1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

FOSAGEN 70 mg (tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each tablet contains 70 mg of alendronic acid.

Contains sugar: Lactose monohydrate 158,88 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White normal bi-convex tablets 9,5 mm in diameter, embossed “AD70” on one side and “G” on the reverse**.**

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FOSAGEN 70 mg is indicated in women for the treatment of postmenopausal osteoporosis to reduce the risk of fractures, including those of the hip and spine (vertebral compression fractures).

4.2 Posology and method of administration

Posology

- It is important to take FOSAGEN 70 mg only as directed.

- The recommended dosage is one FOSAGEN 70 mg tablet (70 mg alendronic acid) once weekly, taken by mouth with a full glass of water, at least 2 hours before/after any food, beverages or other medication is taken.
- It is important to take FOSAGEN 70 mg with plain water only, as other beverages, including mineral water, are likely to reduce the absorption of alendronic acid.
- All patients should take calcium and vitamin D supplements if their diet is inadequate.
- These should be taken at least 30 minutes after taking FOSAGEN 70 mg.
- Remain in an upright position for 30 minutes after taking FOSAGEN 70 mg.
- To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, FOSAGEN 70 mg 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.
- FOSAGEN 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 section 4.4).

Special populations

Elderly population:

No dosage adjustments are necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 ml/min) (see section 4.3).

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to alendronate or any of the other excipients listed in section 6.1.

- Severe renal function impairment when creatinine clearance is less than 35 ml/minute.
- The risk factor should be considered when gastro-intestinal problems such as duodenitis, dysphagia, gastritis, ulcers or symptomatic oesophageal diseases are present.
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.
- As alendronate may exacerbate hypocalcaemia or vitamin D deficiency, these conditions should be corrected before FOSAGEN 70 mg is administered.
- The inability to stand or sit upright for 30 minutes after taking the medicine.
- Safety and efficacy have not been established in children.
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Osteonecrosis of the jaw

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in patients.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with biphosphonates, including FOSAGEN 70 mg, in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

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, angiogenesis inhibitors, smoking,
- a history of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures.

While on treatment, these patients should avoid invasive dental procedure, if possible.
For patients who develop osteonecrosis of the jaw while on biphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of biphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating doctor should guide the management plan of each patient based on individual benefit/risk assessment.

Hypocalcaemia and vitamin D deficiency should be corrected before starting FOSAGEN 70 mg, as FOSAGEN 70 mg may exacerbate these conditions.

Upper gastro-intestinal adverse reactions

The risk benefit should be considered in patients suffering from upper gastro-intestinal diseases, such as dysphagia, duodenitis, gastritis, ulcers or symptomatic oesophageal conditions, because of possible irritant effects of FOSAGEN 70 mg on the upper gastro-intestinal mucosa and a potential for worsening of the underlying disease (see section 4.3).
Oesophageal adverse experiences, such as oesophagitis, oesophageal stricture (see section 4.3), have been reported in patients receiving treatment with FOSAGEN 70 mg. In some cases, these have been severe and required hospitalisation. Doctors should, therefore, be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue FOSAGEN 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 FOSAGEN 70 mg and/or who fail to swallow it with a full glass of water, and/or who continue to take FOSAGEN 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 section 4.2).

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, patients should be instructed to swallow FOSAGEN 70 mg 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 FOSAGEN 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 FOSAGEN 70 mg and consult their doctor.

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

Due to the positive effects of FOSAGEN 70 mg to increase bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

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

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates such as FOSAGEN 70 mg who present with ear symptoms such as pain or discharge, or chronic ear infections.

Musculoskeletal pain

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 treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

Atypical fractures of the femur

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 complete 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.

Renal impairment

Alendronate as contained in FOSAGEN 70 mg is not recommended for patients with renal impairment where creatinine clearance is less than 35 ml/min, (see section 4.2).

Bone and mineral metabolism

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 before starting this medicinal product. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with FOSAGEN 70 mg.
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 hypocalcaemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption).

Use in the Elderly

There is no age-related difference in the efficacy or safety profiles of FOSAGEN 70 mg.

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Lactose warning:

FOSAGEN 70 mg contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take FOSAGEN 70 mg.

4.5 Interaction with other medicines 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 medicines will interfere with absorption of FOSAGEN 70 mg. Patients are advised to wait at least 30 minutes after FOSAGEN 70 mg before taking any other oral medication.

No adverse experiences attributable to the concomitant use of alendronate and oestrogen (intravaginal, transdermal, or oral) in postmenopausal women have been identified.

4.6 Fertility, pregnancy and lactation

Pregnancy

FOSAGEN 70 mg should no be used during pregnancy (see section 4.3).

Breastfeeding

FOSAGEN 70 mg should not be used during breastfeeding (see section 4.3).

Fertility

There are no data on foetal risk in humans. However, there is a theoretical risk of foetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

4.7 Effects on ability to drive and use machines

FOSAGEN 70 mg has no or negligible direct influence on the ability to drive and use machines. Patients may experience certain adverse reactions (for example blurred vision, dizziness and severe bone muscle or joint pain (see section 4.8)), that may influence the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

Of the above adverse experiences, abdominal pain was reported most commonly and the incidences of the other adverse experiences did not exceed 4,1 %.

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Frequent	**Less frequent**	**Frequency not known**
Immune system disorders:		hypersensitivity reactions including urticaria and angioedema	
Metabolism and nutrition disorders:		symptomatic hypocalcaemia, often in association with predisposing conditions[§]	

Nervous system disorders:	headache, dizziness		
Eye disorders:		eye inflammation (uveitis, scleritis, or episcleritis)	
Ear and labyrinth disorders:	vertigo	osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)	
Gastrointestinal disorders:	abdominal pain, dyspepsia, oesophageal ulcer*, dysphagia*, abdominal distention, oesophagitis*, oesophageal erosions*, nausea, vomiting, constipation, diarrhoea, flatulence, acid	oesophageal stricture*, oropharyngeal ulceration*, gastritis, gastric and duodenal ulcers, some severe and with complications, although a causal relationship has not been established, dysgeusia	

	regurgitation and melaena		
Skin and subcutaneous tissue disorders:	alopecia, pruritus	rash (occasionally with photosensitivity) and erythema, rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis	
Musculoskeletal, connective tissue and bone disorders:	musculoskeletal (bone, muscle or joint) pain**, joint swelling	osteonecrosis of the jaw**, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)	
General disorders and administrative site conditions:	asthenia, peripheral oedema,	transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in	

		association with initiation of treatment	
Laboratory test findings:			asymptomatic, mild and transient decreases in serum calcium and phosphate have been observed.

* see section 4.4 and 4.2.

** see section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Symptoms:

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

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

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

Pharmacotherapeutic group and ATC code:

Pharmacodynamic effects:

Biphosphonates are synthetic analogues of pyrophosphate that bind to the hydroxyapatite found in bone. Alendronate sodium is an aminobiphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption.

Alendronate localises preferentially at sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation. During exposure to alendronate, normal bone is formed that incorporates alendronate into its matrix where it is pharmacologically inactive.

5.2 Pharmacokinetic properties

Absorption:

The mean oral bioavailability of alendronate in women is 0.57 % for the 70 mg tablet when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability is decreased by 40 % when alendronate is given either 30 minutes or one hour before breakfast, when compared to taking the tablets two hours before eating. Bioavailability is negligible whether alendronate is administered with or up to two hours after or before a standardised breakfast.

When alendronate is taken with coffee or citrus juice, bioavailability is reduced by 60 %.

Distribution:

Alendronate is transiently distributed to soft tissue and then rapidly redistributed to bone or excreted in the urine. The volume of distribution is at least 28 L in humans.

Biotransformation:

Approximately 78 % in human plasma.

Elimination:

Following a single intravenous dose of 10 mg alendronate, the renal clearance was 71 ml per minute. The systemic clearance was approximately 200 ml/min. After 6 hours the plasma concentrations fell by more than 95 %. The terminal half-life in humans is estimated to exceed 10 years, reflecting release of alendronate from the skeleton.

There is no evidence that alendronate is metabolised in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose (pH 102)

Povidone (K29 - 32)

Croscarmellose sodium

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25 ºC.

Protect from light.

Keep securitainers well-closed.

6.5 Nature and contents of container

4, 8 or 12 tablets in green PVC and aluminium foil blister strips packaged into an outer cardboard carton.

4, 8 or 12 tablets in white securitainers with white polyethylene caps and optional polyethylene ullage filler.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

VIATRIS HEALTHCARE (Pty) Ltd.

4 Brewery Street

Isando

1600

Republic of South Africa

8 REGISTRATION NUMBER(S)

A39/3.2/0597

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 February 2006

10 DATE OF REVISION OF TEXT

06 February 2024