

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Fosalen 10 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg alendronic acid (as sodium alendronate trihydrate).

Excipients:

Each tablet contains 103.95 mg of lactose monohydrate.

For a full list of excipients see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

White to off-white, capsule-shaped tablet, embossed "AN 10" on one side and "Arrow logo" on the other.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Treatment of post-menopausal osteoporosis.

Alendronate reduces the risk of vertebral and hip fractures.

### 4.2 Posology and method of administration

For oral use only.

The recommended dosage is 10 mg once daily.

*To obtain satisfactory absorption of alendronate*

Fosalen tablets must be taken on an empty stomach immediately on rising in the morning, with plain water only, at least 30 minutes before the first food, drink or other medication of the day. Other drinks (including mineral water), food and some medicines are likely to reduce the absorption of alendronate (see section 4.5).

*To assist delivery to the stomach and thus reduce the risk of irritation/side effects locally and in the oesophagus (see section 4.4)*

- Fosalen tablets should only be swallowed on arising for the day with a whole glass of water (not less than 200 ml or 7 fl. oz).
- Fosalen tablets should be swallowed whole. The tablets should not be crushed, chewed, or allowed to dissolve in the mouth on account of the risk of oropharyngeal ulceration.
- Patients should not lie down until after the first meal of the day, which must be at least 30 minutes after taking the tablet.
- Patients should not lie down within 30 minutes of taking Fosalen 10 mg tablets.
- Fosalen 10 mg tablets 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

*Use in elderly patients:*

In clinical trials there was no age-related difference with regard to efficacy or safety profiles of alendronate. Therefore no adjustment of the dose is necessary for elderly patients.

*Use in impaired renal function*

No dose adjustment is necessary in patients with a glomerular filtration rate (GFR) greater than 35 ml/min. Alendronate is not recommended for patients with impaired renal function if the GFR is less than 35 ml/min, as there is no experience of this.

*Use in impaired hepatic function*

No dose adjustment is necessary.

*Use in children (under 18 years)*

Alendronate has been studied in a small number of patients with osteogenesis imperfect under 18 years of age. Results are insufficient to support its use in children.

### 4.3 Contraindications

- Oesophageal abnormalities and other factors that delay oesophageal emptying, such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to alendronate, other bisphosphonates or to any of the excipients.
- Hypocalcaemia.

Also see section 4.4.

### 4.4 Special warnings and precautions for use

Alendronate can cause local irritation to the upper gastrointestinal mucosa. As there is a risk of worsening of the underlying disease, caution should be observed if alendronate is given to patients with active upper gastrointestinal tract problems, such as dysphagia, oesophageal disease, gastritis, duodenitis or ulcers, or in cases of recent (during the last year) severe gastrointestinal disease such as gastric ulcer, active gastrointestinal bleeding or surgery in the upper gastrointestinal tract other than pyloroplasty (see section 4.3 ).

Oesophageal side effects (in some cases severe and requiring hospitalisation) such as oesophagitis, oesophageal ulcers or oesophageal erosions, in rare cases followed by oesophageal stricture, have been reported in patients receiving treatment with alendronate. The physician should therefore be alert to any signs or symptoms of possible oesophageal reaction. The patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

The risk of severe oesophageal side effects is thought to be greater in patients who do not take alendronate correctly and/or continue to take alendronate after developing symptoms indicative of oesophageal irritation. It is very important that complete administration instructions are given to, and understood, by the patient (see section 4.2). Patients should be informed that the risk of oesophageal problems may increase if they do not follow these instructions.

Despite no increased risk having been observed in extensive clinical trials, following marketing of the original preparation there have been reports of rare cases of gastric and duodenal ulcers, some of them severe and with complications. A causal relationship cannot be excluded (see section 4.8).

Patients should be instructed that if they miss a dose of Fosalen, 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 day, as originally scheduled.

Alendronate is not recommended for patients with impaired renal function if the GFR is less than 35 ml/min (see section 4.2).

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

Hypocalcaemia must be corrected before treatment with alendronate is initiated (see section 4.3). Other disorders of mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting alendronate. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during treatment with alendronate.

On account of the positive effects of alendronate on the increase in bone mineralisation, reductions in serum calcium and serum phosphate may occur. These are usually slight and asymptomatic. However, in rare cases, symptomatic hypocalcaemia has been reported which occasionally has been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and in cases of calcium malabsorption).

It is therefore particularly important to ensure that patients taking glucocorticoids have an adequate calcium and vitamin D intake.

Fosalen 10 mg tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimes 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 preventative dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, periodontal disease, smoking).

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.

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). 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.

#### *Atypical stress fractures*

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, 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.

4.5 Interaction with other medicinal products and other forms of interaction

If taken at the same time, it is likely that foods and drinks (including mineral water), calcium supplements, antacids and some oral medicines will affect the absorption of alendronate. Patients must therefore wait for at least 30 minutes after taking alendronate before taking any other oral medicine (see section 4.2).

No other clinically significant drug interactions are expected. A number of patients in the clinical trials received oestrogen (intravaginally, transdermally or orally) concomitantly with alendronate. No undesirable effects could be related to the combination treatment.

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

No specific interaction studies have been carried out, but alendronate was used in clinical trials concomitantly with a number of other commonly prescribed medicines without any evidence of clinically unfavourable interactions.

4.6 Pregnancy and lactation

Use during pregnancy

There are insufficient data regarding the use of alendronate in pregnant women. Animal studies revealed effects on foetal bone formation at high doses. Alendronate given to pregnant rats caused hypocalcaemia-related dystocia (see section 5.3). In view of the indication, alendronate should not be used during pregnancy.

Use during lactation

It is not known whether alendronate is excreted into breast milk in humans. In view of the indication, 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 Fosalen may affect some patients' ability to drive or operate machinery. Individual responses to Fosalen may vary (see section 4.8).

4.8 Undesirable effects

In two three-year studies of almost identical design, with post-menopausal women (alendronate 10 mg: n=196; placebo: n= 397) the overall safety profiles for alendronate 10 mg daily and placebo were similar.

Undesirable effects reported by the investigators as possibly, probably or definitely related to the drug are presented below if they occurred in ≥ 1 % of any in the treatment groups in the one-year study or in ≥ 1 % of the patients who were treated with alendronate 10 mg per day and with an incidence higher than in patients who were treated with placebo in three-year studies.

	The one-year study		Three-year studies	
	Alendronate once-weekly tablet (n=519) %	Alendronate 10 mg daily (n=370) %	Alendronate 10 mg daily (n=196) %	Placebo (n=397) %
Gastrointestinal				
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
Abdominal distension	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 pain (bone, muscle or joints)	2.9	3.2	4.1	2.5
Muscle cramps	0.2	1.1	0.0	1.0
<i>Neurological</i>				
Headache	0.4	0.3	2.6	1.5

The following undesirable effects have also been reported in clinical trials and/or post marketing:

Nervous system disorders:

*Common* ( $\geq 1/100$ ,  $< 1/10$ ): Headache

Eye disorders:

*Rare* ( $\geq 1/10,000$ ,  $< 1/1000$ ): Uveitis, scleritis, episcleritis

Gastrointestinal disorders:

*Common* ( $\geq 1/100$ ,  $< 1/10$ ): Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcers\*, dysphagia\*, abdominal distension, acid regurgitation.

*Uncommon* ( $\geq 1/1000$ ,  $< 1/100$ ): Nausea, vomiting, gastritis, oesophagitis\* oesophageal erosions\*, melaena.

*Rare* ( $\geq 1/10,000$ ,  $< 1/1000$ ): Oesophageal stricture\*, oropharyngeal ulceration\*, upper gastrointestinal PUB (perforations, ulcers, bleeding), a causal relationship cannot be ruled out.

Skin and subcutaneous tissue disorders:

*Uncommon* ( $\geq 1/1000$ ,  $< 1/100$ ): Rash, pruritus, erythema

*Rare* ( $\geq 1/10,000$ ,  $< 1/1000$ ): Rash with photosensitivity, urticaria, angioedema, alopecia

*Very rare* ( $\leq 1/10,000$ ): Isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Musculoskeletal, connective tissue and bone disorders:

*Common* ( $\geq 1/100$ ,  $< 1/10$ ): Musculoskeletal pain (bones, muscles or joints)

*Rare* ( $\geq 1/10,000$ ,  $< 1/1000$ ): Osteonecrosis of the jaw 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; severe musculoskeletal (bone, muscle or joint) pain (see section 4.4)

*Unknown frequency*: Stress fractures of the proximal femoral shaft (see section 4.4)

General disorders and administration site conditions:

*Rare* ( $\geq 1/10,000$ ,  $< 1/1000$ ): Transient symptoms as in an acute phase reaction (myalgia, malaise and in rare cases fever) usually in connection with the start of treatment.

Metabolism and nutrition disorders:

*Rare ( $\geq 1/10,000$ ,  $< 1/1000$ ):* Symptomatic hypocalcaemia, generally in connection with predisposing conditions (see section 4.4).

Immune system disorders:

*Rare ( $\geq 1/10,000$ ,  $< 1/1000$ ):* *Hypersensitivity reactions including urticaria and angioedema.*

\*See section 4.4 and section 4.2.

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

Nervous system disorders: Dizziness, dysgeusia

Ear and labyrinth disorders: Vertigo

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

General disorders and administration site conditions: Asthenia, peripheral oedema

*Laboratory values:* In clinical trials, asymptomatic, slight and transient decreases in serum calcium and serum phosphate were observed in approx. 18 and 10 % respectively of the patients taking alendronate 10 mg/day versus 12 and 3 % respectively of those taking placebo. However, the incidence of reductions in serum calcium to  $< 2.0$  mmol/l and serum phosphate to  $\leq 0.65$  mmol/l was comparable in the two groups.

## 4.9 Overdose

Hypocalcaemia, hypophosphataemia and upper gastrointestinal side effects such as upset stomach, heartburn, oesophagitis, gastritis or ulcer can occur on oral overdosage. There is no specific information available with regard to overdosage with alendronate. Milk or antacids should be given in order to bind alendronate. On account of the risk of oesophageal irritation, vomiting should not be induced and the patient should be kept in an upright position.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs affecting bone structure and mineralisation, bisphosphonates.

ATC code: M05BA04

The active substance in Fosalen 10 mg tablets, sodium alendronate trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption without any direct effect on bone formation. Preclinical studies have demonstrated a preference for localisation of alendronate to sites where active resorption takes place. Osteoclastic activity is inhibited, but formation and binding of the osteoclasts is not affected. Bone formed during treatment with alendronate is of normal quality.

*Treatment of post-menopausal osteoporosis*

**Osteoporosis is defined as bone mineral density (BMD) of the spine or hip 2.5 standard deviations below the mean value of a normal young population or as a previous fragility fracture, irrespective of bone mineral density.**

The effects of alendronate on BMD and fracture incidence in post-menopausal women were studied in two initial efficacy studies of identical design (n=994), and in the *Fracture Intervention Trial* (FIT: n=6459).

In the initial efficacy studies, the increases in BMD with alendronate 10 mg daily relative to placebo after three years were 8.8 %, 5.9 % and 7.8 % at the spine, femoral neck and trochanter respectively. Total BMD also increased significantly. In the patients treated with alendronate, the proportion of patients who suffered one or more vertebral fractures was reduced by 48 % (alendronate 3.2 % versus placebo 6.2 %). In the two-year extensions of these studies the BMD in the spine and trochanter continued to increase. In addition, BMD at the femoral neck and total body was maintained.

The FIT study included two placebo-controlled trials in which alendronate was given daily (5 mg daily for two years and 10 mg daily for a further one or two years).

- FIT 1: A three-year study with 2027 patients who had had at least one baseline vertebral (compression) fracture. In this study alendronate daily reduced the incidence of  $\geq 1$  new vertebral fracture by 47 % (alendronate 7.9 % versus placebo 15.0 %). In addition, a statistically significant reduction in the incidence of hip fractures was confirmed (1.1 % versus 2.2 %, a reduction of 51 %).
- FIT 2: A four-year study with 4432 patients who had a low bone mass but had not had any vertebral fracture at the start of the study. In this study, in a subgroup analysis of osteoporotic women (37 % of the total population who fulfilled the definition of osteoporosis given above) a significant difference was seen in the incidence of hip fractures (alendronate 1.0 % versus placebo 2.2 %, a reduction of 56 %) and in the incidence of  $\geq 1$  vertebral fracture (2.9 % versus 5.8 %, a reduction of 50 %).

#### *Concomitant use with oestrogen/hormone replacement therapy (HRT)*

The effects on BMD of treatment with alendronate 10 mg once-daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year study of hysterectomised, post-menopausal, osteoporotic women. At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or alendronate alone (both 6.0%).

The effects on BMD when 'Fosamax' was added to stable doses (for at least one year) of HRT (oestrogen  $\pm$  progestin) were assessed in a one-year study in post-menopausal, 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 favourable 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.

## **5.2 Pharmacokinetic properties**

### *Absorption*

Compared with an intravenous reference dose, the mean oral bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg given after an overnight fast and two hours before a standardised breakfast.

Bioavailability decreased to an estimated 0.46 % and 0.39 % when alendronate was given an hour or half an hour before a standardised breakfast.

In osteoporosis studies alendronate was effective when it was given at least 30 minutes before the first meal or drink of the day. Bioavailability was negligible irrespective of whether alendronate was given together with or up to two hours after a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approx. 60 %. In healthy persons, oral prednisolone (20 mg three times daily for five days) did not result in any clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 % to 44 %).

### *Distribution*

Studies in rats show that alendronate is initially distributed to soft tissues after intravenous administration of 1 mg/kg, but is then rapidly redistributed to the skeleton or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres 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 metabolised in animals or humans.

*Elimination*

Following a single intravenous dose of ( $^{14}\text{C}$ ) 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 intravenous dose of 10 mg, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within 6 hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten 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 thought 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 intravenous 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 section 4.2).

**5.3 Preclinical safety data**

Conventional studies of general toxicity, genotoxicity and carcinogenicity did not reveal any special risks for humans. Studies in female rats showed that treatment with alendronate during pregnancy was associated with dystocia during parturition, which was related to hypocalcaemia. Studies in which rats were given high doses showed an increased incidence of incomplete foetal bone formation. The relevance for humans is unknown.

**6 PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

Microcrystalline cellulose  
Lactose monohydrate  
Croscarmellose sodium  
Magnesium stearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf Life**

2 years

**6.4 Special precautions for storage**

Do not store above 25°C.

**6.5 Nature and contents of container**

The tablets are supplied in triplex blister (PVC/PE/PVDC/AL) packaging.  
14, 28, 56, 98, 112 and 50 x 1 (unit dose).  
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements



## **7 MARKETING AUTHORISATION HOLDER**

PLIVA Pharma Ltd.  
Vision House,  
Bedford Road,  
Petersfield,  
Hants, GU32 3QB,  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA 585/25/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 8<sup>th</sup> December 2006

Date of last renewal: 3<sup>rd</sup> December 2009

## **10 DATE OF REVISION OF THE TEXT**

September 2010