SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

FOSAVANCE® 5600 Tablets

COMPOSITION

Each FOSAVANCE 5600 Tablet contains alendronate monosodium salt trihydrate which is the molar equivalent to 70 mg alendronic acid (anhydrous free acid), and 140 mcg of cholecalciferol equivalent to 5600 I.U. vitamin D_3.

Excipients: Microcrystalline cellulose, lactose anhydrous, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hydroxytoluene, modified food starch and sodium aluminium silicate.

FOSAVANCE 5600 contains sugar in the form of lactose anhydrous (63 mg) and sucrose (16 mg).

PHARMACOLOGICAL CLASSIFICATION

A.3.2. Connective tissue medicines, non-hormonal preparations

PHARMACOLOGICAL ACTION

Pharmacodynamic Properties

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.

Cholecalciferol

Cholecalciferol (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.

Pharmacokinetic Properties

Absorption

Alendronate Sodium

Relative to an intravenous (IV) reference dose, the mean bioavailability of alendronate in women was 0,57 % for the 70 mg tablet when administered orally after an overnight fast, and 2 hours before a standardised breakfast.

The alendronate in the alendronate/cholecalciferol (70 mg/5600 I.U.) tablets and the alendronate sodium 70 mg tablet is similarly bioavailable.

Bioavailability was decreased similarly (by approximately 40 %) whether alendronate was administered 1 hour or 30 minutes 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 (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Bioavailability was negligible whether alendronate was administered with or up to 2 hours after a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60 %.

Cholecalciferol

Following administration of the 70 mg alendronate/5600 I.U. cholecalciferol tablet after an overnight fast and 2 hours before a meal, the mean area under the serum-concentration-time curve (AUC_{0-80h}) 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 I.U. cholecalciferol tablets is similar to an equal dose of vitamin D_3 administered alone.

Distribution

Alendronate Sodium

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 drug 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 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.

Metabolism

Alendronate Sodium

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 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 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 was almost exclusively as metabolites of the parent.

INDICATIONS

FOSAVANCE 5600 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.

CONTRAINDICATIONS

Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.

Inability to stand or sit upright for at least 30 minutes.

Hypersensitivity to any component of FOSAVANCE 5600.

Hypocalcaemia (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Severe renal insufficiency (creatinine clearance < 35 ml/min).

Pregnancy and lactation (see **"PREGNANCY AND LACTATION"**).

Paediatric age group.

WARNINGS AND SPECIAL PRECAUTIONS

Alendronate Sodium

FOSAVANCE 5600 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 or perforation, have been reported in patients receiving treatment with alendronate as contained in FOSAVANCE 5600. 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 FOSAVANCE 5600, 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 FOSAVANCE 5600, and/or who fail to swallow it with a full glass of water, and/or who continue to take FOSAVANCE 5600 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 **"DOSAGE AND DIRECTIONS FOR USE"**).

While no increased risk was observed in extensive clinical trials with alendronate as contained in FOSAVANCE 5600, there have been reports of gastric and duodenal ulcers, some severe and with complications.

Because of possible irritant effects of alendronate, as contained in FOSAVANCE 5600 on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAVANCE 5600 is given to patients with active upper gastrointestinal problems, such as dysphagia, oesophageal diseases (including known Barrett's oesophagus), gastritis, duodenitis or ulcers.

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation patients should be instructed to swallow FOSAVANCE 5600 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 FOSAVANCE 5600 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 FOSAVANCE 5600 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 FOSAVANCE 5600 and NSAIDs.

Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported with oral bisphosphonates (see **"SIDE EFFECTS"**). Most reported cases of bisphosphonate-associated osteonecrosis of the jaw have been in cancer patients treated with intravenous bisphosphonates. Known risk factors for osteonecrosis of the jaw include a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids), poor oral hygiene and co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, anaemia, coagulopathy, infection and smoking). Patients who develop osteonecrosis of the jaw 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 FOSAVANCE 5600 treatment, of each patient based on individual benefit/risk assessment.

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 **"SIDE EFFECTS"**). 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.

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in long-term (usually longer than 3 years) bisphosphonate-treated patients. Some were stress fractures (some of which were reported as insufficiency fractures) occurring in the absence of apparent trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. Approximately one third of these fractures were bilateral; therefore the contra-lateral femur should be examined in patients who have sustained a femoral shaft stress fracture. Bisphosphonate therapy in patients with stress fractures should be discontinued.

Patients should be instructed that if they miss a dose of FOSAVANCE 5600, they should take 1 tablet on the morning after they remember. They should not take 2 tablets on the same day but should return to taking 1 tablet once a week, as originally scheduled on their chosen day.

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

Hypocalcaemia must be corrected before initiating therapy with FOSAVANCE 5600 (see **"CONTRAINDICATIONS"**). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions serum calcium and symptoms of hypocalcaemia should be monitored during therapy with FOSAVANCE 5600.

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.

Use in the Elderly

In clinical studies, there was no age-related difference in the efficacy or safety profiles of FOSAVANCE 5600.

Effects on Ability to Drive and Use Machines

Adverse reactions that have been reported with FOSAVANCE 5600 may affect the ability of patients to drive or operate machinery.

Excipients

FOSAVANCE 5600 contains lactose and sucrose. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicinal product.

INTERACTIONS

Alendronate Sodium

If taken concomitantly it is likely that calcium supplements, antacids, and other oral medications will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking FOSAVANCE 5600 before taking any other oral medication.

No other interactions of clinical significance are anticipated.

A small number of post-menopausal women in the osteoporosis trials received oestrogen (intra-vaginal, transdermal or oral) while taking FOSAVANCE 5600. 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 FOSAVANCE 5600, was used with a wide range of commonly prescribed medicines without evidence of clinical adverse interactions.

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.

PREGNANCY AND LACTATION

FOSAVANCE 5600 has not been studied in pregnant or breastfeeding women and should not be given to them (see **"CONTRAINDICATIONS"**).

DOSAGE AND DIRECTIONS FOR USE

The recommended dosage is one 70 mg/5600 I.U. tablet once weekly. For most osteoporotic patients the appropriate dose is 70 mg/5600 I.U. once weekly.

FOSAVANCE 5600 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, an ingredient of FOSAVANCE 5600 (see **"INTERACTIONS"**).

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, FOSAVANCE 5600 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. FOSAVANCE 5600 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 **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Patients should receive supplemental calcium and/or vitamin D if intake is inadequate (see **"WARNINGS AND SPECIAL PRECAUTIONS"**). Medical practitioners should consider the vitamin D intake from vitamins and dietary supplements. FOSAVANCE 5600 is intended to provide a week's supply of vitamin D based on a daily dose of 400 I.U. and 800 I.U. in a single, once-weekly dose, respectively.

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 **"CONTRAINDICATIONS"**).

SIDE EFFECTS

The following adverse experiences with alendronate, as contained in FOSAVANCE 5600 have been reported during clinical studies.

[Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100), Rare (≥ 1/10 000, < 1/1 000), Very rare (< 1/10 000 including isolated cases)]

Nervous system disorders

Common: Headache

Gastrointestinal disorders

Common: Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation

Uncommon: Nausea, gastritis, melaena

Rare: Oropharyngeal ulceration*, gastric or duodenal ulcers, some severe and with complications.

*(see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"DOSAGE AND DIRECTIONS FOR USE"**)

Skin and subcutaneous tissue disorders

Uncommon: Rash, erythema

Musculoskeletal, connective tissue and bone disorders

Common: Musculoskeletal (bone, muscle or joint) pain.

Laboratory Test Findings

A decrease in serum calcium and phosphate may occur.

Post-Marketing Experience

The following adverse experiences have been reported during post-marketing use of FOSAVANCE 5600:

Immune system disorders: Hypersensitivity reactions including urticaria and angioedema.

Metabolism and nutrition disorders: Symptomatic hypocalcaemia, generally in association with predisposing conditions (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Nervous system disorders: Dizziness, vertigo, dysgeusia.

Eye disorders: Uveitis, scleritis, episcleritis.

Gastrointestinal disorders: Vomiting, oesophagitis*, oesophageal erosions*, oesophageal stricture*, oesophageal perforations.

*(See **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"DOSAGE AND DIRECTIONS FOR USE"**).

Musculoskeletal, connective tissue and bone disorders: Severe and/or incapacitating bone, joint, and/or muscle pain, (see **"WARNINGS AND SPECIAL PRECAUTIONS"**);

localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, with delayed healing (see "**WARNINGS AND SPECIAL PRECAUTIONS"**)*, joint swelling, low-energy femoral shaft fracture.

Skin and subcutaneous tissue disorders: Pruritus, rash with photosensitivity, alopecia, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

General disorders and administration site conditions: Transient symptoms as in an acute-phase response (myalgia, malaise, asthenia and fever) have been reported with alendronate, usually in association with initiation of treatment, peripheral oedema.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Alendronate Sodium

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

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 I.U./day.

IDENTIFICATION

White to off-white modified rectangular shaped tablet with 270 on one side and a bone shape on the other side.

PRESENTATION

FOSAVANCE 5600 Tablets will be packaged in push-through aluminium blisters in packs containing 4 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from moisture and light. Store tablets in the original blister package until use.

Keep out of reach of children.

REGISTRATION NUMBER

44/3.2/0350

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

Spaces, 1st Floor

22 Magwa Crescent, Gateway West

Waterfall City, Midrand, 2090

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT

11 June 2015

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