PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] RIVA-ALENDRONATE

Alendronate Sodium Tablets

Tablets, 5 mg, 10 mg and 70 mg alendronic acid (as alendronate sodium trihydrate), Oral

House Standard

Bone Metabolism Regulator

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SEP 6, 2017

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APR 26, 2024

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	07/2022
7 WARNINGS AND PRECAUTIONS	04/2024

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RIVA-ALENDRONATE (alendronate sodium) is indicated for:

- The treatment of osteoporosis in postmenopausal women.
    - For the treatment of osteoporosis in postmenopausal women, RIVA-ALENDRONATE increases bone mass and prevents fractures, including those of the hip and spine (vertebral compression fractures).
- The treatment of osteoporosis in men.
    - For the treatment of osteoporosis in men, RIVA-ALENDRONATE increases bone mass and reduces the incidence of fractures.
- The prevention of osteoporosis in postmenopausal women
    - For the prevention of osteoporosis, alendronate sodium may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture.
- The treatment and prevention of glucocorticoid-induced osteoporosis in men and women.
    - Alendronate sodium is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density.

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

1.1 Pediatrics

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

1.2 Geriatrics

Geriatrics (≥65 years of age): In clinical studies, there was no age-related difference in the efficacy or safety profiles of alendronate sodium (see 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

RIVA-ALENDRONATE is contraindicated in patients with

- hypersensitivities to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia.
- the inability to stand or sit upright for at least 30 minutes.
- hypocalcemia (see 7 WARNINGS AND PRECAUTIONS).

- renal insufficiency with creatinine clearance < 0.58 mL/s (< 35 mL/min) (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics, Renal Insufficiency).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. See 7 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 RIVA-ALENDRONATE on an individual patient basis.
- Although no specific studies have been conducted on the effects of switching patients on another therapy for osteoporosis to RIVA-ALENDRONATE there are no known or theoretical safety concerns related to RIVA-ALENDRONATE in patients who previously received any other antiosteoporotic therapy.

4.2 Recommended Dose and Dosage Adjustment

- **Treatment of Osteoporosis in Postmenopausal Women and in Men**

  The recommended dosage is one 70 mg tablet once weekly or one 10 mg tablet once daily.

- **Prevention of Osteoporosis in Postmenopausal Women**

  The recommended dosage is 5 mg once a day.

- **Treatment and Prevention of Glucocorticoid-Induced Osteoporosis in Men and Women**

  The recommended dosage is 5 mg once a day, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is 10 mg once a day.

Dosage Adjustment

Geriatrics (≥ 65 years of age): No dosage adjustment is necessary for the elderly (see 1 INDICATION, 1.2 Geriatrics).

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

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

4.4 Administration

RIVA-ALENDRONATE 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 RIVA-ALENDRONATE (see 9 DRUG INTERACTIONS). Waiting less than 30 minutes will lessen the effect of RIVA-ALENDRONATE by decreasing its absorption into the body.

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

RIVA-ALENDRONATE tablets should not be chewed, sucked, cut, or crushed. (see 7 WARNINGS AND PRECAUTIONS).

4.5 Missed Dose

Patients should be instructed that if they miss a dose of RIVA-ALENDRONATE 70 mg once weekly, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Take RIVA-ALENDRONATE 5 mg and 10 mg once daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule of one tablet once a day.

5 OVERDOSAGE

No specific information is available on the treatment of overdosage with RIVA-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.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets / 5 mg, 10 mg, 70 mg Each tablet contains 6.53, 13.05 or 91.37 mg of alendronate monosodium salt trihydrate, which is the equivalent to 5 mg, 10 mg and 70 mg, respectively, of free acid.	anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose

RIVA-ALENDRONATE 5 mg tablets, a white to off white , round, flat faced beveled edged, uncoated tablet with inscription ‘5’ on one side and plain on the other side. Available in blister packages of 28 tablets.

RIVA-ALENDRONATE 10 mg tablets, a white to off-white, oval biconvex uncoated tablet with inscription ‘10’ on one side and plain on the other side. Available in blister packages of 28 tablets.

RIVA-ALENDRONATE 70 mg tablets, a white to off-white, oval biconvex uncoated tablet with inscription '70' on one side and plain on the other side. Available in blister packages of 4 tablets and bottles of 100 tablets.

RIVA-ALENDRONATE tablets are gluten-free.

7 WARNINGS AND PRECAUTIONS

General

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, patients should be instructed to swallow each tablet of RIVA-ALENDRONATE with a full glass of water. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take RIVA-ALENDRONATE 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 RIVA-ALENDRONATE immediately and consult their physician. (see 4.4 Administration).

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

Endocrine and Metabolism

Hypocalcemia must be corrected before initiating therapy with RIVA-ALENDRONATE (see 2 CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as Vitamin D deficiency) should be treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with RIVA-ALENDRONATE. 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 RIVA-ALENDRONATE for predisposing conditions.

Due to the positive effects of alendronate sodium in increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, in whom the pretreatment rate of bone turnover may be greatly elevated, and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and Vitamin D intake is especially important in patients receiving glucocorticoids.

Gastrointestinal

RIVA-ALENDRONATE, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate sodium. 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 RIVA-ALENDRONATE immediately and seek medical attention if they

develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn (see 8.2 Clinical Trial Adverse Reactions; 8.5 Post-Market Adverse Reactions).

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking alendronate sodium and/or who fail to swallow it with the recommended amount of water, and/or who continue to take alendronate sodium after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see 4 DOSAGE AND ADMINISTRATION).

Because of possible irritant effects of RIVA-ALENDRONATE on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when RIVA-ALENDRONATE is given to patients with active upper gastrointestinal problems, such as dysphagia, esophageal diseases (including known Barrett's esophagus), gastritis, duodenitis, or ulcers.

While no increased risk was observed in extensive clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications.

Musculoskeletal

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

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

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

Osteonecrosis:

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

majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection, including osteomyelitis (see 8.5 Post-Market Adverse Reactions).

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

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

Cases of osteonecrosis of the external auditory canal (cholesteatoma) have been reported in patients treated with RIVA-ALENDRONATE.

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

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

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

Ophthalmologic

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

Renal

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

Reproductive Health: Female and Male Potential

Fertility

The effect of alendronate sodium on human fertility has not been evaluated. Animal study data is included in Section 16 NON-CLINICAL TOXICOLOGY.

7.1 Special Populations

7.1.1 Pregnant Women

RIVA-ALENDRONATE should not be used by pregnant women. RIVA-ALENDRONATE has not been studied in pregnant women.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

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

Osteonecrosis of the Jaw and atypical bone fractures have been observed under post marketing seeting. See 7 WARNINGS AND PRECAUTIONS, Musculoskeletal.

8.2 Clinical Trial Adverse Reactions

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

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 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 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 10 mg/day or placebo are presented in the following table.

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

	Alendronate Sodium 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	0.5	1.0

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

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

In the two-year extension (treatment years 4 and 5) of the above studies, the overall safety profile of alendronate sodium 10 mg/day was similar to that observed during the three-year placebo-controlled period. Additionally, the proportion of patients who discontinued alendronate sodium 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 5 mg/day for two years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo.

Discontinuations due to upper gastrointestinal adverse experiences were: alendronate sodium, 3.2%; placebo, 2.7%. The overall adverse experience profile was similar to that seen in other studies with alendronate sodium 5 or 10 mg/day.

In a one-year, double-blind multicenter study, the overall safety and tolerability profiles of alendronate sodium 70 mg once weekly and alendronate sodium 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:

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

	Alendronate Sodium 70 mg once weekly n = 519 (%)	Alendronate Sodium 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 10 mg/day [n=146] and a one-year study of alendronate sodium 70 mg once weekly [n=109]), the safety profile of alendronate sodium 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 10 mg/day vs. 10.5% for placebo, and 6.4% for alendronate sodium 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 soduim 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 soduim 70 mg once weekly were similar to that of placebo and no difference was seen between men and women.

Prevention of Osteoporosis in Postmenopausal Women:

The safety of alendronate soduim 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 for either two or three years. In these studies, the overall safety profiles of alendronate sodium 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 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 5 mg/day or placebo are presented in the following table:

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

	Alendronate Sodium 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
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.

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 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 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 5 or 10 mg/day or placebo are presented in the following table:

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

	Alendronate Sodium 10 mg/day n = 157 (%)	Alendronate Sodium 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.

8.3 Less Common Clinical Trial Adverse Reactions

Skin: rash and erythema

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

Clinical Trial Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronate sodium versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg P[1]/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.

[1] P: Elemental phosphorus

8.5 Post-Market Adverse Reactions

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

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

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

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

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

Nervous System: dizziness, vertigo, dysgeusia

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

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Specific interaction studies were not performed. Animal studies have demonstrated that alendronate sodium 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 sodium is not expected to interact with other drugs based on effects on protein binding, renal excretion, or metabolism of other drugs.

9.3 Drug-Behavioural 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 (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 RIVA-ALENDRONATE may vary.

9.4 Drug-Drug Interactions

Table 6 - Interaction with Alendronate Sodium

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Calcium supplements, Antacids, other Multivalent Cations and other Oral Medications		Interfere with absorption of alendronate	Wait at least one-half hour after taking RIVA-ALENDRONATE before taking any other oral medication.
Ranitidine	CT	Was shown to double the bioavailability of oral alendronate	The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H2 - antagonists is unknown
Hormone Replacement Therapy (HRT [estrogen ± progestin])	CT	Greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone.	The safety and tolerability profile of the combination was consistent with those of the individual treatments (see 8.2 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.

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

Alendronate sodium was used in osteoporosis studies in men, postmenopausal women, and glucocorticoid users, with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions.

Specific interaction studies were not performed. Alendronate sodium was used in osteoporosis studies in men, postmenopausal women, and glucocorticoid users, with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions.

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving daily therapy with dosages of alendronate sodium greater than 10 mg and acetylsalicylic acid-containing products. This was not observed in a study with alendronate sodium 70 mg once weekly.

RIVA-ALENDRONATE 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 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 RIVA-ALENDRONATE.

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

Herbal products may interfere with the absorption of alendronate. RIVA-ALENDRONATE must be taken at least one-half hour before any herbal products. See 4 DOSAGE AND ADMINISTRATION, Administration.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Alendronate 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.

10.2 Pharmacodynamics

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

Osteoporosis in Postmenopausal Women

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

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

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

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with alendronate sodium. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of alendronate sodium 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment, however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with alendronate sodium 5 mg/day. In a one-year study with alendronate sodium 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 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 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 70 mg once weekly.

Glucocorticoid-Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.
In clinical studies of up to two years' duration, alendronate sodium 5 and 10 mg/day reduced cross-linked N-telopeptides of type 1 collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, alendronate sodium 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

10.3 Pharmacokinetics

Table 7 - Summary of alendronate sodium Pharmacokinetic Parameters in the Normal Population

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

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

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

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

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

Distribution

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%.

Metabolism

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

Elimination

Following a single IV dose of [14C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration.

The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with alendronate sodium (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations and Conditions

- **Pediatrics:** The oral bioavailability in children (4 to 16 years of age) with osteogenesis imperfecta (OI) was similar to that observed in adults; however, RIVA-ALENDRONATE is not indicated for use in children (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).
- **Geriatrics:** Bioavailability and disposition (urinary excretion) were similar in elderly (≥ 65 years of age) and younger patients. No dosage adjustment is necessary (see 4 DOSAGE AND ADMINISTRATION).
- **Sex:** Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.
- **Ethnic Origin:** Pharmacokinetic differences due to race have not been studied.
- **Hepatic Insufficiency:** As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.
- **Renal Insufficiency:** Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 0.58 to 1 mL/s [35 to 60 mL/min]). RIVA-ALENDRONATE is contraindicated for patients with more severe renal insufficiency (creatinine clearance < 0.58 mL/s [< 35 mL/min]). See 2 CONTRAINDICATIONS.

11 STORAGE, STABILITY AND DISPOSAL

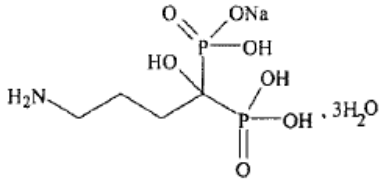
Store at room temperature (15°C - 30°C).

Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	alendronate sodium trihydrate
Chemical name:	RIVA-ALENDRONATE contains alendronate sodium trihydrate, which is described chemically as: (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.
Molecular formula and molecular mass:	$C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and 325.12 g/mol
Structural formula:	
Physicochemical properties:	Alendronate is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of osteoporosis in postmenopausal women

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

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PN035	Double -blind, randomized, placebo-controlled, parallel group multicenter extension study	PBO FOS 5mg FOS 10mg FOS 20/5mg ORAL 3 years	478	45-82	Women
PN037	Double -blind, randomized, placebo-controlled, parallel group multicenter extension study	PBO FOS 5mg FOS 10mg FOS 20/5mg ORAL 3 years	516	44 to 84	Women
PN041	Double-blind, randomized, parallel-group study	PB0 FOS 10mg FOS 20mg sCT ORAL 2 years	286	48-76	Women
PN118	Randomized, Double-blind, multicenter study	FOS 10mg FOS 35mg (twice a week) FOS 70mg (once a week) ORAL 1 year	1258	42-95	Women
PN026	Double-blind, randomized, placebo controlled- parallel group, multicenter study	PBO FOS 5mg FOS 10mg FOS 20mg/PBO FOS 40mg/PBO FOS 40mg/2.5mg ORAL 2 (+1*year)	188	42-75	Women

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PN054	Double-blind, randomized, placebo controlled, parallel-group study	PBO FOS 1mg FOS 2.5mg FOS 5mg ORAL 2 years	359	59-85	Women
FIT 1	Randomized, placebo-controlled	PBO FOS 10mg ORAL 3 years	2027	55-81	Women
FIT 2	Randomized, placebo-controlled	PBO FOS 10mg ORAL 4 years	4432	55-80	Women
PN072	Double-blind, randomized, placebo-controlled, multicenter study	FOS 10mg + conjugated estrogens (0.625 mg) OR conjugated estrogens (0.625 mg) OR PBO OR FOS 10mg ORAL 2 years	425	42-82	Women
PN097	Triple-blind, randomized, placebo-controlled, parallel-group, multicenter study	FOS 10 mg/day + HRT (estrogen + progestin) OR PBO/HRT ORAL 1 year	428	40-84	Women

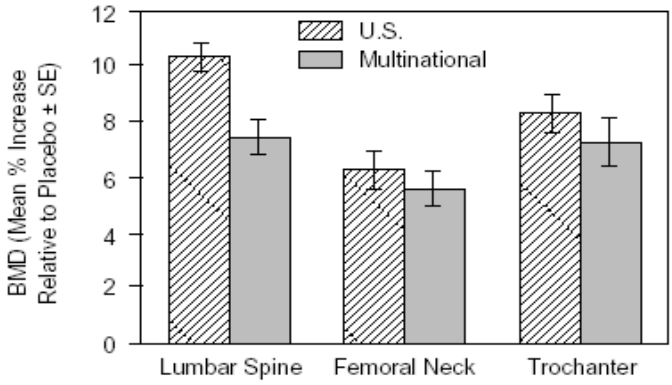
PBO= Placebo; FOS=alendronate (mg/day); sCT=Intranasal salmon calcitonin 100 IU/day; FOS 20/PB0, FOS 40/PBP= alendronate 20 or 40mg for 1 year followed by placebo for 1 year; FOS 40/2.5= alendronate 40mg for 3 months followed by 2.5 for 21 months; FOS 20/5=alendronate 20mg for 2 years followed by 5mg for 1 year

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

Effect on Bone Mineral Density

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

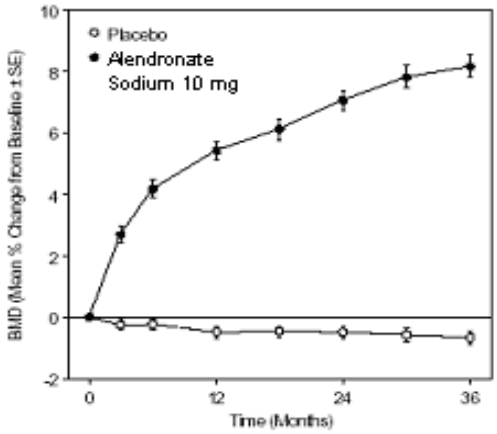
Osteoporosis Treatment Studies in Postmenopausal Women
Increase in BMD
Alendronate Sodium 10 mg/day at Three Years



In the combined studies, after three years, BMD of the lumbar spine, femoral neck and trochanter in placebo-treated patients decreased significantly by between 0.65 and 1.16%. Highly significant increases, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received alendronate sodium 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 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 reverses the progression of osteoporosis. Alendronate sodium was similarly effective regardless of age, race, baseline rate of bone turnover, renal function and use with a wide range of common medications.

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



In a separate study, alendronate sodium 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 70 mg once weekly (n = 519) and alendronate sodium 10 mg daily (n = 370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70-mg once-weekly group and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group. The two treatment groups were also similar with regard to BMD increases at other skeletal sites. In trials with alendronate sodium changes in BMD of this magnitude were associated with a decrease in fracture incidence (see below).

Effects of Withdrawal

In patients with postmenopausal osteoporosis treated with alendronate sodium 10 mg/day for one or two years the effects of treatment withdrawal were assessed. Following discontinuation, bone turnover gradually returned toward pretreatment levels, and BMD no longer increased although accelerated bone loss was not observed. These data indicate that treatment with alendronate sodium must be continuous to produce progressive increases in bone mass.

Effect on Fracture Incidence

To assess the effects of alendronate sodium 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 (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant 48% reduction in the proportion of patients treated with alendronate sodium experiencing one or more vertebral fractures relative to those treated with placebo (3.2% vs 6.2%). An even greater reduction in the total number of vertebral fractures (4.2 vs 11.3 per 100 patients) was also observed. Furthermore, of patients who sustained any vertebral fracture, those treated with alendronate sodium experienced less height loss (5.9 mm vs 23.3 mm) due to a reduction in both the number and severity of fractures.

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

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

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

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

Table 9- Effect of Alendronate Sodium on Fracture Incidence in the Three-Year Study of FIT (Patients with Vertebral Fracture at Baseline)

Patients with:	% of Patients		Reduction (%) in Fracture Incidence
	Alendronate Sodium (n=1022)	Placebo (n=1005)	
Vertebral fractures (diagnosed by X-ray)†			
≥ 1 new vertebral fracture	7.9	15.0	47***
≥ 2 new vertebral fractures	0.5	4.9	90***
Painful (clinical) fractures			
≥ 1 painful vertebral	2.3	5.0	54**
fracture Any painful	13.8	18.1	26**
fracture	1.1	2.2	51*
Hip fracture	2.2	4.1	48*
Wrist (forearm) fracture			

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

* p<0.05

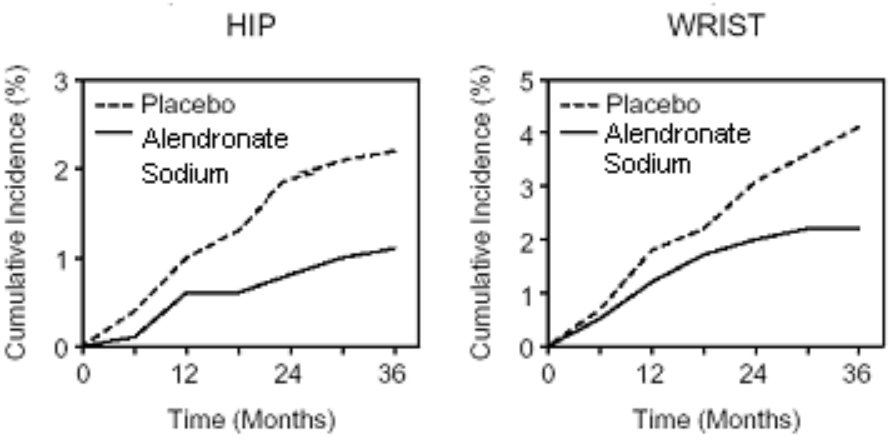
** p<0.01

*** p<0.001

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

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

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



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

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

Table 10 - Effect of Alendronate Sodium 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 (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, n=1426; placebo, n=1428
††† Not significant
** p = 0.01
***p <0.001

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

Combined FIT Studies

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

Table 11 - Effect of Alendronate Sodium on Fracture Incidence in the Combined (Three- and Four-Year) Studies of FIT

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

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

[††] Number evaluable for vertebral fractures: osteoporotic patients, n=4804; all patients,n=6084

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

[‡] Not significant

[‡‡] p=0.059

* p<0.05

** p<0.01

***p<0.001

Consistency of Fracture Results

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

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

Bone Histology

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

Treatment of osteoporosis in men

Table 12 - Summary of patient demographics for clinical trials (treatment of osteoporosis in men)

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

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

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

A two-year, double-blind, placebo-controlled, multicenter study of alendronate sodium 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 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6% (all p≤ 0.001). Consistent with much larger studies in postmenopausal women, in these men, alendronate sodium 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 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 ≤ 0.001); femoral neck, 1.9% (p=0.007); trochanter, 2.0% (p ≤ 0.001); and total body, 1.2% (p=0.018). These increases in BMD were similar to those seen at one year in the 10 mg once-daily study. The trial was not powered to detect a clinical difference in fracture incidence between the alendronate and placebo groups. However, other studies with daily or weekly alendronate administrations have consistently demonstrated a relationship between increases in BMD (a surrogate marker) and decreases in fracture rate (clinical endpoint). Therefore, it can be assumed that this relationship is also true in men given a weekly administration of alendronate

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

Prevention of osteoporosis in postmenopausal women

Table 13 - Summary of patient demographics for clinical trials (prevention of osteoporosis in postmenopausal women)

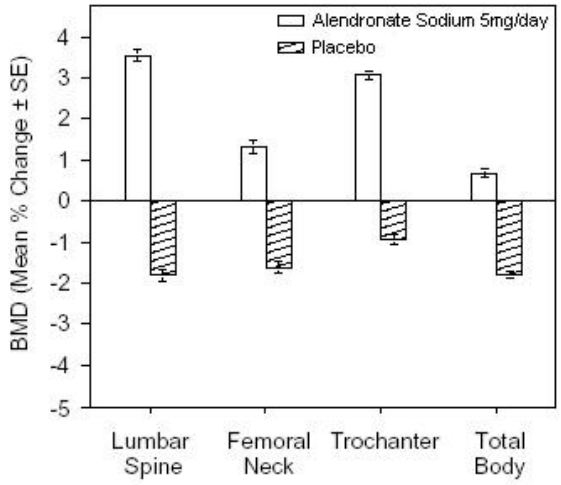
Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PN055	Double-blind, placebo-controlled	PBO FOS 2.5mg FOS 5mg Estrogen/progestin ORAL 2 years	1609	44-60	Women
PN029	Double-blind, placebo-controlled, parallel-group, multicenter study	PBO FOS 1mg FOS 5mg FOS 10mg FOS 20mg/PBO ORAL 3 years	447	40-60	Women

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

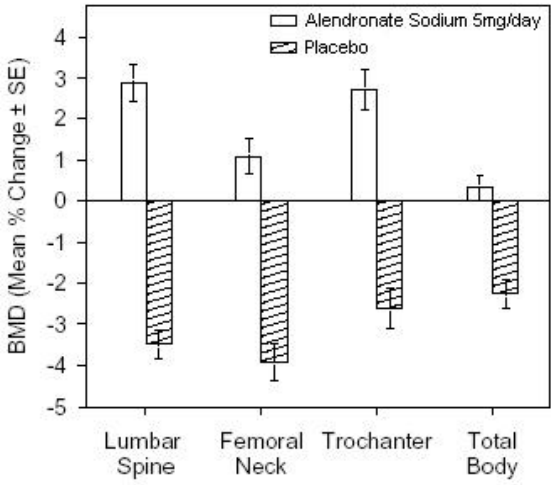
Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40-60 years of age. One thousand six hundred nine patients (alendronate sodium 5 mg/day: n = 498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (alendronate sodium 5 mg/day: n = 88), who were between six months and three years postmenopausal, were treated for up to three years. As expected, in the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, alendronate sodium 5 mg/day effectively prevented bone loss, and induced highly significant increases in bone mass at each of these sites (see following figures). In addition, alendronate sodium 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. Alendronate Sodium 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

Osteoporosis Prevention Studies in Postmenopausal Women

Change in BMD from Baseline
2 – Year Study



Change in BMD from Baseline
3 – Year Studv



Bone Histology

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

Concomitant Use with Estrogen/Hormone Replacement Therapy (HRT)

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

The effects on BMD when alendronate sodium was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of alendronate sodium 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.

Treatment and prevention of glucocorticoid-induced osteoporosis in men and women

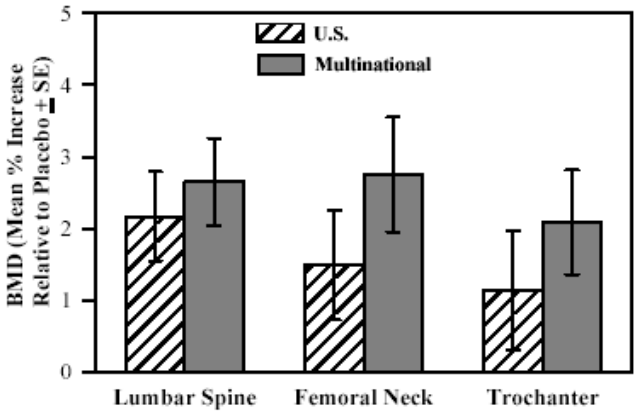
Table 14 - Summary of patient demographics for clinical trials (treatment and prevention of glucocorticoid-induced osteoporosis in men and women)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PN082	Randomized, double-blind placebo-controlled, dose ranging	PBO FOS 2.5 mg FOS 5 mg FOS 10mg 7.5 mg/day prednisone or equivalent ORAL 48 weeks	328	17-79	Men Women
PN083	Randomized, double-blind placebo-controlled, dose ranging	PBO FOS 5mg FOS 10mg 7.5 mg/day prednisone or equivalent ORAL 48 weeks	232	19-83	Men Women

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

The efficacy of alendronate sodium 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design (United States and Multinational [which also included alendronate sodium 2.5 mg/day]). These studies enrolled a total of 560 patients between the ages of 17 and 83. Patients received supplemental calcium and Vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving alendronate sodium 5 mg/day for each study.

Studies in Glucocorticoid - Treated Patients
Increase in BMD
Alendronate Sodium 5 mg/day at One Year



After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received alendronate sodium 5 or 10 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with alendronate sodium 5 or 10 mg/day. The increases in BMD (relative to placebo) with alendronate sodium 10 mg/day were greater than those with alendronate sodium 5 mg/day only in postmenopausal women not receiving estrogen therapy, at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. Alendronate sodium was effective regardless of dose or duration of glucocorticoid use. In addition, alendronate sodium was similarly effective regardless of age (<65 vs. $\geq$ 65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

Bone Histology

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

Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with alendronate sodium 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with alendronate sodium 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with alendronate sodium (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (alendronate sodium 0.7% vs. placebo 6.8%).

14.3 Comparative Bioavailability Studies

A blinded, randomized, single-dose, four-period, 2-sequence, replicate, crossover oral bioequivalence study of RIVA-ALENDRONATE Tablets 10 mg and Fosamax ® Tablets 10 mg tablets was conducted in forty six (46) healthy, male subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Alendronic acid (1 x 10 mg tablets) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %) (n = 86 observations)				
Parameter	**Test*#**	**Reference+**	**% Ratio of Geometric Least Square Means #**	**90% Confidence Interval#**
AUC_T (ng·h/mL)	13.475 15.903 (65.7%)	13.475 15.126 (49.0%)	99.4	88.66-111.55%
AUC_I (ng.h/mL)	14.155 16.701 (65.6%)	14.242 16.047 (50.1%)	98.8	88.01-110.98%
C_{max} (ng/mL)	4.783 5.696 (70.3%)	4.674 5.236 (48.2%)	101.4	90.23-113.99%
T_{max}§ (h)	1.000 (0.250 – 3.000)	1.125 (0.500 – 3.000)	Not applicable	Not applicable
$T_{½}$€ (h)	5.227 (73.4%)	5.699 (88.3%)	Not applicable	Not applicable

*RIVA-ALENDRONATE 10 mg tablets (Laboratoire Riva Inc.)
+ Fosamax® Tablets 10 mg (Merck Frosst Canada Ltd., Canada)
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only
n = 85 observations

A blinded, randomized, single-dose, four-period, 2-sequence, replicate, crossover oral bioequivalence study of RIVA-ALENDRONATE Tablets 70 mg and Fosamax ® Tablets 70 mg tablets was conducted in fifty one (51) healthy, male subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Alendronic acid (1 X 70 mg tablets) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %) (n = 102 observations)				
Parameter	**Test***	**Reference+**	**% Ratio of Geometric Least Square Means**	**90 % Confidence Interval**
AUC_T (ng·h/mL)	100.941 127.421 (70.9%)	94.242 122.633 (77.7%)	107.1	96.35-119.12%
AUC_I (ng.h/mL)	107.056 135.221 (71.0%)	100.012 130.502 (77.6%) [@]	106.6	95.96-118.45%
C_{max} (ng/mL)	34.168 43.706 (80.7%)	32.450 41.872 (82.0%)	105.4	94.60-117.50%
T_{max} [§] (h)	1.250 (0.250 – 2.500)	1.000 (0.250 – 2.500)	Not applicable	Not applicable
$T_{½}$ [€] (h)	6.006 (46.1%)	5.791 (57.5%) [@]	Not applicable	Not applicable

*RIVA-ALENDRONATE 70 mg tablets (Laboratoire Riva Inc.)
+ Fosamax ® Tablets 70 mg (Merck Frosst Canada Ltd., Canada)
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only
@ n=101

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

The oral LD_{50} values of alendronate in female rats and mice were 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2) (equivalent to human oral doses* of 27,600 and 48,300 mg), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2) (equivalent to a human oral dose* of 10,000 mg).

Chronic Toxicity

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.

Carcinogenicity: 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.

Genotoxicity: Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation. Similarly, no evidence of mutagenicity was observed in an *in vitro* mammalian cell mutagenesis assay, an *in vitro* alkaline elution assay in rat hepatocytes, and an *in vivo* chromosomal aberration assay in mice at IV doses up to 25 mg/kg/day (75 mg/m^2). In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate was weakly positive at concentrations $\geq$ 5 mM in the presence of cytotoxicity. This is of no relevance to safety in humans since similar concentrations are not achievable *in vivo* at therapeutic doses. Furthermore, clear negative results in four of five genotoxicity studies, including the most relevant studies for human carcinogenic potential (the *in vivo* chromosomal aberration assay and the microbial mutagenesis assay), and negative carcinogenicity studies in rats and mice lead to the conclusion that there is no evidence of genotoxic or carcinogenic risks from alendronate in humans.

* Based on a patient weight of 50 kg

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

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

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrFOSAMAX® alendronate sodium tablets, 70 mg, submission control 273860, Product Monograph, Organon Canada Inc. (AUG 03, 2023).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] RIVA-ALENDRONATE

Alendronate Sodium Tablets
5 mg or 10 mg alendronate daily dosage

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

What is RIVA-ALENDRONATE used for?

- Prevent osteoporosis in postmenopausal women who are at risk of developing osteoporosis. Osteoporosis is a thinning and weakening of the bones. RIVA-ALENDRONATE is used to maintain bone matter and reduce the risk of future fractures.
- Treat and prevent osteoporosis in men and women caused by corticosteroid hormones. RIVA-ALENDRONATE is used in men and women who take corticosteroid hormone drugs daily and have low bone density.

RIVA-ALENDRONATE is not for use in children under 18 years of age.

How does RIVA-ALENDRONATE work?

RIVA-ALENDRONATE contains a medicinal ingredient called alendronate sodium. Alendronate sodium belongs to a class of non-hormonal drugs called bisphosphonates. The bisphosphonates are similar to a molecule naturally made in your body that will break down bone tissue.Alendronate binds to the receptors in your body to prevent the bone from breaking down. This process also helps rebuild bone.

What are the ingredients in RIVA-ALENDRONATE?

Medicinal ingredient: alendronate sodium.

Non-medicinal ingredients: Anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

RIVA-ALENDRONATE comes in the following dosage forms:

Tablets: 5 mg and 10 mg.

Do not use RIVA-ALENDRONATE if you:

- Have certain disorders of the esophagus (the tube that connects your mouth with your stomach).
- Are unable to stand or sit upright for at least 30 minutes.
- Are allergic to alendronate sodium any other ingredients in RIVA-ALENDRONATE. If you are not sure about this, talk to your healthcare professional before taking RIVA-ALENDRONATE.
- Have low blood calcium.

- Have SEVERE kidney disease. If you have any doubts if this applies to you, speak to your healthcare professional.

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

- have cancer, gum disease, poor oral hygiene, or diabetes.
- get chemotherapyor radiotherapy.
- take corticosteroids, or immunosuppressive drugs.
- take angiogenesis inhibitor; 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 RIVA-ALENDRONATE.

- 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.

Other warnings you should know about:

Talk to your healthcare professional

- If you have ear pain and/or discharge from the ear while taking RIVA-ALENDRONATE as these could be signs of bone damage in the ear.

Use in pregnancy and breast-feeding

Do not take RIVA-ALENDRONATE if you are pregnant or breast-feeding.

Use in children

RIVA-ALENDRONATE is not indicated for use in children under 18 years of age.

Use in elderly

RIVA-ALENDRONATE works equally well in, and is equally well tolerated by, patients older and younger than 65 years of age.

Lifestyle changes

Your healthcare professional 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 physician before you begin any exercise program.

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

Driving and using machines

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

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

The following may interact with RIVA-ALENDRONATE:

- Calcium supplements, antacids, and other oral medications will interfere with the absorption of RIVA-ALENDRONATE if they are taken at the same time. You must wait at least one-half hour after taking RIVA-ALENDRONATE before taking any other oral medication.

How to take RIVA-ALENDRONATE:

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

Usual dose:

Take one RIVA-ALENDRONATE tablet once a day, every day.

Follow these instructions carefully:

1. After getting up for the day and before taking your first food, beverage, or other medication, swallow your RIVA-ALENDRONATE tablet only with plain water. **Do NOT cut, chew, crush or suck on the tablet**. To make sure RIVA-ALENDRONATE is absorbed by your body, do **NOT** take RIVA-ALENDRONATE with:
   - mineral water
   - coffee or tea
   - juice

   If your normal drinking water is classified as “hard water”, you should consider taking this medication with distilled water (i.e., not mineral water).
2. After taking your RIVA-ALENDRONATE 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.
3. Do not take RIVA-ALENDRONATE at bedtime or before getting up for the day. This will help RIVA-ALENDRONATE:
   - reach your stomach quickly and;
   - reduce the potential for irritation of your esophagus (the tube that connects your mouth with your stomach).
4. After taking your RIVA-ALENDRONATE, wait at least 30 minutes before taking your first food, beverage, or other medication of the day. This includes antacids, calcium supplements and vitamins. RIVA-ALENDRONATE is effective only if taken when your stomach is empty.

5. If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking RIVA-ALENDRONATE immediately and call your healthcare professional.

Overdose:

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

If you think you, or a person you are caring for, have taken too much RIVA-ALENDRONATE, 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, do not take an extra dose. Just resume your usual schedule of one tablet once a day.

What are possible side effects from using RIVA-ALENDRONATE?

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

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

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

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to

interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

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

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

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

Storage:

Store at room temperature (15°C - 30°C).

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

Keep out of reach and sight of children.

If you want more information about RIVA-ALENDRONATE:

- 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 Laboratoire Riva Inc. at 1-800-363-7988.

This leaflet was prepared by:

Laboratoire Riva Inc.
660 Boul. Industriel
Blainville, Quebec
J7C 3V4

www.labriva.com

Last revised: April 24, 2024

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr RIVA-ALENDRONATE

Alendronate Sodium Tablets
70 mg alendronate once weekly dosage

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

What is RIVA-ALENDRONATE used for?

RIVA-ALENDRONATE is used in adults to treat osteoporosis in men and postmenopausal women. Osteoporosis is a thinning and weakening of the bones. RIVA-ALENDRONATE helps to rebuild bone and makes bone less likely to fracture.

RIVA-ALENDRONATE is not for use in children under 18 years of age.

How does RIVA-ALENDRONATE work?

RIVA-ALENDRONATE contains a medicinal ingredient called alendronate sodium. Alendronate sodium belongs to a class of non-hormonal drugs called bisphosphonates. The bisphosphonates are similar to a molecule naturally made in your body that will break down bone tissue. Alendronate binds to the receptors in your body to prevent the bone from breaking down. This process also helps rebuild bone.

What are the ingredients in RIVA-ALENDRONATE?

Medicinal ingredient: alendronate sodium.

Non-medicinal ingredients: Anhydrous lactose, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

RIVA-ALENDRONATE comes in the following dosage forms:

Tablet 70 mg.

Do not use RIVA-ALENDRONATE if you:

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

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

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

Other warnings you should know about:

<u>Gastrointestinal Problems</u>

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

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

Muscle and skeletal problems

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

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

Eye problems

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

Bone damage in ear

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

Use in pregnancy and breast-feeding

Do not take RIVA-ALENDRONATE if you are pregnant or breast-feeding.

Lifestyle changes

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

Driving and using machines

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

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

The following may interact with RIVA-ALENDRONATE:

- Calcium supplements, antacids, and other oral medications will interfere with the absorption of RIVA-ALENDRONATE if they are taken at the same time. You must wait at least half an hour after taking RIVA-ALENDRONATE before taking any other oral medication.
- Intravenous ranitidine
- Herbal products, food and beverages other than plain water may impact your ability to absorb RIVA-ALENDRONATE. Wait at least half an hour after taking RIVA-ALENDRONATE before you take any herbal products, food or beverages.

How to take RIVA-ALENDRONATE:

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

Usual dose:

Take one RIVA-ALENDRONATE tablet once a week.

Follow these instructions carefully:

1. Choose the day of the week that best fits your schedule. Every week, take one tablet of RIVA-ALENDRONATE on your chosen day.
2. After getting up for the day and before taking your first food, beverage, or other medication, swallow your RIVA-ALENDRONATE tablet only with plain water (200 to 250 mL). **Do NOT cut, chew, crush or suck on the tablet.** To make sure RIVA-ALENDRONATE is absorbed by your body, do **NOT** take RIVA-ALENDRONATE with:

   - mineral water
   - coffee or tea
   - juice

   If your normal drinking water is classified as “hard water”, you should consider taking this medication with distilled water (i.e., not mineral water).
3. After taking your RIVA-ALENDRONATE, 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 RIVA-ALENDRONATE at bedtime or before getting up for the day. This will help RIVA-ALENDRONATE:

   - reach your stomach quickly and;
   - reduce the potential for irritation of your esophagus (the tube that connects your mouth with your stomach).
5. After taking your RIVA-ALENDRONATE, wait at least 30 minutes before taking your first food, beverage, or other medication of the day. This includes antacids, calcium supplements and vitamins. RIVA-ALENDRONATE 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 RIVA-ALENDRONATE immediately and call your healthcare professional.

Overdose:

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

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

Missed Dose:

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

What are possible side effects from using RIVA-ALENDRONATE?

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

- Digestive problems
    - Acid reflux
    - Bloated feeling in stomach
    - Constipation
    - Diarrhea
    - Excessive gas
    - Nausea
    - Stomach pain
    - Vomiting
- Dizziness, spinning sensation ora changed sense of taste.
- Flu-like symptoms (rarely with fever) and/or generally feeling unwell.
- Joint swelling or swelling in your hands or legs.
- Lack or loss of strength
- Mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.
- Muscle cramps and/or aches
- Skin problems
    - Rash that may be made worse by sunlight
    - Hair loss
    - Itchy skin

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

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

Reporting Side Effects

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

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

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

Storage:

Store at room temperature (15°C - 30°C).

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

Keep out of reach and sight of children.

If you want more information about RIVA-ALENDRONATE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling Laboratoire Riva Inc. at 1-800-363-7988.

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