

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrAPO-ALENDRONATE / VITAMIN D₃

Alendronate Sodium / Cholecalciferol Tablets

Tablets, 70 mg / 70 mcg (2800 IU) and 70 mg / 140 mcg (5600 IU), Oral

Apotex Standard

Bone Metabolism Regulator and Vitamin D

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	03/2024
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-ALENDRONATE / VITAMIN D₃ (alendronate sodium/cholecalciferol) is indicated for:

- The treatment of osteoporosis in postmenopausal women.
- The treatment of osteoporosis in men.

For the treatment of osteoporosis, the alendronate sodium component of APO-ALENDRONATE / VITAMIN D₃ increases bone mass and can prevent fractures, including those of the hip and spine (vertebral compression fractures).

Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2.5 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture.

Patients suffering from osteoporosis are at an increased risk for vitamin D insufficiency, especially those over the age of 70 years, home bound, or chronically ill, and may need to receive vitamin D supplementation in addition to that provided in APO-ALENDRONATE / VITAMIN D₃ (see [4 DOSAGE AND ADMINISTRATION, 4.4 Administration](#)). Those living in high latitudes (including most of Canada) may also need additional supplementation.

An adequate calcium intake is also required.

Patients with gastrointestinal malabsorption may not adequately absorb vitamin D₃ and will also require further supplementation.

APO-ALENDRONATE / VITAMIN D₃ alone should not be used to treat vitamin D deficiency (commonly defined as 25-hydroxyvitamin D <22.5 nmol/L or 9 ng/mL).

Important limitations of use: The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis (see [4 DOSAGE AND ADMINISTRATION](#)).

1.1 Pediatrics

Pediatrics (<18 years of age):

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age):

In clinical studies, there was no age-related difference in the efficacy or safety profiles of alendronate (see [14 CLINICAL TRIALS](#))

Daily requirements of vitamin D₃ may be increased in the elderly.

2 CONTRAINDICATIONS

APO-ALENDRONATE / VITAMIN D₃ is contraindicated in patients with:

- hypersensitivity to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia.
- the inability to stand or sit upright for at least 30 minutes.
- hypocalcemia (see [7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism](#)).
- renal insufficiency with creatinine clearance < 0.58 mL/s (< 35 mL/min) (see [4 DOSAGE AND ADMINISTRATION](#) and [10.3 Pharmacokinetics, Renal Insufficiency](#)).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- All patients must receive supplemental calcium and/or vitamin D, if intake is inadequate. Health Professionals should consider the vitamin D intake from vitamins and dietary supplements. Patients at increased risk for vitamin D insufficiency (e.g. over the age of 70 years, home bound, or chronically ill) should receive APO-ALENDRONATE / VITAMIN D₃ (70 mg/5600 IU) and may also need additional vitamin D supplementation. For patients fifty years and over, the recommended dose is at least 800 IU per day. Those living in high latitudes (including most of Canada) may also need additional supplementation (see [7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism](#)).
- The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of APO-ALENDRONATE / VITAMIN D₃ on an individual patient basis.
- Although no specific studies have been conducted on the effects of switching patients on another therapy for osteoporosis to alendronate sodium /cholecalciferol, there are no

known or theoretical safety concerns related to APO-ALENDRONATE / VITAMIN D₃ in patients who previously received any other antiosteoporotic therapy.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage is one tablet of APO-ALENDRONATE / VITAMIN D₃ (70 mg/2800 IU) or APO-ALENDRONATE / VITAMIN D₃ (70 mg/5600 IU) once weekly. The appropriate dosage of APO-ALENDRONATE / VITAMIN D₃ must be determined by the health professional based on the patient's vitamin D requirement.

Geriatrics (≥65 years of age): No dosage adjustment is necessary for the elderly. See [1.2 Geriatrics](#).

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see [1 INDICATIONS, 1.1 Pediatrics](#)).

Renal Impairment: No dosage adjustment is required for patients with mild-to-moderate renal insufficiency (creatinine clearance 0.58 to 1 mL/s [35 to 60 mL/min]). APO-ALENDRONATE / VITAMIN D₃ is contraindicated for patients with more severe renal insufficiency (creatinine clearance < 0.58 mL/s [< 35 mL/min]) (see [2 CONTRAINDICATIONS](#)).

4.4 Administration

APO-ALENDRONATE / VITAMIN D₃ must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only. Other beverages (including mineral water), food, and some medications are known to reduce the absorption of alendronate (see [9 DRUG INTERACTIONS](#)). Waiting less than 30 minutes will lessen the effect of APO-ALENDRONATE / VITAMIN D₃ by decreasing its absorption into the body.

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, APO-ALENDRONATE / VITAMIN D₃ should only be swallowed upon arising for the day with a full glass of water (200 to 250 mL) and patients should not lie down for at least 30 minutes and until after their first food of the day. APO-ALENDRONATE / VITAMIN D₃ should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see [7 WARNINGS AND PRECAUTIONS](#)).

APO-ALENDRONATE / VITAMIN D₃ tablets should not be chewed, sucked, cut, or crushed (see [7 WARNINGS AND PRECAUTIONS](#)).

4.5 Missed Dose

Patients should be instructed that if they miss a dose of APO-ALENDRONATE / VITAMIN D₃, 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.

5 OVERDOSAGE

Alendronate Sodium

No specific information is available on the treatment of overdosage with alendronate. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

Cholecalciferol

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 D₃ for up to five months was not associated with hypercalciuria or hypercalcemia.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet / 91.37 mg alendronate monosodium salt trihydrate, equivalent to 70 mg of free acid, and 70 mcg of cholecalciferol, equivalent to 2800 International Units (IU) vitamin D ₃ .	Butylated hydroxytoluene, colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, mannitol and microcrystalline cellulose.
Oral	Tablet / 91.37 mg alendronate monosodium salt trihydrate, equivalent to 70 mg of free acid, and 140 mcg of cholecalciferol, equivalent to 5600 International Units (IU) vitamin D ₃ .	Butylated hydroxytoluene, colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, mannitol and microcrystalline cellulose.

APO-ALENDRONATE / VITAMIN D₃ (70 mg/2800 IU) tablets are white to off-white, oval, biconvex tablets, engraved “APO” on one side, “A-D28” on the other side.

APO-ALENDRONATE / VITAMIN D₃ (70 mg/2800 IU) tablets are available in blisters of 4s.

APO-ALENDRONATE / VITAMIN D₃ (70 mg/5600 IU) tablets are white to off-white, biconvex, rectangular tablets, engraved “APO” on one side, “ALE-D56” on the other side.

APO-ALENDRONATE / VITAMIN D₃ (70 mg/5600 IU) tablets are available in blisters of 4s.

7 WARNINGS AND PRECAUTIONS

General

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, patients should be instructed to swallow each tablet of APO-ALENDRONATE / VITAMIN D₃ with a full glass of water (200 to 250 mL) and not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take APO-ALENDRONATE / VITAMIN D₃ at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking APO-ALENDRONATE / VITAMIN D₃ immediately and consult their physician (see [4 DOSAGE AND ADMINISTRATION, 4.4 Administration](#)).

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

Driving and Operating 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 APO-ALENDRONATE / VITAMIN D₃ (e.g., dizziness, vertigo, visual disturbances, and severe bone, muscle or joint pain) may affect some patients' ability to drive or operate machinery. Individual responses to APO-ALENDRONATE / VITAMIN D₃ may vary.

Endocrine and Metabolism

Hypocalcemia must be corrected before initiating therapy with APO-ALENDRONATE / VITAMIN D₃ (see [2 CONTRAINDICATIONS](#)). Other disorders affecting mineral metabolism (such as Vitamin D deficiency) should be treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with APO-ALENDRONATE / VITAMIN D₃. Symptomatic hypocalcemia has been reported rarely, both in patients with

predisposing conditions and patients without known predisposing conditions. Patients should be advised to report to their physicians any symptoms of hypocalcemia, such as paresthesias or muscle spasms. Physicians should carefully evaluate patients who develop hypocalcemia during therapy with APO-ALENDRONATE / VITAMIN D₃ for predisposing conditions.

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

APO-ALENDRONATE / VITAMIN D₃ alone should not be used to treat vitamin D deficiency (commonly defined as 25-hydroxyvitamin D < 22.5 nmol/L or 9 ng/mL).

Patients suffering from osteoporosis are at an increased risk for vitamin D insufficiency, especially those over the age of 70 years, home bound, or chronically ill, and may need to receive vitamin D supplementation in addition to that provided in APO-ALENDRONATE / VITAMIN D₃ (see [4 DOSAGE AND ADMINISTRATION, 4.4 Administration](#)). Those living in high latitudes (including most of Canada) may also need additional supplementation.

Patients with gastrointestinal malabsorption syndromes may also require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered.

Vitamin D₃ supplementation may worsen hypercalcemia and/or hypercalciuria when administered to patients with diseases associated with unregulated overproduction of 1,25 dihydroxyvitamin D (e.g., leukemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.

Gastrointestinal

APO-ALENDRONATE / VITAMIN D₃, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate (see [8.5 Post-Market Adverse Reactions](#)). In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue APO-ALENDRONATE / VITAMIN D₃ immediately and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking alendronate sodium/cholecalciferol tablets and/or who fail to swallow it with the recommended amount of water, and/or who continue to take alendronate sodium/cholecalciferol tablets after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood

by, the patient (see [4 DOSAGE AND ADMINISTRATION](#)).

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 APO-ALENDRONATE / VITAMIN D₃ is given to patients with active upper gastrointestinal problems, such as dysphagia, esophageal diseases (including known Barrett's esophagus), gastritis, duodenitis, or ulcers.

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.

Musculoskeletal

Atypical fractures: Low-energy fractures of the subtrochanteric and proximal femoral shaft and other bones have been reported in some long-term (time to onset in the majority of reports ranged from 18 months to 10 years) alendronate-treated patients. Some were stress fractures (some of which were reported as insufficiency fractures) occurring in the absence of apparent trauma or induced by mild external force. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. Approximately one third of the reported femur fractures were bilateral; therefore, the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. Poor healing of these fractures was also reported. Patients with suspected stress fractures should be evaluated, including evaluation for causes and risk factors of stress fractures (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, lower extremity arthritis or fracture, previous stress fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of alendronate therapy in patients with stress fractures should be considered based on individual benefit/risk assessment (See [8.5 Post-Market Adverse Reactions](#)).

Musculoskeletal Pain: In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis. However, such reports have been infrequent. This category of drugs includes alendronate. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping the medication. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate (see [8.5 Post-Market Adverse Reactions](#)).

In placebo-controlled clinical studies of alendronate, the percentages of patients with these symptoms were similar in the alendronate and placebo groups.

Osteonecrosis: Osteonecrosis of the jaw (ONJ) has been reported in patients receiving treatment regimens including bisphosphonates. The majority of reports occurred following tooth extractions with delayed healing and involved cancer patients treated with intravenous

bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. However, some cases have also occurred in patients receiving oral bisphosphonate treatment for postmenopausal osteoporosis and other diagnoses. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection, including osteomyelitis (see [8.5 Post-Market Adverse Reactions](#)).

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors. Known risk factors for osteonecrosis of the jaw include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors, immunosuppressive drugs), poor oral hygiene, co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, diabetes mellitus), smoking, and heavy alcohol use.

Patients who develop osteonecrosis of the jaw should receive appropriate antibiotic therapy and/or oral surgery and discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment. Dental surgery may exacerbate the condition. For patients requiring dental procedures (e.g. tooth extraction, dental implants), there are no definitive data available to establish whether discontinuation of bisphosphonate treatment reduces the risk of ONJ.

Cases of osteonecrosis of the external auditory canal (cholesteatoma) have been reported in patients treated with alendronate sodium/cholecalciferol tablets.

Clinical judgment of the treating physician and/or oral surgeon should guide the management plan, including bisphosphonate treatment, of each patient based on individual benefit/risk assessment.

The following should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds).
- Route of administration (higher risk for parenteral administration).
- Cumulative dose of bone resorption therapy.
- Co-morbid conditions (e.g. anemia, coagulopathies) and smoking.
- Periodontal disease, poorly fitting dentures, history of dental disease.

Ophthalmologic

Ocular disturbances including conjunctivitis, uveitis, episcleritis and scleritis have been reported with alendronate therapy. Patients with ocular events other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. If ocular inflammatory symptoms are observed, treatment may need to be discontinued (see [8.5 Post-Market Adverse Reactions](#)).

Renal

APO-ALENDRONATE / VITAMIN D₃ is contraindicated for patients with severe renal insufficiency (creatinine clearance < 0.58 mL/s [< 35 mL/min]) (see [2 CONTRAINDICATIONS](#)).

Reproductive Health: Female and Male Potential

- **Fertility**

The effect of alendronate sodium/cholecalciferol on human fertility has not been evaluated. Animal study data is included in Section [16 NON-CLINICAL TOXICOLOGY](#).

7.1 Special Populations

7.1.1 Pregnant Women

APO-ALENDRONATE / VITAMIN D₃ should not be used by pregnant women. Alendronate sodium/cholecalciferol has not been studied in pregnant women.

7.1.2 Breast-feeding

APO-ALENDRONATE / VITAMIN D₃ should not be used during breast-feeding. It is unknown whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

In clinical studies, there was no age-related difference in the efficacy or safety profiles of alendronate (see [14 CLINICAL TRIALS](#)).

Daily requirements of vitamin D₃ may be increased in the elderly.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common drug related adverse reactions include gastrointestinal disorders (abdominal pain, dyspepsia, constipation, diarrhea, flatulence, esophageal ulcer, dysphagia, acid regurgitation, melena, nausea and abdominal distention), musculoskeletal (bone, muscle or joint) pain and headache.

It is important to follow the recommended dosing instructions. See [7 WARNINGS AND PRECAUTIONS, Gastrointestinal](#) and [4.4 Administration](#).

Osteonecrosis of the Jaw and atypical bone fractures have been observed under post marketing setting. See [7 WARNINGS AND PRECAUTIONS, Musculoskeletal](#).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Alendronate

Treatment of Osteoporosis

Postmenopausal Women:

In two, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational) of virtually identical design, with a total of 994 postmenopausal women, the overall safety profiles of alendronate 10 mg/day and placebo were similar. 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 considered by the investigators as possibly, probably, or definitely drug-related in $\geq 1\%$ of patients treated with either alendronate 10 mg/day or placebo are presented in the following table.

Table 2 - Drug-Related* Adverse Experiences Reported in $\geq 1\%$ of Patients Treated for Osteoporosis

	Alendronate 10 mg/day n = 196 (%)	Placebo n = 397 (%)
Gastrointestinal		
abdominal pain	6.6	4.8
nausea	3.6	4.0

	Alendronate 10 mg/day n = 196 (%)	Placebo n = 397 (%)
dyspepsia	3.6	3.5
constipation	3.1	1.8
diarrhea	3.1	1.8
flatulence	2.6	0.5
acid regurgitation	2.0	4.3
esophageal ulcer	1.5	0.0
vomiting	1.0	1.5
dysphagia	1.0	0.0
abdominal distention	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

* Considered possibly, probably, or definitely drug-related as assessed by the investigators.

One patient treated with alendronate (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant acetylsalicylic acid (ASA) developed an anastomotic ulcer with mild hemorrhage, which was considered drug-related. ASA and alendronate were discontinued and the patient recovered.

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 two 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 multicenter study, the overall safety and tolerability profiles of

alendronate 70 mg once weekly and alendronate 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug-related in \geq 1% of patients in either treatment group are presented in the following table:

Table 3 - Drug-Related* Adverse Experiences Reported in \geq 1% of Patients Treated for Osteoporosis

	Alendronate 70 mg once weekly 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 distention	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

* Considered possibly, probably, or definitely drug-related as assessed by the investigators.

Men:

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of alendronate 10 mg/day [n=146] and a one-year study of alendronate 70 mg once weekly [n=109]), the safety profile of alendronate was generally similar to that seen in postmenopausal women. The rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate 10 mg/day vs. 10.5% for placebo, and 6.4% for alendronate 70 mg once weekly vs. 8.6% for placebo.

Other Studies in Men and Women:

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

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

Prevention of Osteoporosis in Postmenopausal Women:

The safety of alendronate 5 mg/day in postmenopausal women 40 to 60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive alendronate for either two or three years. In these studies, the overall safety profiles of alendronate 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with alendronate 5 mg/day and 5.7% of 648 patients treated with placebo. Adverse experiences reported by the investigators as possibly, probably or definitely drug-related in $\geq 1\%$ of patients treated with either alendronate 5 mg/day or placebo are presented in the following table:

Table 4 - Drug-Related* Adverse Experiences Reported in $\geq 1\%$ of Patients. Prevention of Osteoporosis

	Alendronate 5 mg/day n = 642 (%)	Placebo n = 648 (%)
Gastrointestinal		
abdominal pain	1.7	3.4
acid regurgitation	1.4	2.5
diarrhea	1.1	1.7
dyspepsia	1.9	1.7
nausea	1.4	1.4

* Considered possibly, probably, or definitely drug-related as assessed by the investigators.

Concomitant Use with Estrogen/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 estrogen \pm progestin (n=354) was consistent with those of the individual treatments.

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis:

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

Table 5 - Drug-Related* Adverse Experiences Reported in $\geq 1\%$ of Patients. Treatment and Prevention of Glucocorticoid-induced Osteoporosis

	Alendronate 10 mg/day n = 157 (%)	Alendronate 5 mg/day n = 161 (%)	Placebo n = 159 (%)
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
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

* Considered possibly, probably, or definitely drug-related as assessed by the investigators.

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies was consistent with that observed in the first year.

Paget's Disease of Bone:

In clinical studies (Paget's disease and osteoporosis), adverse experiences reported in 175 patients taking alendronate 40 mg/day for 3 to 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 (17.7% alendronate vs. 10.2% placebo). Isolated cases of esophagitis 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. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with alendronate 40 mg/day and 2.4% of patients treated with placebo.

Alendronate/Cholecalciferol

In a fifteen week double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of alendronate/cholecalciferol (70 mg/2800 IU) was similar to that of alendronate 70 mg once weekly. In the 24-week double-blind extension study in women (n=619) and men (n=33), the safety profile of alendronate/cholecalciferol (70 mg/2800 IU) administered with an additional 2800 IU vitamin D₃ was similar to that of alendronate/cholecalciferol (70 mg/2800 IU).

8.3 Less Common Clinical Trial Adverse Reactions

Skin: rash and erythema

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

In double-blind, multicenter, 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 P¹/dL (0.65 mM) were similar in both treatment groups.

In a small, open-label study, at higher doses (80 mg/day) some patients had elevated transaminases. However, this was not observed at 40 mg/day. No clinically significant toxicity was associated with these laboratory abnormalities.

Rare cases of leukemia have been reported following therapy with other bisphosphonates. Any causal relationship to either the treatment or to the patients' underlying disease has not been established.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported in post-marketing use of alendronate:

Body as a Whole: hypersensitivity reactions including urticaria and angioedema; transient symptoms of myalgia, malaise, asthenia and fever have been reported with alendronate typically in association with initiation of treatment; symptomatic hypocalcemia both in association with predisposing conditions and in patients without known predisposing conditions; peripheral edema.

Dental: localized osteonecrosis of the jaw (ONJ) generally associated with local infection (including osteomyelitis) and/or tooth extraction with delayed healing (see [7 WARNINGS AND PRECAUTIONS](#)).

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, esophageal stricture or perforation, and oropharyngeal ulceration; gastric or duodenal ulcers, some severe and with complications (see [7 WARNINGS AND PRECAUTIONS](#) and [4 DOSAGE AND ADMINISTRATION](#)).

¹ P: Elemental phosphorus

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe and/or incapacitating; joint swelling; low-energy fractures of the femoral shaft and other bones (see [7 WARNINGS AND PRECAUTIONS](#)).

Nervous System: dizziness, vertigo, dysgeusia

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

Special Senses: uveitis, scleritis or episcleritis; osteonecrosis of the external auditory canal (cholesteatoma)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Specific interaction studies were not performed.

Animal studies have demonstrated that alendronate is highly concentrated in bone and is retained only minimally in soft tissue. No metabolites have been detected. Although alendronate is bound approximately 78% to plasma protein in humans, its plasma concentration is so low after oral dosing that only a small fraction of plasma-binding sites is occupied, resulting in a minimal potential for interference with the binding of other drugs. 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. In summary, alendronate is not expected to interact with other drugs based on effects on protein binding, renal excretion, or metabolism of other drugs.

9.4 Drug-Drug Interactions

Table 6 - Interaction with Alendronate Sodium

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Calcium supplements, Antacids, other Multivalent Cations and other Oral Medications		Interfere with absorption of alendronate	Wait at least one-half hour after taking APO-ALENDRONATE / VITAMIN D ₃ before taking any other oral medication.
Ranitidine	CT	Was shown to double the bioavailability of oral alendronate	The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H ₂ - antagonists is unknown
Hormone Replacement Therapy (HRT [estrogen ± progestin])	CT	Greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone.	The safety and tolerability profile of the combination was consistent with those of the individual treatments (see 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions , Concomitant Use with Estrogen/Hormone Replacement Therapy). The studies were too small to detect antifracture efficacy, and no significant differences in fracture incidence among the treatment groups were found.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Alendronate was used in osteoporosis studies in men, postmenopausal women, 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 acetylsalicylic acid-containing products. This was not observed in a study with alendronate 70 mg once weekly.

Alendronate sodium / cholecalciferol tablets may be administered to patients taking nonsteroidal anti-inflammatory drugs (NSAIDs). In a three-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of

upper gastrointestinal adverse events was similar in patients taking alendronate 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with APO-ALENDRONATE / VITAMIN D₃.

Interaction with Cholecalciferol

Drugs That May Impair the Absorption of Cholecalciferol

Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g. cholestyramine, colestipol) may impair the absorption of vitamin D.

Drugs That May Increase the Catabolism of Cholecalciferol

Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D.

9.5 Drug-Food Interactions

Food and beverages other than plain water may markedly reduce the absorption and effectiveness of alendronate. APO-ALENDRONATE / VITAMIN D₃ must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only (see [4 DOSAGE AND ADMINISTRATION, 4.4 Administration](#)).

9.6 Drug-Herb Interactions

Herbal products may interfere with the absorption of alendronate. APO-ALENDRONATE / VITAMIN D₃ must be taken at least one-half hour before any herbal products.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

APO-ALENDRONATE / VITAMIN D₃ contains alendronate sodium, a bisphosphonate, and cholecalciferol (vitamin D₃).

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.

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

10.2 Pharmacodynamics

Alendronate Sodium

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in Postmenopausal Women:

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral fracture. Osteoporosis 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. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) 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 deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

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 bone specific alkaline phosphatase

by approximately 50%, and total serum alkaline phosphatase, by approximately 25 to 30%, to reach a plateau after 6 to 12 months. In osteoporosis prevention studies, alendronate 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during a one-year study with alendronate 70 mg once weekly for the treatment of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with alendronate. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of alendronate 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment, however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with alendronate 5 mg/day. In a one-year study with alendronate 70 mg once weekly, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to alendronate but also a decrease in renal phosphate reabsorption.

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. 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 were observed in a one-year study in men with osteoporosis receiving alendronate 70 mg once weekly.

10.3 Pharmacokinetics

Table 7 - Summary of Alendronate Sodium Pharmacokinetic Parameters in the Normal Population

	Mean	90% Confidence Interval
Absolute bioavailability of 5 mg tablet, taken 2 hours before first meal of the day	0.63% (females)	(0.48, 0.83)
Absolute bioavailability of 10 mg tablet, taken 2 hours before first meal of the day	0.78% (females)	(0.61, 1.04)
	0.59% (males)	(0.43, 0.81)

	Mean	90% Confidence Interval
Absolute bioavailability of 40 mg tablet, taken 2 hours before first meal of the day	0.60% (females)	(0.46, 0.78)
Absolute bioavailability of 70 mg tablet, taken 2 hours before first meal of the day	0.57% (females)	(0.44, 0.73)
Renal Clearance mL/s (mL/min) (n=6)	1.18 (71)	(1.07, 1.3) (64, 78)

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 standardized breakfast. Oral bioavailability of the 10 mg tablet in men was 0.59%.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

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

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

Cholecalciferol

Following administration of alendronate/cholecalciferol (70 mg/2800 IU) after an overnight fast and two hours before a standard meal, the mean area under the serum-concentration-time curve ($AUC_{0-120 \text{ hrs}}$) for vitamin D₃ (unadjusted for endogenous vitamin D₃ levels) was 296.4 ng-hr/mL. The mean maximal serum concentration (C_{max}) of vitamin D₃ was 14.8 nmol/L or 5.9 ng/mL, and the median time to maximal serum concentration (T_{max}) was 12 hrs. Following

administration of alendronate/cholecalciferol (70 mg/5600 IU) after an overnight fast and two hours before a meal, the mean area under the serum-concentration-time curve ($AUC_{0-80 \text{ hrs}}$) for vitamin D₃ (unadjusted for endogenous vitamin D₃ levels) was 490.2 ng·hr/mL. The mean maximal serum concentration (C_{max}) of vitamin D₃ was 30.5 nmol/L or 12.2 ng/mL and the median time to maximal serum concentration (T_{max}) was 10.6 hours. The bioavailability of the vitamin D₃ in alendronate/cholecalciferol (70 mg/2800 IU) and alendronate/cholecalciferol (70 mg/5600 IU) is similar to an equal dose of vitamin D₃ administered alone.

Distribution:

Alendronate Sodium

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

Cholecalciferol

Following absorption, vitamin D₃ enters the blood as part of chylomicrons. Vitamin D₃ is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D₃, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D₃ at these sites for later release into the circulation. Circulating vitamin D₃ is bound to vitamin D-binding protein.

Metabolism:

Alendronate Sodium

There is no evidence that alendronate is metabolized in animals or humans.

Cholecalciferol

Vitamin D₃ is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D₃, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D₃, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D₃ undergoes glucuronidation prior to elimination.

Elimination:

Alendronate Sodium

Following a single IV dose of [¹⁴C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with alendronate (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Cholecalciferol

When radioactive vitamin D₃ was administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4%, and the mean fecal 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 D₃ in the serum following an oral dose of alendronate/ cholecalciferol (70 mg/2800 IU) is approximately 24 hours.

Special Populations and Conditions

- **Pediatrics:** Alendronate pharmacokinetics have not been investigated in patients <18 years of age. APO-ALENDRONATE / VITAMIN D₃ is not indicated for use in children (see [7 WARNINGS AND PRECAUTIONS, Special Populations, 7.1.3 Pediatrics](#)).

- **Geriatrics:**
Alendronate Sodium

Bioavailability and disposition (urinary excretion) were similar in elderly (≥ 65 years of age) and younger patients. No dosage adjustment is necessary (see [4 DOSAGE AND ADMINISTRATION](#)).

Cholecalciferol

Dietary requirements of vitamin D₃ may be increased in the elderly.

- **Sex:** Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.
- **Ethnic Origin:** Pharmacokinetic differences due to race have not been studied.
- **Hepatic Insufficiency:** As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Vitamin D₃ may not be adequately absorbed in patients who have malabsorption due to inadequate bile production.

- **Renal Insufficiency:** Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. 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.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 0.58 to 1 mL/s [35 to 60 mL/min]). APO-ALENDRONATE / VITAMIN D₃ is contraindicated for patients with more severe renal insufficiency (creatinine clearance < 0.58 mL/s [< 35 mL/min]) (see [2 CONTRAINDICATIONS](#)).

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature (15°C to 30°C). Protect from moisture and light. Store tablets in the original blister package until use.

Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Alendronate Sodium

Proper name:

alendronate sodium

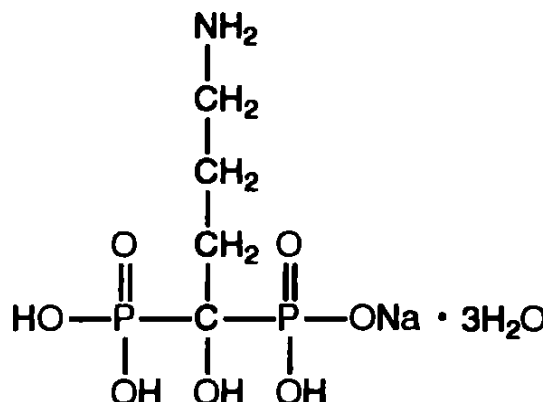
Chemical name:

(4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

Molecular formula and molecular mass:

$C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and 325.12 g/mol

Structural formula:



Physicochemical properties:

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

Cholecalciferol

Proper name:

cholecalciferol

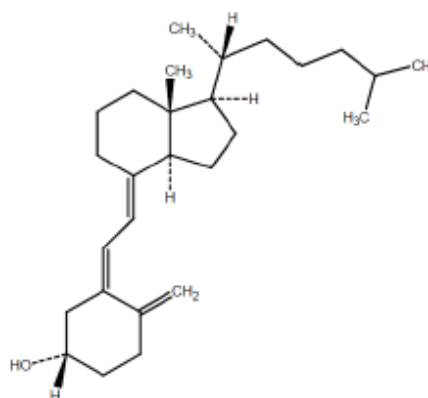
Chemical name:

(3 β ,5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-3-ol

Molecular formula and molecular mass:

$C_{27}H_{44}O$ and 384.64 g/mol

Structural formula:



Physicochemical properties:

Cholecalciferol is a white or yellowish-white powder. Cholecalciferol is practically insoluble in water, freely soluble in usual organic solvents, and slightly soluble in vegetable oils.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Alendronate/Cholecalciferol Studies

Treatment of osteoporosis in men and postmenopausal women

Table 8 - Summary of patient demographics for clinical trials (treatment of osteoporosis in men and postmenopausal women)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PN227	Double-blind, randomized, active-controlled, multicenter study	Base Study: FOV 70 / 2800 FOS 70ORAL 15 weeks	717	67 (35-89)	Men Women
		Extension Study: FOV 70 / 2800 +	652	67 (41-89)	Men Women

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
		cholecalciferol 2800 OR FOV 70 / 2800 + PBO ORAL 24 weeks			

FOV = alendronate (mg/week) / cholecalciferol (IU/week); FOS = alendronate (mg/week); PBO = placebo (mg/week)

In a 15-week trial, 717 postmenopausal women and men, mean age 67 years, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2.5 standard deviations below the premenopausal mean) were randomized to receive either weekly alendronate/cholecalciferol 70 mg/2800 IU vitamin D or weekly alendronate 70 mg alone with no vitamin D supplementation. Patients who were vitamin D deficient (25-hydroxyvitamin D < 22.5 nmol/L or 9 ng/mL) at baseline were excluded. Treatment with alendronate/cholecalciferol 70 mg/2800 IU resulted in a smaller reduction in serum calcium levels (-0.9%) when compared to alendronate 70 mg alone (-1.4%). As well, treatment with alendronate/cholecalciferol 70 mg/2800 IU resulted in a significantly smaller increase in parathyroid hormone levels when compared to alendronate 70 mg alone (14% and 24%, respectively).

The sufficiency of patients' vitamin D status is best assessed by measuring 25-hydroxyvitamin D levels. In the 15-week trial mentioned above, baseline 25-hydroxyvitamin D levels were 55.5 nmol/L (22.2 ng/mL) in the alendronate/cholecalciferol group and 55.3 nmol/L (22.1 ng/mL) in the alendronate only group. After 15 weeks of treatment, the mean levels were 26% higher in the alendronate/cholecalciferol group as compared to the alendronate only group (57.8 nmol/L [23.1 ng/mL] versus 46.0 nmol/L [18.4 ng/mL], respectively). The final levels of 25-hydroxyvitamin D at Week 15 are summarized in the table below. The percentage of patients with serum 25-hydroxyvitamin D < 37.5 nmol/L (15 ng/mL) was significantly lower with alendronate/cholecalciferol 70 mg/2800 IU than alendronate 70 mg (11.5 % vs. 31.9 %), respectively (p < 0.001).

Table 9 - 25-hydroxyvitamin D Levels after Treatment with Alendronate/Cholecalciferol (70 mg/2800 IU) or Alendronate 70 mg at Week 15*

25-hydroxyvitamin D Ranges (nmol/L [ng/mL])	Number (%) of Patients					
	< 22.5 [9]	22.5-35 [9-14]	37.5-47.5 [15-19]	50-60 [20-24]	62.5-72.5 [25-29]	75-155 [30-62]

	Number (%) of Patients					
Alendronate/cholecalciferol (70 mg/2800 IU) (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 or 9 ng/mL) at baseline were excluded.

Patients (n=652) who completed the above 15-week trial continued in a 24-week extension in which all received alendronate/cholecalciferol (70 mg/2800 IU) and were randomly assigned to receive either additional once weekly vitamin D₃ 2800 IU (Vitamin D₃ 5600 IU group) or matching placebo (Vitamin D₃ 2800 IU group). After 24 weeks of extended treatment (Week 39 from original baseline), the mean levels of 25-hydroxyvitamin D were 69.8 nmo/L (27.9 ng/mL) and 64.0 nmol/L (25.6 ng/mL) in the vitamin D₃ 5600 IU group and vitamin D₃ 2800 IU group, respectively. The mean change of 25-hydroxyvitamin D levels from baseline was greater in the Vitamin D₃ 5600 IU group (p < 0.001). The percentage of patients with hypercalciuria at Week 39 was not statistically different between treatment groups.

The distribution of the final levels of 25-hydroxyvitamin D at Week 39 is summarized in the table below. The percentage of patients with serum 25-hydroxyvitamin D < 37.5 nmol/L (15 ng/mL) was non-significantly lower in the Vitamin D₃ 5600 IU group than in the Vitamin D₃ 2800 IU group (3.1 % vs. 5.6 %), respectively (p < 0.12).

Table 10 - 25-hydroxyvitamin D Levels after Treatment with Alendronate/Cholecalciferol at Week 39

25-hydroxyvitamin D Levels after Treatment with Alendronate/Cholecalciferol at Week 39						
	Number (%) of Patients					
25-hydroxyvitamin D Ranges (nmol/L [ng/mL])	< 22.5 [9]	22.5-35 [9-14]	37.5-47.5 [15-19]	50-60 [20-24]	62.5-72.5 [25-29]	75-155 [30-59]
alendronate/cholecalciferol (Vitamin D ₃ 5600 IU group)* (N=321)	0	10 (3.1)	29 (9.0)	79 (24.6)	87 (27.1)	116 (36.1)

25-hydroxyvitamin D Levels after Treatment with Alendronate/Cholecalciferol at Week 39

	Number (%) of Patients					
alendronate/cholecalciferol (Vitamin D ₃ 2800 IU group)** (N=320)	1 (0.3)	17 (5.3)	56 (17.5)	80 (25.0)	74 (23.1)	92 (28.8)

* Patients received alendronate 70 mg or alendronate/cholecalciferol (70 mg/2800 IU) for the 15-week base study followed by alendronate/cholecalciferol (70 mg/2800 IU) and 2800 IU additional vitamin D₃ for the 24-week extension study.

** Patients received alendronate 70 mg or alendronate/cholecalciferol (70 mg/2800 IU) for 15-week base study followed by alendronate/cholecalciferol (70 mg/2800 IU) and placebo for the additional vitamin D₃ for 24-week extension study.

Alendronate Studies

Treatment of osteoporosis in postmenopausal women

Table 11 - Summary of patient demographics for clinical trials (treatment of osteoporosis in postmenopausal women)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PN035	Double -blind, randomized, placebo-controlled, parallel group multicenter extension study	PBO FOS 5 mg FOS 10 mg FOS 20/5 mg ORAL 3 years	478	45-82	Women
PN037	Double -blind, randomized, placebo-controlled, parallel group multicenter extension study	PBO FOS 5 mg FOS 10 mg FOS 20/5 mg ORAL 3 years	516	44-84	Women

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PN041	Double-blind, randomized, parallel-group study	PBO FOS 10 mg FOS 20 mg sCT ORAL 2 years	286	48-76	Women
PN118	Randomized, Double-blind, multicenter study	FOS 10 mg FOS 35 mg (twice a week) FOS 70 mg (once a week) ORAL 1 year	1258	42-95	Women
PN026	Double-blind, randomized, placebo controlled-parallel group, multicenter study	PBO FOS 5 mg FOS 10 mg FOS 20 mg/PBO FOS 40 mg/PBO FOS 40 mg/2.5 mg ORAL 2 (+1*year)	188	42-75	Women
PN054	Double-blind, randomized, placebo controlled, parallel-group study	PBO FOS 1 mg FOS 2.5 mg FOS 5 mg ORAL 2 years	359	59-85	Women
FIT 1	Randomized, placebo-controlled	PBO FOS 10 mg ORAL 3 years	2027	55-81	Women

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
FIT 2	Randomized, placebo-controlled	PBO FOS 10 mg ORAL 4 years	4432	55-80	Women
PN072	Double-blind, randomized, placebo- controlled, multicenter study	FOS 10 mg + conjugated estrogens (0.625 mg) OR conjugated estrogens (0.625 mg) OR PBO OR FOS 10 mg ORAL 2 years	425	42-82	Women
PN097	Triple-blind, randomized, placebo- controlled, parallel-group, multicenter study	FOS 10 mg/day + HRT (estrogen + progestin) OR PBO/HRT ORAL 1 year	428	40-84	Women

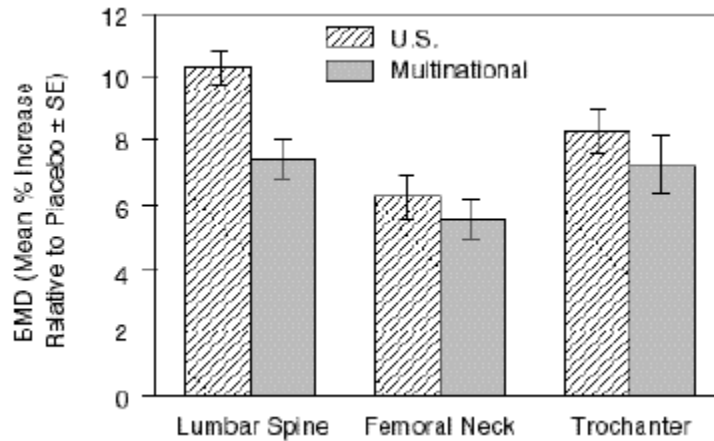
PBO= Placebo; FOS=alendronate (mg/day); sCT=Intranasal salmon calcitonin 100 IU/day; FOS 20/PBO, FOS 40/PBP= alendronate 20 or 40 mg for 1 year followed by placebo for 1 year; FOS 40/2.5= alendronate 40 mg for 3 months followed by 2.5 for 21 months; FOS 20/5=alendronate 20 mg for 2 years followed by 5 mg for 1 year

*Following 2 years of treatment, patients were followed for a further year off treatment.

Effect on Bone Mineral Density

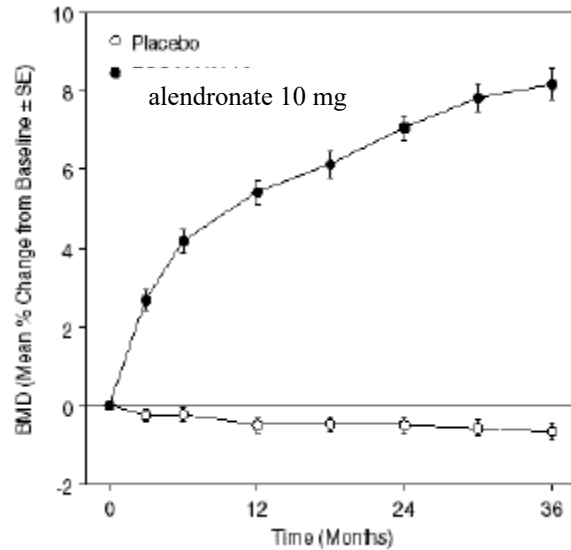
The efficacy of alendronate 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years duration. These included two large three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in 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.

**Osteoporosis Treatment Studies in Postmenopausal Women
Increase in BMD
Alendronate 10 mg/day at Three Years**



In the combined studies, after three years, BMD of the lumbar spine, femoral neck and trochanter in placebo-treated patients decreased significantly by between 0.65 and 1.16%. Highly significant increases, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received alendronate 10 mg/day. Total body BMD also increased significantly in both studies, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the entire three years of treatment (see following figure 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 three and five: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. Thus, alendronate reverses the progression of osteoporosis. Alendronate was similarly effective regardless of age, race, baseline rate of bone turnover, renal function and use with a wide range of common medications.

**Osteoporosis Treatment Studies in Postmenopausal Women
Time Course of Effect of Alendronate 10 mg/day Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline**



In a separate study, alendronate 10 mg/day for two years induced highly significant increases in BMD of the spine, femoral neck, trochanter, and total body relative to either intranasal salmon calcitonin 100 IU/day or placebo.

The therapeutic equivalence of alendronate 70 mg once weekly (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multicenter 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. In trials with alendronate changes in BMD of this magnitude were associated with a decrease in fracture incidence (see below).

Effects of Withdrawal

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, bone turnover gradually returned toward pretreatment levels, and BMD no longer increased although accelerated bone loss was not observed. These data indicate that treatment with alendronate must be continuous to produce progressive increases in bone mass.

Effect on Fracture Incidence

To assess the effects of alendronate on vertebral fracture incidence, the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of alendronate (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year).

There was a statistically significant 48% reduction in the proportion of patients treated with alendronate experiencing one or more vertebral fractures relative to those treated with placebo (3.2% vs 6.2%). An even greater reduction in the total number of vertebral fractures (4.2 vs 11.3 per 100 patients) was also observed. 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.

Additionally, analysis of the data pooled across doses of ≥ 2.5 mg from five placebo-controlled studies of two- or three-years' duration including the U.S. and Multinational studies (alendronate n=1012, placebo: n=590) revealed a significant 29% reduction in non-vertebral fracture incidence (alendronate 9.0% vs placebo, 12.6%). Like the effect on vertebral fracture incidence, these results of alendronate treatment are consistent with the observed increases in bone mass.

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 a baseline vertebral fracture.

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

This randomized, double-blind, placebo-controlled 2027-patient study (alendronate n=1022; placebo, n=1005) demonstrated that treatment with alendronate resulted in statistically significant and clinically meaningful reductions in fracture incidence at three years as shown in the following table.

Table 12 - Effect of Alendronate on Fracture Incidence in the Three-Year Study of FIT (Patients with Vertebral Fracture at Baseline)

Patients with:	% of Patients		Reduction (%) in Fracture Incidence
	Alendronate (n=1022)	Placebo (n=1005)	
Vertebral fractures (diagnosed by X-ray)[†]			
≥ 1 new vertebral fracture	7.9	15.0	47***
≥ 2 new vertebral fractures	0.5	4.9	90***

Patients with:	% of Patients		Reduction (%) in Fracture Incidence
	Alendronate (n=1022)	Placebo (n=1005)	
Painful (clinical) fractures			
≥ 1 painful vertebral fracture	2.3	5.0	54**
Any painful fracture	13.8	18.1	26**
Hip fracture	1.1	2.2	51*
Wrist (forearm) fracture	2.2	4.1	48*

† Number evaluable for vertebral fracture: alendronate, n=984; placebo, n=966

* p < 0.05

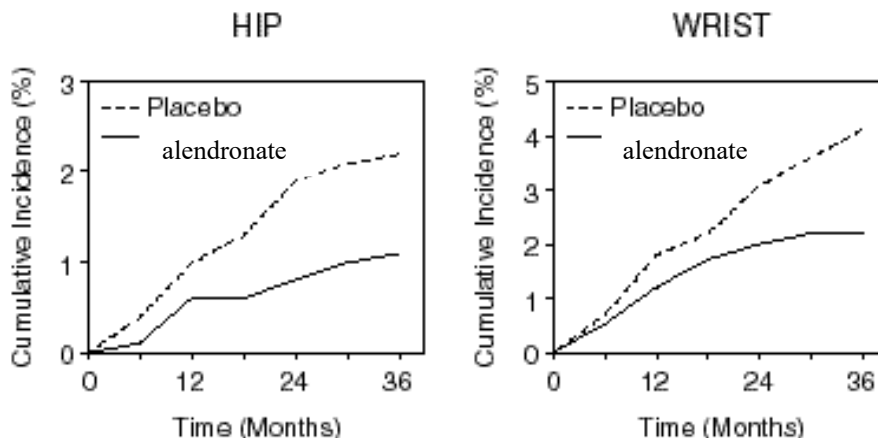
** p < 0.01

*** p < 0.001

Furthermore, in this population of patients with baseline vertebral fracture, treatment with alendronate significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

The following two figures display the cumulative incidence of hip and wrist fractures in the Three-Year Study of FIT. In both figures, the cumulative incidence of these types of fracture is lower with alendronate compared with placebo at all time points. Alendronate reduced the incidence of hip fracture by 51% and wrist fracture by 48%. Proportionately similar reductions of hip and wrist fractures were seen in pooled earlier osteoporosis treatment studies.

**Cumulative Incidence of Hip and Wrist Fractures
in the Three-Year Study of FIT
(Patients with Vertebral Fracture at Baseline)**



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

This randomized, 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 the following table for the patients with osteoporosis.

Table 13 - Effect of Alendronate on Fracture Incidence in Osteoporotic[†] Patients in the Four-Year Study of FIT (Patients without Vertebral Fracture at Baseline)

Patients with:	% of Patients		Reduction (%) in Fracture Incidence
	Alendronate (n=1545)	Placebo (n=1521)	
≥ 1 painful fracture	12.9	16.2	22 ^{**}
≥ 1 vertebral fracture ^{††}	2.5	4.8	48 ^{***}
≥ 1 painful vertebral fracture	1.0	1.6	41 ^{†††}
Hip fracture	1.0	1.4	29 ^{†††}
Wrist (forearm) fracture	3.9	3.8	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

^{†††} Not significant

^{**} p=0.01

^{***} p < 0.001

In all patients (including those without osteoporosis), the reductions in fracture incidence were: ≥ 1 painful fracture, 14% (p=0.072); ≥ 1 vertebral fracture, 44% (p=0.001); ≥ 1 painful vertebral fracture, 34% (p=0.178), and hip fracture, 21% (p=0.44). The incidence of wrist fracture in all patients was alendronate, 3.7%; placebo, 3.2% (not significant).

Combined FIT Studies

The reductions in fracture incidence for the combined Three- and Four-Year Studies of FIT are shown in the following table.

Table 14 - Effect of Alendronate on Fracture Incidence in the Combined (Three- and Four-Year) Studies of FIT

Reduction (%) in Fracture Incidence Alendronate vs. Placebo		
Patients with:	Osteoporotic patients [†] (n=5093)	All patients (n=6459)
Vertebral fractures (diagnosed by X-ray)^{††}		
≥ 1 vertebral fracture	48 ^{***}	46 ^{***}
≥ 2 vertebral fractures	88 ^{***}	84 ^{***}
Painful (clinical) fractures		
Any painful fracture	24 ^{***}	18 ^{**}
Painful vertebral fracture	50 ^{***}	47 ^{***}
Hip fracture	40 [*]	36 ^{‡†}
Wrist (forearm) fracture ^{†††}	18 [‡]	6 [‡]

[†] Includes all patients in the Three-Year Study plus osteoporotic patients (baseline femoral neck BMD at least 2 SD below the mean for young adult women) in the Four-Year Study

^{††} Number evaluable for vertebral fractures: osteoporotic patients, n=4804; all patients, n=6084

^{†††} Significant reduction in wrist fracture incidence was observed in the Three-Year Study (patients with baseline vertebral fracture) but not in the Four-Year Study (patients without baseline vertebral fracture)

[‡] Not significant

^{‡†} p=0.059

^{*} p < 0.05

^{**} 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 U.S. and Multinational (U.S./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; U.S./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 U.S./Mult. and Three-Year FIT Studies (p < 0.001). Thus, alendronate reduces the incidence of vertebral fractures whether or not patients have experienced a previous vertebral fracture.

Overall, these results demonstrate the consistent efficacy of alendronate to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated with the 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 mineralization 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 rats and baboons exposed to long-term alendronate treatment, indicate that bone formed during therapy with alendronate is of normal quality.

Treatment of osteoporosis in men

Table 15 - Summary of patient demographics for clinical trials (treatment of osteoporosis in men)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PN096	Double-blind randomized placebo-controlled, multicenter, multinational study	PBO FOS 10 mg Calcium (500 mg) and Vitamin D (400 IU) supplement daily ORAL 2 years	241	31-87	Men
PN165	Double-blind, placebo-controlled, multicenter study	PBO FOS 70 mg (once weekly) ORAL 1 year	167	38-91	Men

PBO= Placebo; FOS=alendronate (mg/day)

The efficacy of alendronate in men with osteoporosis was demonstrated in two clinical studies.

A two-year, double-blind, placebo-controlled, multicenter study of alendronate 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). At two years, the mean increases relative to placebo in BMD in men receiving alendronate 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6% (all $p \leq 0.001$). Consistent with much larger studies in postmenopausal women, in these men, alendronate 10 mg/day reduced the incidence of new vertebral fracture (assessed 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; $p=0.022$).

A one year, double blind, placebo controlled, multicenter study of alendronate 70 mg once weekly enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). At one year, the mean increases in BMD relative to placebo were significant at the following sites: lumbar spine, 2.8% ($p \leq 0.001$); femoral neck, 1.9% ($p=0.007$); trochanter, 2.0% ($p \leq 0.001$); and total body, 1.2% ($p=0.018$). These increases in BMD were similar to those seen at one year in the 10 mg once daily study. The trial was not powered to detect a clinical difference in fracture incidence between the alendronate and placebo groups. However, other studies with daily or weekly alendronate administrations have consistently demonstrated a relationship between increases in BMD (a surrogate marker) and decreases in fracture rate (clinical endpoint). Therefore, it can be assumed that this relationship is also true in men given a weekly administration of alendronate.

In both studies alendronate was effective regardless of age, gonadal function or baseline BMD (femoral neck and lumbar spine).

Concomitant Use with Estrogen/Hormone Replacement Therapy (HRT)

The effects on BMD of treatment with alendronate 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized 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 estrogen or alendronate alone (both 6.0%).

The effects on BMD when alendronate was added to stable doses (for at least one year) of HRT (estrogen \pm 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 favorable 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. The studies were too small to detect antifracture efficacy, and no significant differences in fracture incidence among the treatment groups were found.

14.2 Comparative Bioavailability Studies

A randomized, two-way, single dose, crossover comparative bioavailability study of APO-ALENDRONATE/ CHOLECALCIFEROL 70 mg/140 mcg (5600 IU) tablets (Apotex Inc.) and P^rFOSAVANCE[®] 70 mg/5600 IU tablets (Merck Canada Inc.) was conducted in healthy male and female subjects under fasting condition. Comparative bioavailability data from the 77 subjects

that were included in the statistical analysis are presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Alendronate (1 x 70 mg alendronate sodium /140 mcg [5600 IU] cholecalciferol) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (pg·h/mL)	78010.22 87110.96 (47.39)	73134.89 83451.24 (54.50)	106.7	98.0 - 116.1
AUC _I (pg·h/mL)	82226.12 91790.62 (47.24)	76965.23 87662.40 (54.31)	106.8	98.2 - 116.3
C _{max} (pg/mL)	26392.83 30676.25 (69.69)	24527.89 27833.05 (53.46)	107.6	97.6 - 118.7
T _{max} ³ (h)	1.02 (0.33-3.03)	1.00 (0.50-2.50)		
T _½ ⁴ (h)	5.96 (21.82)	5.74 (23.85)		
¹ APO-ALENDRONATE / CHOLECALCIFEROL (alendronate sodium /cholecalciferol) tablets, 70 mg/140 mcg (5600 IU) (Apotex Inc.) ² prFOSAVANCE® (alendronate sodium /cholecalciferol) tablets, 70 mg/140 mcg (5600 IU), (Merck Canada Inc.) ³ Expressed as the median (range) only ⁴ Expressed as the arithmetic mean (CV%) only				

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Baseline-Adjusted Cholecalciferol (1 x 70 mg alendronate sodium /140 mcg [5600 IU] cholecalciferol) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng·h/mL)	351.59 363.34 (23.03)	337.44 349.28 (24.62)	104.2	98.7 – 110.0
AUC _I (ng·h/mL)	425.83 440.66 (25.64)	417.44 432.93 (24.34)	102.0	96.3 - 108.1
C _{max}	10.19	9.65	105.6	100.2 - 111.3

Baseline-Adjusted Cholecalciferol (1 x 70 mg alendronate sodium /140 mcg [5600 IU] cholecalciferol) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
(ng/mL)	10.51 (23.35)	10.00 (25.75)		
T _{max} ³ (h)	12.00 (8.00-18.00)	12.00 (8.00-16.00)		
T _{1/2} ⁴ (h)	24.85 (21.97)	25.45 (20.62)		
¹ APO-ALENDRONATE / CHOLECALCIFEROL (alendronate sodium /cholecalciferol) tablets, 70 mg/140 mcg (5600 IU) (Apotex Inc.) ² prFOSAVANCE® (alendronate sodium /cholecalciferol) tablets, 70 mg/5600 IU, (Merck Canada Inc.) ³ Expressed as the median (range) only ⁴ Expressed as the arithmetic mean (CV%) only				

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Alendronate Sodium

The oral LD₅₀ values of alendronate in female rats and mice were 552 mg/kg (3256 mg/m²) and 966 mg/kg (2898 mg/m²) (equivalent to human oral doses* of 27,600 and 48,300 mg), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m²) (equivalent to a human oral dose* of 10,000 mg).

Cholecalciferol

Significant lethality occurred in mice treated with a single high oral dose of calcitriol (4 mg/kg), the hormonal metabolite of cholecalciferol.

Chronic Toxicity

Alendronate Sodium

Alendronate-related changes in the repeated dose-toxicity studies of up to one year in rats and three years in dogs consisted of retention of primary spongiosa of bone in areas of endochondral bone formation, sustained reduction of alkaline phosphatase activities, and transient reduction in serum calcium and phosphate concentrations. These are related to the desired pharmacologic activity of alendronate. The species most sensitive to nephrotoxicity (dogs) required a dose* equivalent to at least 100 mg in humans to manifest nephrotoxicity. Rats also showed evidence of this effect at higher doses. Gastrointestinal toxicity was seen in rodents only. This appears to be due to a direct effect on the mucosa and occurred only at doses greater than 2.5 mg/kg/day.

Cholecalciferol

Cholecalciferol (vitamin D₃)-related changes in a 26-week, repeated-dose oral toxicity study in rats consisted of nephrocalcinosis and pheochromocytomas in the adrenal medulla. These changes were observed at doses \geq 5000 IU/kg/day.

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.

Harderian gland (a retroorbital gland not present in humans) adenomas were increased in high-dose female mice ($p=0.003$) in a 92-week carcinogenicity study at doses of alendronate of 1, 3 and 10 mg/kg/day (males) or 1, 2 and 5 mg/kg/day (females). These doses are equivalent to 0.5 to 4 times the 10 mg human dose based on surface area, mg/m².

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats ($p=0.003$) in a 2-year carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 1 and 3 times the 10 mg human dose based on surface area.

Cholecalciferol

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

Genotoxicity:

Alendronate Sodium

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation. Similarly, no evidence of mutagenicity was observed in an *in vitro* mammalian cell mutagenesis assay, an *in vitro* alkaline elution assay in rat hepatocytes, and an *in vivo* chromosomal aberration assay in mice at IV doses up to 25 mg/kg/day (75 mg/m²). In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate was weakly positive at concentrations \geq 5 mM in the presence of cytotoxicity. This is of no relevance to safety in humans since similar concentrations are not achievable *in vivo* at therapeutic doses. Furthermore, clear negative results in four of five genotoxicity studies, including the most relevant studies for human carcinogenic potential (the *in vivo* chromosomal aberration assay and the microbial mutagenesis assay), and negative carcinogenicity studies in rats and mice lead to the conclusion that there is no evidence of genotoxic or carcinogenic risks from alendronate in humans.

Cholecalciferol

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

Reproductive and Developmental Toxicology:

Alendronate Sodium

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

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

Cholecalciferol

Ergocalciferol (vitamin D₂) at high doses (150,000 to 200,000 IU/kg/day) administered prior to mating resulted in altered estrous cycle and inhibition of pregnancy in rats. The potential effect of cholecalciferol on male fertility is unknown in rats.

No data are available for cholecalciferol (vitamin D₃). Administration of high doses (\geq 10,000 IU/every other day) of ergocalciferol (vitamin D₂) to pregnant rabbits, resulted in higher incidence of fetal aortic stenosis compared to controls. Administration of vitamin D₂ (40,000 IU/day) to pregnant rats, resulted in neonatal death, decreased fetal weight, and impaired

osteogenesis of long bones postnatally.

17 SUPPORTING PRODUCT MONOGRAPHS

1. FOSAVANCE® (alendronate sodium / cholecalciferol tablets, 70 mg / 70 mcg (2800 IU) and 70 mg / 140 mcg (5600 IU), submission control 273858, Product Monograph, Organon Canada Inc. (AUG 03, 2023).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAPO-ALENDRONATE / VITAMIN D₃

Alendronate Sodium / Cholecalciferol Tablets

Read this carefully before you start taking **APO-ALENDRONATE / VITAMIN D₃** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-ALENDRONATE / VITAMIN D₃**.

What is APO-ALENDRONATE / VITAMIN D₃ used for?

APO-ALENDRONATE / VITAMIN D₃ is used in adults:

- to treat osteoporosis in men and postmenopausal women. Osteoporosis is a thinning and weakening of the bones. APO-ALENDRONATE / VITAMIN D₃ helps to rebuild bone and makes bone less likely to fracture.
- that are at an increased risk of vitamin D insufficiency.

APO-ALENDRONATE / VITAMIN D₃ is not for use in children under 18 years of age.

How does APO-ALENDRONATE / VITAMIN D₃ work?

APO-ALENDRONATE / VITAMIN D₃ contains two medicinal ingredients; one called alendronate sodium and another called cholecalciferol (vitamin D₃). Cholecalciferol is the natural form of vitamin D. Alendronate sodium belongs to a class of non-hormonal drugs called bisphosphonates. The bisphosphonates are similar to a molecule naturally made in your body that will break down bone tissue. Alendronate binds to the receptors in your body to prevent the bone from breaking down. This process also helps rebuild bone.

What are the ingredients in APO-ALENDRONATE / VITAMIN D₃?

Medicinal ingredients: Alendronate sodium and cholecalciferol.

Non-medicinal ingredients: Butylated hydroxytoluene, colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, mannitol and microcrystalline cellulose.

APO-ALENDRONATE / VITAMIN D₃ comes in the following dosage forms:

Tablet:

- 70 mg alendronate sodium and 70 mcg (2800 IU) cholecalciferol.

- 70 mg alendronate sodium and 140 mcg (5600 IU) cholecalciferol.

Do not use APO-ALENDRONATE / VITAMIN D₃ if you:

- Have certain disorders of the esophagus (the tube that connects your mouth with your stomach)
- Are unable to stand or sit upright for at least 30 minutes.
- Are allergic to alendronate sodium, cholecalciferol or any other ingredients in APO-ALENDRONATE / VITAMIN D₃. If you are not sure about this, talk to your healthcare professional before taking APO-ALENDRONATE / VITAMIN D₃.
- Have low blood calcium.
- Have SEVERE kidney disease. If you have any doubts if this applies to you, speak to your healthcare professional.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-ALENDRONATE / VITAMIN D₃. Talk about any health conditions or problems you may have, including if you:

- have low blood calcium or a condition that affects your ability to absorb minerals (i.e. Vitamin D deficiency). This condition must be treated before you begin treatment with APO-ALENDRONATE / VITAMIN D₃. Your healthcare professional will monitor your condition during your treatment. You should consume a sufficient amount of calcium and Vitamin D if you are already receiving glucocorticoids medicines. Speak to your healthcare professional if you experience muscle spasms or nerve problems (i.e. abnormal tingling or prickling sensations).
- have digestive problems. These may include difficulty swallowing, esophagus diseases, ulcers, inflammation of the first part of the small intestines, and inflammation of the lining of the stomach.
- may be at risk of developing osteonecrosis (bone damage in the jaw). Speak to your healthcare professional if have a planned dental extraction. Your healthcare professional may request a dental check-up before starting APO-ALENDRONATE / VITAMIN D₃. You may also be at risk of causing bone damage to your jaw if you:
 - have cancer
 - have or had poor dental health, gum or teeth disease
 - have poor oral hygiene, dentures that do not fit well.
 - have anemia (low red blood cell count)
 - have infection
 - have a blood disorder where your blood cannot form clots in the normal way
 - have diabetes (high blood sugar).
 - get chemotherapy, or radiotherapy.
 - take corticosteroids, or immunosuppressive drugs.
 - take angiogenesis inhibitors; they are drugs that slow down the growth of new blood vessels and are used mostly to treat cancer (e.g. bevacizumab).
 - are or have been a smoker.

- are a heavy alcohol user.
- have or have had any medical problems including known kidney disease.
- have any allergies.

Other warnings you should know about:

High calcium levels

Taking APO-ALENDRONATE / VITAMIN D₃ may worsen conditions such as hypercalcemia (high levels of calcium in blood) and/or hypercalciuria (high levels of calcium in urine). This happens when you have a disease that is associated with your body overproduces calcium (e.g., leukemia, lymphoma, sarcoidosis).

Gastrointestinal Problems

Taking APO-ALENDRONATE / VITAMIN D₃ incorrectly may cause you to experience problems with your esophagus. Stop taking APO-ALENDRONATE / VITAMIN D₃ and speak to your healthcare professional if you experience difficulty or pain upon swallowing, chest/breastbone pain or new or worsening heartburn. To avoid problems with your esophagus and allow the drug to reach the stomach, consider the following instructions:

- swallow each tablet of APO-ALENDRONATE / VITAMIN D₃ with a full glass of water.
- do NOT cut, chew, crush or suck the tablet.
- do NOT lie down for at least 30 minutes and until your first meal of the day.
- do NOT take APO-ALENDRONATE / VITAMIN D₃ at bedtime or before starting your day.

Muscle and skeletal problems

Drugs such as APO-ALENDRONATE / VITAMIN D₃ may cause serious bone, joint or muscle pain. You may experience relief from these symptoms after you end your treatment. Long term treatment with APO-ALENDRONATE / VITAMIN D₃ may cause stress fractures (repetitive trauma) or low energy fractures (falls from standing). If you develop new or unusual pain in the hip, thigh or any other bone, contact your healthcare professional. Your healthcare professional will:

- evaluate your condition if they suspect you have developed a fracture.
- examine the cause of the stress fracture and provide appropriate care.
- pause your treatment depending on your condition.

Eye problems

Drugs such as APO-ALENDRONATE / VITAMIN D₃ may cause vision problems. Different parts of your eye may experience inflammation or you may develop an eye infection. Your healthcare professional may end your treatment if they identify symptoms of inflammation.

Bone damage in ear

Treatment with APO-ALENDRONATE / VITAMIN D₃ may cause bone damage in your ear. Talk to your healthcare professional if you have ear pain and/or discharge from the ear while taking APO-ALENDRONATE / VITAMIN D₃.

Use in pregnancy and breast-feeding

Do not take APO-ALENDRONATE / VITAMIN D₃ if you are pregnant or breast feeding.

Lifestyle changes

Consult with your healthcare professional about lifestyle changes when taking APO-ALENDRONATE / VITAMIN D₃. These may include changes to your diet, use of dietary supplements, exercising and stop smoking.

Driving and using machines

Before you do tasks that may require special attention, wait until you know how you respond to APO-ALENDRONATE / VITAMIN D₃. There have been side effects reported with APO-ALENDRONATE / VITAMIN D₃ that may affect your ability to drive or operate machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-ALENDRONATE / VITAMIN D₃:

- Calcium supplements, antacids, and other oral medications will interfere with the absorption of APO-ALENDRONATE / VITAMIN D₃ if they are taken at the same time. You must wait at least half an hour after taking APO-ALENDRONATE / VITAMIN D₃ before taking any other oral medication.
- Intravenous ranitidine
- herbal products, food and beverages other than plain water may impact your ability to absorb APO-ALENDRONATE / VITAMIN D₃. Wait at least half an hour after taking APO-ALENDRONATE / VITAMIN D₃ before you take any herbal products, food or beverages.
- Certain medicines or food additives may prevent the vitamin D in APO-ALENDRONATE / VITAMIN D₃ from getting into your body, including artificial fat substitutes, mineral oils, orlistat and the cholesterol-lowering medicines, cholestyramine and colestipol. Medicines for seizures (convulsions), cimetidine and thiazides (diuretic) may decrease the effectiveness of vitamin D.

How to take APO-ALENDRONATE / VITAMIN D₃:

- Always take APO-ALENDRONATE / VITAMIN D₃ exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- It is important that you continue taking APO-ALENDRONATE / VITAMIN D₃ for as long as your healthcare professional prescribes it.
- Your healthcare professional may ask you to take calcium and vitamin D while you are on APO-ALENDRONATE / VITAMIN D₃ therapy.

Usual dose:

Take one ALENDRONATE / VITAMIN D₃ tablet once a week.

Follow these instructions carefully:

1. Choose the day of the week that best fits your schedule. Every week, take one tablet of APO-ALENDRONATE / VITAMIN D₃ on your chosen day.

2. After getting up for the day and before taking your first food, beverage, or other medication, swallow your APO-ALENDRONATE / VITAMIN D₃ tablet only with plain water (200 to 250 mL).

Do NOT cut, chew, crush or suck on the tablet. To make sure APO-ALENDRONATE / VITAMIN D₃ is absorbed by your body, do **NOT** take APO-ALENDRONATE / VITAMIN D₃ with:

- mineral water
- coffee or tea
- juice

If your normal drinking water is classified as “hard water”, you should consider taking this medication with distilled water (i.e., not mineral water).

3. After taking your APO-ALENDRONATE / VITAMIN D₃, do not lie down — stay fully upright (sitting, standing or walking) for at least 30 minutes and do not lie down until after your first food of the day.

4. Do NOT take APO-ALENDRONATE / VITAMIN D₃ at bedtime or before getting up for the day. This will help APO-ALENDRONATE / VITAMIN D₃:

- reach your stomach quickly and;
- reduce the potential for irritation of your esophagus (the tube that connects your mouth with your stomach).

5. After taking your APO-ALENDRONATE / VITAMIN D₃, wait at least 30 minutes before taking your first food, beverage, or other medication of the day. This includes antacids, calcium supplements and vitamins. APO-ALENDRONATE / VITAMIN D₃ is effective only if taken when your stomach is empty.

6. If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking APO-ALENDRONATE / VITAMIN D₃ immediately and call your healthcare professional.

Overdose:

If you take too much APO-ALENDRONATE / VITAMIN D₃, drink a full glass of milk and contact your healthcare professional immediately. Do not make yourself vomit. Do not lie down.

If you think you, or a person you are caring for, have taken too much APO-ALENDRONATE / VITAMIN D₃, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, just take one dose of APO-ALENDRONATE / VITAMIN D₃ on the morning after you remember. Do NOT take two doses on the same day. Return to taking one dose once a week, as originally scheduled on your chosen day.

What are possible side effects from using APO-ALENDRONATE / VITAMIN D₃?

These are not all the possible side effects you may have when taking APO-ALENDRONATE / VITAMIN D₃. If you experience any side effects not listed here, tell your healthcare professional.

- digestive problems
 - Acid reflux
 - Bloating feeling in stomach
 - Constipation
 - Diarrhea
 - Excessive gas
 - Nausea
 - Stomach pain
 - Vomiting
- dizziness, spinning sensation or a changed sense of taste.
- flu-like symptoms (rarely with fever) and/or generally feeling unwell.
- joint swelling or swelling in your hands or legs.
- lack or loss of strength
- mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.
- muscle cramps and/or aches
- skin problems
 - Rash that may be made worse by sunlight
 - Hair loss
 - Itchy skin

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Allergic reactions such as: - hives - swelling of the face, lips, tongue and/or throat - difficulty in breathing or swallowing			✓
Severe bone, joint, and/or muscle pain		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
New or unusual pain in the hip or thigh		✓	
Esophageal inflammation or ulcers causing: - chest pain - heartburn - difficulty or pain upon swallowing			✓
Stomach inflammation, stomach or other peptic ulcers occasionally associated with black and/or bloody stools			✓
Jaw problems associated with delayed healing and infection, often following tooth extraction			✓
Eye inflammation associated with eye pain; eye redness; sensitivity to light, decreased vision			✓
Stevens-Johnson syndrome and/or toxic epidermal necrolysis (Severe skin reactions): redness, blistering and/or peeling of large areas of the skin			✓
Low blood calcium: - numbness or tingling around the mouth or in the hands or feet - muscle spasms in the face, hands, or feet			✓
RARE			
Persistent ear pain		✓	
UNKNOWN			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
New or unusual pain in locations other than the thigh bone		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at controlled room temperature (15°C to 30°C). Protect from moisture and light. Store tablets in the original blister package until time of use.

Do not use this medicine after the month and year written after EXP (expiry date) on the container.

Keep out of reach and sight of children.

If you want more information about APO-ALENDRONATE / VITAMIN D₃:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (<http://www.apotex.ca/products>), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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