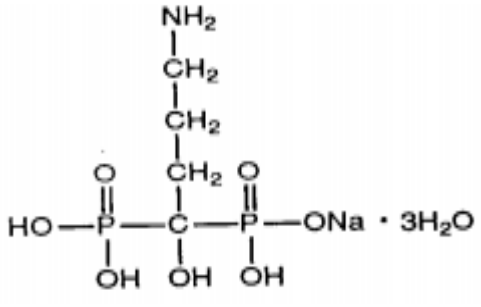
FONATPLUS 70 mg/70 µg TABLET
FONATPLUS 70 mg/140 µg TABLET

NAME OF THE MEDICINE

Alendronate sodium and colecalciferol

Alendronate sodium
Chemical Name: (4-amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt trihydrate.

Structural Formula:



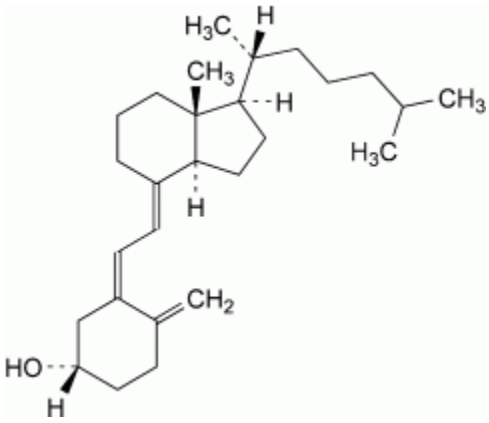
CAS Number: 121268-17-5

Molecular Formula: $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$

Molecular Weight: 325.12

Colecalciferol
Chemical Name: colecalciferol(5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3β-ol. colecalciferol

Structural Formula:



CAS Number: 67-97-0

Molecular Formula: $C_{27}H_{44}O$

Molecular Weight: 384.6

DESCRIPTION

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 is a white or almost white, crystalline powder. It is soluble in water, very slightly soluble in methanol, practically insoluble in methylene chloride.
Colecalciferol (vitamin D_3) is a secosterol that is the natural precursor of the calcium-regulating hormone calcitriol (1,25-dihydroxyvitamin D_3).

Colecalciferol is a white to almost white crystalline powder. Colecalciferol is practically insoluble in water, free soluble in alcohol, soluble in fatty oils.

Each tablet of FonatPlus 70 mg/70 µg contains 91.37 mg of alendronate sodium, which is the molar equivalent to 70 mg of alendronic acid, and 70 mcg of colecalciferol equivalent to 2800 IU vitamin D. Each tablet of FonatPlus 70 mg/140 µg contains 91.37 mg of alendronate sodium, which is the molar equivalent to 70 mg of alendronic acid, and 140 mcg of colecalciferol equivalent to 5600 IU vitamin D. The tablets also contain the following inactive ingredients: cellulose-microcrystalline, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, silica-colloidal anhydrous, magnesium stearate, butylated hydroxytoluene and povidone.

PHARMACOLOGY

Pharmacodynamic Properties

Absorption

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 Clinical Trials section 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.

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.

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 alendronate sodium with colecalciferol (70 mg/70 mcg) 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} alendronate sodium with colecalciferol 70 mg/70 mcg /vitamin D_3 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 (alendronate sodium with colecalciferol 70 mg/70 mcg /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 mcg

(2800 IU) vitamin D_3 in alendronate sodium with colecalciferol (70 mg/70 mcg) is similar to 70 mcg (2800 IU) vitamin D_3 administered alone (using the $AUC_{0\text{-}120\ hrs}$ and C_{max} GMR values).

Following administration of alendronate sodium with colecalciferol 70 mg/140 mcg 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} alendronate sodium with colecalciferol 70 mg/140 mcg /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 (alendronate sodium with colecalciferol 70 mg/140 mcg /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 mcg (5600 IU) vitamin D_3 in alendronate sodium with colecalciferol 70 mg/140 mcg is similar to 140 mcg (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 5ng/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.

Elimination

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 DOSAGE AND 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 mcg is approximately 24 hours.

CLINICAL TRIALS

Treatment of Osteoporosis

Alendronate sodium with colecalciferol studies

The effect of alendronate 70 mg/colecalciferol 70 mcg 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 mcg (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 (22.5nmol/ 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 mcg 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 mcg 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 the table below.

25-hydroxyvitamin D Levels after treatment with alendronate 70mg/colecalciferol 70mcg 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 70 mg/colecalciferol 70 mcg (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 mcg with an additional 70 mcg colecalciferol (2800 IU vitamin D_3) for a total of 140 mcg colecalciferol (5600 IU vitamin D_3) once weekly was compared to 70mg/colecalciferol 70 mcg 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 mcg group received alendronate 70 mg/ colecalciferol 70 mcg (n=305 women, 21 men) and those in the colecalciferol 140 mcg group received alendronate 70 mg /colecalciferol 70 mcg with an additional 70 mcg 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 mcg group and 9/317 (2.8%) for the colecalciferol 70 mcg 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 mcg group and 18/320 (5.6%) in the colecalciferol 70 mcg group.

The percentage of patients with serum 25-hydroxyvitamin D ≥15 ng/mL (37.5 nmol/L) was higher with the colecalciferol 140 mcg group vs. the colecalciferol 70 mcg 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 the table below.

25-hydroxyvitamin D Levels after treatment with alendronate 70 mg/colecalciferol 70 mcg or alendronate 70 mg/colecalciferol 70 mcg plus additional colecalciferol 70 mcg 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 70 mg or alendronate 70 mg/colecalciferol 70 mcg for the 15-week base study followed by alendronate 70mg/colecalciferol 70 mcg and 70 mcg additional colecalciferol for the 24-week extension study.

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

INDICATIONS

FonatPlus 70 mg/70 µg and FonatPlus 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

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 PRECAUTIONS)

PRECAUTIONS

SEVERE OESOPHAGEAL ULCERATION HAS BEEN REPORTED IN PATIENTS TAKING ALENDRONATE. SEE DOSAGE AND ADMINISTRATION. PHYSICIANS SHOULD THEREFORE BE ALERT TO ANY SIGNS OR SYMPTOMS SIGNALING A POSSIBLE OESOPHAGEAL REACTION. PATIENTS SHOULD BE INSTRUCTED TO DISCONTINUE ALENDRONATE SODIUM WITH COLECALCIFEROL 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 alendronate sodium with colecalciferol (See 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 alendronate sodium with colecalciferol. The content of vitamin D in alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) is not suitable for correction of vitamin D deficiency.

Alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) 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 Clinical Trials, alendronate sodium with colecalciferol study). Alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) should not be used to treat osteomalacia. Vitamin D should be used to treat osteomalacia. Alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) 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 alendronate sodium with colecalciferol and/or who fail to swallow it with the recommended amount of water, and/or who continue to take alendronate sodium with colecalciferol after developing symptoms suggestive of oesophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND 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 alendronate sodium with colecalciferol 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 hypercalcemia 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 ADVERSE REACTIONS, 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), 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). 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 ADVERSE REACTIONS, *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.

Renal Insufficiency
Alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) are not recommended for patients with creatinine clearance < 35mL/min (see DOSAGE AND ADMINISTRATION).

Nephrolithiasis and Hypercalciuria
Patients with a history of either nephrolithiasis or hypercalciuria may require special diets that limit their calcium intake. The calcium content of BoneCal should be considered when these diets are prescribed.

Dosing Instructions for Patients
Alendronate sodium with colecalciferol tablets
To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation patients should be instructed to swallow each tablet of alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) 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 alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) 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 alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) and consult their physician.

Patients should be instructed that if they miss a dose of alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg), 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.

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

Alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) 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.

Paediatric use

Alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) have not been studied in children and should not be given to them.

Use in the elderly

In controlled trials, there was no age-related difference in the efficacy or safety profiles of alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg).

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 (≥5mM), 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.

Effect 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.

Effect on ability to drive or use machinery
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 alendronate sodium with colecalciferol may affect some patients' ability to drive or operate machinery. Individual responses to alendronate sodium with colecalciferol may vary (see ADVERSE EFFECTS).

INTERACTIONS WITH OTHER MEDICINES

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 alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) 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 ADVERSE REACTIONS, 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., cholestyramine, colestipol) may impair the absorption of vitamin D. Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D.

ADVERSE EFFECTS

Treatment of osteoporosis
Postmenopausal women
Alendronate 70 mg 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 the following table:

Drug Related Adverse Experiences Reported in ≥1% of Patients		
	alendronate 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
diarrhea	3.1	1.8
constipation	3.1	1.8
flatulence	2.6	0.5
acide regurgitation	2.0	4.3
oesophagael 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		
musculosketelal (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 the following table:

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 alendronate 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 the following table:

Drug Related Adverse Experiences Reported in ≥1% of Patients			
	alendronate 10 mg/day %	alendronate 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.

Alendronate sodium with colecalciferol

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 mcg 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 mcg (vitamin D_3 2800 IU) administered with an additional colecalciferol 70 mcg for a total of 140 mcg colecalciferol (5600 IU vitamin D_3) was similar to that of alendronate 70 mg/colecalciferol 70 mcg (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 mcg group and 2.8% in the colecalciferol 70 mcg group, which was not statistically significant. Overall, the safety profile of alendronate 70 mg/colecalciferol 70 mcg administered with 70 mcg additional colecalciferol for a total of 140 mcg colecalciferol was similar to that of alendronate/colecalciferol 70 mcg.

Alendronate sodium with colecalciferolPost-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 PRECAUTIONS and DOSAGE AND 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 PRECAUTIONS); joint swelling, atypical stress fracture (see PRECAUTIONS).

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.

DOSAGE AND ADMINISTRATION

FonatPlus (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 DRUG INTERACTIONS).

FonatPlus (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, alendronate sodium with colecalciferol brands (70 mg/70 mcg or 70 mg/140 mcg) 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. Alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140mcg) 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 PRECAUTIONS).

SEVERE OESOPHAGEAL ULCERATION HAS BEEN REPORTED IN PATIENTS TAKING ALENDRONATE. SEE PRECAUTIONS. 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 ALENDRONATE SODIUM WITH COLECALCIFEROL (70 mg/70 mcg or 70 mg/140 mcg) AND CONSULT THEIR PHYSICIAN.

In clinical trials, alendronate was administered with appropriate calcium and vitamin D_3 supplementation. The use of vitamin D_3 as the sole treatment of osteoporosis has not been established.

Patients should receive supplemental calcium and/or vitamin D_3, if intake is inadequate (see PRECAUTIONS).

Physicians should consider the vitamin D_3 intake from vitamins and dietary supplements. Alendronate sodium with colecalciferol (70 mg/70mcg) provides 2800 IU (70 mcg) of vitamin D_3 in a single once weekly dose, which is equivalent to seven daily doses of 400 IU (10 micrograms). Alendronate sodium with colecalciferol (70 mg/140 mcg) provides 140 mcg colecalciferol (5600 IU of vitamin D_3) in a single once weekly dose, which is equivalent to seven daily doses of 20 mcg colecalciferol (800 IU vitamin D_3). Additional supplements should not be taken at the same time of day as alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) (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). Alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) 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 alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg), or on another therapy for Paget's disease to alendronate, there are no known or theoretical safety concerns related to alendronate sodium with colecalciferol (70 mg/70 mcg or 70 mg/140 mcg) in patients who previously received any other antiosteoporotic or antipagetic therapy.

FonatPlus (70 mg/70 µg or 70 mg/140 µg)
Treatment of osteoporosis in patients where vitamin D_3 supplementation is recommended

The recommended dose is one tablet of FonatPlus (70 mg/70 µg or 70 mg/140 µg) once weekly.

OVERDOSAGE

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.

Contact the Poisons Information Centre (telephone 13 11 26) for advice regarding management of overdose.

PRESENTATION AND STORAGE CONDITIONS

FonatPlus 70 mg/ 70 µg once weekly tablet is a white to off-white, modified capsule-shaped uncoated tablet, debossed with 'ADC' on one side and '28' on the other side. Available in blister packs (PA/Al/PVC/Al) of 1* and 4 tablets.

FonatPlus 70 mg/ 140 µg, once weekly tablet is a white to off-white, modified capsule-shaped uncoated tablet, debossed with 'ADC' on one side and '56' on the other side. Available in blister packs (PA/Al/PVC/Al) of 1* and 4 tablets.

Store below 25°C. Protect from light and moisture

* Starter packs only

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 16th December 2013

Date of most recent amendment: 26th February 2014