PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1 NAME OF THE MEDICINE

ORTHOCOLE 5 600 (tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ORTHOCOLE contains 70 mg alendronic acid (as alendronate sodium trihydrate) and 140 microgram colecalciferol (equivalent to 5 600 IU vitamin D_3) per tablet.

Excipients with known effect:

Contains sugar.

Each tablet contains lactose (59,14 mg) and sucrose (27,49 mg).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ORTHOCOLE 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

For most osteoporotic patients, the appropriate dose is 70 mg/5 600 IU (one ORTHOCOLE tablet) **once weekly**. For osteoporotic patients receiving a separate vitamin D supplement (400 IU) daily, the appropriate dose is 70 mg/2 800 IU once weekly. As ORTHOCOLE is not available with the lower (2 800 IU) vitamin D content, another alendronate/colecalciferol product that only contains 2 800 IU vitamin D should be used in this case.

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).

Paediatric population

Safety and efficacy in children have not been established (see section 4.3)

Method of administration

ORTHOCOLE must be taken at least one-half hour before the first food, beverage, or medicine of the day with plain water only. Other beverages (including mineral water), food, and some medicines are likely to reduce the absorption of alendronate, an ingredient of ORTHOCOLE (see section 4.5).

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, ORTHOCOLE 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. ORTHOCOLE 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).

Patients should receive supplemental calcium and/or vitamin D, if intake is inadequate (see section 4.4). The medical practitioner should consider the vitamin D intake from vitamins and dietary supplements. ORTHOCOLE is intended to provide a week's supply of vitamin D based on a daily dose of 800 IU in a single, once weekly dose.

4.3 Contraindications

- Hypersensitivity to alendronate, colecalciferol or any of the other excipients of ORTHOCOLE (see section 6.1).
- 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.
- Hypocalcaemia (see section 4.4).
- Severe renal insufficiency (creatinine clearance less than 35 mL/minute).
- Pregnancy and lactation (see section 4.6).
- Paediatric age group.

4.4 Special warnings and precautions for use

Alendronate sodium

Upper gastrointestinal adverse reactions

ORTHOCOLE may cause local irritation of the upper gastrointestinal mucosa.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, in some instances followed by oesophageal stricture, have been reported in patients receiving treatment with alendronate as contained in ORTHOCOLE. 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 ORTHOCOLE 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 ORTHOCOLE and/or who fail to swallow it with a full glass of water, and/or who continue to take ORTHOCOLE 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 instructed that if they miss a dose of ORTHOCOLE, 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.

While no increased risk was reported in clinical trials with alendronate as contained in ORTHOCOLE, there have been reports of gastric and duodenal ulcers, some severe and with complications.

Because of possible irritant effects of alendronate, as contained in ORTHOCOLE, on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when ORTHOCOLE is given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal diseases (including known Barret's oesophagus), gastritis, duodenitis, or ulcers, or with a recent history (within the previous year) of major gastrointestinal diseases such as peptic ulcer, or active gastrointestinal bleeding, or surgery of the upper gastrointestinal tract, other than pyloroplasty.

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation patients should be instructed to swallow ORTHOCOLE 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 ORTHOCOLE 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 ORTHOCOLE and consult their medical practitioner.

Since non-steroidal anti-inflammatory drug (NSAID) use is associated with gastrointestinal irritation, caution is advised with the concomitant use of ORTHOCOLE and NSAIDs.

Osteonecrosis of the jaw

Localised osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported with oral bisphosphonates (see section 4.8). A dental examination with appropriate preventative dentistry should be considered prior to treatment with oral bisphosphonates in patients with poor dental status. Most reported cases of bisphosphonate-associated ONJ have been in cancer patients treated with intravenous bisphosphonates. Known risk factors for ONJ include the potency of the bisphosphonates, route of administration, cumulative dose, a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, invasive dental procedures, poorly fitting dentures and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anaemia, coagulopathy, infection and smoking). Patients who develop ONJ should receive appropriate care by a dental practitioner and discontinuation of

bisphosphonate therapy should be considered based on individual benefit/risk assessment. Dental surgery may exacerbate the condition.

For patients requiring invasive dental surgery (e.g. tooth extraction, dental implants), clinical judgement of the prescribing medical practitioner and treating dental practitioner should guide the management plan, including ORTHOCOLE treatment, of each patient based on individual benefit/risk assessment.

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.

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 medicine or another bisphosphonate.

Atypical fractures of the femur

Atypical, low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in long-term (usually longer than three 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 contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. Bisphosphonate therapy in patients with stress fractures should be discontinued and they should receive appropriate orthopaedic care.

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.

Bone and mineral metabolism

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

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

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 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).

Colecalciferol

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.

Special populations

Elderly patients

No age-related difference is reported in the efficacy or safety profiles of ORTHOCOLE.

Excipients

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

Paediatric population

The safety and efficacy of ORTHOCOLE in children less than 18 years have not been established (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Alendronate sodium

If taken concomitantly it is likely that food and beverages (including mineral water), calcium supplements, antacids and other oral medicines will interfere with the absorption of alendronate. Therefore, patients should be advised to wait at least 30 minutes after taking ORTHOCOLE before taking any other oral medicine (see section 4.2).

Since non-steroidal anti-inflammatory drug (NSAID) use is associated with gastrointestinal irritation, caution is advised with the concomitant use of ORTHOCOLE and NSAIDs.

No other interactions of clinical significance are anticipated.

According to published information a small number of postmenopausal women in the osteoporosis trials received oestrogen (intravaginal, transdermal, or oral) while taking alendronate. No adverse experiences attributable to their concomitant use were identified.

Specific interaction studies were not performed. In postmenopausal osteoporosis studies, alendronate, an ingredient of ORTHOCOLE, was used with a wide range of commonly prescribed medicines without evidence of clinical adverse interactions.

Colecalciferol

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

ORTHOCOLE is only intended for use in postmenopausal women and therefore it should not be used during pregnancy or in breast-feeding women (see section 4.3).

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. Studies in animals have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D. ORTHOCOLE should not be used during pregnancy.

Breast-feeding

It is unknown whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Colecalciferol and some of its active metabolites pass into breast milk. ORTHOCOLE 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

Adverse reactions such as dizziness, blurred vision, severe bone muscle or joint pain (see section 4.8) may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated summary of adverse reactions

Immune system disorders
Frequency unknown: hypersensitivity reactions including urticaria and angioedema

Metabolism and nutrition disorders

Frequency unknown:	symptomatic hypocalcaemia, often in association with predisposing conditions (see section 4.4)

Nervous system disorders

Frequent	headache
Frequency unknown	dizziness, vertigo, dysgeusia

Eye disorders

Frequency unknown	eye inflammation (uveitis, scleritis, or episcleritis)

Ear and labyrinth disorders

Less frequent	osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)

Gastrointestinal disorders

Frequent	abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, dysphagia (see sections 4.4 and 4.2), abdominal distension, acid regurgitation
Less frequent	nausea, gastritis, melena, oropharyngeal ulceration (see sections 4.4 and 4.2), upper gastrointestinal PUBs (perforation, ulcers, bleeding) (see section 4.4)
Frequency unknown	vomiting, oesophagitis, oesophageal erosions, oesophageal stricture, oesophageal perforations (see sections 4.4 and 4.2)

Skin and subcutaneous tissue disorders

Less frequent	rash, erythema
Frequency unknown	pruritus, rash with photosensitivity, alopecia, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders	
Frequent	musculoskeletal (bone, muscle or joint) pain
Less frequent	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), localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, with delayed healing (see section 4.4), joint swelling, low-energy femoral shaft fracture
General disorders and administration site conditions	
Frequency unknown	transient symptoms as in an acute-phase response (myalgia, malaise, asthenia and fever) typically in association with the initiation of treatment, peripheral oedema
Investigations	
Frequency unknown	Asymptomatic, mild and transient decreases in serum calcium and phosphate

Paediatric population

No data are available.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

Alendronate sodium

Symptoms

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

Management

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.

Colecalciferol

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

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 sodium

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

Colecalciferol

Colecalciferol (vitamin D_3) is a secosterol that is 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

Alendronate sodium

Relative to an intravenous (IV) reference dose, the mean bioavailability of alendronate in women is 0,57 % for the 70 mg tablet when administered orally after an overnight fast and two hours before a standardised breakfast.

Bioavailability is decreased similarly (by about 40 %) whether alendronate is administered one or one-half hour before the first food or beverage of the day (see section 4.2). In osteoporosis studies alendronate was effective when administered at least one-half hour before the first food or beverage of the day (see section 4.2).

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 about 60 %.

Colecalciferol

Following administration of 70 mg alendronate/5600 IU colecalciferol after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve

($AUC_{0\text{-}80\ hrs}$) 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 colecalciferol tablets is similar to an equal dose of vitamin D_3 administered alone.

Distribution

Alendronate sodium

Reportedly, studies in rats showed 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 L in humans. Concentrations of medicine in plasma following therapeutic oral doses are too low for analytical detection (less than 5 ng/mL). Protein binding in human plasma is approximately 78 %.

Colecalciferol

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

Alendronate sodium

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

Colecalciferol

Vitamin D_3 is metabolised by hydroxylation in the liver to 25-hydroxyvitamin D_3, and subsequently metabolised in the kidney to 1,25-dihydroxyvitamin D_3, which represents the

biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D_3 undergoes glucuronidation prior to elimination.

Elimination

Alendronate sodium

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 intravenous dose of 10 mg alendronate, the renal clearance was 71 mL/min. The 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.

Colecalciferol

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 was almost exclusively as metabolites of the parent. The mean half-life of vitamin D_3 in the serum following an oral dose of the 70 mg alendronate/2 800 IU colecalciferol tablet is approximately 24 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Microcrystalline cellulose (E460)

Croscarmellose sodium

Magnesium stearate (E572)

Sunflower oil, refined

Butylhydroxytoluene (E 321)

Gelatin

Sucrose

Maize starch

Aluminium magnesium silicate.

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 blister to protect from moisture and light.

6.5 Nature and contents of the container

ORTHOCOLE 5 600 IU tablets are packed in PA/ALL/PVC – Aluminium foil (Alu-Alu blister) foil blister strips. Each pack contains 4 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

Suite C, Rubenstein Ridge

617 Rubenstein Drive

Moreleta Park, 0181

Tel. no.: +27 (0)12 997 6974

8 REGISTRATION NUMBER

57/3.2/0655.654

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Registration date: 22 July 2025

10 DATE OF REVISION OF THE TEXT

Not applicable