1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PREOVIDLEN 70 mg/ 5600 IU tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of PREOVIDLEN contains 70 mg alendronic acid as alendronate sodium trihydrate and 0,14 mg (5 600 IU) cholecalciferol (vitamin D3).

Contains sugar: Lactose anhydrous 59,14 mg, sucrose 27,49 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white, modified rectangle-shaped tablets engraved, mottled, with 5600 on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

PREOVIDLEN 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) and to help ensure vitamin D adequacy.

4.2. Posology and method of administration

Posology

Adults

The recommended dosage is one 70 mg/5 600 IU tablet once weekly. For most osteoporotic patients the appropriate dose is 70 mg/5 600 IU once weekly.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated.

Patients should receive supplemental calcium and/or vitamin D if intake is inadequate (see section 4.4). Additional supplementation with vitamin D should be considered on an individual basis taking into account any vitamin D intake from vitamins and dietary supplements.

PREOVIDLEN is intended to provide a week's supply of vitamin D.

Special populations

Elderly population

In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate as contained in PREOVIDLEN. Therefore, no dose adjustment is necessary for the elderly.

Renal impairment

PREOVIDLEN is not recommended for patients with renal impairment where creatinine clearance is less than 35 mL /min, due to lack of experience. No dose adjustment is necessary for patients with mild to moderate renal insufficiency (creatinine clearance 35 to 60 mL/min).

Method of administration

For oral administration.

PREOVIDLEN 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 medications are likely to reduce the absorption of alendronate, as contained in PREOVIDLEN (see section 4.5).

The following instructions should be followed exactly in order to minimise the risk of oesophageal irritation and related adverse reactions (see section 4.4):

- PREOVIDLEN should only be swallowed after getting up for the day with a full glass of water (not less than 200 ml).
- Patients should only swallow PREOVIDLEN 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 for at least 30 minutes after taking PREOVIDLEN and until after the first food of the day.
- PREOVIDLEN 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 4.8).

4.3. Contraindications

PREOVIDLEN is contraindicated in:

- Patients with hypersensitivity to alendronate and cholecalciferol or to any of the excipients in PREOVIDLEN (see section 6.1).
- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypocalcaemia.
- Severe renal insufficiency (creatinine clearance less than 35 mL/min) (see section 4.2).

- Pregnancy and lactation (see section 4.6).
- Paediatric age group.

4.4. Special warnings and precautions for use

Alendronate

Upper gastrointestinal adverse reactions

Alendronate, as contained in PREOVIDLEN, can cause local irritation of the upper gastrointestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate, as contained in PREOVIDLEN, is given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous year) of major gastrointestinal disease such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastrointestinal tract other than pyloroplasty (see section 4.3). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate, as contained in PREOVIDLEN, on an individual patient basis.

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate, as contained in PREOVIDLEN. Medical practitioners should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate, as contained in PREOVIDLEN and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain or new or worsening heartburn (see section 4.8).

The risk of severe oesophageal adverse reactions appears to be greater in patients who fail to take alendronate, as contained in PREOVIDLEN, properly and/or who continue to take alendronate, as contained in PREOVIDLEN, after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to and are 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.

While no increased risk was observed in extensive clinical trials with alendronate, as contained in PREOVIDLEN, there have been (post-marketing) reports of gastric and duodenal ulcers, some of which were severe and with complications (see section 4.8).

Osteonecrosis of the jaw

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in patients with cancer who are receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates, such as alendronate as in PREOVIDLEN.

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 with oral bisphosphonates, such as alendronate as in PREOVIDLEN in patients with poor dental status.

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 as in PREOVIDLEN, dental surgery may exacerbate the condition. 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, 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.

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. 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 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. Bisphosphonate treatment should be stopped in patients with stress fractures and they should receive appropriate orthopaedic care.

Musculoskeletal pain

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, 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 relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

Patients should be instructed that if they miss a dose of PREOVIDLEN 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.

Due to the nature of the disease process in osteoporosis, PREOVIDLEN is intended for long-term use.

Renal impairment

PREOVIDLEN 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 estrogen deficiency and ageing should be considered. Hypocalcaemia must be corrected before initiating therapy with PREOVIDLEN (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting PREOVIDLEN. The content of vitamin D in PREOVIDLEN is not suitable for correction of vitamin D deficiency. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with PREOVIDLEN.

Due to the positive effects of alendronate, as contained in PREOVIDLEN 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) (see section 4.8).

Cholecalciferol

Vitamin D3, as contained in PREOVIDLEN may increase the magnitude of hypercalcaemia and/or hypercalciuria when administered to patients with disease associated with unregulated overproduction of calcitriol (e.g. leukaemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.

Patients with malabsorption may not adequately absorb vitamin D3 as contained in PREOVIDLEN.

Excipients

PREOVIDLEN contains lactose and sucrose. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, total lactase deficiency, fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take PREOVIDLEN.

PREOVIDLEN 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

Alendronate

If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate as contained in PREOVIDLEN. Therefore, patients must wait at least 30 minutes after taking alendronate as contained in PREOVIDLEN, before taking any other oral medicinal product (see sections 4.2 and 5.2).

Non-steroidal anti-inflammatory drugs (NSAID)

Since non-steroidal anti-inflammatory drug (NSAID) use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate as contained in PREOVIDLEN.

Cholecalciferol

Olestra, mineral oils, orlistat, and bile acid sequestrants

Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g. colestyramine, colestipol) may impair the absorption of vitamin D as contained in PREOVIDLEN.

Anticonvulsants, cimetidine and thiazides

Anticonvulsants, cimetidine and thiazides may increase the catabolism of vitamin D as contained in PREOVIDLEN. Additional vitamin D supplements may be considered on an individual basis.

4.6. Fertility, pregnancy and lactation

PREOVIDLEN is only intended for use in postmenopausal women and therefore it should not be used during pregnancy or in breast-feeding women.

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 as contained in PREOVIDLEN given during pregnancy in rats caused dystocia related to hypocalcaemia (see section 5.3). Studies in animals have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D as contained in PREOVIDLEN (see section 5.3). PREOVIDLEN should not be used during pregnancy (see section 4.3).

Breastfeeding

It is unknown whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Cholecalciferol as contained in PREOVIDLEN and some of its active metabolites pass into breast milk. PREOVIDLEN should not be used during breast-feeding as

safety and efficacy have not been established (see section 4.3).

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

PREOVIDLEN 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

a) Summary of the safety profile

The frequently reported adverse reactions are upper gastrointestinal adverse reactions including abdominal pain, dyspepsia, oesophageal ulcer, dysphagia, abdominal distension and acid regurgitation (> 1 %).

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Immune system disorders		Hypersensitivity reactions including urticaria and angioedema.	
Metabolism and nutrition disorders		Symptomatic hypocalcaemia, often in association with predisposing condition*.	
Nervous system disorders	Headache, dizziness**.	Dysgeusia**.	
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, constipation, diarrhoea, flatulence, oesophageal ulcer***, dysphagia***, abdominal distension, acid regurgitation.	Nausea, vomiting, gastritis, oesophagitis***, oesophageal erosions***, melena** oesophageal stricture***, oropharyngeal ulceration***, upper gastrointestinal PUBs (perforation, ulcers, bleeding)*.	Oesophageal perforations.
Skin and subcutaneous tissue disorders	Alopecia**, pruritus**.	Rash, erythema rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis****.	
Musculoskeletal and connective tissue disorders	Musculoskeletal (bone, muscle or joint) pain which is sometimes severe(**)(*), 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 fever), typically in association with initiation of treatment**.	A decrease in serum calcium and phosphate may occur.

** See section 4.4*

***Frequency in clinical trials was similar in the medicinal product and placebo group*

****See sections 4.2 and 4.4*

*****This adverse reaction was identified through post-marketing surveillance.*

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 SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Alendronate

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

Cholecalciferol

Vitamin D toxicity has not been documented during chronic therapy in generally healthy adults at a dose less than 10,000 IU/day. In a clinical study of healthy adults, a 4,000 IU daily dose of vitamin D3 for up to five months was not associated with hypercalciuria or hypercalcaemia.

Treatment

Alendronate

No specific information is available on the treatment of overdose with alendronate as contained in PREOVIDLEN. In case of overdose with PREOVIDLEN, milk or antacids should be given to bind alendronate. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Pharmacotherapeutic group: Drugs for treatment of bone diseases, Bisphosphonates, combinations,

ATC code: M05BB03

Mechanism of action

Alendronate

Alendronate sodium is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Bisphosphonates are synthetic analogies of pyrophosphate

that bind to the hydroxyapatite found in bone. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Cholecalciferol (vitamin D_3)

Vitamin D3 is produced in the skin by conversion of 7-dehydrocholesterol to vitamin D3 by ultraviolet light. In the absence of adequate sunlight exposure, vitamin D3 is an essential dietary nutrient. Vitamin D3 is converted to 25-hydroxyvitamin D3 in the liver, and stored until needed. Conversion to the active calcium- mobilising hormone 1,25-dihydroxyvitamin D3 (calcitriol) in the kidney is tightly regulated. The principal action of 1,25-dihydroxyvitamin D3 is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption. Vitamin D3 is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in secondary hyperparathyroidism, hypophosphataemia, proximal muscle weakness and osteomalacia, further increasing the risk of falls and fractures in osteoporotic individuals. Supplemental vitamin D reduces these risks and their consequences.

Osteoporosis is defined as bone mineral density (BMD) of the spine or hip 2.5 standard deviations (SD) below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.

5.2. Pharmacokinetic properties

Absorption

Alendronate

Relative to an intravenous reference dose, the oral mean bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability was decreased similarly to an estimated 0.46 % and 0.39 % when alendronate was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronate was effective when administered at least 30 minutes before the first food or beverage of the day.
The alendronate component in the PREOVIDLEN (70 mg/5,600 IU) combination tablet is bioequivalent to the alendronate 70 mg tablet.

Bioavailability was negligible whether alendronate was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60 %.
In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronate (a mean increase ranging from 20 % to 44 %).

Cholecalciferol

In healthy adult subjects (males and females), following administration of 70 mg alendronate/5600 IU cholecalciferol tablets after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve (AUC0-80 hrs) for vitamin D3 (unadjusted for endogenous vitamin D3 levels) was 490.2 ng•hr/ml. The mean maximal serum concentration (Cmax) of vitamin D3 was 12.2 ng/ml and the median time to maximal serum concentration (Tmax) was 10.6 hours. The bioavailability of the 5,600 IU vitamin D3 in 70 mg alendronate/5600 IU cholecalciferol tablets is similar to 5,600 IU vitamin D3 administered alone.

Distribution

Alendronate

Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg intravenous administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres in humans. Concentrations of alendronate in plasma following therapeutic oral doses are too low for analytical detection (< 5 ng/ml). Protein binding in human plasma is approximately 78 %.

Cholecalciferol

Following absorption, vitamin D3 enters the blood as part of chylomicrons. Vitamin D3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D3 at these sites for later release into the circulation. Circulating vitamin D3 is bound to vitamin D-binding protein.

Biotransformation

Alendronate

There is no evidence that alendronate is metabolised in animals or humans.

Cholecalciferol

Vitamin D3 is rapidly metabolised by hydroxylation in the liver to 25-hydroxyvitamin D3, and subsequently metabolised in the kidney to 1,25-dihydroxyvitamin D3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D3 undergoes glucuronidation prior to elimination.

Elimination

Alendronate

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 10 mg intravenous dose, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95 % within six hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten 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.

Cholecalciferol

When radioactive vitamin D3 was administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4 %, and the mean faecal excretion of radioactivity after 4 days was 4.9 %. In both cases, the excreted radioactivity was almost exclusively as metabolites of the parent.

Renal impairment

Preclinical studies show that 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).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Aluminium magnesium silicate, butylhydroxytoluene, croscarmellose sodium, gelatin, lactose anhydrous, magnesium stearate, maize starch, microcrystalline cellulose, sucrose, sunflower oil.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25 °C in the original packaging to protect from moisture and light.

6.5. Nature and contents of container

Silver aluminium/aluminium blister containing 4 tablets, packaged in a cardboard carton.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

Hotline: 0800 122 912

8. REGISTRATION NUMBER

53/3.2/0225

9. DATE OF FIRST AUTHORISATION

25 March 2025

10. DATE OF REVISION OF TEXT

25 March 2025

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.