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S3

1. NAME OF THE MEDICINE

OSTEONATE PLUS 2800 ONCE A WEEK tablets.

OSTEONATE PLUS 5600 ONCE A WEEK tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OSTEONATE PLUS 2800 ONCE A WEEK: Each tablet contains sodium alendronate trihydrate equivalent to 70 mg alendronic acid and cholecalciferol concentrate (powder form) equivalent to 70 mcg cholecalciferol (2800 IU Vitamin D_3).

OSTEONATE PLUS 5600 ONCE A WEEK: Each tablet contains sodium alendronate trihydrate equivalent to 70 mg alendronic acid and cholecalciferol concentrate (powder form) equivalent 140 mcg cholecalciferol (5600 IU vitamin D_3).

OSTEONATE PLUS ONCE A WEEK contains sugar (lactose and sucrose) in the following quantities, respectively:

OSTEONATE PLUS 2800 ONCE A WEEK: 87,140 mg; 13,745 mg

OSTEONATE PLUS 5600 ONCE A WEEK: 59,140 mg; 27,490 mg

For the full list of excipients, see section 6.1

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3. PHARMACEUTICAL FORM

Tablets.

OSTEONATE PLUS 2800 ONCE A WEEK: White to off-white oblong, biconvex tablets, mottled, engraved with 2800 on one side with dimensions 12,3 mm ± 0,2 mm in length and 6,5 ± 0,2 mm in width.

OSTEONATE PLUS 5600 ONCE A WEEK: White to off-white, modified rectangle-shaped tablets, mottled, engraved with 5600 on one side with dimensions 11,4 mm ± 0,2 mm in length and 7,2 ± 0,2 mm in width.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OSTEONATE PLUS ONCE A WEEK 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) and to help ensure vitamin D adequacy.

4.2 Posology and method of administration

Posology

The recommended dosage is 1 (one) OSTEONATE PLUS ONCE A WEEK tablet once a week. For osteoporotic patients receiving a separate vitamin D supplement (400 IU) daily, the appropriate dose of OSTEONATE PLUS ONCE A WEEK is 70mg/2800 IU once weekly.

Patients should receive supplemental calcium and/or vitamin D if intake is inadequate (see section 4.4). Doctors should consider the vitamin D intake of the individual patient from vitamins and dietary supplements. OSTEONATE PLUS ONCE A WEEK provides a week's supply of vitamin D, based on a daily dose of 400 IU and 800 IU respectively, in a single once-a-week dose.

Special populations

Elderly

No dosage adjustment is necessary for the elderly.

Renal insufficiency

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min) (see section 4.3 and 5.2).
In patients with severe renal insufficiency, OSTEONATE PLUS ONCE A WEEK is contraindicated (see section 4.3).

Paediatric population

The safety and efficacy of OSTEONATE PLUS ONCE A WEEK in children less than 18 years of age have not been established.
OSTEONATE PLUS ONCE A WEEK is therefore contraindicated in children below 18 years (see section 4.3).

Method of administration

Oral use.

To facilitate delivery to the stomach and to reduce the potential for oesophageal irritation, OSTEONATE PLUS ONCE A WEEK must be taken at least a ½ hour before the first food, beverage or medication of the day, with a full glass of plain water.

Patients should only swallow OSTEONATE PLUS ONCE A WEEK 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 (see section 4.4).

Other beverages (including mineral water), food and some medicines are likely to reduce the absorption of alendronate, an active ingredient of OSTEONATE PLUS ONCE A WEEK (see section 4.5). Patients should not lie down for at least 30 minutes and not until after they have eaten. OSTEONATE PLUS ONCE A WEEK 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, cholecalciferol or to any of the ingredients of OSTEONATE PLUS ONCE A WEEK.
- abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.
- inability to stand or sit upright for at least 30 minutes.

- hypocalcaemia (see section 4.4).
- severe renal insufficiency (creatinine clearance less than 35 mL/min).
- pregnancy and lactation (see section 4.6).
- children below the age of 18 years.

4.4 Special warnings and precautions for use

Alendronic acid

Upper gastrointestinal adverse reactions

OSTEONATE PLUS ONCE A WEEK may cause local irritation of the upper gastro-intestinal mucosa.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, which may be followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with alendronate, as contained in OSTEONATE PLUS ONCE A WEEK. 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 OSTEONATE PLUS ONCE A WEEK and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

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The risk of severe oesophageal adverse experiences appears to be greater in patients who lie down after taking OSTEONATE PLUS ONCE A WEEK and/or who fail to swallow it with a full glass of water, and/or who continue to take OSTEONATE PLUS ONCE A WEEK after developing symptoms suggestive of oesophageal irritation.

It is therefore very important that the full dosing instructions are provided to, and understood by, the patient (see section 4.2).

Although no increased risk has been observed, there have been reports of gastric and duodenal ulcers, some severe and with complications when taking alendronate, as contained in OSTEONATE PLUS ONCE A WEEK (see section 4.8).

Due to possible irritant effects of alendronate, as contained in OSTEONATE PLUS ONCE A WEEK, on the upper gastro-intestinal mucosa and a potential for worsening of the underlying disease, caution should be used when OSTEONATE PLUS ONCE A WEEK is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal diseases (including known Barrett's oesophagus), gastritis, duodenitis or 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).

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To facilitate delivery to the stomach and therefore reduce the potential for oesophageal irritation, patients should be instructed to swallow OSTEONATE PLUS ONCE A WEEK with a full glass of water and to not lie down for at least 30 minutes and not until they have eaten. 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 PLUS ONCE A WEEK 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 OSTEONATE PLUS ONCE A WEEK and consult their doctor.

Since nonsteroidal anti-inflammatory medicine (NSAID) use is associated with gastrointestinal irritation, caution is advised with the concomitant use of OSTEONATE PLUS ONCE A WEEK and NSAIDs.

Osteonecrosis of the jaw:

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported, mainly in patients with cancer receiving treatment regimens including primarily intravenous administered bisphosphonates. Many of these were receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates, such as OSTEONATE PLUS ONCE A WEEK.

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A dental examination with appropriate preventative dentistry should be considered prior to treatment with bisphosphonates, such as OSTEONATE PLUS ONCE A WEEK, in patients with concomitant risk factors. Known risk factors for osteonecrosis of the jaw include a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene and co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, poorly fitting dentures, anaemia, coagulopathy, infection and smoking).

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 OSTEONATE PLUS ONCE A WEEK, dental surgery may exacerbate the condition.
For patients requiring invasive dental procedures (e.g. tooth extraction, dental implants), there is 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 an 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.

Musculoskeletal pain:

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have sometimes 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 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 three 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 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. Poor healing of these fractures has also been reported.

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

During OSTEONATE PLUS ONCE A WEEK 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.

Bone and mineral metabolism:

Causes of osteoporosis other than oestrogen deficiency and aging should be considered. Hypocalcaemia must be corrected before initiating therapy with OSTEONATE PLUS ONCE A WEEK (see section 4.3).

Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with OSTEONATE PLUS ONCE A WEEK.

Due to the positive effects of alendronate 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).

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Cholecalciferol

Vitamin D_3 may increase the magnitude of hypercalcaemia and/or hypercalciuria when administered to patients with diseases 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 D_3.

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.

Use in the elderly:

In clinical studies, there was no age-related difference in the efficacy or safety profiles of alendronic acid or cholecalciferol, as contained in OSTEONATE PLUS ONCE A WEEK.

Sugar:

OSTEONATE PLUS ONCE A WEEK contains lactose.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take OSTEONATE PLUS ONCE A WEEK.

OSTEONATE PLUS ONCE A WEEK contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Alendronic acid

It is likely that food and beverages (including mineral water) (see section 4.2), calcium supplements, antacids and other oral medicines, if taken concomitantly, will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking OSTEONATE PLUS ONCE A WEEK before taking any other oral medicine. No other interactions of clinical significance are anticipated.

A small number of post-menopausal women in the osteoporosis trials received oestrogen (intravaginal, transdermal or oral) while taking OSTEONATE PLUS ONCE A WEEK. No adverse experiences attributable to their concomitant use were identified.

Specific interaction studies were not performed. In post-menopausal osteoporosis studies, alendronate, an ingredient of OSTEONATE PLUS ONCE A WEEK, was used with a wide range of commonly prescribed medicines without evidence of clinical adverse interactions. Since nonsteroidal anti-inflammatory medicine (NSAID) use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

Cholecalciferol

Olestra, mineral oils, orlistat and bile acid sequestrants (e.g. cholestyramine, colestipol) may impair the absorption of vitamin D.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

OSTEONATE PLUS ONCE A WEEK has not been studied in pregnant women and is therefore contraindicated (see section 4.3). Studies in animals have shown reproductive toxicity.

Breastfeeding

OSTEONATE PLUS ONCE A WEEK is contraindicated in breastfeeding women as safety and efficacy have not been established (see section 4.3).

Fertility

There is 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

Certain adverse reactions that have been reported with OSTEONATE PLUS ONCE A WEEK may affect patients' ability to drive or operate machinery e.g. blurred vision, dizziness and severe bone muscle or joint pain (see section 4.8). Patients should be warned not to drive or use machines until they know how this medicine affect them.

4.8 Undesirable effects

a). Summary of the safety profile

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

b). Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects

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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	Headache, dizziness*
	Less frequent	Dysgeusia*
Eye disorders	Less frequent	Eye inflammation (Uveitis*, scleritis*, episcleritis*)
Ear and labyrinth disorders	Frequent	Vertigo*
	Less frequent	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Gastrointestinal disorders	Frequent	Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation

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	Less frequent	Nausea, vomiting*, gastritis, oesophagitis*, oesophageal erosions*, melaena, oesophageal stricture*, oropharyngeal ulceration, gastric or duodenal ulcers, some severe and with complications, upper gastrointestinal PUBs (perforation, ulcers, bleeding)
	Frequency unknown	Oesophageal perforations* (see section 4.4)
Skin and subcutaneous tissue disorders	Frequent	Alopecia, pruritus
	Less frequent	Rash, erythema, rash with photosensitivity*, severe skin reactions* including Stevens-Johnson syndrome* and toxic epidermal necrolysis*
Musculoskeletal, connective tissue and bone disorders	Frequent	Musculoskeletal (bone, muscle or joint) pain which is sometimes severe, joint swelling*

	Less frequent	Localised osteonecrosis of the jaw*, generally associated with tooth extraction and/or local infection, with delayed healing (see section 4.4), atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)
	Frequency unknown	Severe and/or incapacitating bone, joint, and/or muscle pain* (see section 4.4), low-energy femoral shaft fracture*
General disorders and administrative site conditions	Frequent	Asthenia*, peripheral oedema*
	Frequency unknown	Transient symptoms as in an acute-phase response* (myalgia*, malaise*and rarely, fever*) have been reported with alendronate, usually in association with initiation of treatment, and typically in association with the initiation of treatment
Investigations	Frequency unknown	Asymptomatic, mild and transient decreases in serum calcium and phosphate

*Post marketing adverse reactions.

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 asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

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:

Alendronic acid

Hypocalcaemia, hypophosphataemia and upper gastro-intestinal side effects, such as upset stomach, heartburn, oesophagitis, gastritis or ulcer, may result from oral overdosage.

Cholecalciferol

Vitamin D toxicity may occur with hypercalcaemia or hypercalciuria. This has not been documented during chronic therapy in generally healthy adults at a dose < 10 000 IU/day.

In a clinical study of healthy adults, a 4 000 IU daily dose of vitamin D_3 for up to five months was not associated with hypercalciuria or hypercalcaemia.

Management of overdose:

Alendronic acid

No specific information is available on the treatment of overdosage with alendronate, as contained in OSTEONATE PLUS ONCE A WEEK.

Milk or antacids should be given to bind alendronate. Due to the risk of oesophageal irritation, vomiting should not be induced, and the patient should remain fully upright.

Cholecalciferol

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: M05BB03

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

Mechanism of action

Alendronic acid

Alendronic acid, a bisphosphonate, acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogues of pyrophosphate that bind to the hydroxyapatite found in bone.

Cholecalciferol

Cholecalciferol (vitamin D_3) is a secosterol; the natural precursor of the calcium-regulating hormone calcitriol (1,25-dihydroxyvitamin D_3).

Vitamin D_3 is converted to 25-hydroxyvitamin D_3 in the liver. Conversion to the active calcium-mobilising hormone 1,25-dihydroxyvitamin D_3 (calcitriol) occurs in the kidney. The principal action of 1,25-dihydroxyvitamin D_3 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.

5.2 Pharmacokinetic properties

Absorption:

Alendronic acid

The mean oral bioavailability of alendronate in women is 0,57 % for the 70 mg tablet when administered after an overnight fast, and 2 hours before a standardised breakfast. The alendronate in the alendronate/cholecalciferol tablet and an alendronic acid 70 mg tablet show similar bioavailability.

Bioavailability is decreased similarly (by approximately 40 %) whether alendronate is administered 1 hour or ½ hour prior to a standardised breakfast. Alendronate is effective when administered at least ½ hour before the first food or beverage of the day (see section 4.2).

Bioavailability is negligible whether alendronate is administered with or up to two hours after a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduces bioavailability by approximately 60 %.

Cholecalciferol

Following administration of an alendronate/cholecalciferol 70 mg/2800 IU tablet after an overnight fast and 2 hours before a standard meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}120\ hrs}$) for vitamin D_3 was 296,4 ng-hr/mL. The mean maximal serum concentration (C_{max}) of vitamin D_3 is 5,9 ng/mL, and the median time to maximal serum concentration (T_{max}) was 12 hours. The bioavailability of the 2800 IU vitamin D_3 from an alendronate/cholecalciferol tablet is similar to 2800 IU vitamin D_3 administered alone.

Following administration of the 70 mg alendronate/5600 IU cholecalciferol tablet after an overnight fast and 2 hours before a meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}80h}$) for vitamin D_3 was 490,2 ng-hr/mL. The mean maximal serum concentration (C_{max}) of vitamin D_3 was 12,2 ng/mL, and the median time to maximal serum concentration (T_{max}) was 10,6 hours. The bioavailability of the vitamin D_3 in 70 mg alendronate/5600 IU cholecalciferol tablet is similar to an equal dose vitamin D_3 administered alone.

Distribution:

Alendronic acid

Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg IV 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 the plasma, following therapeutic oral doses, are too low for analytical detection (less than 5 ng/mL). Protein binding in human plasma is approximately 78 %.

Cholecalciferol

Following absorption, vitamin D_3 enters the blood as part of chylomicrons. Vitamin D_3 is distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D_3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D_3 at these sites for later release into the circulation. Circulating vitamin D_3 is bound to vitamin D-binding protein.

Biotransformation:

Alendronic acid

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

Cholecalciferol

Vitamin D_3 is metabolised by hydroxylation in the liver to 25-hydroxyvitamin D_3, and subsequently metabolised in the kidney to the biologically active form - 1,25-dihydroxyvitamin D_3. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D_3 undergoes glucuronidation prior to elimination.

Elimination:

Alendronic acid

Following a single IV 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 IV dose, the renal clearance of alendronate was 71 mL /min. Plasma concentrations fell by more than 95 % within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, reflecting release of alendronate from the skeleton.

Cholecalciferol

When radioactive vitamin D_3 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 is almost exclusively as metabolites of the parent compound. The mean half-life of vitamin D_3 in the serum following an oral dose of the 70 mg alendronate, 2800 IU cholecalciferol tablet is approximately 24 hours.

Pharmacokinetics in special patient groups

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 also sections 4.2 and 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium magnesium silicate

Butylhydroxytoluene (BHT) E321

Croscarmellose sodium

Gelatin (100 Bloom)

Lactose

Magnesium stearate

Maize Starch

Microcrystalline cellulose

Sunflower oil (refined)

Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original blister in order to protect from moisture and light.

6.5 Nature and contents of container

OSTEONATE PLUS ONCE A WEEK tablets are packed in PA/ALL/PVC - aluminium foil (Alu–Alu) blister strips, inside a carton. Each carton contains 4 tablets.

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, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

OSTEONATE PLUS 2800 ONCE A WEEK: A50/3.2/0636*

OSTEONATE PLUS 5600 ONCE A WEEK: A50/3.2/0637

**Not all strengths may be marketed*

9. DATE OF FIRST AUTHORISATION

June 2022

10. DATE OF REVISION OF THE TEXT

14 December 2022