SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

DENSATE 70 mg (Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DENSATE 70 mg:

Each uncoated tablet contains sodium alendronate equivalent to alendronic acid 70 mg.

Sugar free.

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

DENSATE 70 mg: White to off-white, oval shaped, biconvex, uncoated tablets, debossed with ‘F’ on one side and ‘21’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DENSATE 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).
- for the treatment of primary/idiopathic osteoporosis in men and to reduce the risk of vertebral fractures associated with primary/idiopathic osteoporosis.

4.2 Posology and method of administration

Posology

Treatment of postmenopausal osteoporosis:

The recommended dosage is one 70 mg tablet once weekly.

Treatment of primary/idiopathic osteoporosis in men:

The recommended dosage is one 70 mg tablet once weekly.

Special populations

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 30 to 80 mL/min) (see section 4.3).

Method of administration

For oral use.

- DENSATE 70 mg must be taken at least half an 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 DENSATE 70 mg (see section 4.5).
- Patients should take calcium and vitamin D supplements if their dietary intake is inadequate (see section 4.4). These should be taken at least 30 minutes after taking DENSATE 70 mg.
- Patients should be advised to remain in an upright position for 30 minutes after taking DENSATE 70 mg tablets.
- To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, DENSATE 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. DENSATE 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).

4.3 Contraindications

- Hypersensitivity to alendronate or to any of the excipients of DENSATE 70 mg listed in section 6.1.
- Severe renal function impairment when creatinine clearance is less than 35 mL/minute.
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.
- The inability to stand or sit upright for 30 minutes after taking the medicine.
- Pregnancy and lactation (see section 4.6).
- Hypocalcaemia (see section 4.4).
- ***Paediatric age group***: Safety and efficacy have not been established.

4.4 Special warnings and precautions for use

– Fractures of the subtrochanteric and proximal shaft of the femur with minimal trauma (a fall from a standing height) after prolonged use (see section 4.4).

– Potential for oesophageal neoplastic change

Low energy fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate as contained in DENSATE 70 mg in long-term (usually longer than three years) bisphosphonate-treated treatment 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. Bisphosphonate such as DENSATE 70 mg therapy in patients with stress fractures should be discontinued.

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.

Osteonecrosis of the jaw (ONJ)

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported with oral bisphosphonates (see section 4.8). Most reported cases of bisphosphonate-associated osteonecrosis of the jaw 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, and co-morbid disorders (e.g., periodontal and /or other pre-existing dental disease, anaemia, coagulopathy, infection and smoking).

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates, including DENSATE 70 mg, in patients with poor dental status.

While on treatment, these patients should avoid invasive dental procedures (e.g., tooth extraction, dental implants), if possible.

For patients who develop osteonecrosis of the jaw while on DENSATE 70 mg therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of DENSATE 70 mg 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.

During bisphosphonate (e.g., DENSATE 70 mg) 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.

Upper gastro-intestinal adverse reactions

DENSATE 70 mg can cause local irritation to the mucous membrane in the upper part of the gastrointestinal tract.

As there is a risk of worsening of the underlying disease, caution should be used when DENSATE 70 mg 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 severe 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). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of DENSATE 70 mg on an individual patient basis.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, infrequently followed by oesophageal stricture, have been reported in patients receiving treatment with DENSATE 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 DENSATE 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 DENSATE 70 mg and/or who fail to swallow it with a full glass of water, and/or who continue to take DENSATE 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).

There have been less-frequent (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications (see section 4.8).

To facilitate delivery to the stomach and therefore reduce the potential for oesophageal irritation, patients should be instructed to swallow DENSATE 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.

As DENSATE 70 mg may exacerbate hypocalcaemia or vitamin D deficiency, these conditions should be corrected before DENSATE 70 mg is administered.

Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take DENSATE 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 DENSATE 70 mg and consult their doctor.

Since NSAID use is associated with gastrointestinal irritation, caution is advised with the concomitant use of DENSATE 70 mg and NSAIDs.

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with DENSATE 70 mg, 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 (e.g., DENSATE 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 DENSATE 70 mg. In post-marketing experience, these symptoms have less frequently 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 medicine or another bisphosphonate.

Renal impairment

DENSATE 70 mg should not be given for patients with renal impairment where creatinine clearance is less than 35 mL/min (see section 4.3).

Bone and mineral metabolism

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

Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting DENSATE 70 mg. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with DENSATE 70 mg.

Due to the positive effects of DENSATE 70 mg 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 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).

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

Use in the Elderly:

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

Patients should be instructed that if they miss a dose of DENSATE 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 on their chosen day, as originally scheduled.

DENSATE 70 mg contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

An increased incidence of upper gastrointestinal adverse events may occur in patients taking DENSATE 70 mg concomitantly with NSAIDs.

There may be additive hypocalcaemic effects with aminoglycosides.

Substances such as calcium supplements, osmotic laxatives, antacids, food and beverages will interfere with the absorption of DENSATE 70 mg. Patients are advised to wait at least 30 minutes after taking DENSATE 70 mg before taking any other medication, or food.

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

The safety of DENSATE 70 mg has not been established in pregnancy (see section 4.3).

Breastfeeding

The safety of DENSATE 70 mg has not been established in lactation (see section 4.3)

Fertility

There are no data on foetal risk in humans.

4.7 Effects on ability to drive and use machines

There are no data to suggest that DENSATE 70 mg affects the ability to drive or use machines.

However, 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

The following adverse reactions have been reported with DENSATE 70 mg:

MedDRA System Organ Class	**Frequency**	**Adverse reaction**
Neoplasms benign malignant and unspecified (including cysts and polyps)	*Less frequent*	Oesophageal cancer.
Immune system disorders	*Less frequent*	Hypersensitivity reactions, including urticaria and angioedema.
Blood and lymphatic system disorders	*Less frequent*	Anaemia, leucopenia, thrombocytopenia.
Metabolism and nutrition disorders	*Less frequent*	Symptomatic hypocalcaemia, generally in association with predisposing conditions (see section 4.4), hypophosphatemia.
Nervous system disorders	*Frequent*	Headache, dizziness
	Less frequent	Dysgeusia.
Eye disorders	*Less frequent*	Eye inflammation (uveitis, scleritis or episcleritis), diplopia with conjunctival swelling, eyelid oedema, non-specific conjunctivitis, blurred vision.
Ear and labyrinth disorders	*Frequent*	Vertigo.
	Less frequent	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).
Cardiac disorders	*Less frequent*	Atrial fibrillation.

Gastrointestinal disorders	*Frequent*	Abdominal pain, dyspepsia, oesophageal ulcer*, dysphagia*, abdominal distention, constipation, diarrhoea, flatulence, acid regurgitation**,** oesophageal stricture*.
	Less frequent	Nausea, vomiting, oesophagitis*, oesophageal erosions*, oropharyngeal ulceration*, gastritis, melaena, gastric and duodenal ulcers, some severe and with complications, oesophageal perforations (see section 4.4), ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding) (see section 4.4).
* See sections 4.2 and 4.4		
Hepato-biliary disorders	*Less frequent*	Raised liver enzymes, hepatitis, hepatocellular damage.
Skin and subcutaneous tissue disorders	*Frequent*	Alopecia, pruritus.
	Less frequent	Rash (occasionally with photosensitivity), erythema and, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.
Musculoskeletal and connective tissue	*Frequent*	Musculoskeletal (bone, muscle or joint) pain which is sometimes

disorders		severe (see section 4.4), joint swelling.
	Less frequent	Osteonecrosis of the jaw (see section 4.4), synovitis, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction), low-energy femoral shaft fracture.
Renal and urinary disorders	*Less frequent*	Renal Failure.
General disorders and administration site conditions	*Frequent*	Asthenia, peripheral oedema.
	Less frequent	Transient symptoms as in an acute-phase response (myalgia, malaise, fever), typically in association with initiation of treatment.

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. Health care 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

Symptoms

Hypocalcaemia, hypophosphatemia and upper gastrointestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage.

Management

The administration of milk or antacids may be of benefit.

Because of the risk of oesophageal irritation, vomiting should not be induced. Keep the patient in an upright position.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.3.2. Connective tissue medicines, non-hormonal preparations.

Pharmacotherapeutic group: Bisphosphonate, for the treatment of bone diseases

ATC Code: M05B A04

Bisphosphonates are synthetic analogues of pyrophosphate 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.

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 after oral administration in men (0,6 %) is very similar to that in women.

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 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 per minute. Within 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

Cellulose microcrystalline

Magnesium stearate

Maize starch

Povidone

Sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a dry place at or below 25 °C. Do not remove blisters from carton until required for use. Keep original containers well closed.

6.5 Nature and contents of container

DENSATE 70 mg:

Tablets are packed in printed aluminium foil with heat seal lacquer and clear PVC laminated with aclar. Each blister contains 4 tablets.

Pack size: 4's – Each carton contains 1 blister of 4 tablets each.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd.

Office 2, 100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

0157

Pretoria

South Africa

8 REGISTRATION NUMBER(S)

45/3.2/0581

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 01 March 2013

10 DATE OF REVISION OF THE TEXT

To be allocated.

Access to the corresponding Patient Information Leaflet

https://www.novagenpharma.co.za/products/ osteoporosis/