PROFESSIONAL INFORMATION

OSTEONATE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

OSTEONATE 70 mg, tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each OSTEONATE 70 mg tablet contains trihydrate monosodium alendronate which is equivalent to alendronic acid 70 mg.

OSTEONATE 70 mg tablets are sugar free and essentially 'sodium free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

OSTEONATE 70 mg tablets are white, oval, flat, with dimensions 14 x 8 mm, and marked on one face with "70".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OSTEONATE 70 mg is indicated for the treatment of:

Post-menopausal osteoporosis in women to reduce the risk of fractures, including those of the hip and spine (vertebral compression fractures).

Primary hypogonadal osteoporosis in men and to reduce the risk of vertebral fractures.

4.2 Posology and method of administration Posology

Treatment of post-menopausal osteoporosis:

The recommended dosage is one 70 mg tablet once weekly.

Treatment of primary hypogonadal osteoporosis in men:

The recommended dosage is one 70 mg tablet once weekly.

OSTEONATE 70 mg must be taken at least 30 minutes before the first food, beverage or medication of the day with plain water only. Other beverages (including mineral water), food and some medicines are likely to reduce the absorption of OSTEONATE 70 mg (see section 4.5).

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see section 4.4).

Special populations

Elderly patients:

No dosage adjustment is necessary for the elderly.

Renal impairment:

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency. OSTEONATE 70 mg is contraindicated in patients with creatinine clearance (35 - 60 mL/min) (see section 4.3).

Paediatric population

The safety and efficacy of OSTEONATE 70 mg in children less than 18 years of age has not been established.

Method of administration

For oral use.

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, OSTEONATE 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. OSTEONATE 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 (section 4.4).

Missed dose:

Medical practitioners should advise patients who forget to take OSTEONATE 70 mg to take the missed dose on the morning after they remember. They should not take two tablets on the same day. They should then return to take one tablet once a week on the same day of the week as originally scheduled.

4.3 Contraindications

- hypersensitivity to alendronate or to any of the components of OSTEONATE 70 mg
- severe renal function impairment when creatinine clearance is less than 35 mL/minute
- 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
- the inability to stand or sit upright for at least 30 minutes after taking the medicine
- paediatric age group: safety and efficacy have not been established
- pregnancy and lactation
- hypocalcaemia.

4.4 Special warnings and precautions for use

Osteonecrosis:

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection with

delayed healing, has been reported with oral bisphosphonates, such as OSTEONATE 70 mg. Most reported cases of bisphosphonate-associated osteonecrosis of the jaw have been in cancer patients treated with intravenous bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment of bisphosphonates, including OSTEONATE 70 mg, in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, smoking, co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection, diabetes, obesity) and increasing age.

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. Appropriate care by oral surgeon and discontinuation of therapy should be considered. 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 medical practitioner 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.

Osteonecrosis of the external auditory canal:

Osteonecrosis of the external auditory canal has been reported with bisphosphonates (as in OSTEONATE 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 who present with ear symptoms such as pain or discharge, or chronic ear infections.

Upper gastrointestinal disease:

OSTEONATE 70 mg is contraindicated in patients suffering from upper gastrointestinal diseases, such as dysphagia, duodenitis, gastritis, ulcers or symptomatic oesophageal conditions (including known Barrett's oesophagus), 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, because of possible irritant effects of OSTEONATE 70 mg on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease (see section 4.3).

Oesophageal adverse experiences such as oesophagitis, oesophageal ulcers and oesophageal erosions, followed rarely by oesophageal stricture or perforation, have been reported in patients receiving treatment with OSTEONATE 70 mg. In some cases, these have been severe and required hospitalisation. medical practitioners should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue OSTEONATE 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 OSTEONATE 70 mg and/or who fail to swallow it with a full glass of water, and/or who continue to take OSTEONATE 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 OSTEONATE 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 OSTEONATE 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. Causes of osteoporosis other than oestrogen deficiency, aging and glucocorticoid use should be considered.

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 (see section 4.8).

Hypocalcaemia:

Hypocalcaemia and other disorders affecting mineral metabolism (such as vitamin D deficiency) should be corrected before starting OSTEONATE 70 mg therapy, as OSTEONATE 70 mg may exacerbate these conditions. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with OSTEONATE 70 mg.

Due to positive effects of OSTEONATE 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.

Bone and mineral metabolism:

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

Musculoskeletal effects:

Bone, joint and/or muscle pain have been reported in patients taking bisphosphonates such as OSTEONATE 70 mg. These symptoms may be severe and/or incapacitating (see section 4.8). The time to onset of symptoms varies from one day to several months after starting treatment. Most patients had a relief of symptoms after stopping treatment. A subset had a recurrence of symptoms when re-challenged with the same medicine or another bisphosphonate.

Atypical fractures of the femur:

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a

small number of long-term (usually longer than 3 years) bisphosphonate-treated 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 contra-lateral femur should be examined in patients who have sustained a femoral shaft stress fracture. Stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g. vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care. Bisphosphonate therapy in patients with stress fractures should be discontinued.

During OSTEONATE 70 mg 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:

OSTEONATE 70 mg is not recommended for patients with renal impairment where creatinine clearance is less than 35 mL/min, (see section 4.2 and 4.3).

Use in the elderly:

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

Excipients with known effect

Sodium

OSTEONATE 70 mg contains less than 1 mmol sodium (0.023g) per tablet, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicines and other forms of interaction

Other oral medications, such as mineral supplements and antacids, containing aluminium, calcium, iron or magnesium and some osmotic laxatives will interfere with the absorption of OSTEONATE 70 mg. Patients are advised to wait at least 30 minutes after OSTEONATE 70 mg before taking any other oral medication.

No other interactions of clinical significance are anticipated.

No adverse experiences attributable to the concomitant use of alendronate and oestrogen (intravaginal, transdermal or oral) in post-menopausal women have been identified.
There may be additive hypocalcaemic effects with aminoglycosides.
Patients should be advised to be cautious when using nonsteroidal anti-inflammatory drugs (NSAIDs) while taking OSTEONATE 70 mg, as these NSAIDs are associated with gastrointestinal irritation.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of OSTEONATE 70 mg has not been established in pregnancy and therefore, should not be used during pregnancy (see section 4.3).

Breastfeeding

The safety of OSTEONATE 70 mg has not been established in lactation.
A risk to the newborn/infant cannot be excluded. OSTEONATE 70 mg should not be used during breastfeeding.

Fertility

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the

amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use (see section 5.2). 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

OSTEONATE 70 mg has no or negligible direct influence on the ability to drive and use machines. There are no data to suggest that OSTEONATE 70 mg affects the ability to drive or use machines. However, certain adverse reactions (for example blurred vision, dizziness and severe bone muscle or joint pain) that have been reported with OSTEONATE 70 mg may affect some patient's ability to drive and use machines. Individual responses to OSTEONATE 70 mg may vary (see section 4.8).

4.8 Undesirable effects

a. *Summary of the safety profile*

In a one-year study in postmenopausal women with osteoporosis the overall safety profiles of once weekly dose formulation of alendronate 70 mg and a daily formulation of alendronate 10 mg were similar. In two three-year studies of virtually identical design, in postmenopausal women (alendronate 10 mg: n=196, placebo: n=397) the overall safety profiles of alendronate 10 mg/day and placebo were similar.

b. Tabulated list of adverse effects

The frequencies of adverse events are ranked according to the following:

Frequent = Common (≥ 1/100 to < 1/10) and very common (1>10).

Less frequent = Infrequent (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000);

Very rare (<1/10 000).

Frequency not known = cannot be estimated from the available data.

System Organ Class	Frequency	Side effects
Neoplasms benign and malignant (including cysts and polyps)	*Less frequent* *Frequency unknown*	Oesophageal cancer Barrett's oesophagus
Immune system disorders	*Less frequent*	Hypersensitivity reactions including urticaria and angioedema.
Metabolism and nutrition disorders	*Less frequent*	Symptomatic hypocalcaemia, generally in association with predisposing conditions
Nervous system disorders	*Frequent* *Less frequent*	Headache Dysgeusia, dizziness
Eye disorders	*Less frequent*	Uveitis, scleritis, episcleritis, non-specific conjunctivitis, abnormal or blurred vision, iritis, serious ocular reactions and optic neuritis, diplopia with conjunctival swelling, eyelid oedema
Ear and labyrinth disorders	*Frequent* *Less frequent*	Vertigo Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Cardiac disorders	*Less frequent*	Increased risk of arterial fibrillation

Gastrointestinal disorders	*Frequent*	Abdominal pain, dyspepsia, dysphagia, oesophageal ulcer, abdominal distention, oesophagitis, constipation, diarrhoea, flatulence, acid regurgitation
	Less frequent	Gastritis, nausea, melaena oesophageal erosions, oesophageal stricture, vomiting, oropharyngeal ulceration, oesophageal perforations, gastric and duodenal ulcers, ulcer bleeding
Hepatobiliary disorders	*Less frequent*	Hepatitis
Skin and subcutaneous tissue disorders	*Less frequent*	Rash, erythema, pruritus, photosensitivity, alopecia, Stevens Johnson syndrome, toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders	*Frequent*	Musculoskeletal pain (severe and/or incapacitating bone, muscle or joint), muscle cramp
	Less frequent	Joint swelling, low- energy femoral shaft fracture, localised osteonecrosis of the jaw (generally associated with tooth extraction and/or local infection, with delayed healing)
	Frequency unknown	Transient acute symmetrical polyarthritis, synovitis (possibly causing carpal tunnel syndrome)*, low impact atypical fractures in the subtrochanteric region and prodromal symptoms (thigh pain, vague discomfort, subjective weakness)*
General disorders and administrative site conditions	*Less frequent*	Transient symptoms as in an acute-phase response (myalgia, arthralgia, bone pain, malaise, asthenia and fever, chills, fatigue), typically at the start of treatment, peripheral oedema
Investigations	*Frequency unknown*	Asymptomatic, mild and transient decreases in serum calcium and phosphate*

*Post marketing

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 professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

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

Management of overdose:

The administration of milk and 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

Pharmacotherapeutic group: Bisphosphonate, for the treatment of bone diseases

ATC code: M05BA04

Pharmacological classification: A.3.2 Connective tissue medicines, non-hormonal preparations.

Mechanism of action

Bisphosphonates 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 to sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation. Since bone formation and bone resorption are coupled, bone formation is also reduced, but less so than resorption, leading to progressive gains in bone mass.

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. At 0,6 %, bioavailability in men is similar to that in women.

Bioavailability is decreased by 40 % when alendronate is given ½ - 1 hour before breakfast, when compared to taking the tablet two hours before eating.

Absorption is negligible when alendronate is administered 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 the soft tissue and then rapidly redistributed to bone or excreted in the urine. The volume of distribution is at least 28 L in humans.

Plasma concentrations of alendronate after oral dosing are lower than 5 ng/mL. Protein binding is approximately 78 %.

Biotransformation:

There is no evidence that alendronate is metabolised by humans.

Elimination:

Following a single intravenous dose of 10 mg alendronate, the renal clearance was 71 mL/min. Systematic clearance does not exceed 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.

Pharmacokinetics in special patient groups

Renal impairment:

Alendronate 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Studies in rats have shown that treatment with alendronate during pregnancy was associated with dystocia in dams during parturition which was related to hypocalcaemia.

In studies, rats given high doses showed an increased incidence of incomplete foetal ossification. The relevance to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline

Crospovidone (Type A)

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture and direct light.

Keep blisters in outer carton until required for use.

6.5 Nature and contents of container

OSTEONATE 70 mg tablets are packed in an OPA/Al/PVC/Al blister pack containing 4 tablets in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, 7945

Cape Town, South

Africa

TEL: + 27 21 707 7000

or 0860-PHARMA (742 762)

8. REGISTRATION NUMBER

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ZIMBABWE

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