

## EUROPEAN UNION CORE SAFETY PROFILE

### FOSAMAX (Alendronic acid as alendronate sodium trihydrate)

#### 4.2 Posology and method of administration

The recommended dosage is one 70 mg tablet once weekly. The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of ‘Fosamax’ on an individual patient basis, particularly after 5 or more years of use.

*To permit adequate absorption of alendronate:*

‘Fosamax’ must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see section 4.5 ~~‘Interaction with other medicinal products and other forms of interaction’~~).

*To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see section 4.4 ~~‘Special warnings and precautions for use’~~):*

- ‘Fosamax’ should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
- Patients should only swallow ‘Fosamax’ whole. Patients should not crush or chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
- Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.
- Patients should not lie down for at least 30 minutes after taking ‘Fosamax’.
- ‘Fosamax’ should not be taken at bedtime or before arising for the day.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see section 4.4 ~~‘Special warnings and precautions for use’~~).

*Use in the elderly:* In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate. Therefore no dosage adjustment is necessary for the elderly.

*Use in renal impairment:* No dosage adjustment is necessary for patients with GFR greater than 35 ml/min. Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

*Use in children (under 18 years):* Alendronate has been studied in a small number of patients with osteogenesis imperfecta under 18 years of age. Results are insufficient to support its use in children.

'Fosamax' Once Weekly 70 mg has not been investigated in the treatment of glucocorticoid-induced osteoporosis.

#### **4.3 Contraindications**

- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to alendronate or to any of the excipients.
- Hypocalcaemia.
- See also section 4.4.

#### **4.4 Special warnings and precautions for use**

Alendronate can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty (see section 4.3 'Contraindications'). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient (see section 4.2 'Posology and method of administration'). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

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.

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. The following risk factors should be considered when evaluating an individual's risk of developing osteonecrosis of the jaw:

- potency of the bisphosphonate (highest for zoledronic acid), route of administration (see above) and cumulative dose
- cancer, chemotherapy, radiotherapy, corticosteroids, ~~smoking~~
- a history of dental disease, poor oral hygiene, periodontal disease, ~~smoking~~invasive dental procedures and poorly fitting dentures.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with oral bisphosphonates in patients with poor dental status.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, 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 of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

During bisphosphonate treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.

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 'section 4.8 Undesirable 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. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Stress fractures (also known as insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long term with alendronic acid (time to onset in the majority of cases ranged from 18 months to 10 years). The fractures occurred after minimal or no trauma and some patients experienced thigh pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures were often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures was also reported.

Discontinuation of bisphosphonate therapy in patients with stress fracture is advisable pending evaluation of the patient, based on an individual benefit risk assessment.

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique, fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported.

Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

In post-marketing experience, there have been rare reports of severe skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis.

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.

Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see section 4.2) ~~'Posology and method of administration'~~.

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

Hypocalcaemia must be corrected before initiating therapy with alendronate (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with 'Fosamax'.

Due to the positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur especially in patients taking glucocorticoids in whom calcium absorption may be decreased. These are usually small and asymptomatic. However, there have been rare reports of symptomatic hypocalcemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption).

Ensuring adequate calcium and vitamin D intake is particularly important in patients receiving glucocorticoids.

#### *Excipients*

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### **4.5 Interaction with other medicinal products and other forms of interaction**

If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking alendronate before taking any other oral medicinal product (see sections 4.2 ~~'Posology and method of administration'~~ and and 5.2 ~~'Pharmacokinetic properties'~~).

No other interactions with medicinal products of clinical significance are anticipated. A number of patients in the clinical trials received oestrogen (intravaginal, transdermal, or oral) while taking alendronate. No adverse experiences attributable to their concomitant use were identified.

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

Although specific interaction studies were not performed, in clinical studies alendronate was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions.

#### 4.6 Pregnancy and lactation

##### *Use during pregnancy*

Alendronate should not be used during pregnancy. There are no adequate data from the use of alendronate in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, or postnatal development. Alendronate given during pregnancy in rats caused dystocia related to hypocalcemia (see section 5.3 ~~‘Preclinical safety data’~~).

##### *Use during lactation*

It is not known whether alendronate is excreted into human breast milk. Alendronate should not be used by breast-feeding women.

#### 4.7 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’ may affect some patients' ability to drive or operate machinery. Individual responses to ‘Fosamax’ may vary. ~~(See (see section 4.8-))~~

#### 4.8 Undesirable effects

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of ‘Fosamax’ Once Weekly 70 mg (n=519) and alendronate 10 mg/day (n=370) were similar.

In two three-year studies of virtually identical design, in post-menopausal women (alendronate 10 mg: n=196, placebo: n=397) the overall safety profiles of alendronate 10 mg/day and placebo were similar.

Adverse experiences reported by the investigators as possibly, probably or definitely drug-related are presented below if they occurred in  $\geq 1\%$  in either treatment group in the one-year study, or in  $\geq 1\%$  of patients treated with alendronate 10 mg/day and at a greater incidence than in patients given placebo in the three-year studies:

	One-Year Study		Three-Year Studies	
	‘Fosamax’ Once Weekly 70 mg (n=519) %	alendronate 10 mg/day (n=370) %	alendronate 10 mg/day (n=196) %	Placebo (n=397) %
<i>Gastro-intestinal</i>				
abdominal pain	3.7	3.0	6.6	4.8
Dyspepsia	2.7	2.2	3.6	3.5
acid regurgitation	1.9	2.4	2.0	4.3
Nausea	1.9	2.4	3.6	4.0

	One-Year Study		Three-Year Studies	
	'Fosamax' Once Weekly 70 mg (n=519) %	alendronate 10 mg/day (n=370) %	alendronate 10 mg/day (n=196) %	Placebo (n=397) %
abdominal distention	1.0	1.4	1.0	0.8
Constipation	0.8	1.6	3.1	1.8
Diarrhoea	0.6	0.5	3.1	1.8
Dysphagia	0.4	0.5	1.0	0.0
Flatulence	0.4	1.6	2.6	0.5
Gastritis	0.2	1.1	0.5	1.3
gastric ulcer	0.0	1.1	0.0	0.0
oesophageal ulcer	0.0	0.0	1.5	0.0
<i>Musculoskeletal</i>				
musculoskeletal (bone, muscle or joint) pain	2.9	3.2	4.1	2.5
muscle cramp	0.2	1.1	0.0	1.0
<i>Neurological</i>				
Headache	0.4	0.3	2.6	1.5

The following adverse experiences have also been reported during clinical studies and/or post-marketing use:

[Common ( $\geq 1/100$ ,  $< 1/10$ ), Uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ), Rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ), Very rare ( $< 1/10,000$  including isolated cases)] [Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$ ,  $< 1/10$ ), Uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ), Rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ), Very rare ( $< 1/10,000$  including isolated cases)]

<b><i>Immune system disorders:</i></b>	<i>Rare:</i> hypersensitivity reactions including urticaria and angioedema
<b><i>Metabolism and nutrition disorders:</i></b>	<i>Rare:</i> symptomatic hypocalcaemia, often in association with predisposing conditions. <sup>§</sup> (see section 4.4)
<b><i>Nervous system disorders:</i></b>	<i>Common:</i> headache, <u>dizziness</u> <sup>†</sup> <i>Uncommon:</i> <u>dysgeusia</u> <sup>†</sup>
<b><i>Eye disorders:</i></b>	<i>Uncommon:</i> <u>eye inflammation</u> (uveitis, scleritis, episcleritis)
<b><i>Ear and labyrinth disorders:</i></b>	<i>Common:</i> <u>vertigo</u> <sup>†</sup>
<b><i>Gastrointestinal disorders</i></b>	<i>Common:</i> abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation <i>Uncommon:</i> nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena <sup>‡</sup> <i>Rare:</i> oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding) <sup>§</sup> (see section 4.4)*See sections 4.2 and 4.4

<b><i>Skin and subcutaneous tissue disorders:</i></b>	<u>Common: alopecia<sup>†</sup>, pruritus<sup>†</sup></u> <u>Uncommon: rash, pruritus, erythema</u> <u>Rare: rash with photosensitivity<sup>‡</sup></u> <u>Very rare and isolated cases: isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis<sup>‡</sup></u>
<b><i>Musculoskeletal and connective tissue disorders:</i></b>	<u>Very common: musculoskeletal (bone, muscle or joint) pain which is sometimes severe<sup>†§</sup> (see section 4.4)</u> <u>Common: musculoskeletal (bone, muscle or joint) pain joint swelling<sup>†</sup></u> <u>Rare: Osteonecrosis of the jaw<sup>‡§</sup> has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and/or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4); severe musculoskeletal (bone, muscle or joint) pain (see section 4.4) stress fractures of the proximal femoral shaft<sup>‡</sup> (see section 4.4) atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)<sup>†</sup></u>
<b><i>General disorders and administration site conditions:</i></b>	<u>Common: asthenia<sup>†</sup>, peripheral oedema<sup>†</sup></u> <u>Rare-Uncommon: transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment<sup>†</sup>.</u>
<sup>§</sup> See section 4.4 <sup>†</sup> Frequency in Clinical Trials was similar in the drug and placebo group. <sup>*</sup> See sections 4.2 and 4.4 <sup>‡</sup> This adverse reaction was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trials <sup>†</sup> Identified in postmarketing experience.	

During post-marketing experience the following reactions have been reported (frequency unknown):

***Nervous system disorders:*** — dizziness, dysgeusia

***Ear and labyrinth disorders:*** — vertigo

***Skin and subcutaneous tissue disorders:***  
 — alopecia

***Musculoskeletal, connective tissue and bone disorders:*** joint swelling.  
 — joint swelling, stress fractures of the proximal femoral shaft (see section 4.4)

***General disorders and administration site conditions:***  
 — asthenia, peripheral oedema

#### *Laboratory test findings*

In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronate 10 mg/day versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in

serum calcium to  $<8.0$  mg/dl ( $2.0$  mmol/l) and serum phosphate to  $\leq 2.0$  mg/dl ( $0.65$  mmol/l) were similar in both treatment groups.

#### **4.9 Overdose**

Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage.

No specific information is available on the treatment of overdosage with alendronate. Milk or antacids should be given to bind alendronate. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.