APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ALENDRONATE UNICORN 70

Strength: 70 mg Trihydrate monosodium alendronate equivalent to alendronic acid

Pharmaceutical form: tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **ALENDRONATE UNICORN 70** tablet contains alendronate

monosodium trihydrate which is equivalent to 70 mg of the free acid.

ALENDRONATE UNICORN 70 is sugar free.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

ALENDRONATE UNICORN 70 tablets are white, oval, smooth, flat and marked in one face with

"70".

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ALENDRONATE UNICORN 70 is indicated for the treatment of:

- Postmenopausal 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

It is important to take **ALENDRONATE UNICORN 70** only as directed.

The recommended dosage is one **ALENDRONATE UNICORN 70** tablet (70 mg alendronic acid) once weekly.

Patients should be instructed that if they miss a dose of **ALENDRONATE UNICORN 70**, 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, as originally scheduled on their chosen day.

Special Populations

No dosage adjustment is 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

Oral use.

To permit adequate absorption of alendronate

ALENDRONATE UNICORN 70 is taken by mouth with a full glass of water, at least 30 minutes before/after any food, beverages or medication is taken. It is important to take **ALENDRONATE UNICORN 70** with plain water only, as other beverages, including mineral water, are likely to reduce the absorption of alendronic acid.

All patients should take calcium or Vitamin D supplements if their diet is inadequate. These should be taken at least 30 minutes after taking **ALENDRONATE UNICORN 70.**

1. Remain in an upright position for 30 minutes after taking **ALENDRONATE UNICORN 70** tablets.
2. **ALENDRONATE UNICORN 70** should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml) and patients should not lie down for at least 30 minutes and until after their first food of the day.

ALENDRONATE UNICORN 70 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 any other components of the formulation.
- 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.
- As alendronate may exacerbate hypocalcaemia or vitamin D deficiency, these conditions should be corrected before **ALENDRONATE UNICORN 70** is administered.
- 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.

4.4 Special warnings and precautions for use

Osteonecrosis of the jaw

Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local

infection with delayed healing (including osteomyelitis), has been reported in patients with cancer receiving treatment regimens including primarily intravenous administered bisphosphonates. A diagnosis of cancer, concomitant therapies (e.g. pre-existing dental disease, anemia, coagulopathy and infection) have been identified as risk factors. Patients should obtain appropriate care by an oral surgeon and individual benefit/risk assessment is necessary to determine whether bisphosphonate therapy should be discontinued. Many of these patients were receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates, such as **ALENDRONATE UNICORN 70.**

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.

A dental examination with appropriate preventive dentistry should be considered prior to treatment of bisphosphonates, including **ALENDRONATE UNICORN 70**, 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 aging.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, such as **ALENDRONATE UNICORN 70,** 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 doctor 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.

Upper gastrointestinal adverse reactions

The risk should be considered in patients suffering from upper gastrointestinal diseases, such as dysphagia, duodenitis, gastritis, ulcers, oesophageal disease, or with a 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 or symptomatic oesophageal conditions (including known Barrett's oesophagus), because of possible irritant effects of **ALENDRONATE UNICORN 70** on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease. In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, infrequently followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with **ALENDRONATE UNICORN 70**. 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 **ALENDRONATE UNICORN 70** 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 **ALENDONATE UNICORN 70** and/or who fail to swallow it with a full glass of water, and/or who continue to take **ALENDRONATE UNICORN 70** 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). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, patients should be instructed to swallow **ALENDRONATE UNICORN 70** 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 **ALENDRONATE UNICORN 70** 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.

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 who present with ear symptoms such as pain or discharge, or chronic ear infections.

Bone and mineral metabolism

Causes of osteoporosis other than oestrogen deficiency and ageing should be considered. Hypocalcaemia and other disorders affecting mineral metabolism (such as vitamin D deficiency) should be corrected before starting **ALENDRONATE UNICORN 70** therapy, as **ALENDRONATE UNICORN 70** may exacerbate these conditions. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with **ALENDRONATE UNICORN 70.**

Due to positive effects of **ALENDRONATE UNICORN 70** 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. 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).
Ensuring adequate calcium and vitamin D intake is especially important in patients receiving glucocorticoids.

Musculoskeletal pain

Bone, joint and/or muscle pain have been reported in patients taking bisphosphonates such as **ALENDRONATE UNICORN 70**. In some cases, these symptoms have 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 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

Atypical, low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported with long-term use (usually longer than 3 years) in bisphosphonate-treated patients. These transverse or short oblique, fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. Some were stress fractures (also 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 and receive appropriate orthopaedic care. 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. **ALENDRONATE UNICORN 70** treatment should be stopped in patients with stress fractures and they should receive appropriate orthopaedic care, 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 is not recommended for patients with renal impairment where creatinine clearance is less than 35 ml/min,(see section 4.2).

Sodium

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

Use in the Elderly:

There is no age-related difference in the efficacy or safety profiles of **ALENDRONATE UNICORN 70**.

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 will interfere with the absorption of **ALENDRONATE UNICORN 70.**

Patients are advised to wait at least 30 minutes after taking **ALENDRONATE UNICORN 70** 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.

There may be additive hypocalcaemic effects with aminoglycosides.

Patients are advised to be cautious when using non-steroidal anti-inflammatory drugs (NSAIDs) while taking **ALENDRONATE UNICORN 70**, as these NSAIDs are associated with gastrointestinal irritation.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of alendronate in pregnant women.

Studies in animals have shown reproductive toxicity. Alendronate given during pregnancy in rats caused dystocia related to hypocalcaemia.

ALENDRONATE UNICORN 70 should not be used during pregnancy.

Breastfeeding

It is unknown whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. **ALENDRONATE UNICORN 70** should not be used during breast-feeding.

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

There are no data to suggest that **ALENDRONATE UNICORN 70** affects the ability to drive or 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

System Organ Class	**Frequency**	**Side effects**
Neoplasms benign and malignant (including cysts and polyps):	Less frequent:	Oesophageal cancer.
	Frequency unknown:	Barrett's oesophagus.
Blood and lymphatic system disorders:	Frequency unknown:	Anaemia, thrombocytopenia, leucopenia.
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 (see section 4.4).
Psychiatric disorders:	Frequency unknown:	Auditory hallucinations, red-coloured visual disturbances.
Nervous system disorders:	Frequent:	Headache.
	Less Frequent:	Vertigo, dysgeusia and dizziness.

Eye disorders:	Less frequent:	Eye inflammation (Uveitis, scleritis, episcleritis)
	Frequency unknown:	Non-specific conjunctivitis, abnormal or blurred vision, iritis, serious ocular reactions and optic neuritis.
Ear and labyrinth disorders	Very Rare	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Cardiac disorders:	Frequency unknown:	Serious atrial fibrillation adverse events.

Gastrointestinal disorders:	Frequent:	Abdominal pain, dyspepsia, dysphagia*, oesophageal ulcer*, abdominal distention, oesophagitis*, nausea, vomiting, constipation, diarrhoea, flatulence, acid regurgitation and melaena.
	Less frequent:	Gastritis, oesophageal stricture*, oesophageal erosions*, oropharyngeal ulceration*, isolated cases of esophageal perforations, ulcers and bleeding (PUBs), gastric and duodenal ulcers (some severe and with complications).
* see section 4.4 and section 4.2.		
Hepato-biliary disorders:	Less frequent:	Hepatitis, hepatocellular damage with

		raised liver enzyme concentrations.
Skin and subcutaneous tissue disorders:	Less frequent:	Rash (occasionally with photosensitivity), erythema, pruritus, alopecia and severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.
Musculoskeletal, connective tissue and bone disorders:	Frequent:	Musculoskeletal pain (severe and/or incapacitating bone, muscle or joint)*.
	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), stress fractures of the proximal femoral shaft (see section 4.4).
* see section 4.4".		

Renal and urinary disorders:	Frequency unknown:	Acute renal failure.
General disorders and administrative site conditions:	Less frequent:	Hypersensitivity reactions (including urticaria and angioedema). Transient symptoms as in an acute-phase response (myalgia, arthralgia, bone pain, malaise, asthenia, peripheral oedema and rarely, fever, chills, fatigue), typically at the start of treatment.
Ear and labyrinth disorders:	Frequent:	vertigo
	Less frequent:	osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Investigations:	Frequency unknown:	Asymptomatic, mild and transient decreases in serum calcium and phosphate

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 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 the SAHPRA website.

Side effects must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to vigilance@unicornpharma.co.za.

4.9 Overdose

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

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 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. In osteoporosis studies, alendronate was effective when administered at least 30 minutes before the first food or beverage of the day.

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 were found to be lower than 5 ng/ml. A high protein binding of approximately 78 % has been found in humans.

Metabolism

There is no evidence that alendronate is metabolised in humans.

Elimination

Following a single intravenous dose of [^{14}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 alendronate, the renal

clearance was 71 ml per 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. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline, crospovidone, 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

ALENDRONATE UNICORN 70 tablets are packed in an aluminium and PVC/PVDC or polyamide, aluminium, PVC blister pack containing 4 tablets in an outer carton.

6.6 Special precautions for disposal and other handling

This medicine does not require any special storage conditions.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

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8 REGISTRATION NUMBER(S)

43/3.2/0266

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 02 March 2012

10 DATE OF REVISION OF THE TEXT

30 January 2025