SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

FOSAVANCE™ 2800 Tablets

FOSAVANCE™ 5600 Tablets

COMPOSITION

Each FOSAVANCE 2800 contains alendronate monosodium salt trihydrate which is the molar equivalent to 70 mg of free acid, and 70 mcg of cholecalciferol equivalent to 2800 IU vitamin D_3.

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 IU vitamin D_3.

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

FOSAVANCE 2800 contains sugar in the form of lactose anhydrous (62 mg) and sucrose (8 mg).

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

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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 two hours before a standardised breakfast.

The alendronate in the alendronate/cholecalciferol (70 mg/2800 IU and 70 mg/5600 IU) tablets and the alendronate sodium 70 mg tablet is similarly bioavailable.

Bioavailability was decreased similarly (by approximately 40 %) whether alendronate was administered one or one-half hour before a standardised breakfast. In osteoporosis studies alendronate was effective when administered at least one-half hour 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 two 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/2800 IU cholecalciferol tablet after an overnight fast and two 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 was 5,9 ng/ml, and the median time to maximal serum concentration (T_{max}) was 12 hrs. Following administration of 70 mg alendronate/5600 IU cholecalciferol 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/2800 IU cholecalciferol and 70 mg alendronate/5600 IU 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 L in humans. Concentrations of drug 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 %.

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. 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.

INDICATIONS

FOSAVANCE 2800 and FOSAVANCE 5600 are 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.

CONTRA-INDICATIONS

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.

Hypocalcaemia (see WARNINGS AND SPECIAL PRECAUTIONS).

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

Pregnancy and lactation (see PREGNANCY AND LACTATION).

Paediatric age group.

WARNINGS AND SPECIAL PRECAUTIONS

Alendronate Sodium

FOSAVANCE may cause local irritation of the upper gastro-intestinal 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. 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 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 and/or who fail to swallow it with a full glass of water, and/or who continue to take FOSAVANCE 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, 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 on the upper gastro-intestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAVANCE is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal diseases (including known Barret's oesophagus), gastritis, duodonitis, or ulcers.

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

Since NSAID use is associated with gastrointestinal irritation, caution is advised with the concomitant use of FOSAVANCE and NSAIDs.

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 SIDE EFFECTS). Most reported cases of bisphosphonate-associated ONJ have been in cancer patients treated with intravenous bisphosphonates. Known risk factors for ONJ 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 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 FOSAVANCE 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 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.

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

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

Hypocalcaemia must be corrected before initiating therapy with FOSAVANCE (see **CONTRA-INDICATIONS**). 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.

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.

Effects on ability to drive and use machines

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

Excipients

FOSAVANCE 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 one-half hour after taking FOSAVANCE before taking any other oral medication.

No other interactions of clinical significance are anticipated.

A small number of postmenopausal women in the osteoporosis trials received oestrogen (intravaginal,

transdermal, or oral) while taking FOSAVANCE. No adverse experiences attributable to their concomitant use were identified.

Specific interaction studies were not performed. In postmenopausal osteoporosis studies, alendronate, an ingredient of FOSAVANCE, 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 has not been studied in pregnant or breast-feeding women and should not be given to them (see **CONTRA-INDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

The recommended dosage is one 70 mg/2800 IU or one 70 mg/5600 IU tablet once weekly. For most osteoporotic patients the appropriate dose is 70 mg/5600 IU once weekly. For osteoporotic patients receiving a separate vitamin D supplement (400 IU) daily, the appropriate dose of FOSAVANCE is 70mg/2800 IU once weekly.

FOSAVANCE must be taken at least one-half hour 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 (see **INTERACTIONS).**

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, FOSAVANCE 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 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 practitioner should consider the vitamin D intake from vitamins and dietary supplements. FOSAVANCE 2800 and FOSAVANCE 5600 are intended to provide a week's supply of vitamin D based on a daily dose of 400 IU and 800 IU 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 **CONTRA-INDICATIONS**)

SIDE EFFECTS

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

[Common (greater than or equal to 1/100, less than 1/10), Uncommon (greater than or equal to 1/1000, less than1/100), Rare (greater than or equal to 1/10,000, less than 1/1000), Very rare (less than 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:

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**)

Muscoloskeletal, 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, hypophosphataemia and upper gastro-intestinal 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 less than 10,000 IU/day.

IDENTIFICATION

FOSAVANCE 2800 Tablet: White to off-white modified capsule shaped tablet with “710” on one side and a bone shape on the other side.

FOSAVANCE 5600 Tablet: White to off-white modified rectangular shaped tablet with "270" on one side and a bone shape on the other side.

PRESENTATION

FOSAVANCE 2800 and 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

FOSAVANCE 2800: A40/3.2/0259

FOSAVANCE 5600: 44/3.2/0350

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

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