SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FOSAVANCE® 70 mg/5,600 IU tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FOSAVANCE 70 mg/5,600 IU tablets
Each tablet contains 70 mg alendronic acid (as sodium trihydrate) and 140 micrograms (5,600 IU) colecalciferol (vitamin D_3).

Excipients with known effect
Each tablet contains 63 mg lactose (as lactose anhydrous) and 16 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
FOSAVANCE 70 mg/5,600 IU tablets
Modified rectangle-shaped, white to off-white tablets, marked with an outline of a bone image on one side, and '270' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FOSAVANCE is indicated for the treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency. It reduces the risk of vertebral and hip fractures.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet once weekly.

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.

Due to the nature of the disease process in osteoporosis, FOSAVANCE is intended for long-term use.
The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of FOSAVANCE on an individual patient basis, particularly after 5 or more years of use.

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

FOSAVANCE® 70 mg/2,800 IU tablets
The equivalence of intake of 2,800 IU of vitamin D_3 weekly in FOSAVANCE to daily dosing of vitamin D 400 IU has not been studied.

FOSAVANCE 70 mg/5,600 IU tablets
The equivalence of intake of 5,600 IU of vitamin D_3 weekly in FOSAVANCE to daily dosing of vitamin D 800 IU has not been studied.

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

Renal impairment
FOSAVANCE is not recommended for patients with renal impairment where creatinine clearance is less than 35 ml/min, due to lack of experience. No dose adjustment is necessary for patients with a creatinine clearance greater than 35 ml/min.

Paediatric population
The safety and efficacy of FOSAVANCE in children less than 18 years of age have not been established. This medicinal product should not be used in children less than 18 years of age because no data are available for the alendronic acid/colecalciferol combination. Currently available data for alendronic acid in the paediatric population is described in section 5.1.

Method of administration

Oral use.

To permit adequate absorption of alendronate:

FOSAVANCE must be taken with water only (not mineral water) at least 30 minutes before the first food, beverage, or medicinal product (including antacids, calcium supplements and vitamins) of the day. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see sections 4.5 and 4.8).

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

- FOSAVANCE should only be swallowed after getting up for the day with a full glass of water (not less than 200 ml).
- Patients should only swallow FOSAVANCE whole. Patients should not crush or chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
- Patients should not lie down for at least 30 minutes after taking FOSAVANCE and until after the first food of the day.
- FOSAVANCE should not be taken at bedtime or before arising for the day.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypocalcaemia.

4.4 Special warnings and precautions for use

Alendronate

Upper gastrointestinal adverse reactions

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

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

The risk of severe oesophageal adverse reactions appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and are understood by the patient (see section 4.2). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

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

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

The following risk factors should be considered when evaluating an individual's risk of developing osteonecrosis of the jaw:

- potency of the bisphosphonate (highest for zoledronic acid), route of administration (see above) and cumulative dose
- cancer, chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors, smoking
- a history of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures

A dental examination with appropriate preventive dentistry should be considered prior to treatment with oral bisphosphonates in patients with poor dental status.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

During bisphosphonate treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms such as pain or discharge, or chronic ear infections.

Musculoskeletal pain
Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see section 4.8). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique, fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.
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.

Atypical fractures of other bones
Atypical fractures of other bones, such as the ulna and tibia have also been reported in patients receiving long-term treatment. As with atypical femoral fractures, these fractures occur after minimal, or no trauma and some patients experience prodromal pain prior to presenting with a completed fracture. In cases of ulna fracture, this may be associated with repetitive stress loading associated with the long-term use of walking aids.

Renal impairment
FOSAVANCE is not recommended for patients with renal impairment where creatinine clearance is less than 35 ml/min (see section 4.2).

Bone and mineral metabolism
Causes of osteoporosis other than oestrogen deficiency and ageing should be considered.

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

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).

Colecalciferol
Vitamin D_3 may increase the magnitude of hypercalcaemia and/or hypercalciuria when administered to patients with disease associated with unregulated overproduction of calcitriol (e.g. leukaemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.

Patients with malabsorption may not adequately absorb vitamin D_3.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Since Non Steroidal Anti-Inflammatory Drug (NSAID) use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

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

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

Pregnancy

There are no or limited amount of data from the use of alendronate in pregnant women. Studies in animals have shown reproductive toxicity. Alendronate given during pregnancy in rats caused dystocia related to hypocalcaemia (see section 5.3). Studies in animals have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D (see section 5.3). FOSAVANCE 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. FOSAVANCE 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

FOSAVANCE has no or negligible direct influence on the ability to drive and use machines. Patients may experience certain adverse reactions (for example, blurred vision, dizziness and severe bone muscle or joint pain (see section 4.8)) that may influence the ability to drive and use machines.

4.8 Undesirable effects

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 %).

Tabulated list of adverse reactions

The following adverse reactions have been reported during clinical studies and/or post-marketing use with alendronate.

No additional adverse reactions have been identified for the combination of alendronate and colecalciferol.

Frequencies are defined as: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reactions
Immune system disorders	Rare	hypersensitivity reactions including urticaria and angioedema
Metabolism and nutrition disorders	Rare	symptomatic hypocalcaemia, often in association with predisposing condition,[§]
Nervous system disorders	Common	headache, dizziness[†]
	Uncommon	dysgeusia[†]
Eye disorders	Uncommon	eye inflammation (uveitis, scleritis, or episcleritis)
Ear and labyrinth disorders	Common	vertigo[†]
	Very rare	osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Gastrointestinal disorders	Common	abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation
	Uncommon	nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena[†]
	Rare	oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding)[§]
Skin and subcutaneous tissue disorders	Common	alopecia[†], pruritus[†]
	Uncommon	rash, erythema
	Rare	rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis[‡]
Musculoskeletal and connective tissue disorders	Very common	musculoskeletal (bone, muscle or joint) pain which is sometimes severe[†§]
	Common	joint swelling[†]
	Rare	osteonecrosis of the jaw[‡§]; atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)
	Not known	atypical fractures of other bones
General disorders and administration site conditions	Common	asthenia[†], peripheral oedema[†]
	Uncommon	transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever), typically in association with initiation of treatment[†]

[§]*See section 4.4*
[†]*Frequency in Clinical Trials was similar in the medicinal product and placebo group.*
**See sections 4.2 and 4.4*
[‡]*This adverse reaction was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trials.*

Description of selected adverse reactions

Atypical subtrochanteric and diaphyseal femoral fractures
Although the pathophysiology is uncertain, consistent evidence from epidemiological studies suggests an increased risk of atypical subtrochanteric and diaphyseal femoral fractures with long-term bisphosphonate therapy for postmenopausal osteoporosis, particularly beyond three to five years of use. The absolute risk of atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction) remains rare.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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

Colecalciferol
Vitamin D toxicity has not been documented during chronic therapy in generally healthy adults at a dose less than 10,000 IU/day. In a clinical study of healthy adults a 4,000 IU daily dose of vitamin D_3 for up to five months was not associated with hypercalciuria or hypercalcaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases, Bisphosphonates, combinations, ATC code: M05BB03

Mechanism of action

Alendronate
Alendronate sodium is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Colecalciferol (vitamin D_3)
Vitamin D_3 is produced in the skin by conversion of 7-dehydrocholesterol to vitamin D_3 by ultraviolet light. In the absence of adequate sunlight exposure, vitamin D_3 is an essential dietary nutrient. Vitamin D_3 is converted to 25-hydroxyvitamin D_3 in the liver, and stored until needed. Conversion to the active calcium-mobilising hormone 1,25-dihydroxyvitamin D_3 (calcitriol) in the kidney is tightly regulated. 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.

Vitamin D_3 is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in secondary hyperparathyroidism, hypophosphataemia, proximal muscle weakness and osteomalacia, further increasing the risk of falls and fractures in osteoporotic individuals. Supplemental vitamin D reduces these risks and their consequences.

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

Clinical efficacy and safety

FOSAVANCE studies
The effect of the lower dose of FOSAVANCE (alendronate 70 mg/vitamin D_3 2,800 IU) on vitamin D status was demonstrated in a 15-week, multinational study that enrolled 682 osteoporotic post-menopausal women (serum 25-hydroxyvitamin D at baseline: mean, 56 nmol/l [22.3 ng/ml]; range, 22.5-225 nmol/l [9-90 ng/ml]). Patients received the lower strength (70 mg/2,800 IU) of FOSAVANCE (n=350) or FOSAMAX (alendronate) 70 mg (n=332) once a week; additional vitamin D supplements were prohibited. After 15 weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher (26 %) in the FOSAVANCE (70 mg/2,800 IU) group (56 nmol/l [23 ng/ml]) than in the alendronate-only group (46 nmol/l [18.2 ng/ml]). The percentage of patients with vitamin D insufficiency (serum 25-hydroxyvitamin D < 37.5 nmol/l [< 15 ng/ml]) was significantly reduced by 62.5 % with FOSAVANCE (70 mg/2,800 IU) vs. alendronate-only (12 % vs. 32 %, respectively), through week 15. The percentage of patients with vitamin D deficiency (serum 25-hydroxyvitamin D < 22.5 nmol/l [< 9 ng/ml]) was significantly reduced by 92 % with FOSAVANCE (70 mg/2,800 IU) vs. alendronate-only (1 % vs 13 %, respectively). In this study, mean 25-hydroxyvitamin D levels in patients with vitamin D insufficiency at baseline (25-hydroxyvitamin D, 22.5 to 37.5 nmol/l [9 to < 15 ng/ml]) increased from 30 nmol/l (12.1 ng/ml) to 40 nmol/l (15.9 ng/ml) at week 15 in the FOSAVANCE (70 mg/2,800 IU) group (n=75) and decreased from 30 nmol/l (12.0 ng/ml) at baseline to 26 nmol/l (10.4 ng/ml) at week 15 in the

alendronate-only group (n=70). There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups.

The effect of the lower dose of FOSAVANCE (alendronate 70 mg/vitamin D_3 2,800 IU) plus an additional 2,800 IU Vitamin D_3 for a total of 5,600 IU (the amount of vitamin D_3 in the higher dose of FOSAVANCE) once weekly was demonstrated in a 24-week, extension study that enrolled 619 osteoporotic post-menopausal women. Patients in the Vitamin D_3 2,800 group received FOSAVANCE (70 mg/2,800 IU) (n=299) and patients in the Vitamin D_3 5,600 group received FOSAVANCE (70 mg/2,800 IU) plus an additional 2,800 IU vitamin D_3 (n=309) once a week; additional vitamin D supplements were allowed. After 24-weeks of treatment, the mean serum 25-hydroxyvitamin D levels were significantly higher in the Vitamin D_3 5,600 group (69 nmol/l [27.6 ng/ml]) than in the Vitamin D_3 2,800 group (64 nmol/l [25.5 ng/ml]). The percentage of patients with vitamin D insufficiency was 5.4 % in the Vitamin D_3 2,800 group vs. 3.2 % in the Vitamin D_3 5,600 group through the 24-week extension. The percentage of patients with vitamin D deficiency was 0.3 % in the Vitamin D_3 2,800 group vs. zero in the Vitamin D_3 5,600 group. There were no differences in mean serum calcium, phosphate, or 24-hour urine calcium between treatment groups. The percentage of patients with hypercalciuria at the end of the 24-week extension was not statistically different between treatment groups.

Alendronate studies
The therapeutic equivalence of alendronate once weekly 70 mg (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study of post-menopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1 % (95 % CI: 4.8, 5.4 %) in the 70 mg once-weekly group and 5.4 % (95 % CI: 5.0, 5.8 %) in the 10 mg daily group. The mean BMD increases were 2.3 % and 2.9 % at the femoral neck and 2.9 % and 3.1 % at the total hip in the 70 mg once weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.

The effects of alendronate on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459).

In the initial efficacy studies, the mean BMD increases with alendronate 10 mg/day relative to placebo at three years were 8.8 %, 5.9 % and 7.8 % at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. There was a 48 % reduction (alendronate 3.2 % vs placebo 6.2 %) in the proportion of patients treated with alendronate experiencing one or more vertebral fractures relative to those treated with placebo. In the two-year extension of these studies BMD at the spine and trochanter continued to increase and BMD at the femoral neck and total body were maintained.

FIT consisted of two placebo-controlled studies using alendronate daily (5 mg daily for two years and 10 mg daily for either one or two additional years):

- FIT 1: A three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture. In this study alendronate daily reduced the incidence of ≥ 1 new vertebral fracture by 47 % (alendronate 7.9 % vs. placebo 15.0 %). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1 % vs. 2.2 %, a reduction of 51 %).

- FIT 2: A four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37 % of the global population who correspond with the above definition of osteoporosis) in the incidence of hip fractures (alendronate 1.0 % vs. placebo 2.2 %, a reduction of 56 %) and in the incidence of ≥ 1 vertebral fracture (2.9 % vs. 5.8 %, a reduction of 50 %).

Laboratory test findings
In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 % and 10 %, respectively, of patients taking alendronate 10 mg/day versus approximately 12 % and 3 % of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≤ 2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

Paediatric population
Alendronate sodium has been studied in a small number of patients with osteogenesis imperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfecta.

5.2 Pharmacokinetic properties

Alendronate

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

The alendronate component in the FOSAVANCE (70 mg/2,800 IU) combination tablet and the FOSAVANCE (70 mg/5,600 IU) combination tablet is bioequivalent to the alendronate 70 mg tablet.

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

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronate (a mean increase ranging from 20 % to 44 %).

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

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

Elimination
Following a single intravenous dose of [^{14}C]alendronate, approximately 50 % of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg intravenous dose, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95 % within six hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

<u>Colecalciferol</u>

Absorption
In healthy adult subjects (males and females), following administration of FOSAVANCE 70 mg/2,800 IU tablets after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}120\ hrs}$) for vitamin D_3 (unadjusted for endogenous vitamin D_3 levels) 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 hours. The bioavailability of the 2,800 IU vitamin D_3 in FOSAVANCE is similar to 2,800 IU vitamin D_3 administered alone.

In healthy adult subjects (males and females), following administration of FOSAVANCE 70 mg/5,600 IU 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 (unadjusted for endogenous vitamin D_3 levels) 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 5,600 IU vitamin D_3 in FOSAVANCE is similar to 5,600 IU vitamin D_3 administered alone.

Distribution
Following absorption, vitamin D_3 enters the blood as part of chylomicrons. Vitamin D_3 is rapidly 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
Vitamin D_3 is rapidly 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
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 FOSAVANCE (70 mg/2,800 IU) is approximately 24 hours.

Renal impairment
Preclinical studies show that alendronate that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative intravenous doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see section 4.2).

5.3 Preclinical safety data

Non-clinical studies with the combination of alendronate and colecalciferol have not been conducted.

Alendronate
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in rats have shown that treatment with alendronate during pregnancy was associated with dystocia in dams during parturition which was related to hypocalcaemia. In studies, rats given high doses showed an increased incidence of incomplete foetal ossification. The relevance to humans is unknown.

Colecalciferol
At doses far higher than the human therapeutic range, reproductive toxicity has been observed in animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Lactose anhydrous
Medium chain triglycerides
Gelatin
Croscarmellose sodium
Sucrose
Colloidal silicon dioxide
Magnesium stearate (E572)
Butylhydroxytoluene (E321)
Modified starch (maize)
Sodium aluminium silicate (E554)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

FOSAVANCE 70 mg/5,600 IU tablets
Aluminium/aluminium blisters, in cartons containing 2, 4 or 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Organon Pharma (UK) Limited
Shotton Lane
Cramlington
United Kingdom
NE23 3JU

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00025/0649

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

26/02/2025