AUSTRALIAN PRODUCT INFORMATION-

FOSAMAX PLUS™ (alendronate sodium/colecalciferol)

1 NAME OF THE MEDICINE

FOSAMAX PLUS tablets contain alendronate sodium and colecalciferol (vitamin D_3).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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.

Each tablet of FOSAMAX PLUS 70 mg/70 µg contains 91.4 mg of alendronate sodium, which is the molar equivalent to 70 mg of alendronic acid, and 70 µg of colecalciferol equivalent to 2800 IU vitamin D.

Each tablet of FOSAMAX PLUS 70 mg/140 µg contains 91.4 mg of alendronate sodium, which is the molar equivalent to 70 mg of alendronic acid, and 140 µg of colecalciferol equivalent to 5600 IU vitamin D.

List of excipients with known effect: lactose, sucrose

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

3 PHARMACEUTICAL FORM

FOSAMAX PLUS (alendronate sodium/colecalciferol) 70 mg/ 70 µg Once Weekly Tablet, providing 2800 IU vitamin D_3. White to off-white, modified capsule-shaped tablet with the outline of a bone image on one side and 710 on the other.

FOSAMAX PLUS (alendronate sodium/colecalciferol) 70 mg/ 140 µg, once weekly tablet, providing 5600 IU vitamin D_3. White to off-white, modified rectangle-shaped tablet with "270" on one side and a bone image on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FOSAMAX PLUS Once Weekly tablet and FOSAMAX PLUS 70 mg/140 µg are indicated for the treatment of:

- Osteoporosis* in select patients where vitamin D supplementation is recommended

* Prior to treatment, osteoporosis must be confirmed by:

- the finding of low bone mass of at least 2 standard deviations below the gender specific mean for young adults or by
- the presence of osteoporotic fracture

4.2 DOSE AND METHOD OF ADMINISTRATION

FOSAMAX PLUS brands (70 mg/70 µg or 70 mg/140 µg) must be taken at least 30 minutes before the first food, beverage or medication of the day with plain water only. Other beverages

(including mineral water), food and some medications are likely to reduce the absorption of alendronate (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

FOSAMAX PLUS brands (70 mg/70 μg or 70 mg/140 μg) should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, FOSAMAX PLUS brands (70 mg/70 μg or 70 mg/140 μg) tablets should only be swallowed with a full glass of water.

Patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX PLUS brands (70 mg/70 μg or 70 mg/140 μg) 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).

SEVERE OESOPHAGEAL ULCERATION HAS BEEN REPORTED IN PATIENTS TAKING ALENDRONATE. (SEE SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 (70 mg/70 μg or 70 mg/140 μg) AND CONSULT THEIR PHYSICIAN.

In clinical trials, alendronate was administered with appropriate calcium and vitamin D supplementation. The use of vitamin D as the sole treatment of osteoporosis has not been established.

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 μg) provides 2800 IU (70 micrograms) of vitamin D in a single once weekly dose, which is equivalent to seven daily doses of 400 IU (10 micrograms). FOSAMAX PLUS (70 mg/140 μg) provides 140 μg colecalciferol (5600 IU of vitamin D_3) in a single once weekly dose, which is equivalent to seven daily doses of 20 μg colecalciferol (800 IU vitamin D_3). Additional supplements should not be taken at the same time of day as FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg) (see above).

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 (70 mg/70 μg or 70 mg/140 μg) is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min).

Although no specific studies have been conducted on the effects of switching patients on another therapy for osteoporosis to FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg), or on another therapy for Paget's disease, there are no known or theoretical safety concerns related to FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg) in patients who previously received any other antiosteoporotic or antipagetic therapy.

FOSAMAX PLUS brands (70 mg/70 μg or 70 mg/140 μg)

Treatment of osteoporosis in patients where vitamin D supplementation is recommended

The recommended dose is one tablet of FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg) once weekly. FOSAMAX PLUS should always be taken on the same day each week.

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 Adverse Effects (Undesirable Effects), Clinical studies).

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 any component of this product
- Hypocalcaemia (see Section 4.4 Special Warnings and Precautions for Use)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

SEVERE OESOPHAGEAL ULCERATION HAS BEEN REPORTED IN PATIENTS TAKING ALENDRONATE. SEE SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION. PHYSICIANS SHOULD THEREFORE BE ALERT TO ANY SIGNS OR SYMPTOMS SIGNALING A POSSIBLE OESOPHAGEAL REACTION. PATIENTS SHOULD BE INSTRUCTED TO DISCONTINUE FOSAMAX PLUS AND SEEK MEDICAL ATTENTION IF THEY DEVELOP DYSPHAGIA, ODYNOPHAGIA OR RETROSTERNAL PAIN.

General

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

If there are clinical reasons to suspect hypocalcaemia and/or vitamin D deficiency (serum levels 25 hydroxyvitamin D < 9 nmol/L), the appropriate diagnostic tests should be performed. Hypocalcaemia must be corrected before initiating therapy with FOSAMAX PLUS (see Section 4.3 Contraindications). Other disturbances of 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. The content of vitamin D in FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg) is not suitable for correction of vitamin D deficiency.

FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg) should not be used as sole treatment for osteoporotic patients with a vitamin D deficiency (defined as serum 25-hydroxyvitamin D < 9 ng/mL (22.5 nmol/L) (see Section 5.1 Pharmacodynamic Properties, Clinical trials, FOSAMAX PLUS study). FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg) should not be used to treat osteomalacia. Vitamin D should be used to treat osteomalacia. FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg) has not been studied in patients with vitamin D deficiency.

Small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated, and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Alendronate

Alendronate, like other bisphosphonates, 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.

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 the recommended amount 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, 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.

Colecalciferol

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

Patients with malabsorption may not adequately absorb vitamin D_3.

Dental

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 including alendronate (see Section 4.8 Adverse Effects (Undesirable Effects), Post-marketing experience). As of May 2004, ONJ after bisphosphonate treatment has been described in a total of 99 cases in two large case series, 7 of which were taking oral bisphosphonates. As of 3 Nov 2006, the Australian Adverse Drug Reactions Advisory Committee has received 25 reports of ONJ in patients receiving alendronate. 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.

Prior to treatment with bisphosphonates, a dental examination with appropriate preventative dentistry should be considered in patients with possible risk factors.

Before commencing invasive dental procedures, patients and their dentist should be advised of the risks and reports of osteonecrosis of the jaw so that dental symptoms, including toothache, developing during treatment can be fully assessed for cause before treatment of the tooth commences.

For patients requiring invasive dental surgery (eg. tooth extraction, dental implants), there are no definitive data available to establish whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Therefore clinical judgment of the treating physician and/or oral surgeon should guide the management plan, including discontinuation of bisphosphonate treatment, of each patient based on individual benefit/risk assessment.

In patients who develop ONJ while on bisphosphonate therapy, the clinical judgment of the treating physician should guide the management plan to include appropriate care by an oral

surgeon and discontinuation of bisphosphonate therapy should be based on individual benefit/risk assessment. Surgery at the affected area may exacerbate the condition.

Atypical stress fractures

A small number of long-term (usually longer than three years) alendronate-treated patients developed stress fractures of the proximal femoral shaft (also known as insufficiency fractures), some of which occurred 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. The number of reported cases of this condition is very low (some 40 reported cases world-wide in connection with alendronate as of 2008). 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. Discontinuation of bisphosphonate therapy in patients with stress fractures is advisable pending evaluation of the patient, based on individual benefit/risk assessment. A cause and effect relationship between bisphosphonate use and stress fractures has not been excluded.

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 Adverse Effects (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 drug or another bisphosphonate.

Nephrolithiasis and hypercalciuria

Patients with a history of either nephrolithiasis or hypercalciuria may require special diets that limit their calcium intake.

Dosage instructions for patients

FOSAMAX PLUS tablets

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 (70 mg/70 μg or 70 mg/140 μg) with a full glass of water. Patients should be instructed 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 (70 mg/70 μg or 70 mg/140 μg) 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 (70 mg/70 μg or 70 mg/140 μg) and consult their physician.

Patients should be instructed that if they miss a dose of FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg), 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.

Use in renal impairment

FOSAMAX PLUS (70mg/70 μg or 70 mg/140 μg) are not recommended for patients with creatinine clearance < 35 mL/min (see Section 4.2 Dose and Method of Administration).

Use in the elderly

In controlled trials, there was no age-related difference in the efficacy or safety profiles of FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg).

Paediatric use

FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg) have not been studied in children and should not be given to them.

Effects on laboratory tests

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 alendronate 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.

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 (70 mg/70 μg or 70 mg/140 μg) before taking any other oral medication.

No other drug interactions of clinical significance are anticipated though the concomitant medication with two or more bisphosphonates cannot be recommended because of the lack of clinical data.

Concomitant use of HRT (oestrogen ± progestin) and alendronate was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of alendronate 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 Adverse Effects (Undesirable Effects), Clinical studies, Concomitant use with oestrogen/hormone replacement therapy).

Specific interaction studies were not performed. alendronate (10 mg and 5 mg/day) was used in studies of treatment and prevention of osteoporosis in postmenopausal women, men and glucocorticoid users, with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions. In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving daily therapy with dosages of alendronate greater than 10 mg and aspirin-containing products. However, this was not observed in studies with alendronate once weekly 70 mg.

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., colestyramine, 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

Effects on fertility

Alendronate sodium
Alendronate sodium had no effect on fertility in male and female rats at oral doses of up to 9 and 15 mg/kg/day.

No studies on the effects on fertility have been carried out using the alendronate and colecalciferol combination.

Use in pregnancy

(Category B3)

Alendronate sodium
Alendronate has not been studied in pregnant women and should not be given to them. In studies with pregnant rats, oral alendronate doses of 2 mg/kg/day and above resulted in dystocia due to maternal hypocalcaemia. Foetal weight was reduced in rats at maternal doses greater than 5 mg/kg/day. No teratogenic effects were seen in rats or rabbits at oral doses up to 25 and 35 mg/kg/day, respectively.

Colecalciferol
No data are available for colecalciferol (vitamin D_3). Intramuscular 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.

No studies on the reproductive toxicity potential of the alendronate and colecalciferol combination have been carried out in animals.

Use in lactation

FOSAMAX PLUS (70 mg/70 μg or 70 mg/140 μg) have not been studied in breast-feeding women and should not be given to them. No studies using the combination of alendronate and colecalciferol have been carried out in lactating animals.

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 PLUS may affect some patients' ability to drive or operate machinery. Individual responses to FOSAMAX PLUS may vary (see Section 4.8 Adverse Effects (Undesirable Effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

CLINICAL STUDIES

FOSAMAX

In clinical studies alendronate 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

Alendronate has been evaluated for safety in clinical studies in approximately 5000 postmenopausal patients. In two three-year, placebo controlled, double blind multicentre studies, discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with alendronate 10 mg/day and 6.0% of 397 patients treated with placebo. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in ≥1% of patients treated with either alendronate 10 mg/day or placebo are presented in Table 1:

Table 1
Drug Related Adverse Experiences Reported in ≥1% of Patients

	FOSAMAX 10 mg/day % (n=196)	PLACEBO % (n=397)
Gastrointestinal		
abdominal pain	6.6	4.8
nausea	3.6	4.0
dyspepsia	3.6	3.5
diarrhoea	3.1	1.8
constipation	3.1	1.8
flatulence	2.6	0.5
acid regurgitation	2.0	4.3
oesophageal ulcer	1.5	0.0
vomiting	1.0	1.5
dysphagia	1.0	0.0
abdominal distension	1.0	0.8
gastritis	0.5	1.3
Musculoskeletal		
musculoskeletal (bone, muscle or joint) pain	4.1	2.5
muscle cramp	0.0	1.0
Nervous System/Psychiatric		
headache	2.6	1.5
dizziness	0.0	1.0
Special Senses		
taste perversion	0.5	1.0

Rarely, rash and erythema have occurred.

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

In the Fracture Intervention Trial, discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with alendronate 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were:

alendronate, 3.2%; placebo, 2.7%. The overall adverse experience profile was similar to that seen in other studies with alendronate 5 or 10 mg/day.

In a one-year, double-blind, multicentre study, the overall safety and tolerability profiles of alendronate once weekly 70 mg (n = 519) and alendronate 10 mg daily (n = 370) were similar. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in ≥1% of patients treated with either patient group are presented in Table 2:

Table 2
Drug Related Adverse Experiences Reported in ≥ 1% of Patients

	alendronate once weekly 70 mg % (n = 519)	alendronate 10 mg/day % (n = 370)
Gastrointestinal		
Abdominal pain	3.7	3.0
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
Gastritis	0.2	1.1
Gastric ulcer	0.0	1.1
Musculoskeletal		
Musculoskeletal (bone, muscle or joint) pain	2.9	3.2
muscle cramp	0.2	1.1

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 alendronate 10 mg once daily and oestrogen ± progestin (n=354) was consistent with those of the individual treatments.

Men

In a two year, placebo-controlled, double-blind, multicentre study, the safety profile of FOSAMAX 10 mg daily in 146 men 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 years) no difference was seen in upper gastrointestinal tract lesions between alendronate once weekly 70 mg and placebo.

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

Prevention of osteoporosis

The safety of alendronate in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomised to receive alendronate for either two or three years. In these studies, the safety and tolerability

profile of alendronate 5 mg/day (n=642) was similar to that of placebo (n=648). The only adverse experience reported by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with alendronate 5 mg/day and at a greater incidence than placebo was dyspepsia (alendronate, 1.9% vs. placebo, 1.7%).

Treatment and prevention of glucocorticoid - induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicentre studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of alendronate 5 and 10 mg/day were generally similar to that of placebo. Adverse experiences reported by the investigators as possibly, probably or definitely drug related in ≥1% of patients treated with either alendronate 5 mg/day, 10 mg/day or placebo are presented in Table 3:

Table 3
Drug Related Adverse Experiences Reported in ≥ 1% of Patients

	FOSAMAX 10 mg/day %	FOSAMAX 5 mg/day %	PLACEBO %
Gastrointestinal			
Abdominal pain	3.2	1.9	0.0
Acid regurgitation	2.5	1.9	1.3
Constipation	1.3	0.6	0.0
Melena	1.3	0.0	0.0
Nausea	0.6	1.2	0.6

Paget's disease of bone

In clinical studies (Paget's disease and osteoporosis), adverse experiences reported in patients taking alendronate 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with alendronate 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking alendronate 40 mg/day. Isolated cases of oesophagitis and gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal pain (bone, muscle or joint), which has been described in patients with Paget's disease treated with other bisphosphonates, was reported by the investigators as possibly, probably or definitely drug related in approximately 6% of patients treated with alendronate 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy.

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 alendronate 70 mg/colecalciferol 70 µg was similar to that of alendronate once weekly 70 mg. In the 24-week double-blind extension study in women (n=619) and men (n=33), the safety profile of alendronate 70 mg/ colecalciferol 70 µg (vitamin D_3 2800 IU) administered with an additional colecalciferol 70 µg for a total of 140 µg colecalciferol (5600 IU vitamin D_3) was similar to that of alendronate 70 mg/colecalciferol 70 µg (2800 IU vitamin D_3). The primary endpoint was the proportion of patients who developed hypercalciuria at Week 39, with 4.2% noted in the colecalciferol 140 µg group and 2.8% in the colecalciferol 70 µg group, which was not statistically significant. Overall, the safety profile of alendronate 70 mg/colecalciferol 70 µg administered with 70 µg additional colecalciferol for a total of 140 µg colecalciferol was similar to that of alendronate/colecalciferol 70 µg.

Alendronate/FOSAMAX PLUS 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. 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 and/or stomatitis; 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), often with delayed healing, has been reported rarely.

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (see Section 4.4 Special Warnings and Precautions for Use), joint swelling, atypical stress fracture (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.

Reporting suspected adverse effects

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 http://www.tga.gov.au/reporting-problems.

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. Administration of milk or antacids, to bind alendronate, should be considered.

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 hypercalcemia.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Alendronate sodium

Alendronate is a bisphosphonate that, in animal studies, localises preferentially to sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation. Since bone formation and bone resorption are coupled, bone formation is also reduced, but less so than resorption, leading to progressive gains in bone mass (see Section 5.1 Pharmacodynamic Properties, Clinical trials for details). Following exposure to alendronate, normal bone is formed that incorporates alendronate into its matrix where it is pharmacologically inactive.

The relative inhibitory activities on bone resorption and mineralisation of alendronate and etidronate were compared in growing rats. The lowest dose of alendronate that interfered with bone mineralisation (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding safety margin for etidronate was one to one. These data indicate that, unlike etidronate, alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

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. Optimal serum levels of 25-hydroxyvitamin D are unknown. Vitamin D insufficiency may be seen with serum levels below 30 - 50 nmol/L. Severe vitamin D deficiency is commonly associated with levels <12.5 nmol/L. 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 is associated with reduced risk of vitamin D insufficiency as defined by serum hydroxyvitamin D of < 37.5 nmol/L.

OSTEOPOROSIS

WHO utilises the definition of osteoporosis as a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. The diagnosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the gender specific mean for young adults) or by the presence or history of osteoporotic fracture. It occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation, leading to loss of bone mass.

OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

Daily oral doses of alendronate in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as hydroxyproline, deoxypyridinoline, and cross-linked N-telopeptides of type I collagen). These biochemical changes returned toward baseline values as early as three weeks following the discontinuation of alendronate despite the long retention of alendronate in the skeleton.

Long-term treatment of osteoporosis with alendronate 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received alendronate 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with alendronate. In osteoporosis treatment studies alendronate 10 mg/day decreased the markers of bone formation, osteocalcin and total serum alkaline phosphatase, by approximately 50% and 25-30%, respectively, to reach a plateau after 6 to 12 months. Similar though slightly lower reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with alendronate once weekly 70 mg for the treatment of osteoporosis. In osteoporosis prevention studies alendronate 5 mg/day decreased these markers by approximately 40% and 15%, respectively.

OSTEOPOROSIS IN MEN

Even though osteoporosis is less prevalent in men than in postmenopausal women, a significant proportion of osteoporotic fractures occur in men. The prevalence of vertebral deformities appears to be similar in men and women. All men with osteoporosis should be investigated for hypogonadism and, if necessary, treated for this condition. Treatment of men with osteoporosis with alendronate 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions in cross-linked N-telopeptides of type I collagen were seen in men receiving alendronate 70 mg once weekly.

Clinical trials

TREATMENT OF OSTEOPOROSIS

FOSAMAX PLUS studies

The effect of alendronate 70 mg/colecalciferol 70 µg on vitamin D status was demonstrated in a 15-week, double-blind, multinational study of 717 osteoporotic postmenopausal women and men (serum 25-hydroxyvitamin D at baseline: mean, 22.2 ng/mL [56 nmol/L]; range, 9-90 ng/mL [22.5-225 nmol/L]). Patients received alendronate 70 mg/colecalciferol 70 µg (2800 IU) (n=350 women, 10 men) or alendronate (alendronate 70 mg (n=332 women, 25 men) once a week; additional vitamin D supplements were prohibited. Patients who were vitamin D deficient [defined as serum 25-hydroxyvitamin D < 9 ng/mL (22.5 nmol/L)] at baseline were excluded. Patients with vitamin D insufficiency at baseline were defined as having serum 25-hydroxyvitamin D levels between 9 ng/mL (22.5 nmol/L) and 15 ng/mL (37.5 nmol/L).

The percentage of patients with serum 25-hydroxyvitamin D ≥15 ng/mL (37.5 nmol/L) was significantly higher with alendronate 70 mg/colecalciferol 70 µg vs. alendronate only (89% vs. 68%, respectively). The percentage of patients with serum 25-hydroxyvitamin D ≥9 ng/mL (22.5 nmol/L) was significantly higher with alendronate 70 mg/colecalciferol 70 µg vs. alendronate only (99% vs. 87%, respectively). There were no differences in mean serum

calcium, phosphate or 24-hour urine calcium between treatment groups. The final levels of 25-hydroxyvitamin D at week 15 are summarised in Table 4 below.

Table 4
25-hydroxyvitamin D Levels after treatment with alendronate 70mg/colecalciferol 70μg and alendronate 70 mg at Week 15*
Number (%) of Patients

25-hydroxyvitamin D Ranges (nmol/L)	< 22.5	22.5-35	37.5-47.5	50-60	62.5-72.5	75-155
alendronate 70mg/colecalciferol 70 μg (N=357)	4 (1.1)	37 (10.4)	87 (24.4)	84 (23.5)	82 (23.0)	63 (17.7)
alendronate 70 mg (N=351)	46 (13.1)	66 (18.8)	108 (30.8)	58 (16.5)	37 (10.5)	36 (10.3)

* Patients who were vitamin D deficient (25-hydroxyvitamin D < 22.5 nmol/L) at baseline were excluded.

The effect of alendronate 70 mg/colecalciferol 70 µg with an additional 70 µg colecalciferol (2800 IU vitamin D_3) for a total of 140 µg colecalciferol (5600 IU vitamin D_3) once weekly was compared to 70 mg/colecalciferol 70 µg weekly in a 24-week, extension study that enrolled 652 osteoporotic men and post-menopausal women who completed the above 15-week study. Patients in the colecalciferol 70 µg group received alendronate 70 mg/colecalciferol 70 µg (n=305 women, 21 men) and those in the colecalciferol 140 µg group received alendronate 70 mg/colecalciferol 70 µg with an additional 70 µg colecalciferol (n=314 women, 12 men) once a week; additional vitamin D supplements were allowed. The primary endpoint was incidence of hypercalciuria, defined as an increase of greater than 25% from baseline in 24-hour urine calcium and to a value greater than the upper limit of normal (300 mg in women, 350 mg in men). The rate of hypercalciuria was 13/311 (4.2%) for the colecalciferol 140 µg group and 9/317 (2.8%) for the colecalciferol 70 µg group, relative risk 1.48 (95% CI 0.64, 3.40).

Secondary endpoints included 25 hydroxyvitamin D levels. The proportions of patients with vitamin D insufficiency (< 37.5 nmol/L) after 39 weeks was 10/321 (3.1%) in the colecalciferol 140 µg group and 18/320 (5.6%) in the colecalciferol 70 µg group.

The percentage of patients with serum 25-hydroxyvitamin D ≥15 ng/mL (37.5 nmol/L) was higher with the colecalciferol 140 µg group vs. the colecalciferol 70 µg group (96.9% vs. 94.4%, respectively), although not statistically significant.

There were no differences detected between mean serum calcium, mean serum phosphate, or mean 24-hour urine calcium between groups. The distribution of the final levels of 25-hydroxyvitamin D at week 39 is summarised in Table 5 below.

Table 5
25-hydroxyvitamin D Levels after treatment with alendronate 70 mg/colecalciferol 70 μg or alendronate 70 mg/colecalciferol 70 μg plus additional colecalciferol 70 μg at week 39 in extension study

Number (%) of Patients

25-hydroxyvitamin D Ranges (nmol/L)	< 22.5	22.5-35	37.5-47.5	50-60	62.5-72.5	75-155
Vitamin D_3 5600 IU group*(N=321)	0	10 (3.1)	29 (9.0)	79 (24.6)	87 (27.1)	116 (36.1)
Vitamin D_3 2800 IU group**(N=320)	1 (0.3)	17 (5.3)	56 (17.5)	80 (25.0)	74 (23.1)	92 (28.7)

* Patients received alendronate 70mg or alendronate 70mg/colecalciferol 70 μg for the 15-week base study followed by alendronate 70mg/colecalciferol 70 μg and 70 μg additional colecalciferol for the 24-week extension study.
** Patients received alendronate 70mg or alendronate 70mg/colecalciferol 70 μg for the 15-week base study followed by alendronate 70mg/colecalciferol 70 μg and placebo for the additional colecalciferol for 24 week extension study.

Alendronate Studies

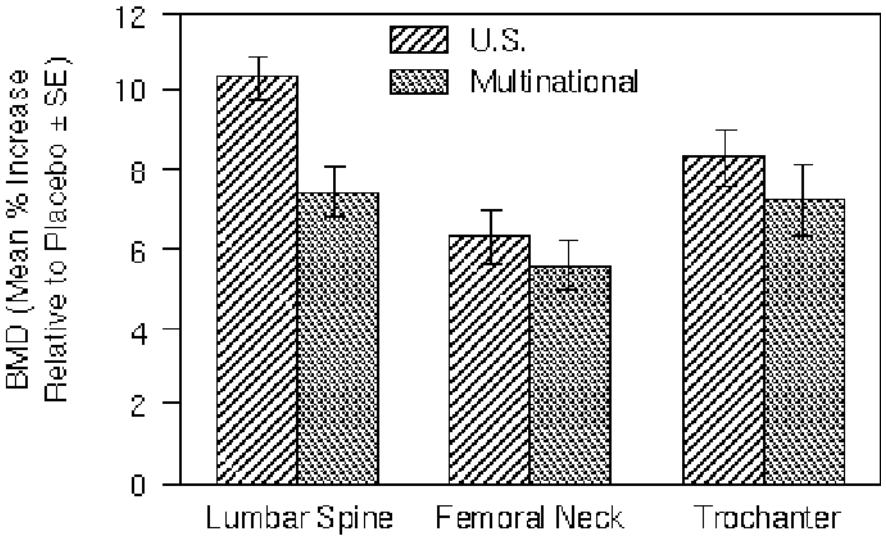
Postmenopausal women

Effect on bone mineral density

The efficacy of alendronate 10 mg once daily in postmenopausal women with osteoporosis was demonstrated in two large three year multicentre studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in bone mineral density (BMD) of the lumbar spine, femoral neck and trochanter in patients receiving alendronate 10 mg/day relative to placebo-treated patients at three years for each of these studies.

Figure 1

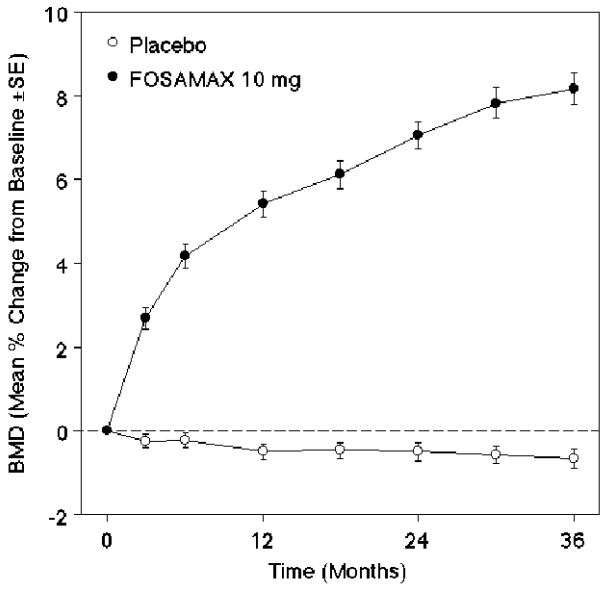
Increase in BMD
FOSAMAX 10 mg/day in Two Studies at Three Years



These increases were highly significant relative both to baseline and placebo at each measurement site in each study. Increases in BMD were evident as early as three months and continued throughout the entire three years of treatment (see Figure 2 below for lumbar spine results). In the two-year extension of these studies, treatment with alendronate 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine 0.94%; trochanter 0.88%). BMD at the femoral neck, forearm and total body were maintained. Thus, alendronate appears to reverse the progression of osteoporosis as assessed by increased bone mineral density. Alendronate was similarly effective regardless of age, race, baseline rate of bone turnover, renal function and use of concomitant medications.

Figure 2

Time Course of Effect of FOSAMAX 10 mg/day versus Placebo:
Lumbar Spine BMD Percent Change from Baseline



In patients with postmenopausal osteoporosis treated with alendronate 10 mg/day for one or two years the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those in the placebo groups. These data indicate that continuous treatment with alendronate is required to produce progressive increases in bone mass.

The therapeutic equivalence of alendronate once weekly 70 mg (n = 519) and alendronate 10 mg daily (n = 370) was demonstrated in a one-year, double-blind, multicentre study of postmenopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70 mg once weekly group and 5.4% (5.0, 5.8%; 95% CI) in the 10 mg daily group. The two treatment groups were also similar with regard to BMD increases at other skeletal sites. While there are no placebo-controlled fracture data for the once weekly 70 mg tablet, the increases in bone density support the expectation that alendronate once weekly 70 mg will have effects to reduce the incidence of fractures similar to those of the 10 mg daily treatment (see below). The study was not designed to evaluate the relative compliance of alendronate once weekly 70 mg and 10 mg daily.

Effect on fracture incidence

Although the US and Multinational studies (see above) were not designed to assess fracture rates as the primary endpoint, preplanned analysis of the data pooled across once daily doses at three years revealed a statistically significant and clinically meaningful 48% reduction in the proportion of patients treated with alendronate experiencing one or more vertebral fractures (3.2%) relative to those treated with placebo (6.2%). Furthermore, of patients who sustained any vertebral fracture, those treated with alendronate experienced less height loss (5.9 mm vs 23.3 mm) due to a reduction in both the number and severity of fractures.

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline vertebral (compression) fracture and the Four-Year Study of patients with low bone mass but without baseline vertebral fracture.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline vertebral fracture)

This randomised, double-blind, placebo-controlled 2027-patient study, (alendronate n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in clinically significant reductions in fracture incidence at three years as shown in Table 6 below. Data also showed statistically significant reductions in painful vertebral fractures and clinical fractures at other sites. Similar reductions of hip and wrist fractures were seen in five pooled osteoporosis treatment studies of two or three years duration.

Table 6
Effect of alendronate on Fracture Incidence in the Three-Year Study of FIT (% of patients with vertebral fracture at baseline)

	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %	P Value
Patients with:					
≥ 1 new vertebral fracture	7.9	15.0	7.1	47	<.001*
≥ 2 new vertebral fractures	0.5	4.9	4.4	90	<.001*
≥ 1 painful vertebral fracture	2.3	5.0	2.7	54	<.002**
Any painful (inc. vertebral) fracture	13.8	18.1	4.3	26	0.007**
Hip fractures	1.1	2.2	1.1	51	0.047**

Wrist (forearm) fractures	2.2	4.1	1.9	48	0.013**
* Mantel-Haenzel chi^2 **Log Rank test					

Furthermore, in this population of patients with baseline vertebral fracture, treatment with alendronate significantly reduced the incidence of hospitalisations resulting from any cause (25.0% vs. 30.7%, a 20% relative risk reduction). This difference appears to be related, at least in part, to the reduction in fracture incidence.

Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline vertebral fracture)

This randomised, double-blind, placebo-controlled, 4432-patient study (alendronate, n=2214; placebo, n=2218) further demonstrated the reduction in fracture incidence due to alendronate. The intent of the study was to recruit women with osteoporosis, i.e. with a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in Table 7 below for the patients with osteoporosis.

Table 7
Effect of alendronate on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT
(patients without vertebral fracture at baseline)

	% of Patients			
	Alendronate (n=1545)	**Placebo (n=1521)**	**Absolute Reduction in Fracture Incidence**	**Relative Reduction in Fracture Risk %**
Patients with:				
≥ 1 painful fracture	12.9	16.2	3.3	22**
≥ 1 vertebral fracture††	2.5	4.8	2.3	48***
≥ 1 painful vertebral fracture	1.0	1.6	0.6	(NS)
Hip fracture	1.0	1.4	0.4	(NS)
Wrist (forearm) fracture	3.9	3.8	-0.1	None

†Baseline femoral neck BMD at least 2 SD below the mean for young adult women
††Number evaluable for vertebral fracture: alendronate, n=1426; placebo, n=1428
nsNot significant. This study was not powered to detect differences at these sites.
**p = 0.01, ***p <0.001

Consistency of fracture results

The reductions in the incidence of vertebral fractures (alendronate vs. placebo) in the Three and Four-Year Studies of FIT were consistent with that in the combined US and Multinational (US/Mult) treatment studies (see above), in which 80% of the women did not have a vertebral fracture at baseline. During these studies, treatment with alendronate reduced the proportion of women experiencing at least one new vertebral fracture by approximately 50% (Three-Year FIT: 47% reduction, p<0.001; Four-Year FIT: 44% reduction, p=0.001 US/Mult, 48% reduction, p=0.034). In addition, alendronate reduced the proportion of women experiencing multiple (two or more) new vertebral fractures by approximately 90% in the US/Mult and Three-Year FIT studies (p<0.001). Thus, alendronate reduced the incidence of vertebral fractures whether or not patients had experienced a previous vertebral fracture.

Overall, these results demonstrate the consistent efficacy of alendronate in reducing the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with greatest morbidity.

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with alendronate at doses ranging from 1 to 20 mg/day for one, two or three years revealed normal mineralisation and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in ovariectomised rats and baboons exposed to long term alendronate treatment, indicate that bone formed during therapy with alendronate is of normal quality.

Concomitant Use with Oestrogen/Hormone Replacement Therapy

The effects on BMD of treatment with alendronate 10 mg once daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomised postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or alendronate alone (both 6.0%).

The effects on BMD when alendronate was added to stable doses (for at least one year) of HRT (oestrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of alendronate 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favourable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Men

The efficacy of alendronate 10 mg once daily in men with osteoporosis was demonstrated in a two-year, double-blind, placebo-controlled, multicentre study, which enrolled 241 osteoporotic men between the ages of 31 and 87 years. All patients in the study (97.5% of whom were Caucasian) had either: 1) a BMD T-score ≤ -2 at the femoral neck and ≤ -1 at the lumbar spine or 2) a baseline osteoporotic fracture and a BMD T-score of ≤ -1 at the femoral neck. At two years the mean increases relative to placebo in BMD in men receiving alendronate 10 mg daily were; lumbar spine 5.3%; femoral neck 2.6%; trochanter 3.1% and total body 1.6% (all $p \leq 0.001$). Alendronate was effective regardless of age, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with the much larger studies in postmenopausal women, in these men alendronate 10 mg daily reduced the incidence of new vertebral fracture (post-hoc analysis; assessment by quantitative radiography) relative to placebo (0.8% vs 7.1%, respectively; $p = 0.017$) and correspondingly, also reduced height loss (-0.6 vs -2.4 mm, respectively; $p = 0.022$).

The effects of discontinuation of alendronate treatment have not been studied in this population.

Prevention of osteoporosis

For the prevention of osteoporosis, alendronate may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.

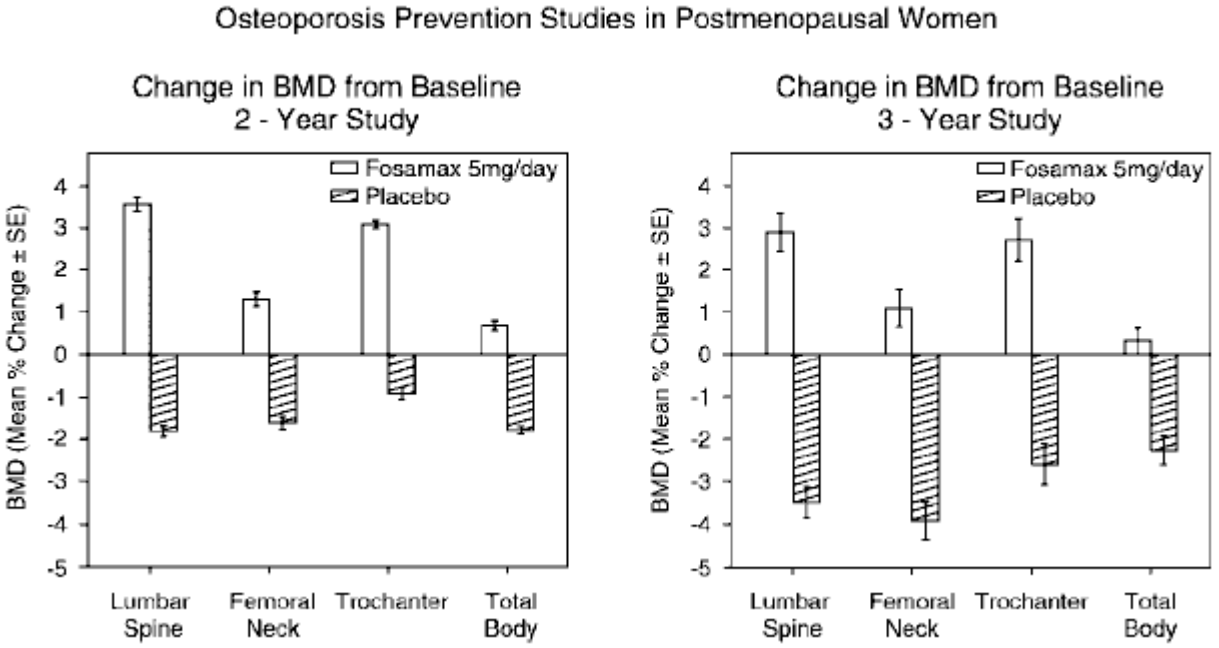
Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women; thin body build and family history of osteoporosis). The presence of such risk factors may be important when considering the use of alendronate for prevention of osteoporosis.

Prevention of bone loss was demonstrated in both a two-year (n=1609) and a three-year (n=447) study of women 40-60 years of age who were at least 6 months postmenopausal. In these studies, alendronate or matching placebo was administered once daily to non-osteoporotic women (overall baseline spine BMD approximately one SD lower that the premenopausal mean BMD).

As expected, in the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, alendronate 5 mg/day effectively prevented bone loss, and induced highly significant increases in bone mass at each of these sites. The mean percent increase in BMD from baseline at the lumbar spine, femoral neck, trochanter and total body at the end of the two-year study were 3.46%, 1.27%, 2.98% and 0.67%, respectively, and those at the end of the three-year study were 2.89%, 1.10%, 2.71% and 0.32%, respectively (see Figure 3 below).

In addition, alendronate 5 mg/day reduced the rate of bone loss in the forearm by approximately half relative to placebo. Alendronate 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

Figure 3



In the two year study (n=1609), of 435 women willing to be randomised to an open-label oestrogen/progestin therapy subgroup, 55 in the US centres received conjugated equine oestrogens 0.625 mg daily (Premarin™) in combination with medroxyprogesterone acetate 5 mg daily (Provera™), whilst 55 in the European centres received higher doses of oestrogen given as 17β-oestradiol 2 mg daily in combination with norethisterone acetate 1 mg daily (10 days per 28 day cycle) (Trisequens™). Only women in the European centres using Trisequens experienced increases in BMD at the spine, hip and total body that were different from those in women using FOSAMAX 5 mg. At these centres, two-year increases in BMD at the lumbar

spine were 5.1% and 3.3%, femoral neck 2.4% and 1.4%, trochanter 4.8% and 2.8%, and total body 2.6% and 0.6% in the Trisequens and alendronate 5 mg groups, respectively. Increases with Premarin and Provera in the US centres were not statistically different to those obtained with alendronate 5 mg. Both alendronate 5 mg and oestrogen/progestin therapy prevented bone loss in these non-osteoporotic women.

Bone histology was normal in the 28 patients biopsied at the end of three years who received alendronate doses of up to 10 mg/day.

Glucocorticoid - Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip and rib). It occurs both in males and females of all ages. Bone loss occurs as a result of a lower rate of bone formation relative to that of bone resorption. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of one year's duration, alendronate 5 and 10 mg/day reduced cross-linked N-telopeptides of type 1 collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 25 to 30% and 12 to 15%, respectively. As a result of inhibition of bone resorption, alendronate 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1%) and serum phosphate (approximately 2 to 7%).

The efficacy of alendronate 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year placebo-controlled, double-blind, multicentre studies (n: total = 560, males = 176) of virtually identical design. Most of the patients were ambulant, Caucasian and non-smokers. The study population included patients with rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus, pemphigus, asthma, myositis, inflammatory bowel disease, giant cell arteritis, sarcoidosis, myasthenia gravis, chronic obstructive pulmonary disease and nephrotic syndrome. The range and duration of prior corticosteroid use in the studies was 0 to 538 months with a mean of 43.6 months and a median of 12 months. The range of prednisone dose at study commencement was 5 to 135 mg/day with a mean of 18.4 mg and a median of 10 mg daily. Fifty-seven percent of patients had osteopenia/osteoporosis at study commencement. Patients received supplemental calcium and vitamin D. At one year, the mean increases relative to placebo in BMD in patients receiving alendronate 5 mg/day from the combined studies were: lumbar spine, 2.41%; femoral neck, 2.19%; and trochanter, 1.65%. These increases were significant at each site. Total body BMD was maintained with alendronate 5 mg/day indicating that the increase in bone mass of the spine and hip did not occur at the expense of other sites. The increases in BMD with alendronate 10 mg/day were similar to those with alendronate 5 mg/day in all patients except for postmenopausal women not receiving oestrogen therapy. In these women, the increases (relative to placebo) with alendronate 10 mg/day were greater than those with alendronate 5 mg/day at the lumbar spine (4.11% vs. 1.56%) and trochanter (2.84% vs. 1.67%), but not at other sites. Alendronate was effective regardless of dose or duration of glucocorticoid use. In addition, alendronate was similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races), gender, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone histology was normal in the 49 patients biopsied at the end of one year who received alendronate at doses of up to 10 mg/day.

Paget's disease of bone

Paget's disease of bone is a chronic, focal skeletal disorder characterised by greatly increased and disorderly bone remodelling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganised, enlarged and weakened bone structure.

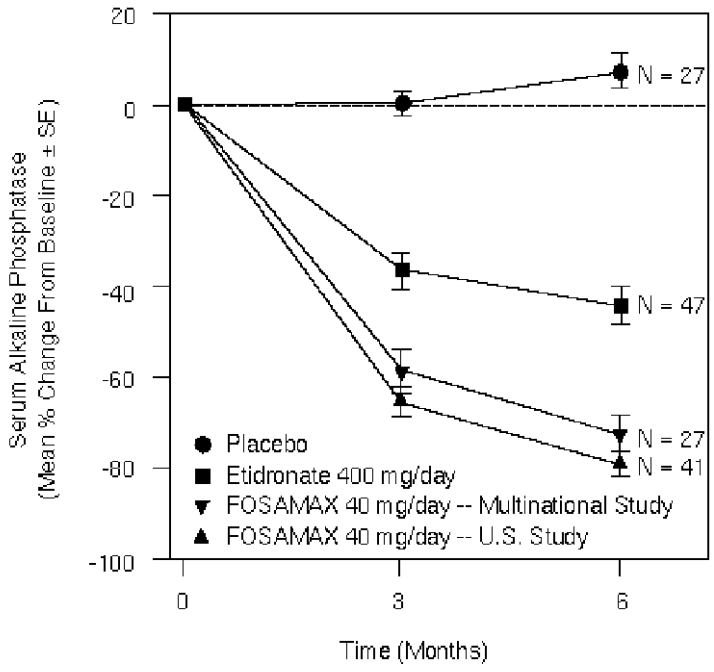
Alendronate decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. Alendronate 40 mg once daily for six months produced highly significant decreases in serum alkaline phosphatase, an objective measure of disease severity. Furthermore, normal lamellar bone was produced during treatment with alendronate, even where pre-existing bone was woven and disorganised.

As a result of the inhibition of bone resorption, alendronate induced generally mild, transient and asymptomatic decreases in serum calcium and phosphate.

The efficacy of alendronate 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled multinational study and a US comparative study with etidronate disodium 400 mg/day. The following Figure 4 shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomised treatment.

Figure 4

Effect on Serum Alkaline Phosphatase of FOSAMAX 40 mg/day
Versus Placebo or Etidronate 400 mg/day



At six months, the mean percent suppression from baseline in serum alkaline phosphatase in patients treated with alendronate (-79% and -73% in the two studies) was significantly greater than that achieved with etidronate disodium 400 mg/day (-44%) and contrasted with the complete lack of response in placebo-treated patients (+8.0%). Response (defined as either normalisation of serum alkaline phosphatase or decrease from baseline ≥ 60%) occurred in approximately 85% of patients treated with alendronate in the combined studies versus 30% in the etidronate group and 0% in the placebo group. FOSAMAX was similarly effective

irrespective of age, gender, race, renal function, concomitant medications, prior use of other bisphosphonates, or baseline alkaline phosphatase.

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. There was substantial variability both within and between patients, coefficient of variation 63% and 77%, respectively. Oral bioavailability in men (0.6%) was similar to that in women.

In two two-period cross-over studies, the alendronate in the FOSAMAX PLUS (70 mg/70 μg and 70 mg/140 μg) tablet was shown to be bioequivalent to the alendronate in the alendronate 70 mg tablet.

Bioavailability was decreased similarly (by approximately 40%) whether alendronate was administered one or one-half hour before a standardised breakfast. In osteoporosis and Paget's disease studies, alendronate 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 normal subjects, oral prednisone (20 mg three times daily for five days) did not substantially alter the oral bioavailability of alendronate (alendronate alone, 0.73%; alendronate plus prednisone, 0.87%).

Colecalciferol

Following administration of FOSAMAX PLUS (70 mg/70 μg) Once Weekly Tablet after an overnight fast and two hours before a standard meal, the baseline unadjusted mean area under the serum-concentration-time curve ($AUC_{0\text{-}120\ hrs}$) for vitamin D_3 was 296.4 ng-hr/mL (Geometric Mean Ratio [{GMR} FOSAMAX PLUS 70 mg/70 μg /vitamin D3 only]: 0.88; 90% CI: 0.81, 0.95). The baseline unadjusted mean maximal serum concentration (C_{max}) of vitamin D_3 was 5.9 ng/mL, [GMR (FOSAMAX PLUS 70 mg/70 μg /vitamin D_3 only): 0.89; 90% CI: 0.84, 0.95] and the median time to maximal serum concentration (T_{max}) was 12 hrs. The bioavailability of the 70 μg (2800 IU) vitamin D_3 in FOSAMAX PLUS (70 mg/70 μg) is similar to 70 μg (2800 IU) vitamin D_3 administered alone (using the $AUC_{0\text{-}120\ hr}$ and C_{max} GMR values).

Following administration of FOSAMAX PLUS 70 mg/140 μg after an overnight fast and two hours before a standard meal, the mean area under the serum-concentration-time curve ($AUC_{0\text{-}80\ hrs}$) (unadjusted for endogenous vitamin D_3 levels) for vitamin D_3 was 490.2 ng-hr/mL (Geometric Mean Ratio [{GMR} FOSAMAX PLUS 70 mg/140 μg /vitamin D_3 only]: 0.94; 90% CI 0.89, 1.00). The baseline unadjusted mean maximal serum concentration (C_{max}) of vitamin D_3 was 12.2 ng/mL, [GMR (FOSAMAX PLUS 70 mg/140 μg /vitamin D_3 only 0.94; 90% CI: 0.88, 1.00] and the median time to maximal serum concentration (T_{max}) was 10.6 hrs. The bioavailability of the 140 μg (5600 IU) vitamin D_3 in FOSAMAX PLUS 70 mg/140 μg is similar to 140 μg (5600 IU) vitamin D_3 administered alone (using the $AUC_{0\text{-}80\ hr}$ and C_{max} GMR values).

Distribution

Alendronate sodium

Preclinical studies show that alendronate transiently distributes to soft tissues following 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 alendronate in plasma following therapeutic oral doses are generally below the limits of quantification (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.

Metabolism

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.

Excretion

Alendronate sodium
Following a single 10 mg 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; the renal clearance of alendronate was 71 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration, due to distribution to the bone and excretion in the urine. The terminal half-life in humans is estimated to exceed 10 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 drugs by those systems in humans.

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 over three weeks in rats, with a cumulative IV dose of 35 mg/kg. 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).

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 alendronate 70 mg/colecalciferol 70 µg is approximately 24 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Alendronate sodium
Alendronate did not cause gene mutations in bacteria or in mammalian cells *in vitro,* nor did it cause DNA damage in rat hepatocytes *in vitro* (alkaline elution assay). In assays of chromosomal damage, alendronate was weakly positive in an *in vitro* assay using Chinese

hamster ovary cells at cytotoxic concentrations (≥5 mM), but was negative at IV doses up to 25 mg/kg/day (75 mg/m^2) in an *in vivo* assay (chromosomal aberrations in mouse bone marrow).

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

No studies on the genotoxic potential have been carried out using the alendronate and colecalciferol combination.

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.

The carcinogenic potential of colecalciferol alone or the alendronate and colecalciferol combination has not been studied.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each FOSAMAX PLUS 70 mg/70 μg and 70 mg/140 μg tablet contains the following inactive ingredients: microcrystalline cellulose, lactose, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal anhydrous silica, magnesium stearate, Dry Vitamin D3 100, purified water, butylated hydroxytoluene, modified food starch and aluminium sodium silicate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Protect FOSAMAX PLUS (70 mg/ 70 μg and 70 mg/ 140 μg) tablets from moisture and light, and store tablets in original blister package until use.

6.5 NATURE AND CONTENTS OF CONTAINER

FOSAMAX PLUS 70 mg/ 70 μg Once Weekly Tablet are supplied in blister packs of 1* and 4 tablets.

FOSAMAX PLUS 70 mg/ 140 μg once weekly tablet are supplied in blister packs of 1* and 4 tablets.

*Supplied as starter packs only.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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.

Alendronate sodium is described chemically as: (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate. The empirical formula is $C_4H_{12}NNaO_7P_2 \bullet 3H_2O$. The formula weight is 325.12.

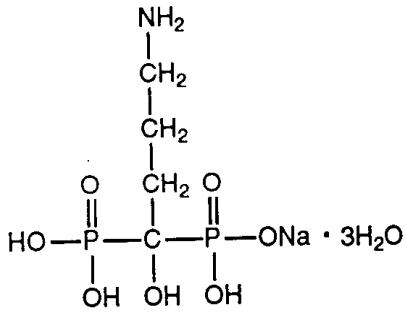
Colecalciferol

Colecalciferol (vitamin D3) is a secosterol that is the natural precursor of the calcium-regulating hormone calcitriol (1,25-dihydroxyvitamin D3).

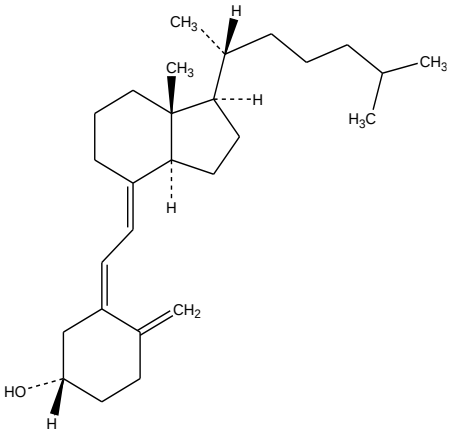
The chemical name of colecalciferol is (3β,5Z,7E)-9,10-secocholesta- 5,7,10(19)-trien-3-ol. The empirical formula of colecalciferol is $C_{27}H_{44}O$ and its molecular weight is 384.6.

Chemical structure

The structural formula of alendronate sodium is:



The structural formula of colecalciferol is:



CAS number

The CAS Registry Numbers are 121268-17-5 (alendronate sodium); 67-97-0 (colecalciferol).

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

8 March 2006

10 DATE OF REVISION

27 March 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	PI reformat
All sections	Deletion of text relating to 5, 10, 40, 70 mg and Plus D-Cal strengths