

In animal studies alendronate localises 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.

PHARMACOKINETICS

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0,57 % for the 70 mg tablet when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability after oral administration in men (0,6 %) was very similar to that in women.

Bioavailability was decreased similarly (by approximately 40 %) whether alendronate was administered one or one-half hour before a standardised breakfast. In two large controlled studies that demonstrated efficacy in post menopausal women with osteoporosis, alendronate sodium 10 mg/day was administered at least one-half hour before the first food or beverage of the day. Therefore, bioavailability and therapeutic response should be similar to that seen in these studies if alendronate sodium is taken as directed (see **DOSAGE AND DIRECTIONS FOR USE**).

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

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 (less than 5 ng/ml). Protein binding in human plasma is approximately 78 %.

Metabolism

There is no evidence that alendronate is metabolised 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 faeces. 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.

PHARMACODYNAMICS

Osteoporosis in post menopausal women

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in post menopausal 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 therapy with alendronate and did not differ from placebo after 7 months despite the long retention of alendronate in the skeleton.

Long-term treatment of osteoporosis with alendronate sodium 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50 and 70 % respectively to reach levels similar to those seen in healthy premenopausal women. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with alendronate sodium. In osteoporosis treatment studies, alendronate sodium 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 – 30 % to a plateau after 6 to 12 months. Similar reductions in the rate of bone

turnover were observed in post menopausal women during a one-year study with alendronate sodium once weekly 70 mg for the treatment of osteoporosis. Alendronate thus reduces the elevated rate of bone turnover observed in post menopausal women to approximate more closely that in premenopausal women.

As a result of inhibition of bone resorption asymptomatic reductions from baseline in serum calcium (approximately 2 %) and phosphate (approximately 4 to 6 %) were evident the first month after the initiation of alendronate sodium 10 mg. No further decreases in serum calcium were observed for the five year duration of the treatment; however, serum phosphate returned towards prestudy levels during years 3 through 5. In a one-year study with alendronate sodium once weekly 70 mg, similar reductions were observed at 6 and 12 months.

Osteoporosis in men

Treatment of men with osteoporosis with alendronate sodium 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 alendronate sodium once weekly 70 mg.

INDICATIONS

FOSAMAX Once Weekly 70 mg is indicated

- for the treatment of post menopausal osteoporosis to reduce the risk of fractures, including those of the hip and spine (vertebral compression fractures)
- for the treatment of primary hypogonadal osteoporosis in men and to reduce the risk of vertebral fractures.

CONTRA-INDICATIONS

Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.

Inability to stand or sit upright for at least 30 minutes.

Hypersensitivity to any component of this product.

Hypocalcaemia (see **SIDE EFFECTS AND SPECIAL PRECAUTIONS, SPECIAL PRECAUTIONS**).

Severe renal insufficiency (creatinine clearance less than 35 ml/min).

Paediatric age group.

WARNINGS

None

INTERACTIONS

If taken concomitantly it is likely that calcium supplements, antacids, and other oral medications will interfere with absorption of FOSAMAX Once Weekly 70 mg. Therefore, patients must wait at least one-half hour after taking FOSAMAX Once Weekly 70 mg before taking any other oral medication.

No other interactions of clinical significance are anticipated.

Concomitant use of HRT (oestrogen with or without progestin) and FOSAMAX Once Weekly 70 mg was assessed in two clinical studies of one or two years' duration in post menopausal osteoporotic women. Combined use of FOSAMAX Once Weekly 70 mg 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.

Specific interaction studies were not performed. FOSAMAX Once Weekly 70 mg was used in osteoporosis studies in men and post menopausal 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.

PREGNANCY AND LACTATION

FOSAMAX Once Weekly 70 mg has not been studied in pregnant or breast feeding women and should not be given to them.

DOSAGE AND DIRECTIONS FOR USE

Treatment of post menopausal osteoporosis:

The recommended dosage is one 70 mg tablet once weekly.

Treatment of primary hypogonadal osteoporosis in men:

The recommended dosage is one 70 mg tablet once weekly.

FOSAMAX Once Weekly 70 mg 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 Once Weekly 70 mg (see **INTERACTIONS**).

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, FOSAMAX Once Weekly 70 mg should only be swallowed upon arising for the day with a **full** glass of

water. Patients should not lie down for at least 30 minutes **and** until after their first food of the day. FOSAMAX Once Weekly 70 mg should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of oesophageal adverse experiences (see **SIDE EFFECTS AND SPECIAL PRECAUTIONS, SPECIAL PRECAUTIONS**).

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see **SIDE EFFECTS AND SPECIAL PRECAUTIONS, SPECIAL 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). (see **CONTRA-INDICATIONS**)

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

The following adverse experiences have been reported during clinical studies with FOSAMAX Once Weekly 70 mg.

[Common (greater than or equal to 1/100, less than 1/10), Uncommon (greater than or equal to 1/1000, less than 1/100), Rare (greater than or equal to 1/10 000, less than 1/1000), Very rare (less than 1/10 000 including isolated cases)]

Nervous system disorders:

Common: headache

Gastro-intestinal disorders:

Common: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*****, dysphagia*****, abdominal distension, acid regurgitation

Uncommon: nausea, gastritis, melaena

Rare: oropharyngeal ulceration*****, gastric or duodenal ulcers, some severe and with complications.

*****(See **SPECIAL PRECAUTIONS and DOSAGE AND DIRECTIONS FOR USE**)

Skin and subcutaneous tissue disorders:

Uncommon: rash, erythema

Musculoskeletal, connective tissue and bone disorders:

Common: musculoskeletal (bone, muscle or joint) pain

LABORATORY TEST FINDINGS

In double-blind multicentre, controlled studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed more frequently in patients taking FOSAMAX Once Weekly 70 mg than in those taking placebo.

Post-Marketing Experience:

The following adverse experiences have been reported during post-marketing use of FOSAMAX Once Weekly 70 mg.

Immune system disorders:

Rare: hypersensitivity reactions including urticaria and angio-oedema

Metabolism and nutrition disorders:

Rare: Symptomatic hypocalcaemia, generally in association with predisposing conditions. (see **SPECIAL PRECAUTIONS**)

Nervous system disorders:

Rare: dizziness, vertigo, dysgeusia

Eye disorders:

Rare: uveitis, scleritis, episcleritis

Gastro-intestinal disorders:

Uncommon: vomiting, oesophagitis*****, oesophageal erosions*****

Rare: oesophageal stricture*****.

Very rare and isolated cases: Isolated cases of oesophageal perforations have been reported.

*****(See **SPECIAL PRECAUTIONS** and **DOSAGE AND DIRECTIONS FOR USE**)

Muscoloskeletal, connective tissue and bone disorders:

Rare: severe and/or incapacitating bone, joint, and/or muscle pain, (see **SPECIAL PRECAUTIONS**); joint swelling, low-energy femoral shaft fracture (see **SPECIAL PRECAUTIONS**). Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, with delayed healing has been reported rarely (see **SPECIAL PRECAUTIONS**)

Skin and subcutaneous tissue disorders:

Uncommon: pruritis

Rare: rash with photosensitivity, alopecia

Very rare and isolated cases: Isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

General disorders and administration site conditions:

Rare: transient symptoms as in an acute-phase response (myalgia, malaise, asthenia and rarely, fever) have been reported with alendronate, typically in association with initiation of treatment.

Peripheral oedema

SPECIAL PRECAUTIONS

FOSAMAX Once Weekly 70 mg may cause local irritation of the upper gastro-intestinal mucosa.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, infrequently followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with FOSAMAX Once Weekly 70 mg. In some cases these have been severe and required hospitalisation. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue FOSAMAX Once Weekly 70 mg and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who lie down after taking FOSAMAX Once Weekly 70 mg and/or who fail to swallow it with a full glass of water, and/or who continue to take FOSAMAX Once Weekly 70 mg after developing symptoms suggestive of oesophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see **DOSAGE AND DIRECTIONS FOR USE**)

While no increased risk was observed in extensive clinical trials, there have been occasional reports of gastric and duodenal ulcers, some severe and with complications.

Because of possible irritant effects of FOSAMAX Once Weekly 70 mg on the upper gastro-intestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX Once Weekly 70 mg is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal diseases (including known Barrett's oesophagus), gastritis, duodonitis, or ulcers.

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation patients should be instructed to swallow FOSAMAX Once Weekly 70 mg with a **full** glass of water. Patients should be instructed 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 Once Weekly 70 mg at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems. Patients should be instructed that if they develop symptoms of oesophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX Once Weekly 70 mg and consult their physician.

Localised osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection with delayed healing, has been reported with oral bisphosphonates such as FOSAMAX Once Weekly 70 mg (see **SIDE EFFECTS**). 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. pre-existing dental disease, anaemia, 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 judgement 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 such as FOSAMAX Once Weekly 70 mg. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see **SIDE EFFECTS**). 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 70 mg, 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.

Causes of osteoporosis other than oestrogen deficiency and ageing should be considered.

Hypocalcaemia must be corrected before initiating therapy with FOSAMAX Once Weekly 70 mg (see **CONTRA-INDICATIONS**). 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 hypocalcaemia should be monitored during therapy with FOSAMAX Once Weekly 70 mg.

Use in the Elderly

In clinical studies, there was no age-related difference in the efficacy or safety profiles of FOSAMAX Once Weekly 70 mg.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with FOSAMAX Once Weekly 70 mg may affect some patient's ability to drive or operate machinery. Individual responses to FOSAMAX Once Weekly 70 mg may vary (see **SIDE EFFECTS**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No specific information is available on the treatment of overdosage with FOSAMAX Once Weekly 70 mg. Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

IDENTIFICATION

White, oval tablet with the outline of a bone image on one side and the code number "31" on the other side.

PRESENTATION

FOSAMAX Once Weekly 70 mg Tablets are supplied in aluminium/aluminium blisters strips in packs containing 2, 4 or 12 tablets.
Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store in a dry place below 25 °C.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

35/3.2/0371

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