PRODUCT MONOGRAPH

JAMP Alendronate / Vitamin D3 70/2800

Alendronic Acid and Cholecalciferol Tablets, Manufacturer's Standard

70 mg Alendronic Acid (as Sodium Alendronate Trihydrate) +
70 mcg Cholecalciferol (2800 IU vitamin D3)

JAMP Alendronate / Vitamin D3 70/5600

Alendronic Acid and Cholecalciferol Tablets, Manufacturer's Standard

70 mg Alendronic Acid (as Sodium Alendronate Trihydrate) +
140 mcg Cholecalciferol (5600 IU vitamin D3)

Bone Metabolism Regulator and Vitamin D

JAMP Pharma Corporation
1310 rue Nobel
Boucherville, Québec
J4B 5H3

Date of Preparation:
August 30, 2021

Submission Control No: 232157

TABLE OF CONTENTS

JAMP Alendronate / Vitamin D3

Alendronic Acid and Cholecalciferol Tablets, Manufacturer's Standard

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet Alendronate 70 mg Cholecalciferol 70 mcg (2800 IU vitamin D_3) or Alendronate 70 mg Cholecalciferol 140 mcg (5600 IU vitamin D_3)	Butylated hydroxytoluene, colloidal silicon dioxide, croscarmellose sodium, gelatin, lactose, magnesium stearate, medium chain triglycerides, microcrystalline cellulose, pregelatinized starch and sucrose.

INDICATIONS AND CLINICAL USE

JAMP Alendronate / Vitamin D3 (alendronic acid (as sodium alendronate trihydrate)/ 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 JAMP Alendronate / Vitamin D3 increases bone mass and can prevent fractures, including those of the hip and spine (vertebral compression fractures).

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

Patients suffering from osteoporosis are at an increased risk for vitamin D insufficiency, especially those over the age of 70 years, home bound, or chronically ill, and may need to receive vitamin D supplementation in addition to that provided in JAMP Alendronate / Vitamin D3 (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.
JAMP Alendronate / Vitamin D3 alone should not be used to treat vitamin D deficiency (commonly defined as 25-hydroxyvitamin D <22.5 nmol/L or 9 ng/mL).

Geriatrics (≥65 years of age):

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

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

Pediatrics (<18 years of age):

Alendronic acid / cholecalciferol tablets has not been studied in patients <18 years of age and should not be given to them.

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 JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 at bedtime or before arising for the day. Patients should be informed

that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking JAMP Alendronate / Vitamin D3 immediately and consult their physician.

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

Osteonecrosis

Osteonecrosis of the jaw (ONJ) has been reported in patients receiving treatment regimens including bisphosphonates. The majority of reports occurred following tooth extractions with delayed healing and involved cancer patients treated with intravenous bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. However, some cases have also occurred in patients receiving oral bisphosphonate treatment for postmenopausal osteoporosis and other diagnoses. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection, including osteomyelitis.

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

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

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

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

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

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

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 tablets (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 tablets, the percentages of patients with these symptoms were similar in the alendronate sodium tablets 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 JAMP Alendronate / Vitamin D3 (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 JAMP Alendronate / Vitamin D3. Symptomatic hypocalcemia has been reported rarely, both in patients with predisposing conditions and patients without known predisposing conditions. Patients should be advised to report to their physicians any symptoms of hypocalcemia, such as paresthesias or muscle spasms. Physicians should carefully evaluate patients who develop hypocalcemia during therapy with JAMP Alendronate / Vitamin D3 for predisposing conditions.

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

Cholecalciferol

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

Patients suffering from osteoporosis are at an increased risk for vitamin D insufficiency, especially those over the age of 70 years, home bound, or chronically ill, and may need to receive vitamin D supplementation in addition to that provided in JAMP Alendronate / Vitamin D3 (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

JAMP Alendronate / Vitamin D3, 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 JAMP Alendronate / Vitamin D3 immediately and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking JAMP Alendronate / Vitamin D3 and/or who fail to swallow it with a full glass (200–250 mL) of water, and/or who continue to take JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 is given to patients with active upper gastrointestinal problems, such as dysphagia, esophageal diseases (including known Barrett's esophagus), gastritis, duodenitis, or ulcers.

While no increased risk was observed in extensive clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers 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:
Alendronic acid / cholecalciferol tablets has not been studied in pregnant women and should not be given to them.

Nursing Women:
Alendric acid / cholecalciferol tablets has not been studied in nursing mothers and should not be given to them.

Pediatrics (<18 years of age):
Alendronic acid / cholecalciferol tablets has not been studied in patients <18 years of age and should not be given to them.

Geriatrics (≥65 years of age):

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

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 tablets
In clinical studies, alendronate sodium tablets 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 tablets 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 sodium tablets 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 sodium tablets 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 sodium tablets 10 mg/day or placebo are presented in the following table.

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

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

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

One patient treated with alendronate sodium tablets (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 tablets 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 sodium tablets 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued alendronate sodium tablets 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 sodium tablets 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 tablets, 3.2%; placebo, 2.7%. The overall adverse experience profile was similar to that seen in other studies with alendronate sodium tablets 5 or 10 mg/day.

In a one-year, double-blind multicenter study, the overall safety and tolerability profiles of alendronate sodium tablets 70 mg once weekly and alendronate sodium tablets 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 sodium tablets 70 mg Once Weekly % (n=519)	**alendronate sodium tablets 10 mg/day % (n=370)**
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle or joint) pain	2.9	3.2
muscle cramp	0.2	1.1

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

Men:

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of alendronate sodium tablets 10 mg/day [n=146] and a one-year study of alendronate sodium tablets 70 mg once weekly [n=109]), the safety profile of alendronate sodium tablets 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 sodium tablets 10mg/day vs. 10.5% for placebo, and 6.4% for alendronate sodium tablets 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 sodium tablets 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 sodium tablets 70 mg once weekly were similar to that of placebo and no difference was seen between men and women.

Other Studies with alendronate sodium tablets

Prevention of Osteoporosis in Postmenopausal Women:
The safety of alendronate sodium tablets 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive alendronate sodium tablets for either two or three years. In these studies the overall safety profiles of alendronate sodium tablets 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 sodium tablets 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 sodium tablets 5 mg/day or placebo are presented in the following table:

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

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

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

Concomitant Use with Estrogen/Hormone Replacement Therapy:
In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with alendronate sodium tablets 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 sodium tablets 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 sodium tablets 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 sodium tablets 10 mg/day % (n=157)	alendronate sodium tablets 5 mg/day % (n=161)	Placebo % (n=159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

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

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

Paget's Disease of Bone:

In clinical studies (Paget's disease and osteoporosis), adverse experiences reported in 175 patients taking alendronate sodium tablets 40 mg/day for 3–12 months were similar to those in postmenopausal women treated with alendronate sodium tablets 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking alendronate sodium tablets 40 mg/day (17.7% alendronate sodium tablets 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 sodium tablets 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 sodium tablets 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 sodium / cholecalciferol tablets (70 mg/2800 IU) was similar to that of alendronate sodium tablets 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 sodium / cholecalciferol tablets (70 mg/2800 IU) administered with an additional 2800 IU vitamin D_3 was similar to that of alendronate sodium / cholecalciferol tablets (70 mg/2800 IU).

Less Common Clinical Trial Adverse Drug Reactions (≤1%)

Skin: rash and erythema

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 tablets 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

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

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

Dental: localized osteonecrosis of the jaw (ONJ) is generally associated with local infection (including osteomyelitis) and/or tooth extraction with delayed healing (see WARNINGS AND PRECAUTIONS, General)

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

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

Nervous System: dizziness, vertigo, dysgeusia

* P: Elemental phosphorus

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

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

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 JAMP Alendronate / Vitamin D3 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 tablets was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. Combined use of alendronate sodium tablets 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 tablets 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 sodium tablets greater than 10 mg and ASA- containing products. This was not observed in a study with alendronate sodium tablets 70 mg once weekly.

JAMP Alendronate / Vitamin D3 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 sodium tablets 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 JAMP Alendronate / Vitamin D3.

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. JAMP Alendronate / Vitamin D3 must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only (see DOSAGE AND ADMINISTRATION, Administration).

Drug-Herb Interactions

Herbal products may interfere with the absorption of alendronate. JAMP Alendronate / Vitamin D3 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 tablets (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 JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 (70 mg/2800 IU) or JAMP Alendronate / Vitamin D3 (70 mg/5600 IU) once weekly. The appropriate dosage of JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 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]). JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

Administration

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

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, JAMP Alendronate / Vitamin D3 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. JAMP Alendronate / Vitamin D3 should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see 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 JAMP Alendronate / Vitamin D3 (70 mg/5600 IU) and may also need additional vitamin D supplementation. For patients fifty years and over, the recommended dose is at least 800 IU per day. Those living in high latitudes (including most of

Canada) may also need additional supplementation.

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

OVERDOSAGE

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

Dialysis would not be beneficial.

Cholecalciferol
Vitamin D toxicity has not been documented during chronic therapy in generally healthy adults at a dose less than 10,000 IU/day. In a clinical study of healthy adults, a 4000 IU daily dose of vitamin D_3 for up to five months was not associated with hypercalciuria or hypercalcemia.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
JAMP Alendronate / Vitamin D3 contains alendronate sodium, a bisphosphonate, and cholecalciferol (vitamin D_3).

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

Cholecalciferol (vitamin 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 sodium tablets 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 tablets. In osteoporosis treatment studies, alendronate sodium tablets 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 sodium tablets 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 tablets. 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 sodium tablets 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 sodium tablets 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 sodium tablets 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 sodium tablets 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 sodium tablets 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)	(0.61, 1.04)
	0.59% (males)	(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)
Absolute bioavailability of 70 mg tablet, taken 2 hours before first meal of the day	0.57% (females)	(0.44, 0.73)
Renal Clearance mL/s (mL/min) (n=6)	1.18 (71)	(1.07, 1.3) (64, 78)

Absorption:
Alendronate Sodium
Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men was 0.59%.

The alendronate in the alendronate sodium / cholecalciferol tablets (70 mg/2800 IU) and alendronate sodium / cholecalciferol tablets (70 mg/5600 IU) tablets and the alendronate sodium tablets (alendronate sodium) 70 mg tablet were found to be equally bioavailable.

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 sodium / cholecalciferol tablets (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 sodium / cholecalciferol tablets (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 sodium / cholecalciferol tablets (70 mg/2800 IU) and alendronate sodium / cholecalciferol tablets (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 sodium tablets (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 sodium / cholecalciferol tablets (70 mg/2800 IU) is approximately 24 hours.

Special Populations and Conditions
Pediatrics (<18 years of age):
Alendronate pharmacokinetics have not been investigated in patients <18 years of age.

Geriatrics (≥65 years of age):
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]). JAMP Alendronate / Vitamin D3 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, but can be stored between 15°C and 30°C. Protect from moisture and light. Store tablets in the original blister package until use.

DOSAGE FORMS, COMPOSITION AND PACKAGING
Dosage Forms
JAMP Alendronate / Vitamin D3 (70 mg/2800 IU) tablets are a white caplet shaped tablets debossed "28" on one side and plain on the other side. Available in blister packages of 4 tablets.

JAMP Alendronate / Vitamin D3 (70 mg/5600 IU) tablets are white modified rectangle shaped tablets, debossed "56" on one side and plain on the other side. Available in blister packages of 4 tablets.

Composition
Each tablet of JAMP Alendronate / Vitamin D3 contains 91.37 mg of alendronate monosodium salt trihydrate, the molar equivalent of 70 mg of free acid, and 70 or 140 mcg of cholecalciferol equivalent to 2800 or 5600 International Units (IU) vitamin D3, respectively. Each tablet contains the following non-medicinal ingredients: butylated hydroxytoluene, colloidal silicon dioxide, croscarmellose sodium, gelatin, lactose, magnesium stearate, medium chain triglycerides, microcrystalline cellulose, pregelatinized starch and sucrose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper names:

Sodium Alendronate Trihydrate

cholecalciferol

Chemical names:

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

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

Molecular formulas:

$C_4H_{12}NNaO_7P_2 \bullet 3H_2O$

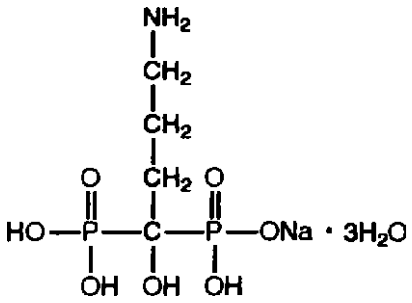
$C_{27}H_{44}O$

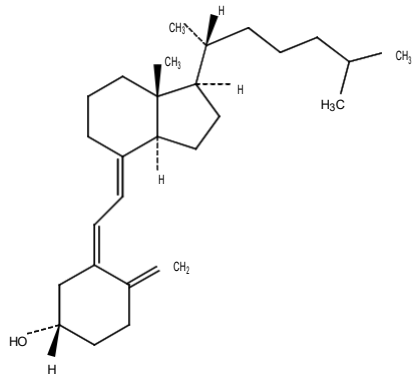
Molecular mass:

325.12

384.6

Structural formulas:





Physicochemical properties:

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

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

CLINICAL TRIALS

Comparative Bioavailability Study

A randomized, four-period, two-treatment, two-sequence, crossover, single dose (1 x 70 mg/140 mcg (5600 IU)) comparative bioavailability study of JAMP Alendronate / Vitamin D3 (JAMP Pharma Corporation) and FOSAVANCE (Merck Canada Inc.) was conducted in healthy, adult male subjects under fasting conditions. A summary of the data from the 50 subjects that were included in the statistical analysis is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Alendronic Acid (1 x 70 mg/140 mcg (5600 IU)) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	132.664 161.975 (67.7)	128.765 152.175 (58.8)	103.0	94.0 - 113.0
AUC_I (ng.h/mL)	142.900 173.885 (67.0)	138.759 163.091 (57.8)	103.0	94.1 -112.8
C_{max} (ng/mL)	40.528 50.343 (74.6)	39.346 47.793 (65.0)	103.0	92.9 - 114.2
T_{max}[3] (h)	1.316 (0.500 - 2.500)	1.333 (0.500 - 4.000)		
$T_{½}$[4] (h)	10.580 (25.7)	10.710 (26.2)		

[1] JAMP Alendronate / Vitamin D3 (alendronic acid (as sodium alendronate trihydrate) / cholecalciferol) tablets 70 mg/140 mcg (5600 IU) (JAMP Pharma Corporation)

[2] FOSAVANCE (alendronate as alendronate sodium/ cholecalciferol) tablets 70 mg/140 mcg (5600 IU) (Merck Canada Inc.)

[3] Expressed as the median (range)

[4] Expressed as the arithmetic mean (CV%) only.

Treatment of Osteoporosis alendronate sodium / cholecalciferol tablets 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 sodium / cholecalciferol tablets 70 mg/2800 IU vitamin D or weekly alendronate sodium tablets 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 sodium / cholecalciferol tablets 70 mg/2800 IU resulted in a smaller reduction in serum calcium levels (-0.9%) when compared to alendronate sodium tablets 70 mg alone (-1.4%). As well, treatment with alendronate sodium / cholecalciferol tablets 70 mg/2800 IU resulted in a significantly smaller increase in parathyroid hormone levels when compared to alendronate sodium tablets 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 tablets group and 55.3 nmol/L (22.1 ng/mL) in the alendronate sodium tablets only group. After 15 weeks of treatment, the mean levels were 26% higher in the alendronate sodium / cholecalciferol tablets group as compared to the alendronate sodium tablets 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 sodium / cholecalciferol tablets 70 mg/2800 IU than alendronate sodium tablets 70 mg (11.5 % vs. 31.9 %), respectively ($p < 0.001$).

25-hydroxyvitamin D Levels after Treatment with alendronate sodium / cholecalciferol tablets (70 mg/2800 IU) or alendronate sodium tablets 70						
	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 sodium/ cholecalciferol tablets (70 mg/2800 IU)	4 (1.1)	37 (10.4)	87 (24.4)	84 (23.5)	82 (23.0)	63 (17.7)
alendronate sodium tablets 70 mg	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 sodium / cholecalciferol tablets (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 tablets at						
	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 tablets (Vitamin D_3 5600 IU	0	10 (3.1)	29 (9.0)	79 (24.6)	87 (27.1)	116 (36.1)
alendronate sodium/ cholecalciferol tablets (Vitamin D_3 2800 IU	1 (0.3)	17 (5.3)	56 (17.5)	80 (25.0)	74 (23.1)	92 (28.8)

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

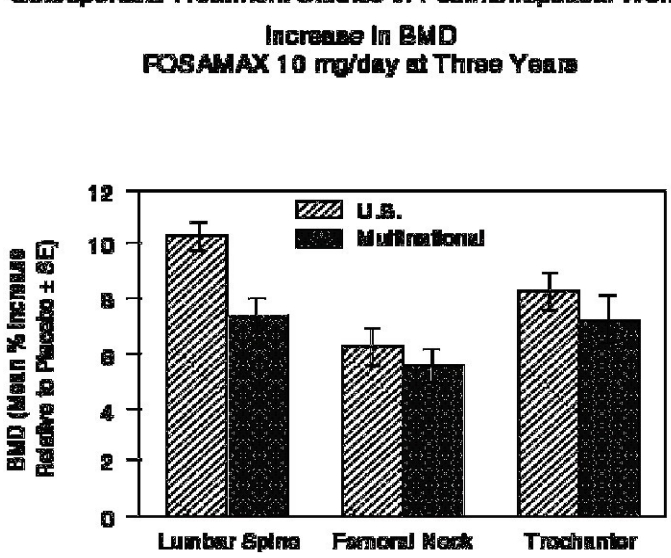
** Patients received alendronate sodium tablets 70 mg or alendronate sodium / cholecalciferol tablets (70 mg/2800 IU) for 15-week base study followed by alendronate sodium / cholecalciferol tablets (70 mg/2800 IU) and placebo for the additional vitamin D3 or 24-week extension study.

Alendronate sodium tablets Studies

Postmenopausal Women

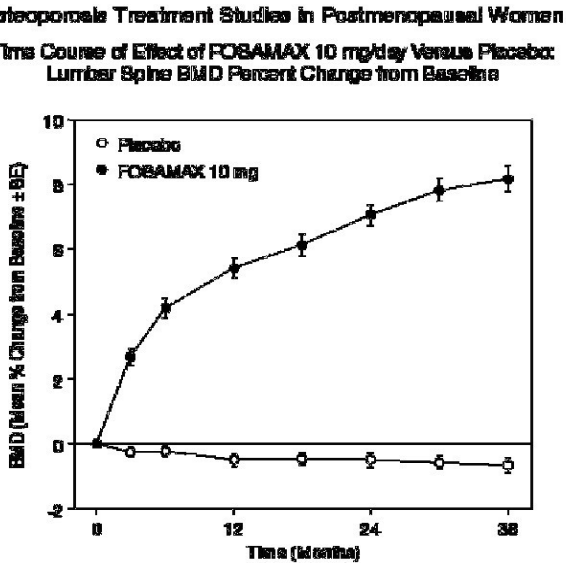
Effect on Bone Mineral Density

The efficacy of alendronate sodium tablets 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 sodium tablets 10 mg/day relative to placebo-treated patients at three years for each of these studies.



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 sodium tablets 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 sodium tablets 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 sodium tablets reverses the progression of osteoporosis. alendronate sodium tablets was similarly effective regardless of age, race, baseline rate of bone turnover, renal function and use with a wide range of common medications.



In a separate study, alendronate sodium tablets 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 sodium tablets 70 mg once weekly (n=519) and alendronate sodium tablets 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 tablets 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 sodium tablets 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 tablets must be continuous to produce progressive increases in bone mass.

Effect on Fracture Incidence

To assess the effects of alendronate sodium tablets 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 sodium tablets (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 tablets 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 tablets 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 tablets: n=1012, placebo: n=590) revealed a significant 29% reduction in non-vertebral fracture incidence (alendronate sodium tablets, 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 tablets, n=1022; placebo, n=1005) demonstrated that treatment with alendronate sodium tablets resulted in statistically significant and clinically meaningful reductions in fracture incidence at three years as shown in the following table.

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

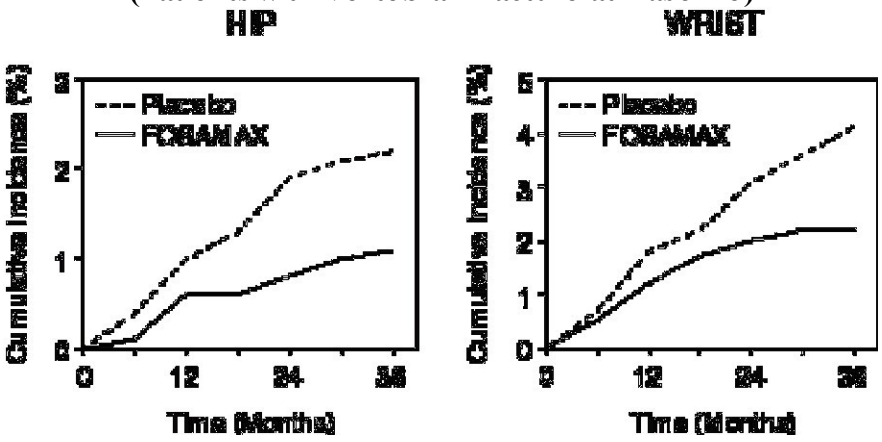
Patients with:	% of Patients alendronate sodium tablets (n=1022)	Placebo (n=1005)	Reduction (%) in Fracture Incidence
Vertebral fractures (diagnosed by X-ray)†			
≥ 1 new vertebral fracture	7.9	15.0	47***
≥ 2 new vertebral fractures	0.5	4.9	90***
Painful (clinical) fractures			
≥ 1 painful vertebral 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 tablets, 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 tablets 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 tablets compared with placebo at all time points. alendronate sodium tablets 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 tablets, n=2214; placebo, n=2218) further demonstrated the reduction in fracture incidence due to alendronate sodium tablets. 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 tablets on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT (Patients without Vertebral Fracture at Baseline)

Patients with:	% of Patients		Reduction (%) in Fracture Incidence
	alendronate sodium tablets (n=1545)	Placebo (n=1521)	
≥ 1 painful fracture	12.9	16.2	22**
≥ 1 vertebral fracture††	2.5	4.8	48***
≥ 1 painful vertebral fracture	1.0	1.6	41†††
Hip fracture	1.0	1.4	29†††
Wrist (forearm) fracture	3.9	3.8	none

† Baseline femoral neck BMD at least 2 SD below the mean for young adult women

†† Number evaluable for vertebral fracture: alendronate sodium tablets, 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 tablets, 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 tablets on Fracture Incidence in the Combined (Three- and Four-Year) Studies of		
	Reduction (%) in Fracture Incidence alendronate sodium tablets vs.	
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 tablets 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 tablets 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 tablets 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 tablets 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 tablets 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 sodium tablets 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 tablets is of normal quality.

Men

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

A two-year, double-blind, placebo-controlled, multicenter study of alendronate sodium tablets 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 sodium tablets 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 sodium tablets 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 sodium tablets 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 REFERENCES).

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

The effects on BMD when alendronate sodium tablets 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 sodium tablets 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.

Comparative Bioavailability Studies

The alendronate in the alendronate sodium / cholecalciferol tablets (70 mg alendronate/2800 IU vitamin D_3) and alendronate sodium tablets (70 mg alendronate) tablet is equally bioavailable as demonstrated in a single-dose, open-label, randomized, crossover study conducted following fasting overnight and for two hours post dose in 207 healthy male and female volunteers. The results are presented in the table below:

Alendronate (1 × 70 mg alendronate/2800 IU vitamin D_3 versus 1 × 70 mg alendronate, fasted) From Measured Data Uncorrected for Potency Geometric Mean* Arithmetic Mean (CV %)				
Parameter	**alendronate sodium / cholecalciferol tablets 70 mg alendronate/2800 IU vitamin D_3**	**alendronate sodium tablets 70 mg alendronate**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
Ae_{0-T}‡ (mcg)	197.5 296.7 (126.8)	191.9 287.3 (89.7)	102.9	90.7–116.8
R_{max}† (mcg/h)	21.0 31.6 (121.6)	20.8 30.9 (89.7)	100.8	89.3–114.0

* Least-squares Mean.
‡ Amount of alendronate excreted unchanged in the urine from time 0 to 36 hours.
† Maximum urinary excretion rate of alendronate (base on four sampling times [pre-dose, 8h, 24h and 36h]).

The alendronate in the alendronate sodium / cholecalciferol tablets (70 mg alendronate/5600 IU vitamin D_3) and alendronate sodium tablets (70 mg alendronate) tablet is equally bioavailable as demonstrated in a single-dose, open-label, randomized, crossover study conducted following fasting overnight and for two hours post dose in 220 healthy male and female volunteers. The results are presented in the table below:

Alendronate (1 × 70 mg alendronate/5600 IU vitamin D_3 versus 1 × 70 mg alendronate, fasted) From Measured Data Uncorrected for Potency Geometric Mean* Arithmetic Mean (CV %)				
Parameter	**alendronate sodium / cholecalciferol tablets 70 mg alendronate/5600 IU vitamin D_3**	**alendronate sodium tablets 70 mg alendronate**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
Ae_{0-T}‡ (mcg)	133.6 228.3 (307.3)	132.2 257.9 (306.5)	101.0	92.2–110.8
R_{max}† (mcg/h)	14.5 24.9 (346.6)	14.2 23.7 (168.3)	101.8	92.9–111.5

* Least-squares Mean.
‡ Amount of alendronate excreted unchanged in the urine from time 0 to 36 hours.
† Maximum urinary excretion rate of alendronate (base on four sampling times [pre-dose, 8h, 24h and 36h]).

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[1] 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 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.

[1] Based on a patient weight of 50 kg

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 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 tablets.

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.

* Based on a patient weight of 50 kg

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
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 ≥ 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*

* Based on a patient weight of 50 kg

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 (≥ 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.

REFERENCES

1. Balena R, Toolan BC, Shea M, Markatos A, Myers ER, Lee SC, Opas EE, Seedor JG, Klein H, Frankenfield D, Quartuccio H, Fioravanti C, Clair J, Brown E, Hayes WC, Rodan GA. The effects of 2-year treatment with the aminobisphosphonate alendronate on bone metabolism. Bone histomorphometry, and bone strength in ovariectomized nonhuman primates. J Clin Invest 1993;92:2577–86.

2. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535–41.

3. Black DM, Reiss TF, Nevitt MC, Cauley J, Karpf D, Cummings SR. Design of the fracture intervention trial. Osteoporosis Int 1993;Suppl. 3:S29–39.

4. Cummings SR, Black DM, Thompson DE, Applegate WB, Barret-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ. Effects of alendronate on risk of fracture in women with low bone density but without vertebral fractures. JAMA 1998;280(24):2077–82.

5. Hosking D, Chilvers CED, Christiansen C, Ravn P, Wasnich R, Ross P, McClung M, Balske A, Thompson D, Daley M, Yates AJ. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. N Engl J Med 1998;338:485–92.

6. Jablonski NG, Chaplin G. Evolution of human skin coloration. J of Human Evolution 2000;39:57–106.

7. Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Johnston CC, Adami S, Harris ST, Santora II AC, Hirsch LJ, Oppenheimer L, Thompson D. Prevention of nonvertebral fractures by alendronate. A Meta-Analysis. JAMA 1997;277:1159–64.

8. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, Adami S, Weber K, Lorenc R, Pietschmann P, Vandormael K, Lombardi A. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000;343:604–10.

9. Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, Thamsborg G, Liberman UA, Delmas PD, Malice MP, Czachur M, Daifotis AG. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998;339:292–9.

10. Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, Kiel D, Felsenberg D, Recker RR, Tonino RP, Roux C, Pinchera A, Foldes AJ, Greenspan SL, Levine MA, Emkey R, Santora II AC, Kaur A, Thompson DE, Yates J, Orloff JJ. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Aging Clin Exp Res 2000;12(1):1–12.

11. Selby PL, Davies M, Adams JE. Do men and women fracture bones at similar bone densities? Osteoporosis Int 2000;11:153–7.

12. Siris E, Weinstein RS, Altman R, Conte JM, Favus M, Lombardi A, Lyles K, McIlwain H, Murphy WA Jr, Reda C, Rude R, Seton M, Tiegs R, Thompson D, Tucci JR, Yates AJ, Zimering M. Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. J Clin Endocrinol Metab 1996;81(3):961–7.

13. Tucci JR, Tonino RP, Emkey RD, Peverly CA, Kher U, Santora AC. Effect of three years of oral alendronate treatment in postmenopausal women with osteoporosis. Am J Med 1996;101:488–501.

14. Webb AR, Kline I, Holick MF. Influence of seasons and latitude on the cutaneous synthesis of vitamin D_3: Synthesis in human skin. Journal of Clinical Endocrinology 1988;67:373–378.

15. Yamamoto M, Markatos A, Seedor JG, Masarachia P, Gentile M, Rodan GA, Balena R. The effects of the aminobisphosphonate alendronate on thyroid hormone-induced osteopenia in rats. Calcif Tissue Int 1993;53:278–82.

16. Brown JP, Josse RG, Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002;167(10 suppl):S1–S34.

17. Pr FOSAVANCE, Control #250920, Product Monograph. Organon Canada Inc. Date of revision: May 11, 2021.

PART III: CONSUMER INFORMATION

JAMP Alendronate / Vitamin D3 70/2800

Alendronic Acid and Cholecalciferol Tablets,
Manufacturer's Standard
Once Weekly Tablets
70 mg Alendronic Acid (as Sodium Alendronate Trihydrate) +
70 mcg Cholecalciferol (2800 IU vitamin D3)

JAMP Alendronate / Vitamin D3 70/5600

Alendronic Acid and Cholecalciferol Tablets,
Manufacturer's Standard
Once Weekly Tablets
70 mg Alendronic Acid (as Sodium Alendronate Trihydrate) +
140 mcg Cholecalciferol (5600 IU vitamin D3)

This leaflet is Part III of a three-part "Product Monograph" published when JAMP Alendronate / Vitamin D3 was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JAMP Alendronate / Vitamin D3. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this insert carefully before starting JAMP Alendronate / Vitamin D3 and every time your prescription is renewed.

ABOUT THIS MEDICATION

WHAT THE MEDICATION IS USED FOR:
JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 because you have a disease known as osteoporosis. JAMP Alendronate / Vitamin D3 is indicated for treatment of osteoporosis in post-menopausal women and in men.

Since it is not known how long JAMP Alendronate / Vitamin D3 should be continued for osteoporosis, you should discuss the need to stay on this medication with your doctor regularly to determine if JAMP Alendronate / Vitamin D3 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.

JAMP Alendronate / Vitamin D3 alone should not be used to treat vitamin D deficiency.

How can JAMP Alendronate / Vitamin D3 treat your osteoporosis?
Your doctor has prescribed JAMP Alendronate / Vitamin D3 to treat your osteoporosis. The alendronate sodium component of JAMP Alendronate / Vitamin D3 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, JAMP

Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3. Because winter sunlight in Canada is too weak to produce vitamin D, most people living in Canada may also need additional vitamin D.

JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 if you:

- Have certain disorders of the esophagus (the tube that connects your mouth with your stomach).
- Are unable to stand or sit upright for at least 30 minutes.
- Are allergic to 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 JAMP Alendronate / Vitamin D3 (70 mg/2800 IU) contains 70 mg of alendronate and 70 mcg of cholecalciferol (2800 IU of vitamin D_3).

Each tablet of JAMP Alendronate / Vitamin D3 (70 mg/5600 IU) contains 70 mg of alendronate and 140 mcg of cholecalciferol (5600 IU of vitamin D_3).

WHAT THE NONMEDICINAL INGREDIENTS ARE:

Butylated hydroxytoluene, colloidal silicon dioxide, croscarmellose sodium, gelatin, lactose, magnesium stearate, medium chain triglycerides, microcrystalline cellulose, pregelatinized starch and sucrose.

WHAT DOSAGE FORMS IT COMES IN:

JAMP Alendronate / Vitamin D3 (70 mg/2800 IU) tablets are a white caplet shaped tablets debossed "28" on one side and plain on the other side.

JAMP Alendronate / Vitamin D3 (70 mg/5600 IU) tablets are white modified rectangle shaped tablets, debossed "56" on one side and plain on the other side.

WARNINGS AND PRECAUTIONS

BEFORE you use JAMP Alendronate / Vitamin D3 talk to your doctor or pharmacist if you:

- have cancer, gum disease, poor oral hygiene, or diabetes.
- get chemotherapy, or radiotherapy.
- take corticosteroids, or immunosuppressive drugs.
- take angiogenesis inhibitors; they are drugs that slow down the growth of new blood vessels and are used mostly to treat cancer (e.g. bevacizumab).
- are or have been a smoker.
- are a heavy alcohol user.

If any of the above apply to you, have a dental check-up before starting JAMP Alendronate / Vitamin D3.

- have or have had any medical problems including known kidney disease.
- have or have had any dental problems.
- have any allergies.
- have any swallowing or digestive problems. Your doctor may check if you:
  - smoke.
  - have or have had teeth and/or gum disease.
  - have dentures that do not fit well.
  - have other relevant medical conditions at the same time, such as; low red blood cell count (called anemia) or if your blood cannot form clots in the normal way.

Digestive problems

Some patients may experience digestive problems while taking JAMP Alendronate / Vitamin D3, 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 JAMP Alendronate / Vitamin D3 and/or if they lie down in less than 30 minutes or before their first food of the day.

Talk to your doctor:

- if you have ear pain and/or discharge from the ear while taking JAMP Alendronate / Vitamin D3 as these could be signs of bone damage in the ear.

Use in pregnancy and breast-feeding

Do not take JAMP Alendronate / Vitamin D3 if you are pregnant or breast- feeding.

Use in children

JAMP Alendronate / Vitamin D3 is not indicated for anyone under 18 years of age and should not be given to them.

Use in elderly

JAMP Alendronate / Vitamin D3 works equally well in, and is equally well tolerated by, patients older and younger than 65

years of age.

There have been side effects reported with JAMP Alendronate / Vitamin D3 that may affect your ability to drive or operate machinery. Individual responses to JAMP Alendronate / Vitamin D3 may vary.

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 JAMP Alendronate / Vitamin D3 before taking any other oral medication.

It is likely that certain medicines or food additives may prevent the vitamin D in JAMP Alendronate / Vitamin D3 from getting into your body, including artificial fat substitutes, mineral oils, orlistat and the cholesterol-lowering medicines, cholestyramine and colestipol.

Medicines for seizures (convulsions), cimetidine and thiazides (diuretic) may decrease the effectiveness of vitamin D.

PROPER USE OF THIS MEDICATION

USUAL DOSE:
These are the important things you must do to help make sure you will benefit from JAMP Alendronate / Vitamin D3:

1. **Choose the day of the week that best fits your schedule. Every week, take one JAMP Alendronate / Vitamin D3 tablet on your chosen day.**

2. **After getting up for the day and before taking your first food, beverage, or other medication, swallow your JAMP Alendronate / Vitamin D3 tablet with a full glass (200-250 mL) of plain water only.**

Do **NOT** take JAMP Alendronate / Vitamin D3 with:
- Mineral water
- Coffee or tea
- Juice

Although it has not been tested, because of high mineral content, "hard water" may decrease absorption of JAMP Alendronate / Vitamin D3. 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 JAMP Alendronate / Vitamin D3.

3. **After swallowing your JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 at bedtime or before getting up for the day.**

The above actions will help the JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 tablet, wait at least 30 minutes before taking your first food, beverage, or other medication of the day,** including antacids, calcium supplements and vitamins. JAMP Alendronate / Vitamin D3 is effective only if taken when your stomach is empty.

6. **If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking JAMP Alendronate / Vitamin D3 immediately and call your doctor.**

7. It is important that you continue taking JAMP Alendronate / Vitamin D3 for as long as your doctor prescribes it. JAMP Alendronate / Vitamin D3 can treat your osteoporosis only if you continue to take it.

It is important to take JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 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.

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

MISSED DOSE:
If you miss a dose, just take one JAMP Alendronate / Vitamin D3 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.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

JAMP Alendronate / Vitamin D3 may have unintended or undesirable effects.
- digestive problems such as nausea, vomiting, diarrhea or constipation.

disorders of your esophagus (the tube that connects your mouth with your stomach) including irritation which can cause chest pain, heartburn or difficulty or pain upon swallowing.

Esophageal reactions may worsen if patients continue to take JAMP Alendronate / Vitamin D3 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 JAMP Alendronate / Vitamin D3 immediately and call your doctor.

- bone, muscle and/or joint pain which is rarely severe.
- joint swelling or swelling in their hands or legs.
- transient flu-like symptoms (rarely with fever).
- rash that may be made worse by sunlight, hair loss.
- 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.
- dizziness, vertigo (spinning sensation) or a changed sense of taste.
- symptoms of low blood calcium (for example, numbness or tingling around the mouth or in the hands or feet; muscle spasms in the face, hands, or feet).
- mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.

If any of these affects you severely, tell your doctor or your pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / effects	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
Allergic reactions such as: - hives - swelling of the face, lips, tongue and/or throat - difficulty in breathing or swallowing			✓
Severe bone, joint, and/or muscle pain		✓	
New or unusual pain in the hip or thigh		✓	
Esophageal ulcers causing: - chest pain - heartburn - difficulty or pain upon swallowing			✓
Stomach or other peptic ulcers occasionally associated with black and/or bloody stools			✓
Jaw problems associated with delayed healing and infection, often following tooth extraction			✓
Eye inflammation associated with eye pain; eye redness; sensitivity to light, decreased vision			✓
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			✓
Rare			
Persistent ear pain		✓	

This is not a complete list of side effects. For any unexpected effects while taking JAMP Alendronate / Vitamin D3, contact your doctor or pharmacist.

REPORTING SIDE EFFECTS

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

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

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

HOW TO STORE IT

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

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

Remember to keep JAMP Alendronate / Vitamin D3 and all medications safely away from children.

MORE INFORMATION

If you want more information about JAMP Alendronate / Vitamin D3:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling the sponsor JAMP Pharma Corporation at 1-866-399-9091.

This leaflet was prepared by JAMP Pharma Corporation
1310 rue Nobel
Boucherville, Québec
J4B 5H3

Date prepared: August 30, 2021