PRODUCT MONOGRAPH

[Pr] Sandoz Alendronate/Cholecalciferol

alendronate sodium/cholecalciferol tablets

70 mg alendronate (as alendronate sodium) + 140 mcg cholecalciferol (5600 IU vitamin D_3)

Bone Metabolism Regulator and Vitamin D

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Date of Preparation:
July 30, 2014

Submission Control No: 161092

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet: Alendronate 70 mg Cholecalciferol 140 mcg (5600 IU vitamin D_3)	all-rac-α-tocopherol, crospovidone, magnesium stearate, medium chain triglycerides, microcrystalline cellulose, modified starch, silicon dioxide colloidal, sodium ascorbate, sucrose.

INDICATIONS AND CLINICAL USE

Sandoz Alendronate/Cholecalciferol (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 Sandoz Alendronate/Cholecalciferol 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 Sandoz Alendronate/Cholecalciferol (see DOSAGE AND ADMINISTRATION, 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 D_3 and will also

require further supplementation.

Sandoz Alendronate/Cholecalciferol 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 DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypocalcemia (see WARNINGS AND PRECAUTIONS).
- Renal insufficiency with creatinine clearance <0.58 mL/s [<35 mL/min] (see DOSAGE AND ADMINISTRATION).

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 Sandoz Alendronate/Cholecalciferol with a full glass of water (200-250 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 Sandoz Alendronate/Cholecalciferol tablets 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 Sandoz Alendronate/Cholecalciferol tablets immediately and consult their physician.

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

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer 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.

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, immunosuppressive drugs), poor oral hygiene, comorbid 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.

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.

Musculoskeletal
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 (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs includes alendronate sodium. 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.

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

Low-energy fractures of the subtrochanteric and proximal femoral shaft 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. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. Approximately one third of these fractures were bilateral; therefore the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. 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.

Endocrine and Metabolism

Alendronate Sodium

Hypocalcemia must be corrected before initiating therapy with Sandoz Alendronate/Cholecalciferol (see 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 Sandoz Alendronate/Cholecalciferol. 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 Sandoz Alendronate/Cholecalciferol for predisposing conditions.

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

Cholecalciferol

Sandoz Alendronate/Cholecalciferol 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 Sandoz Alendronate/Cholecalciferol (see DOSAGE AND ADMINISTRATION, 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 D_3 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

Sandoz Alendronate/Cholecalciferol, like other bisphosphonate-containing products, 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. 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 Sandoz Alendronate/Cholecalciferol 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 tablet and/or who fail to swallow it with a full glass (200-250 mL) of water, and/or who continue to take alendronate sodium/cholecalciferol tablet 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 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 Sandoz Alendronate/Cholecalciferol 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 (postmarketing) reports of gastric and duodenal ulcers with alendronate, some severe and with complications.

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.

Special Populations

Pregnant Women:
Sandoz Alendronate/Cholecalciferol has not been studied in pregnant women and should not be given to them.

Nursing Women:
Sandoz Alendronate/Cholecalciferol has not been studied in nursing mothers and should not be given to them.

Pediatrics (<*18 years of age*):
Sandoz Alendronate/Cholecalciferol has not been studied in patients < 18 years of age and should not be given to them.

Geriatrics:
Alendronate Sodium
In clinical studies, there was no age-related difference in the efficacy or safety profiles of alendronate sodium.

Cholecalciferol
Daily requirements of vitamin D_3 may be increased in the elderly.

Monitoring and Laboratory Tests
Not Applicable.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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

Alendronate sodium has been evaluated for safety in clinical studies in approximately 7200 postmenopausal women.

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 ≥ 1% of patients treated with either alendronate 10 mg/day or placebo are presented in the following table.

Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients Treated for Osteoporosis

	Alendronate 10mg/day % (n=196)	Placebo % (n=397)
Gastrointestinal		
abdominal pain	6.6	4.8
nausea	3.6	4.0
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 distension	1.0	0.8
gastritis	0.5	1.3
Musculoskeletal		
musculoskeletal (bone, muscle or joint) pain	4.1	2.5
muscle cramp	0.0	1.0
Nervous System/Psychiatric		
headache	2.6	1.5
dizziness	0.0	1.0
Special Senses		
taste perversion	0.5	1.0

* 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 sodium 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 sodium, 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 ≥ 1% of patients in either treatment group are presented in the following table:

Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients Treated for Osteoporosis

	Alendronate 70mg/weekly % (n=519)	Alendronate 10mg/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 10mg/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.

Other Studies with alendronate sodium

Prevention of Osteoporosis in Postmenopausal Women

The safety of alendronate 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1400 patients randomized to receive alendronate sodium 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 ≥ 1% of patients treated with either alendronate 5 mg/day or placebo are presented in the following table:

Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients Prevention of Osteoporosis

	Alendronate 5mg/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 ± 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 ≥ 1% of patients treated with either alendronate 5 or 10 mg/day or placebo are presented in the following table:

Drug-Related* Adverse Experiences Reported in ≥ 1% of Patients Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

	Alendronate 10mg/day % (n=157)	Alendronate 5mg/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 - 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 sodium/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 D_3 was similar to that of alendronate/cholecalciferol (70 mg/2800 IU).

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Skin: Rarely, rash and erythema have occurred.

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory Tests
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 sodium versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg P*/dL (0.65 mM) were similar in both treatment groups.

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.

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

Body as a Whole: Hypersensitivity reactions including urticaria and rarely angioedema. As with other bisphosphonates, transient symptoms as in an acute-phase response (myalgia, malaise,

* P: Elemental phosphorus

asthenia and rarely, fever) have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, both in association with predisposing conditions and in patients without known predisposing conditions. Rarely, peripheral edema.

Dental: Localized osteonecrosis of the jaw (ONJ) has been reported rarely with oral bisphosphonate treatment. ONJ is generally associated with local infection (including osteomyelitis), tooth extraction with delayed healing (see WARNINGS AND PRECAUTIONS, General).

Gastrointestinal: Esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Some of these have been serious and required hospitalization. Rarely, gastric or duodenal ulcers, some severe and with complications (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (see WARNINGS AND PRECAUTIONS); joint swelling; low-energy femoral shaft fracture (see WARNINGS AND PRECAUTIONS).

Nervous System: dizziness, vertigo, dysgeusia.

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

Special Senses: Rarely uveitis, scleritis or episcleritis.

DRUG INTERACTIONS

Overview

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.

Drug-Drug Interactions

Alendronate Sodium

If taken at the same time it is likely that calcium supplements, antacids, other multivalent cations and other oral medications will interfere with absorption of alendronate. Therefore, patients must

wait at least one-half hour after taking Sandoz Alendronate/Cholecalciferol before taking any other oral medication.

Intravenous ranitidine 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; no other specific drug interaction studies were performed.

Concomitant use of hormone replacement therapy (HRT [estrogen ± progestin]) and alendronate sodium was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of alendronate sodium and HRT resulted in greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments (see ADVERSE REACTIONS, Clinical Trial Adverse Drug 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.

Specific interaction studies were not performed. Alendronate sodium 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 ASA-containing products. This was not observed in a study with alendronate 70 mg once weekly.

Sandoz Alendronate/Cholecalciferol 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 Sandoz Alendronate/Cholecalciferol.

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.

Drug-Food Interactions

Food and beverages other than **plain water** may markedly reduce the absorption and effectiveness of alendronate. Sandoz Alendronate/Cholecalciferol must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only (see DOSAGE AND ADMINISTRATION, Administration).

Drug-Herb Interactions
Herbal products may interfere with the absorption of alendronate. Sandoz Alendronate/Cholecalciferol must be taken at least one-half hour before any herbal products.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with alendronate sodium/cholecalciferol (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 Sandoz Alendronate/Cholecalciferol may vary.

DOSAGE AND ADMINISTRATION

Recommended Dose
Treatment of Osteoporosis in Postmenopausal Women
Treatment of Osteoporosis in Men
The recommended dosage is one tablet of Sandoz Alendronate/Cholecalciferol (70 mg/5600 IU) once weekly. The appropriate dosage of Sandoz Alendronate/Cholecalciferol must be determined by the physician based on the patient's vitamin D requirement.

All patients must receive supplemental calcium and/or vitamin D, if intake is inadequate (see WARNINGS AND PRECAUTIONS).

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 Sandoz Alendronate/Cholecalciferol on an individual patient basis.

Dosage Adjustment
No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 0.58 to 1 mL/s [35 to 60 mL/min]). Sandoz Alendronate/Cholecalciferol is not recommended for patients with more severe renal insufficiency (creatinine clearance <0.58 mL/s [<35 mL/min]) due to lack of experience.

Missed Dose
Patients should be instructed that if they miss a dose of Sandoz Alendronate/Cholecalciferol 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.

Administration

Sandoz Alendronate/Cholecalciferol tablet 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 DRUG INTERACTIONS). Waiting less than 30 minutes will lessen the effect of Sandoz Alendronate/Cholecalciferol by decreasing its absorption into the body.

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, Sandoz Alendronate/Cholecalciferol should only be swallowed upon arising for the day with a full glass of water (200-250 mL) and patients should not lie down for at least 30 minutes and until after their first food of the day. Sandoz Alendronate/Cholecalciferol 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 WARNINGS AND PRECAUTIONS).

All patients must receive supplemental calcium and/or vitamin D, if intake is inadequate. Physicians 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 Sandoz Alendronate/Cholecalciferol (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.

Although no specific studies have been conducted on the effects of switching patients on another therapy for osteoporosis to Sandoz Alendronate/Cholecalciferol, there are no known or theoretical safety concerns related to Sandoz Alendronate/Cholecalciferol in patients who previously received any other antiosteoporotic therapy.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

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 D_3 for up to five months was not associated with hypercalciuria or hypercalcemia.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Sandoz Alendronate/Cholecalciferol contains alendronate sodium, a bisphosphonate, and cholecalciferol (vitamin D_3).

Alendronate sodium is a bisphosphonate that acts as a potent, specific inhibitor of osteoclastmediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

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

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. Increased bone turnover is an independent risk factor of fractures. 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. 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 sodium. 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. 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 sodium. 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 pre-study levels during years three through five. 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.

Pharmacokinetics

Summary of Pharmacokinetic Parameters of alendronate 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) 0.59% (males)	(0.61, 1.04) (0.43, 0.81)
Absolute bioavailability of 40 mg tablet, taken 2 hours before first meal of the day	0.60% (females)	(0.46, 0.78)

	Mean	90% Confidence Interval
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	1.18	(1.07, 1.3)
(mL/min) (n=6)	(71)	(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 ($AUC_{0\text{-}120\ hrs}$) for vitamin D_3 (unadjusted for endogenous vitamin D_3 levels) was 296.4 ng-hr/mL. The mean maximal serum concentration (C_{max}) of vitamin D_3 was 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 ($AUC_{0\text{-}80\ hrs}$) for vitamin D_3 (unadjusted for endogenous vitamin D_3 levels) was 490.2 ng•hr/ml. The mean maximal serum concentration (C_{max}) of vitamin D_3 was 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 D_3 in alendronate/cholecalciferol (70 mg/2800 IU) and alendronate/cholecalciferol (70 mg/5600 IU) is similar to an equal dose of vitamin D_3 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 D_3 enters the blood as part of chylomicrons. Vitamin D_3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D_3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D_3 at these sites for later release into the circulation. Circulating vitamin D_3 is bound to vitamin D-binding protein.

Metabolism:
Alendronate Sodium
There is no evidence that alendronate is metabolized in animals or humans.

Cholecalciferol
Vitamin D_3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D_3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D_3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D_3 undergoes glucuronidation prior to elimination.

Excretion:
Alendronate Sodium
Following a single IV dose of [^{14}C]-alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the 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 D_3 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 D_3 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.

Geriatrics:
Alendronate Sodium
Bioavailability and disposition of alendronate (urinary excretion) were similar in elderly (≥ 65 years of age) and younger patients. No dosage adjustment of alendronate is necessary (see DOSAGE AND ADMINISTRATION).

Cholecalciferol
Dietary requirements of vitamin D_3 may be increased in the elderly.

Gender:
Bioavailability and the fraction of an IV dose of alendronate excreted in urine were similar in men and women.

Race:
Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency:
Alendronate Sodium
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.

Cholecalciferol
Vitamin D_3 may not be adequately absorbed in patients who have malabsorption due to inadequate bile production.

Renal Insufficiency:
Alendronate Sodium
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]). Sandoz Alendronate/Cholecalciferol is not recommended for patients with more severe renal insufficiency (creatinine clearance <0.58 mL/s [<35 mL/min]) due to lack of experience.

STORAGE AND STABILITY

Store at 25°C, excursions permitted to 15°C - 30°C. Protect from moisture and light. Store tablets in the original blister package until use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

Sandoz Alendronate/Cholecalciferol (70 mg/5600 IU) tablets are white to almost white, oval shaped tablets debossed with 714 on one side. Available in blister packages of 4 tablets.

Composition

Each tablet of Sandoz Alendronate/Cholecalciferol contains 91.35 mg of alendronate monosodium salt trihydrate, the molar equivalent of 70 mg of free acid, 140 mcg of cholecalciferol equivalent to 5600 International Units (IU) vitamin D_3, respectively. Each tablet contains the following non-medicinal ingredients: all-rac-α-tocopherol, crospovidone, magnesium stearate, medium chain triglycerides, microcrystalline cellulose, modified starch, silicon dioxide colloidal, sodium ascorbate, sucrose.

Sandoz Alendronate/Cholecalciferol tablets are gluten free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

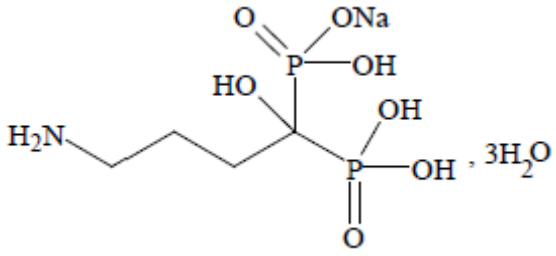
Proper name: Alendronate sodium trihydrate

Chemical name: (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate

Molecular formula: $C_4H_{12}NNaO_7P_2.3H_2O$

Molecular mass: 325.12 g/mol

Structural formula:



Physicochemical properties: Alendronate is a white or almost white crystalline powder. It is sparingly soluble in water, practically insoluble in organic solvents (methanol, chloromethane and ethanol).

Drug Substance

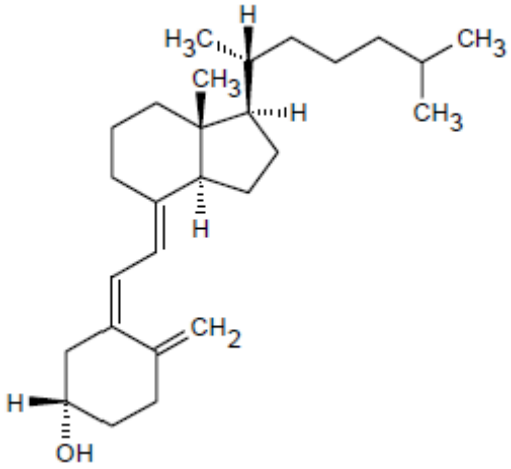
Proper name: Cholecalciferol

Chemical name: (3ß,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3-ol

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

Molecular mass: 384.64 g/mol

Structural formula:



Physicochemical properties: White, odorless, crystalline powder. Cholecalciferol is practically insoluble in water, freely soluble in usual organic solvents, and slightly soluble in vegetable oils

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative, randomised, single dose, full replicate crossover bioequivalence study of Sandoz Alendronate/Cholecalciferol (70 mg alendronate as alendronate sodium + 140 mcg cholecalciferol equivalent to 5600 IU vitamin D_3) tablets and Fosavance® (70 mg alendronate as alendronate sodium + 140 mcg cholecalciferol equivalent to 5600 IU vitamin D_3) tablets in sixty-nine (69) healthy subjects (35 male and 34 female; between the ages of 18 and 55), was conducted under fasting conditions. A summary of the bioavailability data is presented in the table below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Alendronate 1 x 70 mg/ 140 mcg (alendronate sodium/cholecalciferol) tablet From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	37.56 45.94 (72)	37.36 46.90 (85)	100.53	91.44 - 110.54
AUC_I (ng*h/mL)	39.33 48.06 (72)	38.90 48.98 (87)	101.13	91.95 – 111.22
C_{max} (ng/mL)	13.55 17.04 (81)	14.14 18.35 (100)	95.84	86.66 - 105.99
T_{max}§ (h)	1.14 (48)	1.07 (38)		
$T_{½}$§ (h)	1.59 (11)	1.61 (13)		

* Sandoz Alendronate/Cholecalciferol 70 mg/140 mcg (5600 IU) tablets (manufactured for Sandoz Canada Inc.)

† Fosavance® 70 mg/140 mcg (5600 IU) tablets (Merck Frosst Canada Ltd., Canada) were purchased in Canada.

§ Expressed as the arithmetic mean (CV %) only

Treatment of Osteoporosis

Alendronate sodium/cholecalciferol Studies

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 sodium/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 sodium/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 ($p<0.001$).

25-hydroxyvitamin D Levels after Treatment with alendronate/cholecalciferol (70 mg/2800 IU) or alendronate 70 mg at Week 15*

	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 [30-62]**
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 D_3 2800 IU (Vitamin D_3 5600 IU group) or matching placebo (Vitamin D_3 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 D_3 5600 IU group and vitamin D_3 2800 IU group, respectively. The mean change of 25-hydroxyvitamin D levels from baseline was greater in the Vitamin D_3 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 D_3 5600 IU group than in the Vitamin D_3 2800 IU group (3.1 % vs. 5.6 %), respectively ($p<0.12$).

25-hydroxyvitamin D Levels after Treatment with alendronate sodium/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 sodium/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)
Alendronate sodium/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 D_3 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 D_3 for 24-week extension study.

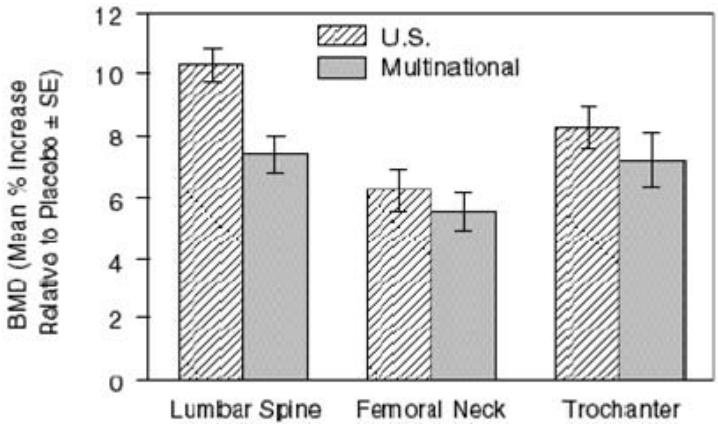
Alendronate sodium Studies

Postmenopausal Women

Effect on Bone Mineral Density

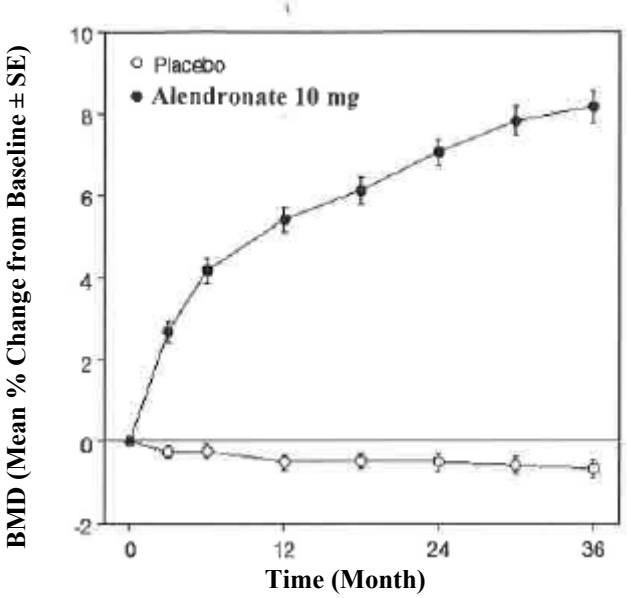
The efficacy of alendronate 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine BMD of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years duration. These 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 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 sodium 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 sodium 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 pre-treatment levels, and BMD no longer increased although accelerated bone loss was not observed. These data indicate that treatment with alendronate sodium 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 sodium 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 sodium 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 sodium: n=1012, placebo: n=590) revealed a significant 29% reduction in non-vertebral fracture incidence (alendronate sodium, 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 sodium, n=1022; placebo, n=1005) demonstrated that treatment with alendronate sodium resulted in

statistically significant and clinically meaningful reductions in fracture incidence at three years as shown in the following table.

Effect of alendronate sodium on Fracture Incidence in the Three-Year Study of FIT (Patients with Vertebral Fracture at Baseline)

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

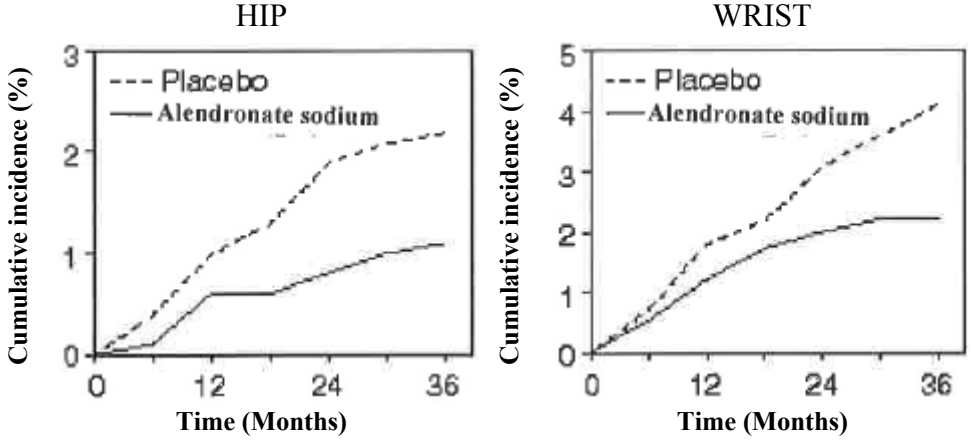
† Number evaluable for vertebral fracture: alendronate sodium, n=984; placebo, n=966

* p<0.05, ** p<0.01, *** p<0.001

Furthermore, in this population of patients with baseline vertebral fracture, treatment with alendronate sodium 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 sodium compared with placebo at all time points. Alendronate sodium 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 sodium,

n=2214; placebo, n=2218) further demonstrated the reduction in fracture incidence due to alendronate sodium. 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.

Effect of alendronate sodium on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT (Patients without Vertebral Fracture at Baseline)

	% of Patients		
Patients with:	**Alendronate sodium (n=1545)**	**Placebo (n=1521)**	**Reduction (%) in Fracture Incidence**
≥ 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 sodium, 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 sodium, 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.

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

	Reduction (%) in Fracture Incidence Alendronate sodium 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
* $p<0.05$, ** $p<0.01$, *** $p<0.001$, ‡‡ $p=0.059$

Consistency of Fracture Results
The reductions in the incidence of vertebral fractures (alendronate sodium 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 sodium 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 sodium 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 sodium 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 sodium 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 sodium is of normal quality.

Men
The efficacy of alendronate sodium 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 (see SELECTED BIBLIOGRAPHY).

In both studies alendronate sodium 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 sodium alone (both 6.0%).

The effects on BMD when alendronate sodium was added to stable doses (for at least one year) of HRT (estrogen ± 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.

DETAILED PHARMACOLOGY

Mechanism of Action

Alendronate sodium
Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration, in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix, where it is no longer pharmacologically active. Thus, alendronate

must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Cholecalciferol
Vitamin D_3 is produced in the skin by photochemical conversion of 7-dehydrocholesterol to previtamin D_3 by ultraviolet light. This is followed by non-enzymatic isomerization to vitamin D_3. In the absence of adequate sunlight exposure, vitamin D_3 is an essential dietary nutrient. Vitamin D_3 in skin and dietary vitamin D_3 (absorbed into chylomicrons) is converted to 25-hydroxyvitamin D_3 in the liver. Conversion to the active calcium-mobilizing hormone 1,25-dihydroxyvitamin D_3 (calcitriol) in the kidney is stimulated by both parathyroid hormone and hypophosphatemia. The principal action of 1,25-dihydroxyvitamin D_3 is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption.

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

Animal Pharmacology
The ability of alendronate to prevent or reverse the bone loss associated with estrogen deficiency was tested *in vivo* in baboons and rats.

Ovariectomized adult baboons undergo bone changes similar to those caused by estrogen deficiency in women. In both, these are reflected early on by increases in biochemical markers of bone resorption (such as urinary deoxypyridinoline) and bone formation (such as serum alkaline phosphatase and osteocalcin). Alendronate, administered for 24 months intravenously every two weeks at 0.05 mg/kg or 0.25 mg/kg (equivalent to human oral doses[*] of approximately 25 and 125 mg/day), maintained or slightly reduced the levels of biochemical markers in a dose-dependent manner. Importantly, continuous treatment did not cause progressive suppression of bone turnover during this 24-month study. Histomorphometric analysis of trabecular bone after 24 months of treatment showed that alendronate, in a dose-dependent manner, prevented the increase in bone turnover caused by ovariectomy and significantly increased the vertebral bone volume. Alendronate also decreased bone turnover in the cortical bone of the radius and prevented an increase in cortical bone porosity. Both in trabecular and cortical bone, there was a positive bone balance at the level of individual remodeling sites (basic multicellular units, BMUs). Bone histology at all sites examined was normal. Furthermore, alendronate significantly increased the BMD of the lumbar spine and the mechanical strength of vertebral trabecular bone. A highly significant positive correlation was found between lumbar spine BMD and bone

[*] Based on a patient weight of 50 kg

strength. In summary, these studies indicate that even at doses equivalent to a human oral dose* of approximately 125 mg/day alendronate maintains normal bone quality while increasing both bone mass and bone strength.

Also, alendronate increased bone mass and vertebral strength in ovariectomized rats. Three-month-old rats were ovariectomized and four months later were treated with alendronate 0, 0.28, 2.8, or 28 mcg/kg subcutaneously twice weekly (equivalent to human oral doses* of 0, 0.57, 5.7, and 57 mg/day for six months). Measurements of the mechanical properties of the lumbar vertebrae showed that ovariectomy caused a significant reduction in stiffness and ultimate strength. In alendronate-treated rats, the strength and trabecular bone mass of vertebral bone showed a dose-dependent increase relative to control animals.

In a second study, 6.5-month-old rats were ovariectomized; alendronate treatment was started six months later and was continued for one year. Alendronate was given subcutaneously twice weekly at 1.8 and 18 mcg/kg (equivalent to human oral doses* of 3.7 and 37 mg/day). Alendronate treatment dose-dependently reduced bone turnover and increased bone mass, both in trabecular and cortical bone. The observed increases in bone mass correlated with increased vertebral strength, both of which were significant relative to the control group at the higher dose. In the alendronate-treated rats, the histology of bone was normal, rates of mineralization were normal, and there were no signs of osteomalacia.

In a study of prevention of bone loss due to estrogen deficiency, 4-month-old rats were ovariectomized and, beginning the next day, alendronate 0.1 or 0.5 mg/kg/day was administered daily by oral gavage for one year. Alendronate treatment at 0.5 mg/kg/day prevented the ovariectomy-induced bone loss and loss of bone strength observed in untreated ovariectomized controls. Alendronate treatment also maintained the histomorphometric parameters at the levels seen in untreated non-ovariectomized controls.

Two-year treatment (starting from the age of six weeks) of normal growing rats of both sexes with doses up to 3.75 mg/kg/day also produced similar findings, including increased bone mass, increased bone strength, and normal bone histology.

The resorbability of bone produced during alendronate treatment was also studied in rats in a model of rapid bone formation following bone marrow injury. Bone formed during daily treatment with 1 mcg/kg subcutaneously (equivalent to a 7.1 mg/day human oral dose*) was completely resorbed at a rate indistinguishable from controls. Bone formed at 2 mcg/kg/day subcutaneously was completely resorbed 24 days after cessation of treatment versus 14 days in controls. Bone formed at 8 and 40 mcg/kg/day subcutaneously was also resorbed, albeit at slower rates, indicating that even at doses equivalent to a human oral dose* of 285 mg/day bone resorption is not completely inhibited by alendronate treatment.

In a three-year study with alendronate in normal mature dogs at doses up to 1 mg/kg/day given

* Based on a patient weight of 50 kg
* Based on a patient weight of 50 kg

orally (equivalent to a human oral dose* of 50 mg/day), there was no evidence of osteomalacia or spontaneous fractures. Histomorphometric evaluation of static and dynamic variables of bone remodeling in the lumbar vertebrae showed: (1) no effect on the cortical and trabecular bone mass or trabecular bone architecture; (2) the expected slight decrease in the rate of bone turnover; and (3) no effect on osteoid maturation time, which is a measure of the time between bone matrix deposition and mineralization. Biomechanical testing showed no deleterious effect on bone strength. The amount of alendronate in bone after three years of treatment at human oral doses* equivalent to 50 mg/day was insignificant (12 ppm) in relation to the total amount of mineral in bone.

Oral treatment with alendronate at 2 mg/kg/day (equivalent to a human oral dose* of 100 mg/day) for 9 weeks before and/or for 16 weeks after an experimental fracture had no deleterious effects on fracture healing in dogs. However, there was a delay in callus remodeling.

Ancillary pharmacology studies evaluating the effects of alendronate on different organ systems showed no important changes in cardiovascular, renal, gastric, and respiratory function in dogs or in central nervous system function in mice.

Four hours after IV administration to mice, [^{3}H]alendronate localization on osteoclast surfaces was about 10-fold higher than on osteoblast surfaces over a wide range of doses, showing selectivity of alendronate for resorption surfaces.

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization was 6000-fold the antiresorptive dose, suggesting a safety margin for drug-induced osteomalacia. The relevance of these findings to humans is unknown.

TOXICOLOGY

The following data are based on findings for the individual components of alendronate sodium/cholecalciferol tablet.

Acute Toxicity

Alendronate Sodium

The oral LD_{50} values of alendronate in female rats and mice were 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2) (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/m^2) (equivalent to a human oral dose* of 10,000 mg).

Cholecalciferol

* Based on a patient weight of 50 kg

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 D_3)-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 ≥ than 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/m^2.

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.

Mutagenesis
Alendronate Sodium
Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation. Similarly, no evidence of mutagenicity was observed in an *in vitro* mammalian cell mutagenesis assay, an *in vitro* alkaline elution assay in rat hepatocytes, and an in *vivo* chromosomal aberration assay in mice at IV doses up to 25 mg/kg/day (75 mg/m^2). In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate was weakly positive at concentrations ≥ 5 mM in the presence of cytotoxicity. This is of no relevance to safety in humans since similar concentrations are not achievable *in vivo* at therapeutic doses.

Furthermore, clear negative results in four of five genotoxicity studies, including the most relevant studies for human carcinogenic potential (the *in vivo* chromosomal aberration assay and the microbial mutagenesis assay), and negative carcinogenicity studies in rats and mice lead to the conclusion that there is no evidence of genotoxic or carcinogenic risks from alendronate in humans.

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.

Reproduction
Alendronate Sodium
Alendronate had no effect on fertility or reproductive performance (male or female) in rats at oral doses up to 5 mg/kg/day. The only 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.

Cholecalciferol
Ergocalciferol (vitamin D_2) 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.

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

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

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PART III: CONSUMER INFORMATION

PrSandoz® Alendronate/Cholecalciferol
(alendronate sodium/cholecalciferol)
Once Weekly Tablets
70 mg alendronate (as alendronate sodium)/ 140 mcg cholecalciferol (5600 IU vitamin D_3)

This leaflet is part III of a three-part "Product Monograph" published when Sandoz Alendronate/Cholecalciferol was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Sandoz Alendronate/Cholecalciferol Contact your doctor or pharmacist if you have any questions about the drug.

Please read this insert carefully before starting Sandoz Alendronate/Cholecalciferol and every time your prescription is renewed.

ABOUT THIS MEDICATION

What the medication is used for:

Sandoz Alendronate/Cholecalciferol is the brand name for a tablet that contains alendronate sodium and cholecalciferol (vitamin D_3) as the active ingredients. It is available **only on prescription** from your doctor. Alendronate sodium is a member of a class of non-hormonal drugs called bisphosphonates. Cholecalciferol is the natural form of vitamin D.

Your doctor has prescribed Sandoz Alendronate/Cholecalciferol because you have a disease known as osteoporosis. Sandoz Alendronate/Cholecalciferol is indicated for treatment of osteoporosis in post-menopausal women and in men.

Since it is not known how long Sandoz Alendronate/Cholecalciferol should be continued for osteoporosis, you should discuss the need to stay on this medication with your doctor regularly to determine if Sandoz Alendronate/Cholecalciferol is still right for you.

What it does:

How is normal bone maintained?

Bone undergoes a normal process of rebuilding that occurs continuously throughout your skeleton. First, old bone is removed (resorbed), then new bone is laid down (formed). This balanced process of resorbing and forming bone keeps your skeleton healthy and strong.

What is osteoporosis and why should it be treated?

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause and may also occur in men. Osteoporosis often occurs in women several years after the menopause, which occurs when the ovaries stop producing the female hormone, estrogen, or are removed (which may occur, for example, at the time of a hysterectomy). The earlier a woman reaches the menopause, the greater the risk of osteoporosis. Osteoporosis can also occur in men due to several causes, including aging and/or a low level of the male hormone, testosterone. In all instances, bone is removed faster than it is formed, so bone loss occurs and bones become weaker. Therefore, maintaining bone mass and preventing further bone loss are important to keep your skeleton healthy. Early on, osteoporosis usually has no symptoms. If left untreated, however, it can result in fractures (broken bones). Although fractures usually cause pain, fractures of the bones of the spine may go unnoticed until they cause height loss. Fractures may occur during normal, everyday activity, such as lifting, or from minor injury that would not ordinarily fracture normal bone. Fractures usually occur at the hip, spine, or wrist and can lead not only to pain, but also to considerable deformity and disability (such as stooped posture from curvature of the spine, and loss of mobility).

What should I know about vitamin D?

Vitamin D is an essential nutrient, required for calcium absorption and healthy bones. The main source is through exposure to summer sunlight, which makes vitamin D in our skin. Winter sunlight in Canada is too weak to produce vitamin D. Even in the summer, clothing or sun block can prevent enough sunlight from getting through. In addition, as people age, their skin becomes less able to make vitamin D. Very few foods are natural sources of vitamin D. Some foods (for example, milk, select brands of orange juice and breakfast cereals) are fortified with vitamin D.

Too little vitamin D leads to inadequate calcium absorption and low phosphate – the minerals that make bones strong. Even if you are eating a diet rich in calcium or taking a calcium supplement, your body cannot absorb calcium properly unless you have enough vitamin D. Too little vitamin D may lead to bone loss and osteoporosis, and severe vitamin D deficiency may cause muscle weakness which can lead to falls, and greater risk of fracture. Vitamin D supplements reduce these risks and their consequences.

Sandoz Alendronate/Cholecalciferol alone should not be used to treat vitamin D deficiency.

How can Sandoz Alendronate/Cholecalciferol treat your osteoporosis?

Your doctor has prescribed Sandoz Alendronate/Cholecalciferol to treat your osteoporosis. The alendronate sodium component of Sandoz Alendronate/Cholecalciferol not only prevents the loss of bone but actually helps to rebuild bone you may have lost and increases your bone mass. This makes bone stronger and less likely to fracture. Thus, Sandoz Alendronate/Cholecalciferol reverses the progression of osteoporosis.

If you are over the age of 70, home bound, or suffer from a long-term illness, you may need to receive vitamin D in addition to that provided in Sandoz Alendronate/Cholecalciferol. Because winter sunlight in Canada is too weak to produce vitamin D, most people living in Canada may also need additional vitamin D.

Sandoz Alendronate/Cholecalciferol does not contain calcium. Your doctor may recommend calcium supplements.

In addition, your doctor may recommend one or more of the following lifestyle changes:

Stop smoking. Smoking appears to increase the rate at which you

lose bone and, therefore, may increase your risk of fracture.

Exercise. Like muscles, bones need exercise to stay strong and healthy. Consult your doctor before you begin any exercise program.

Eat a balanced diet. Your doctor can advise you whether to modify your diet or to take any dietary supplements.

Reduce the use of alcohol.

When it should not be used:
Do not take Sandoz Alendronate/Cholecalciferol 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 any of its ingredients.
- Have low blood calcium.
- Have SEVERE kidney disease. If you have any doubts if this applies to you, speak to your doctor.

What the medicinal ingredients are:
Each tablet of Sandoz Alendronate/Cholecalciferol (70 mg/5600 IU) contains 70 mg of alendronate and 140 mcg of cholecalciferol (5600 IU of vitamin D_3).

What the important nonmedicinal ingredients are:
all-rac-α-tocopherol, crospovidone, magnesium stearate, medium chain triglycerides, microcrystalline cellulose, modified starch, silicon dioxide colloidal, sodium ascorbate, sucrose.

Sandoz Alendronate/Cholecalciferol tablets are gluten free.

What dosage forms it comes in:

Sandoz Alendronate/Cholecalciferol (70 mg/5600 IU) is available as white to almost white, oval shaped tablets debossed with 714 on one side.

WARNINGS AND PRECAUTIONS

BEFORE you use Sandoz Alendronate/Cholecalciferol talk to your doctor or pharmacist:

- If you have cancer, gum disease, poor oral hygiene, or diabetes. If you are receiving chemotherapy, radiotherapy, corticosteroids, or immunosuppressive drugs. If you are or have been a smoker, or are a heavy alcohol user. If you have any of these conditions you should consider having a dental examination before starting Sandoz Alendronate/Cholecalciferol.
- About any medical problems you have or have had, including known kidney disease.
- About any dental problems you have or have had.
- About any allergies.
- If you have any swallowing or digestive problems.

Digestive problems:
Some patients may experience digestive problems while taking Sandoz Alendronate/Cholecalciferol, which may be severe, including irritation or ulceration of the esophagus (the tube that connects your mouth with your stomach), which can cause chest pain, heartburn or difficulty or pain upon swallowing. These reactions may occur especially if patients do not drink the recommended amount of water with Sandoz Alendronate/Cholecalciferol and/or if they lie down in less than 30 minutes or before their first food of the day.

Use in pregnancy and breast-feeding
Do not take Sandoz Alendronate/Cholecalciferol if you are pregnant or breast-feeding.

Use in children
Sandoz Alendronate/Cholecalciferol is not indicated for anyone under 18 years of age and should not be given to them.

Use in elderly
Sandoz Alendronate/Cholecalciferol works equally well in, and is equally well tolerated by, patients older and younger than 65 years of age.

Can I drive or operate machinery while using Sandoz Alendronate/Cholecalciferol?
There have been side effects reported with alendronate sodium/cholecalciferol that may affect your ability to drive or operate machinery. Individual responses to Sandoz Alendronate/Cholecalciferol may vary (See SIDE EFFECTS AND WHAT TO DO ABOUT THEM).

INTERACTIONS WITH THIS MEDICATION

You should always tell your doctor about all drugs you are taking or plan to take, including those obtained without a prescription, vitamins, and herbal products.

It is likely that calcium supplements, antacids, and some oral medicines will interfere with the absorption of alendronate if taken at the same time of the day. You must wait at least one-half hour after taking Sandoz Alendronate/Cholecalciferol before taking any other oral medication.

It is likely that certain medicines or food additives may prevent the vitamin D in Sandoz Alendronate/Cholecalciferol 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.

PROPER USE OF THIS MEDICATION

Usual dose:
How should I take Sandoz Alendronate/Cholecalciferol?
These are the important things you must do to help make sure you will benefit from Sandoz Alendronate/Cholecalciferol:

1. Choose the day of the week that best fits your schedule. Every week, take one Sandoz Alendronate/Cholecalciferol tablet on your chosen day.

2. After getting up for the day and before taking your first food, beverage, or other medication, swallow your Sandoz Alendronate/Cholecalciferol tablet with a full glass (200-250 mL) of plain water only.

Do **not** take Sandoz Alendronate/Cholecalciferol with:

- Mineral water
- Coffee or tea
- Juice

Although it has not been tested, because of high mineral content, "hard water" may decrease absorption of Sandoz Alendronate/Cholecalciferol. If your normal drinking water is classified as "hard water", you should consider taking this medication with distilled water (i.e., not mineral water).

Do not chew or suck on a tablet of Sandoz Alendronate/Cholecalciferol.

3. After swallowing your Sandoz Alendronate/Cholecalciferol tablet, 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 Sandoz Alendronate/Cholecalciferol at bedtime or before getting up for the day.

The above actions will help the Sandoz Alendronate/Cholecalciferol tablet reach your stomach quickly and help reduce the potential for irritation of your esophagus (the tube that connects your mouth with your stomach).

5. After swallowing your Sandoz Alendronate/Cholecalciferol tablet, wait at least 30 minutes before taking your first food, beverage, or other medication of the day, including antacids, calcium supplements and vitamins. Sandoz Alendronate/Cholecalciferol 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 Sandoz Alendronate/Cholecalciferol immediately and call your doctor.

7. It is important that you continue taking Sandoz Alendronate/Cholecalciferol for as long as your doctor prescribes it. Sandoz Alendronate/Cholecalciferol can treat your osteoporosis only if you continue to take it.

It is important to take Sandoz Alendronate/Cholecalciferol over the long-term to continue to help rebuild bone you may have lost. It is, therefore, important to follow your doctor's instructions for taking Sandoz Alendronate/Cholecalciferol without skipping doses or varying from your prescribed treatment schedule. It is also important to continue to follow your doctor's advice on lifestyle changes.

Overdose:
If you take too many tablets, drink a full glass of milk and contact your doctor immediately. Do not induce vomiting. Do not lie down.

In case of drug overdose, contact a healthcare practitioner, 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 Sandoz Alendronate/Cholecalciferol tablet on the morning after you remember. *Do not take two tablets on the same day*. Return to taking one tablet once a week, as originally scheduled on your chosen day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most patients do not have side effects from alendronate sodium /cholecalciferol: however, as with any medicine, Sandoz Alendronate/Cholecalciferol may have unintended or undesirable effects. Side effects usually have been mild. Some patients may experience digestive problems such as nausea, vomiting or black and/or bloody stools. Some digestive problems may be severe including irritation or ulceration of the esophagus (the tube that connects your mouth with your stomach) which can cause chest pain, heartburn or difficulty or pain upon swallowing. Esophageal reactions may worsen if patients continue to take Sandoz Alendronate/Cholecalciferol after developing symptoms suggesting irritation of the esophagus.

If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking Sandoz Alendronate/Cholecalciferol immediately and call your doctor.

Some patients may experience bone, muscle and/or joint pain which is rarely severe. Patients who develop severe bone, joint, and/or muscle pain should contact their doctor. Most patients experienced relief after stopping the drug. Rarely, patients may also experience joint swelling or swelling in their hands or legs. Transient flu-like symptoms (rarely with fever), typically at the start of treatment, have occurred. In rare cases, patients taking Sandoz Alendronate/Cholecalciferol may get itching or eye pain, or a rash that may be made worse by sunlight. Hair loss has been reported. Rarely, severe skin reactions may occur. Allergic reactions such as hives or, rarely, swelling of the face, lips, tongue and/or throat, which may cause difficulty in breathing or swallowing, may occur. Patients may experience dizziness, vertigo (spinning sensation) or a changed sense of taste. Rarely, symptoms of low blood calcium may occur (for example, numbness or tingling around the mouth or in the hands or feet; muscle spasms in the face, hands, or feet). Rarely, stomach or other peptic ulcers (some severe) have occurred. Mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.

Rarely, patients have had jaw problems associated with delayed healing and infection, often following tooth extraction.

Rarely, patients have experienced fracture in a specific part of the thigh bone. If you develop new or unusual pain in the hip or thigh, contact your doctor.

Anytime you have a medical problem you think may be from taking Sandoz Alendronate/Cholecalciferol, even if it is not listed above, talk to your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical attention**
		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			✓
	Bone, joint, and/or muscle pain		✓	
	New or unusual pain in the hip or thigh		✓	
	Digestive problems causing: -chest pain -heartburn -difficulty or pain upon swallowing -black and/or bloody stools			✓
	Esophageal, stomach or other peptic ulcers			✓
	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			✓
	Severe skin reactions			✓
	Symptoms of low blood calcium: -numbness or tingling around the mouth or in the hands or feet -muscle spasms in the face, hands, or feet			✓

This is not a complete list of side effects. For any unexpected effects while taking Sandoz Alendronate/Cholecalciferol contact your doctor or pharmacist.

HOW TO STORE IT

Should be stored at 25°C but can be kept between 15°C - 30°C. Protect from moisture and light. Store tablets in the original blister package until the time of use.

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

Remember to keep Sandoz Alendronate/Cholecalciferol and all medications safely away from children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Sandoz Canada Inc., at:

1-800-361-3062

or by written request at:
145 Jules-Léger
Boucherville, Québec
J4B 7K8

Or by e-mail at :
medinfo@sandoz.com
This leaflet was prepared by Sandoz Canada Inc.

Last revised: July 30, 2014