NEW ZEALAND DATA SHEET

1 FOSAMAX PLUS™ 70/70 (70 mg/70 mcg tablet)

FOSAMAX PLUS™ 70/140 (70 mg/140 mcg tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alendronate sodium/colecalciferol 70 mg/70 mcg tablet (No longer available in New Zealand).
Each tablet contains 70 mg of alendronate sodium and 70 mcg (2800 IU) of Vitamin D_3.

Alendronate sodium/colecalciferol 70 mg/140 mcg tablet.
Each tablet contains 70 mg of alendronate sodium and 140 mcg (5600 IU) of Vitamin D_3.

Composition
Active Ingredients:
Each tablet of FOSAMAX PLUS contains 91.37 mg of alendronate monosodium salt trihydrate which is the molar equivalent to 70.0 mg of free acid, and 70 mcg or 140 mcg of colecalciferol equivalent to 2800 IU or 5600 IU vitamin D, respectively.

Excipients with known effect

- Lactose

For the full list of excipients, see **Section 6.1 List of excipients.**

3 PHARMACEUTICAL FORM

70 mg/70 mcg: White to off white modified capsule shaped tablet marked with 710 on one side and a bone shape on the other. Dimensions are 12.065 mm x 6.35 mm. (No longer available in New Zealand.)

70 mg/140 mcg: White to off white modified rectangle shaped tablet marked with 270 on one side and a bone shape on the other. Dimensions are 11.201 mm x 6.985 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FOSAMAX PLUS is indicated for the treatment of osteoporosis in select patients where vitamin D supplementation is recommended.

4.2 Dose and method of administration

Dose

The recommended dosage is one 70 mg/70 mcg or one 70 mg/140 mcg tablet once weekly. For most osteoporotic patients the appropriate dose is 70 mg/140 mcg once weekly. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis (see **Section 4.8 Undesirable effects**, **Clinical Studies**).

Patients should receive supplemental calcium and/or vitamin D, if intake is inadequate (see **Section 4.4 Special warnings and precautions for use**). Physicians should consider the vitamin D intake from vitamins and dietary supplements. FOSAMAX PLUS 70 mg/70 mcg and 70 mg/140 mcg are intended to provide seven days' worth of 400 and 800 IU daily vitamin D in a single, once-weekly dose, respectively.

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). FOSAMAX PLUS is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience.

Paediatric population

See **Section 4.4 Special warnings and precautions for use.**

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

Method of administration

FOSAMAX PLUS 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 (see **Section 4.5 Interactions with other medicines and other forms of interactions**).

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, FOSAMAX PLUS 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. FOSAMAX PLUS 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 Special warnings and precautions for use**).

Do not halve, crush or chew the tablets (See **Section 4.4 Special warnings and precautions for use**).

4.3 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 the active substance or to any of the excipients listed in **Section 6.1 List of excipients**.
- Hypocalcaemia (see **Section 4.4 Special warnings and precautions for use**).

4.4 Special warnings and precautions for use

Alendronate Sodium

FOSAMAX PLUS, like other bisphosphonate-containing products, may cause local irritation of the upper gastrointestinal mucosa.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with alendronate. In some cases these have been severe and required hospitalisation. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue FOSAMAX PLUS 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 FOSAMAX PLUS and/or who fail to swallow it with a full glass of water, and/or who continue to take FOSAMAX PLUS 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 Dose and method of administration**).

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 severe and with complications.

Because of possible irritant effects of alendronate on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when FOSAMAX PLUS 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 each tablet of FOSAMAX PLUS 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 FOSAMAX PLUS 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 FOSAMAX PLUS and consult their physician.

Localised osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, has been reported rarely with oral bisphosphonates (see **Section 4.8 Undesirable effects**, **Post-Marketing Experience**). 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, angiogenesis inhibitors), poor oral hygiene, 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 an oral surgeon 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 judgment of the treating physician and/or oral surgeon should guide the management plan, including bisphosphonate 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 rarely been severe and/or incapacitating (see **Section 4.8 Undesirable effects**, **Post-Marketing Experience**). 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 and other bones have been reported in a small number of 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 or induced by mild external force. 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 the reported femur fractures were bilateral; therefore the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. Stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g. vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

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

Hypocalcaemia must be corrected before initiating therapy with FOSAMAX PLUS (see **Section 4.3 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 FOSAMAX PLUS.

Due to the positive effects of alendronate in increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur.

FOSAMAX PLUS contains lactose (see **Section 6.1 List of excipients**) which is not suitable for some patients.

Colecalciferol

Vitamin D_3 may increase the magnitude of hypocalcaemia 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.

Renal impairment

FOSAMAX PLUS is not recommended for patients with creatinine clearance < 35 mL/min (see **Section 4.2 Dose and method of administration**).

Paediatric population

FOSAMAX PLUS has not been studied in children and should not be given to them.

Use in the elderly

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

4.5 Interactions with other medicines and other forms of interactions

Alendronate Sodium
If taken at the same time 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 FOSAMAX PLUS before taking any other oral medication.

No other medicine interactions of clinical significance are anticipated.

Concomitant use of HRT (oestrogen ± progestin) and FOSAMAX® (alendronate sodium) was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of FOSAMAX and HRT resulted in greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments (see **Section 4.8 Undesirable effects, Clinical Studies, Concomitant use with oestrogen/hormone replacement therapy**).

Specific interaction studies were not performed. FOSAMAX was used in osteoporosis studies in men, postmenopausal women and glucocorticoid users, with a wide range of commonly prescribed medicines without evidence of clinical adverse interactions.

In a three year controlled clinical study (n = 2027) during which a majority of patients received concomitant NSAIDs, the incidence of ulcer-related adverse events was similar in patients taking FOSAMAX 5 or 10 mg compared to those taking placebo.

However, the incidence of upper gastrointestinal adverse events was increased in the patients receiving daily therapy with dosages of FOSAMAX greater than 10 mg and aspirin- containing products in other clinical studies. However this was not observed in studies with FOSAMAX once weekly 70 mg.

Since 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

FOSAMAX PLUS has not been studied in pregnant women and should not be given to them.

Breast-feeding

FOSAMAX PLUS has not been studied in breast-feeding women and should not be given to them.

Fertility

See **Section 5.3 Preclinical safety data, Animal Toxicology, Reproduction.**

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with FOSAMAX may affect some patients' ability to drive or operate machinery. Individual responses to FOSAMAX may vary (see **Section 4.8 Undesirable effects**).

4.8 Undesirable effects

Clinical Studies

FOSAMAX®
In clinical studies FOSAMAX was generally well tolerated. In studies of up to five years in duration, side effects, which usually were mild, generally did not require discontinuation of therapy.

Treatment of Osteoporosis

Postmenopausal Women

In two three-year, placebo-controlled, double-blind, multicentre studies (United States and Multinational) of virtually identical design, the overall safety profiles of FOSAMAX 10 mg/day and placebo were similar. The following upper gastrointestinal adverse experiences were reported by the investigators as possibly, probably, or definitely medicine related in ≥ 1% of patients treated with FOSAMAX 10 mg/day and at a greater incidence than in patients treated with placebo: abdominal pain (FOSAMAX, 6.6% vs. placebo, 4.8%), dyspepsia (3.6%, 3.5%), oesophageal ulcer (1.5%, 0.0%), dysphagia (1.0%, 0.0%), and abdominal distension (1.0%, 0.8%).

Rarely, rash and erythema have occurred.

Additionally, the following adverse experiences were reported by the investigators as possibly, probably, or definitely medicine related in ≥ 1% of patients treated with FOSAMAX 10 mg/day and at a greater incidence than in patients treated with placebo: musculoskeletal (bone, muscle or joint) pain (FOSAMAX, 4.1% vs. placebo, 2.5%), constipation (3.1%, 1.8%), diarrhoea (3.1%, 1.8%), flatulence (2.6%, 0.5%), and headache (2.6%, 1.5%).

In the two-year extension (treatment years 4 and 5) of the above studies, the overall safety profile of FOSAMAX 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued FOSAMAX 10 mg/day due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicentre study, the overall safety and tolerability profiles of FOSAMAX once weekly 70 mg (n = 519) and FOSAMAX 10 mg daily (n = 370) were similar. The following adverse experiences were reported by the investigators as possibly, probably, or definitely medicine related in ≥ 1% of patients in either treatment group: abdominal pain (FOSAMAX once weekly 70 mg, 3.7%; FOSAMAX 10 mg daily, 3.0%), musculoskeletal (bone, muscle or joint) pain (2.9%, 3.2%), dyspepsia (2.7%, 2.2%), acid regurgitation (1.9%, 2.4%), nausea (1.9%, 2.4%), abdominal distension (1.0%, 1.4%), constipation (0.8%, 1.6%), flatulence (0.4%, 1.6%), muscle cramp (0.2%, 1.1%), gastritis (0.2%, 1.1%), and gastric ulcer (0.0%, 1.1%).

Men

In two, placebo-controlled, double-blind, multicentre studies in men (a two-year study of FOSAMAX 10 mg/day [n = 146] and a one-year study of FOSAMAX once weekly 70 mg [n = 109]), the safety profile of FOSAMAX was generally similar to that seen in postmenopausal women.

Other Studies in Men and Women

In a ten-week endoscopy study in men and women (n = 277; mean age: 55) no difference was seen in upper gastrointestinal tract lesions between FOSAMAX once weekly 70 mg and placebo.

In an additional one-year study in men and women (n = 335; mean age: 50) the overall safety and tolerability profiles of FOSAMAX once weekly 70 mg were similar to that of placebo and no difference was seen between men and women.

In two one-year studies in men and women (n = 477) receiving glucocorticoids, melena was reported in two patients treated with FOSAMAX 10 mg/day.

Concomitant use with oestrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n = 853), the safety and tolerability profile of combined treatment with FOSAMAX 10

mg once daily and oestrogen ± progestin (n = 354) was consistent with those of the individual treatments.

FOSAMAX PLUS
In a 15-week, double-blind, multinational study in osteoporotic postmenopausal women (n = 682) and men (n = 35), the safety profile of once weekly FOSAMAX PLUS (alendronate 70 mg/vitamin D_3 70 mcg) was similar to that of FOSAMAX once weekly 70 mg. In the 24-week double-blind extension study in women (n = 619) and men (n = 33), the safety profile of FOSAMAX PLUS (70 mg/70 mcg) administered with an additional 70 mcg (2800 IU) vitamin D_3 for a total of 140 mcg (5600 IU) was similar to that of FOSAMAX PLUS (70 mg/70 mcg).

Post-Marketing Experience
The following adverse reactions have been reported in post-marketing use with alendronate:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. As with other bisphosphonates, transient symptoms as in an acute-phase response (myalgia, malaise, asthenia and rarely, fever) have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcaemia has occurred, generally in association with predisposing conditions. Rarely, peripheral oedema.

Gastrointestinal: nausea, vomiting, oesophagitis, oesophageal erosions, oesophageal ulcers, rarely oesophageal stricture or perforation, and oropharyngeal ulceration; rarely, gastric or duodenal ulcers, some severe and with complications (see **Section 4.4 Special warnings and precautions for use** and **Section 4.2 Dose and method of administration**). Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), with delayed healing has been reported rarely. (See **Section 4.4 Special warnings and precautions for use**.)

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (see **Section 4.4 Special warnings and precautions for use**); joint swelling; low-energy fractures of the femoral shaft and other bones (see **Section 4.4 Special warnings and precautions for use**).

Nervous System: dizziness, vertigo, dysgeusia.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis. Cholesteatoma of the external auditory canal (focal osteonecrosis) has been reported rarely.

Laboratory Test Findings
In double-blind, multicentre, controlled studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking FOSAMAX versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg P/dL (0.65 mM) were similar in both treatment groups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Alendronate Sodium

No specific information is available on the treatment of overdosage with alendronate. Hypocalcaemia, hypophosphataemia, 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.

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 4000 IU daily dose of vitamin D_3 for up to five months was not associated with hypercalciuria or hypocalcaemia.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonates, combinations; ATC code: M05BB03

FOSAMAX PLUS contains alendronate sodium and colecalciferol (vitamin D_3).

Alendronate Sodium
Alendronate sodium is a bisphosphonate that acts as a potent, specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs 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).

Mechanism of action

Alendronate Sodium
Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localisation to sites of bone resorption specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localisation of radioactive [^{3}H] alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H] alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix, where it is no longer pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e. the number of sites at which bone is remodelled). In addition, bone formation exceeds bone resorption at these remodelling sites, leading to progressive gains in bone mass.

Colecalciferol
Vitamin D_3 is produced in the skin by photochemical conversion of 7-dehydrocholesterol to previtamin D_3 by ultraviolet light. This is followed by non-enzymatic isomerisation to vitamin D_3. In the absence of adequate sunlight exposure, vitamin D_3 is an essential dietary nutrient. Vitamin D_3 in skin and dietary vitamin D_3 (absorbed into chylomicrons) is converted to 25-hydroxyvitamin D_3 in the liver. Conversion to the active calcium-mobilising hormone 1,25-dihydroxyvitamin D_3 (calcitriol) in the kidney is stimulated by both parathyroid hormone and

hypophosphataemia. 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.

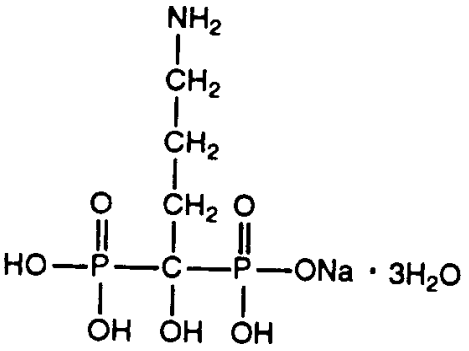
Vitamin D_3 is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in secondary 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.

Chemistry

FOSAMAX PLUS contains alendronate sodium and colecalciferol (vitamin D_3).

Alendronate sodium is described chemically as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

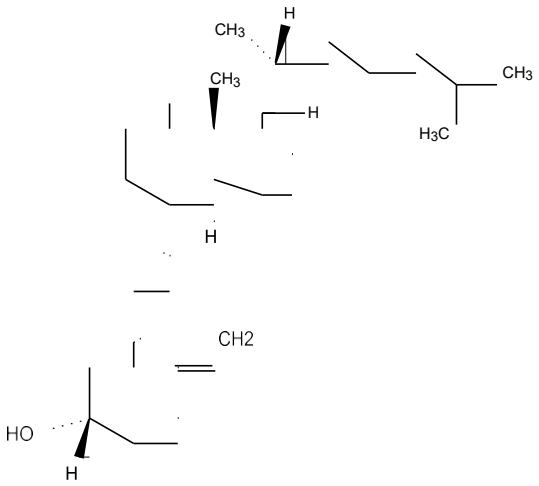
The empirical formula is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$. The formula weight is 325.12. The structural formula is:



Alendronate is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

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

The chemical name of colecalciferol is (3β,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3-ol. The empirical formula of colecalciferol is $C_{27}H_{44}O$ and its molecular weight is 384.6. The structural formula is:



Colecalciferol is a white, crystalline, odourless powder. Colecalciferol is practically insoluble in water, freely soluble in usual organic solvents, and slightly soluble in vegetable oils.

5.2 Pharmacokinetic properties

Absorption

Alendronate Sodium
Relative to an intravenous (IV) reference dose, the mean oral 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. Oral bioavailability in men (0.6%) was similar to that in women.

The alendronate in the FOSAMAX PLUS (70 mg/70 mcg) and FOSAMAX PLUS (70 mg/140 mcg) tablets and the FOSAMAX 70 mg tablet is bioequivalent.

Bioavailability was decreased similarly (by approximately 40%) whether alendronate was administered one or one-half hour before a standardised breakfast. In osteoporosis studies, FOSAMAX was effective when administered at least 30 minutes before the first food or beverage of the day.

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 the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Colecalciferol
Following administration of FOSAMAX PLUS (70 mg/70 mcg) 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 (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 hrs. Following administration of FOSAMAX PLUS (70 mg/140 mcg) 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 vitamin D_3 in FOSAMAX

PLUS (70 mg/70 mcg) and FOSAMAX PLUS (70 mg/140 mcg) 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 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 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

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

Colecalciferol
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

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, and systemic clearance did not exceed 200 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.

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 FOSAMAX PLUS (70 mg/70 mcg) is approximately 24 hours.

Characteristics in patients

Preclinical studies show that the 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 IV 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 Dose and method of administration**).

5.3 Preclinical safety data

Animal Toxicology

Carcinogenicity

Alendronate Sodium

No evidence of carcinogenic effect was observed in a 105-week study in rats receiving oral doses up to 3.75 mg/kg/day and in a 92-week study in mice receiving oral doses up to 10 mg/kg/day.

Colecalciferol

The carcinogenic potential of colecalciferol has not been studied in rodents.

Mutagenesis

Alendronate Sodium

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation. Similarly, no evidence of mutagenicity was observed in an *in vitro* mammalian cell mutagenesis assay, an *in vitro* alkaline elution assay in rat hepatocytes, and an *in vivo* chromosomal aberration assay in mice at IV doses up to 25 mg/kg/day (75 mg/m^2). In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate was weakly positive at concentrations ≥ 5 mM in the presence of cytotoxicity. This is of no relevance to safety in humans since similar concentrations are not achievable *in vivo* at therapeutic doses. Furthermore, clear negative results in four of five genotoxicity studies, including the most relevant studies for human carcinogenic potential (the *in vivo* chromosomal aberration assay and the microbial mutagenesis assay), and negative carcinogenicity studies in rats and mice lead to the conclusion that there is no evidence of genotoxic or carcinogenic risks from alendronate in humans.

Colecalciferol

Calcitriol, the hormonal metabolite of colecalciferol, was not genotoxic in the microbial mutagenesis assay with or without metabolic activation, and in an *in vivo* micronucleus assay in mice.

Reproduction

Alendronate Sodium

Alendronate had no effect on fertility or reproductive performance (male or female) in rats at oral doses up to 5 mg/kg/day. The only medicine related effect seen in these studies was difficulty in parturition in rats, which is directly related to pharmacologically mediated hypocalcaemia. This effect can be prevented in rats by calcium supplementation. Furthermore, a clear no-effect level of 1.25 mg/kg/day was established.

Colecalciferol

Ergocalciferol (vitamin D_2) at high doses (150,000 to 200,000 IU/kg/day) administered prior to mating resulted in altered oestrous cycle and inhibition of pregnancy in rats. The potential effect of colecalciferol on male fertility is unknown in rats.

Development

Alendronate Sodium

In developmental toxicity studies with alendronate, there were no adverse effects at doses up to 25 mg/kg/day in rats and 35 mg/kg/day in rabbits.

Colecalciferol

No data are available for colecalciferol (vitamin D_3). Administration of high doses (≥ 10,000 IU/every other day) of ergocalciferol (vitamin D_2) to pregnant rabbits resulted in higher incidence of foetal aortic stenosis compared to controls. Administration of vitamin D_2 (40,000 IU/day) to pregnant rats resulted in neonatal death, decreased foetal weight, and impaired osteogenesis of long bones postnatally.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store at or below 30°C. Protect from moisture and light. Store tablets in the original blister package until use.

6.5 Nature and contents of container

FOSAMAX PLUS 70 mg/70 mcg tablets are available in packs of 4 tablets. (No longer available in New Zealand.)

FOSAMAX PLUS 70 mg/140 mcg tablets are available in packs of 4 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine

8 SPONSOR

Organon New Zealand Limited
Level 7, 36 Brandon Street
Wellington 6100

Tel: 0800 111 700

9 DATE OF FIRST APPROVAL

16 November 2006

10 DATE OF REVISION

18 April 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4, 4.8	Added “low energy fractures of other bones” as a Precaution and Post Marketing Adverse Event.