SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:
DENSALEN70 (Tablets)
DENSALEN70 tablet contains: 91,35 mg alendronate sodium equivalent to 70 mg alendronic acid.

Excipients:
Carrageenan, colloidal anhydrous silica, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol.
Sugar free

PHARMACOLOGICAL CLASSIFICATION:
A 3.2 Connective tissue medicines, non-hormonal preparations

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
Bisphosphonates are synthetic analogues of pyrophosphates that bind to the hydroxyapatite found in bone. Alendronate sodium is an amino bisphosphonate 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.

Pharmacokinetic properties:

Absorption:
The 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.

Protein binding:
Approximately 78 % in human plasma.

Elimination:
Following a single intravenous dose of 10 mg alendronate, the renal clearance was
71 mℓ /min. 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.

INDICATIONS:

DENSALEN70 is indicated in women for the treatment of post menopausal osteoporosis to reduce the risk of fractures, including those of the hip and spine (vertebral compression fractures).

CONTRAINDICATIONS:

- Hypersensitivity to alendronate or any other components of the formulation.
- Severe renal function impairment when creatinine clearance is less than 35 mℓ /min.
- The risk factor should be considered when gastrointestinal 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 DENSALEN70 is administered.
- The inability to stand or sit upright for 30 minutes after taking the medicine.
- Paediatric age group: Safety and efficacy have not been established.
- Pregnancy and lactation (see PREGNANCY AND LACTATION).
- A low energy stress fracture of the femur shaft while on DENSALEN70, is a contradiction to restarting therapy (see “WARNINGS AND SPECIAL PRECAUTIONS”).

WARNINGS AND SPECIAL PRECAUTIONS:

The risk benefit should be considered in patients suffering from upper gastrointestinal diseases, such as dysphagia, duodenitis, gastritis, ulcers or symptomatic oesophageal conditions, because of possible irritant effects of DENSALEN70 on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease.
In patients with known Barrett’s oesophagus, DENSALEN70 is not recommended.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, infrequently followed by oesophageal stricture, have been reported in patients receiving treatment with DENSALEN70. In some cases these have been severe and required hospitalisation. Medical practitioner should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue DENSALEN70 and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain, new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who lie down after taking DENSALEN70 and/or who fail to swallow it with a full glass of water and/or who continue to take DENSALEN70 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”).

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates, including DENSALEN70, in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

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 is no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgment 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 “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. A subset had recurrence of symptoms when rechallenged with the same medicine 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).

These fractures occur after minimal or no trauma and some patients experienced thigh or groin 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 DENSALEN70 patients who have sustained a femoral shaft fracture. Poor healing of these fractures was also reported. Discontinuation of DENSALEN70 in patients with stress fracture is recommended (see “CONTRAINDICATIONS”).

During DENSALEN70 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 DENSALEN70 once weekly formulation, they should take on DENSALEN70 on the morning after they remember. They should not take two DENSALEN70 tablets on the same day, but should return to taking one DENSALEN70 once a week, as originally scheduled on their chosen day.

DENSALEN70 is not recommended for patients with impaired renal function where GFR is less than 35 mℓ /min (see “DOSAGE AND DIRECTIONS FOR USE”).

Causes of osteoporosis other than oestrogen deficiency and aging should be considered.
Hypocalcaemia must be corrected before initiating therapy with DENSALEN70 (see “Contraindications”). 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 hypocalcaemia should be monitored during therapy with DENSALEN70.

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

Effects on the 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 DENSALEN70 may affect some patients' ability to drive or operate machinery. Individual responses to DENSALEN70 may vary (see “SIDE EFFECTS”).

INTERACTIONS:

Other oral medications, such as calcium supplements and antacids medicines will interfere with the absorption of DENSALEN70. Patients are advised to wait at least 30 minutes after taking DENSALEN70 before taking any other oral mediation (see “DOSAGE AND DIRECTIONS FOR USE”).

No adverse experiences attributable to the concomitant use of alendronate and oestrogen (intravaginal, transdermal, or oral) in postmenopausal women have been identified.
The co-administration of DENSALEN70 with NSAID use is associated with an increased risk of gastrointestinal irritation and gastric ulceration.
Caution should be used during concomitant use with DENSALEN70.

PREGNANCY AND LACTATION:
DENSALEN70 is contraindicated in pregnancy or lactation (see “CONTRAINDICATIONS”).

DOSAGE AND DIRECTIONS FOR USE:

It is important to take DENSALEN70 only as directed.
The recommended dosage is one DENSALEN70 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.

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 DENSALEN70 on an individual patient basis, particularly after 5 or more years of use.

It is important to take DENSALEN70 with plain water only, as other beverages including mineral water are likely to reduce the absorption of alendronic acid.
To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see “WARNINGS AND SPECIAL PRECAUTIONS”):

- DENSALEN70 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 DENSALEN70 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 DENSALEN70.
- DENSALEN70 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 “WARNINGS AND SPECIAL PRECAUTIONS”).

Use in the elderly
In clinical studies there was no age-related difference in the efficacy or safety profiles of DENSALEN70.
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. DENSALEN70 is not recommended for patients with renal impairment where GFR is less than 35 mℓ /min, due to lack of experience.

Paediatric patients
Alendronate sodium is not recommended for use in children under the age of 18 years due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis.

DENSALEN70 has not been investigated in the treatment of glucocorticoid-induced osteoporosis.

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

Immune system disorders:
Less frequent: Hypersensitivity reactions including urticaria and angioedema

Metabolism and nutrition disorders:

Less frequent: Metabolism and nutrition disorders: Symptomatic hypocalcaemia, often in association with predisposing conditions (see “WARNINGS AND SPECIAL PRECAUTIONS”).

Nervous system disorders:
Frequent: Headache , dizziness†

Eye disorders:
Less frequent: Eye inflammation (uveitis, scleritis, episcleritis)

Ear and labyrinth disorders:
Frequent: Vertigo†

Gastrointestinal disorders:-

Frequent: Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, dysphagia (see “DOSAGE AND DIRECTIONS FOR USE” and “WARNINGS AND SPECIAL PRECAUTIONS”), abdominal distension, acid regurgitation

Less frequent: Nausea, vomiting, gastritis, oesophagitis, esophageal erosions, oesophageal stricture, oropharyngeal ulceration (see “DOSAGE AND DIRECTIONS FOR USE” and “WARNINGS AND SPECIAL PRECAUTIONS”), melaena†, upper gastrointestinal PUBs (perforation, ulcers, bleeding). (See “WARNINGS AND SPECIAL PRECAUTIONS”)

Skin and subcutaneous tissue disorders:
Frequent: Alopecia†, pruritus†
Less frequent: Rash, erythema, rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders:
Frequent: Musculoskeletal (bone, muscle or joint) pain which is sometimes severe† (see “WARNINGS AND SPECIAL PRECAUTIONS”), and joint swelling†.

Less frequent: Osteonecrosis of the jaw† (see “WARNINGS AND SPECIAL PRECAUTIONS”).

General disorders and administration site conditions:

Frequent: Asthenia†, peripheral oedema†

Less frequent: Transient symptoms as in an acute phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment†.

Post-marketing data
In addition to the adverse reactions reported during clinical studies and listed above, the following side effects have been reported in post-marketing experience.

Nervous system disorders:
Less frequent: Dysgeusia†

Skin and subcutaneous tissue disorders:
Less frequent: toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:
Less frequent: atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

†Frequency in clinical Trials was similar in the drug and placebo group.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Hypocalcaemia, hypophosphataemia and upper gastrointestinal 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 DENSALEN70. Milk or antacids should be given to bind DENSALEN70. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

IDENTIFICATION:
A white, round, biconvex film-coated tablet debossed with “ALN 70” on one side.

PRESENTATION:
4 tablets packed in aluminium foil blister packed in an outer cardboard carton.

STORAGE INSTRUCTIONS:
Store at or below 25 °C in the original package. Protect from light and moisture. Keep the blisters in the carton until required for use.
KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:
A40/3.2/0515

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION:
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DATE OF PUBLICATION OF THE PACKAGE INSERT:
Date of registration: 01 December 2006
Date of the most recently approved package insert: 22 August 2019

Additional countries registration details:

Country	***Product name***	**Scheduling status (or Category of distribution)**	***Registration number***
Namibia	DENSALEN70	NS2	12/3.2/0063

[1] Company Reg. No.: 1990/001979/07