PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]AA-RISEDRONATE DR

Risedronate Sodium Delayed-Release Tablets

Delayed-Release Tablets, 35 mg (as the hemi-pentahydrate), Oral

Bisphosphonates (ATC Code: M05BA07)

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RECENT MAJOR LABEL CHANGES

Not Applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AA-RISEDRONATE DR (risedronate sodium delayed-release tablets) is indicated for:

- The treatment of osteoporosis in postmenopausal women

Postmenopausal Osteoporosis: In the treatment of osteoporosis in postmenopausal women at risk of fracture, AA-RISEDRONATE DR prevents vertebral and nonvertebral osteoporosis- related (fragility) fractures and increase bone mineral density (BMD) at all measured skeletal sites of clinical importance for osteoporotic fractures, including spine, hip, and wrist.

Osteoporosis may be confirmed by the presence or history of osteoporotic fracture, or by the finding of low bone mass (e.g., at least 2 standard deviation [SD] below the premenopausal mean).

Factors such as family history of osteoporosis (particularly maternal history), age, previous fracture, smoking, moderately low BMD, high bone turnover, thin body frame, Caucasian or Asian race, and early menopause are associated with an increased risk of developing osteoporosis and fractures.

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 risedronate sodium tablets and risedronate sodium delayed-release tablets osteoporosis studies, 26 to 46% of patients were between 65 and 75 years of age and 10 to 23% were over 75 years of age. No overall differences in efficacy or safety were observed between these patients and younger patients (< 65 years) in the above osteoporosis studies. See 14 CLINICAL TRIALS.

2 CONTRAINDICATIONS

AA-RISEDRONATE DR are contraindicated in:

- Patients who are hypersensitive 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.

- Hypocalcemia. See 7 WARNINGS AND PRECAUTIONS.

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.

4.2 Recommended Dose and Dosage Adjustment

- **For all indications and doses:** The patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to instructions.
- **Treatment of Postmenopausal Osteoporosis:** The recommended regimen is weekly (35 mg Once-a-Week delayed-release tablets), taken orally.
- **Renal Impairment:** No dosage adjustment is necessary in patients with a creatinine clearance ≥ 30 mL/min or in the elderly. Not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).
- **Pediatrics (<18 years of age):** Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** No dosage adjustment is necessary in elderly patients. See 1.2 Geriatrics.

4.4 Administration

AA-RISEDRONATE DR (risedronate sodium) delayed-release tablets

- AA-RISEDRONATE DR should be taken in the morning, with breakfast, this may include high fat foods, coffee, tea, milk, orange juice etc. See 4.2 Recommended Dose and Dosage Adjustment. A higher incidence of upper abdominal pain was seen when AA-RISEDRONATE DR was taken in a fasted state before breakfast. See 9.5 Drug-Food Interactions.
- Each AA-RISEDRONATE DR tablet should be swallowed whole while the patient is in an upright position and with sufficient plain water (≥ 120 mL) to facilitate delivery to the stomach.
- Patients taking AA-RISEDRONATE DR should not lie down for at least 30 minutes after taking the medication. See 7 WARNINGS AND PRECAUTIONS.
- AA-RISEDRONATE DR tablets should not be chewed, cut, or crushed. Care should be taken not to break the outer coating which is designed to remain intact until the tablet reaches

the small intestine where the tablet coating dissolves and releases the active ingredient. See 7 WARNINGS AND PRECAUTIONS.

- Calcium supplements and antacids can interfere with the absorption of AA-RISEDRONATE DR. These medications should be administered at a different time of the day than AA-RISEDRONATE DR.
- 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 AA-RISEDRONATE DR on an individual patient basis.

4.5 Missed Dose

Weekly: Patients should be instructed that if they miss a dose of AA-RISEDRONATE DR 35 mg Once-a-Week on their regularly scheduled day, they should take 1 tablet on the day they first remember missing their dose. Patients should then return to taking 1 tablet once a week as originally scheduled on their chosen day. Patients should not take 2 tablets on the same day.

5 OVERDOSAGE

Decreases in serum calcium following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients.

Milk or antacids containing calcium, magnesium, and aluminum may be given to bind risedronate sodium tablets and reduce absorption of the drug; the impact of this intervention for risedronate sodium delayed-release tablets has not been evaluated. The risedronate sodium delayed release tablets formulation is less sensitive to the binding effects of divalent cations. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug if performed within 30 minutes of ingestion. Standard procedures that are effective for treating hypocalcemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.

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	AA-RISEDRONATE DR enteric-coated, delayed-release tablet 35 mg	Colloidal silicon dioxide, disodium edetate, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polysorbate 80, sodium starch glycolate, stearic acid, talc, triethyl citrate, yellow ferric oxide.

AA-RISEDRONATE DR: yellow, oval, biconvex, coated tablet. Engraved “35” on one side, plain on the other side.

Available in blister packages of 4 and bottles of 30 tablets.

The AA-RISEDRONATE DR tablet has an enteric coating, which delays the release of risedronate until the small intestine.

7 WARNINGS AND PRECAUTIONS

General

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting AA-RISEDRONATE DR therapy.

Adequate intake of calcium and vitamin D is important in all patients.

AA-RISEDRONATE DR delayed release tablets are formulated to release in the small intestine to provide effective absorption of risedronate when taken as directed with breakfast. Other risedronate sodium tablets formulations should be taken on an empty stomach at least 30 minutes before first food of the day. For this reason, risedronate sodium tablets 35 mg should not be substituted for AA-RISEDRONATE DR 35 mg.

Detailed dosing instructions (see 4.2 Recommended Dose and Dosage Adjustment and 4.4 Administration) are provided to ensure correct dosing of AA-RISEDRONATE DR therapy.

Gastrointestinal

Bisphosphonates may cause upper gastrointestinal (GI) disorders such as dysphagia, esophagitis, esophageal ulcer, and gastric ulcer (see 8.1 Adverse Reaction Overview). Since some bisphosphonates have been associated with esophagitis and esophageal ulcerations, to facilitate delivery to the stomach and minimize the risk of these events, patients should take

AA-RISEDRONATE DR while in an upright position (i.e., sitting or standing) and with sufficient plain water (≥ 120 mL). Patients should not lie down for at least 30 minutes after taking the drug. Health professionals should be particularly careful to emphasize the importance of the dosing instructions to patients with a history of esophageal disorders (e.g., inflammation, stricture, ulcer, or disorders of motility).

Monitoring and Laboratory Tests

***Osteonecrosis of the jaw*:** Prior to treatment with AA-RISEDRONATE DR, a routine oral examination should be performed. Patients with positive risk factors (e.g. cancer, chemotherapy, immunosuppression, angiogenesis inhibitors, head and neck radiotherapy, corticosteroids, poor oral hygiene, and diabetes) should be referred to a dentist for examination and appropriate preventative dentistry should be performed prior to treatment with AA-RISEDRONATE DR. Patients should receive routine dental check-ups while taking AA-RISEDRONATE DR.

Musculoskeletal

***Osteonecrosis of the Jaw*:** Osteonecrosis of the jaw (ONJ) has been reported post-market in patients treated with bisphosphonates as well as with other oral and intravenous bisphosphonates, including in, but not limited to, patients with cancer receiving treatment or patients that underwent invasive dental procedures such as root canal or dental extraction (see 8.5 Post-Market Adverse Reactions).

Prior to treatment with AA-RISEDRONATE DR, a routine oral examination should be performed. Patients with possible risk factors (e.g., cancer, immunosuppression, chemotherapy, angiogenesis inhibitors, head and neck radiotherapy, corticosteroids, poor oral hygiene, and diabetes) should be referred to a dentist for examination and appropriate preventative dentistry should be performed prior to treatment with AA-RISEDRONATE DR.

During treatment with risedronate sodium, patients should maintain good oral hygiene, undergo routine dental check-ups and immediately report any oral symptoms. While on treatment, these patients should avoid invasive dental procedures if possible but should continue with regular dental cleaning and oral hygiene. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment prior to the procedure reduces the risk of ONJ. In patients who develop ONJ while on bisphosphonate therapy, surgery at the affected area may exacerbate the condition. Clinical judgment of the treating physician should guide the management of patients undergoing dental procedures, based on individual benefit/risk assessment.

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

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds),

- Route of administration (higher risk for parenteral administration),
- Cumulative dose of bone resorption therapy.
- Co-morbid conditions (e.g. anaemia, coagulopathies) and smoking,
- Periodontal disease, poorly fitting dentures, history of dental disease.

***Atypical Subtrochanteric and Diaphyseal Femoral Fractures*:** Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.

Atypical femur fractures most commonly occur with minimal or no impact trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. Poor healing of these fractures was also reported.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contra-lateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment. Although causality has not been established, the role of bisphosphonates cannot be ruled out.

***Musculoskeletal Pain*:** In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates (see 8.1 Adverse Reactions Overview). 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 of patients had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.

Ophthalmologic
Ocular disturbances including conjunctivitis, uveitis, episcleritis, iritis, and scleritis have been reported with risedronate sodium 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 have to be discontinued.

Renal
Risedronate sodium is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).

7.1 Special Populations

7.1.1 Pregnant Women

Risedronate sodium is not intended for use during pregnancy. There are no studies of risedronate sodium in pregnant women.

7.1.2 Breast-feeding

Risedronate sodium is not intended for use with nursing mothers. It is not known whether risedronate is excreted in human milk. Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period post-dosing, indicating a small degree of lacteal transfer. Since many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from bisphosphonates, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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 risedronate sodium tablets and risedronate sodium delayed release tablets osteoporosis studies, 26 to 46% of patients were between 65 and 75 years of age and 10 to 23% were over 75 years of age. No overall differences in efficacy or safety were observed between these patients and younger patients (< 65 years of age) in the above osteoporosis studies. See 14 CLINICAL TRIALS.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Bisphosphonates may cause upper gastrointestinal disorders such as dysphagia, esophagitis, esophageal ulcer and gastric ulcer. It is therefore important to follow the recommended dosing instructions. See 4.4 Administration.

Musculoskeletal pain, rarely severe, has been reported as a common adverse event in patients who received risedronate sodium tablets and risedronate sodium delayed release tablets for all indications and dosage forms.

In risedronate sodium delayed release tablets osteoporosis studies, the most commonly reported adverse reactions were abdominal pain, dyspepsia and nausea. In addition, diarrhea was the most commonly reported adverse reaction for the highest risedronate sodium tablets monthly dose.

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 Postmenopausal Osteoporosis: Risedronate sodium tablets 5 mg daily has been studied for up to 3 years in over 5000 women enrolled in Phase III clinical trials for treatment or prevention of postmenopausal osteoporosis. Most adverse events reported in these trials were either mild or moderate in severity, and did not lead to discontinuation from the study. The distribution of severe adverse events was similar across treatment groups. In addition, the overall incidence of adverse events (AEs) was found to be comparable amongst risedronate sodium tablets and placebo-treated patients.

Table 2 lists adverse events considered possibly or probably drug-related, reported in ≥ 1% of risedronate sodium tablets 5 mg daily-treated patients, in Phase III postmenopausal osteoporosis trials.

Discontinuation of therapy due to serious clinical adverse events occurred in 5.5% of risedronate sodium tablets 5 mg daily-treated patients and 6.0% of patients treated with placebo.

Table 2 Drug-Related* Adverse Events Reported in ≥ 1% of risedronate sodium tablets 5 mg Daily-Treated Patients in Combined Phase III Postmenopausal Osteoporosis Trials

	Risedronate sodium tablets 5 mg n = 1742 (%)	placebo n = 1744 (%)
Body as a Whole		
Abdominal Pain	4.1	3.3
Headache	2.5	2.3
Asthenia	1.0	0.7
Digestive System		
Dyspepsia	5.2	4.8
Nausea	4.8	5.0
Constipation	3.7	3.6
Diarrhea	2.9	2.5
Flatulence	2.1	1.8

	Risedronate sodium tablets 5 mg n = 1742 (%)	placebo n = 1744 (%)
Gastritis	1.1	0.9
Skin and Appendages		
Rash	1.4	0.9
Pruritus	1.0	0.5
* Considered to be possibly or probably causally related by clinical study Investigators		

Weekly Dosing: In the 1-year, double-blind, multicentre study comparing risedronate sodium tablets 35 mg Once-a-Week to risedronate sodium tablets 5 mg daily for the treatment of osteoporosis in postmenopausal women, the overall safety and tolerability profiles of the 2 oral dosing regimens were similar.

The proportion of patients who experienced an upper gastrointestinal adverse event and the pattern of those events were found to be similar between the risedronate sodium tablets 35 mg Once-a-Week and risedronate sodium tablets 5 mg daily-treated groups. In addition to the previously described adverse reactions reported in risedronate sodium tablets osteoporosis clinical trials, arthralgia (risedronate sodium tablets 35 mg, 2.1%; risedronate sodium tablets 5 mg, 1.3%) was reported in ≥ 1% of patients and in more risedronate sodium tablets 35 mg weekly treated patients than in risedronate sodium tablets 5 mg daily treated patients.

In the 1-year, double-blind, multicentre study comparing risedronate sodium tablets 35 mg Once-a-Week to placebo for the prevention of osteoporosis in postmenopausal women, the overall safety and tolerability profiles of the two groups were comparable with the exception of arthralgia.

Specifically, 1.5% of patients taking risedronate sodium tablets 35 mg Once-a-Week experienced arthralgia compared to 0.7% of placebo patients. The overall safety profile observed in this study showed no substantive difference from that observed in the risedronate sodium tablets 5 mg daily versus risedronate sodium tablets 35 mg Once-a-Week treatment study.

Risedronate sodium delayed release tablets - In a 2-year, double-blind, multicentre study comparing risedronate sodium delayed release tablets 35 mg weekly taken following breakfast to risedronate sodium tablets 5 mg daily for the treatment of osteoporosis in postmenopausal women, gastrointestinal adverse events were reported in 38.8% of patients taking risedronate sodium delayed release tablets 35 mg, compared to 34.9% of patients taking risedronate sodium tablets 5 mg. Abdominal pain, vomiting, and upper abdominal pain were reported more frequently by patients taking risedronate sodium delayed release tablets (6.2%, 4.9%, 3.6%) compared to patients taking risedronate sodium tablets 5 mg (3.3%, 3.3%, 2.6%). Other events reported more frequently by patients taking risedronate sodium delayed release tablets included diarrhea, constipation, nasopharyngitis, upper respiratory tract infection, and

pharyngitis.

Endoscopic Findings: Endoscopies were performed on 75 patients treated with 5 mg risedronate sodium tablets once daily and 75 patients treated with placebo who had moderate-to-severe gastrointestinal complaints.

Across treatment groups, the percentage of patients with normal esophageal, gastric and duodenal mucosa on endoscopy was similar (21% risedronate sodium tablets; 20% placebo). Positive findings on endoscopy were also generally comparable across treatment groups. There were a higher number of reports of mild duodenitis in the risedronate sodium tablets group; however, there were more duodenal ulcers in the placebo group. Clinically important findings (perforations, ulcers or bleeding) among this symptomatic population were similar between groups (39% risedronate sodium tablets; 51% placebo).

At the 1-year time point in studies, comparing risedronate sodium delayed release tablets 35 mg weekly to risedronate sodium tablets 5 mg daily in the treatment of postmenopausal osteoporosis, endoscopies performed during the studies revealed no dose dependent pattern in the number of patients with positive endoscopic findings or in the anatomical location of abnormalities detected. Endoscopies were conducted only on consenting patients experiencing moderate to severe gastrointestinal complaints.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse drug reactions were reported in ≤1% of patients who received risedronate sodium tablets for all indications:

- Eye Disorders: iritis (0.1 to 1.0%)
- Gastrointestinal Disorders: duodenitis (0.1 to 1.0%), glossitis (<0.1%)
- Investigations: abnormal liver function tests (<0.1%)

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

Clinical Trial Findings

Asymptomatic mild decreases in serum calcium and phosphorus levels have been observed in some patients. Asymptomatic elevations in PTH levels were observed in some patients receiving risedronate sodium delayed release tablets. See 10.2 Pharmacodynamics.

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

8.5 Post-Market Adverse Reactions

Hypersensitivity and Skin Reactions: angioedema, generalized rash and bullous skin reactions, some severe.

Musculoskeletal and Connective tissue: low-energy femoral shaft fractures, osteonecrosis of the jaw. See Musculoskeletal.

Ophthalmologic: conjunctivitis, episcleritis, iritis, scleritis and uveitis. See Ophthalmologic.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No specific drug-drug interaction studies were performed with risedronate sodium film-coated tablets. Animal studies have demonstrated that risedronate is highly concentrated in bone and is retained only minimally in soft tissue. No metabolites have been detected systemically or in bone. The binding of risedronate to plasma proteins in humans is low (24%), resulting in minimal potential for interference with the binding of other drugs. In an additional animal study, there was also no evidence of hepatic microsomal enzyme induction. In summary, risedronate sodium is not systemically metabolized, does not induce cytochrome P_{450} enzymes and has low protein binding.

Risedronate sodium is therefore not expected to interact with other drugs based on the effects of protein binding displacement, enzyme induction or metabolism of other drugs.

In vitro studies suggest that the amount of EDTA contained in the risedronate sodium delayed release tablets formulation (approximately 1.5 mM) will not significantly affect aqueous solubility of antivirals (nelfinavir, lamivudine, emtricitabin) and drugs with a narrow therapeutic index (digoxin, lithium carbonate, potassium chloride). Thus, co-administration with risedronate sodium delayed release tablets is not likely to alter their absorption.

9.3 Drug-Behavioural Interactions

No drug-behavioural interactions have been identified.

9.4 Drug-Drug Interactions

Patients in the clinical trials were exposed to a wide variety of commonly used concomitant medications (including NSAIDs, H_2-blockers, proton pump inhibitors, antacids, calcium channel blockers, beta-blockers, thiazides, glucocorticoids, anticoagulants, anticonvulsants, cardiac glycosides). While there was no apparent evidence of clinically relevant interactions in the clinical trials, such interactions cannot be ruled out on the basis on these data.

The drugs listed in Table 5 are based on either drug interaction case reports or predicted interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical Comment
Antacids and calcium supplements which contain polyvalent cations (e.g., calcium, magnesium, aluminum and iron)	CT/T	Interference with the absorption of risedronate sodium tablets and risedronate sodium delayed-release tablets. Co-administration of risedronate sodium delayed-release tablets with calcium supplement after breakfast reduced bioavailability of risedronate sodium by approximately 38%.	Such medications should be administered at a different time of the day from AA-RISEDRONATE DR (see 4.4 Administration).
Hormone replacement therapy (HRT)	CT	No clinically significant effect for risedronate sodium tablets	If considered appropriate, risedronate sodium tablets may be used concomitantly with HRT (see Combined Administration with Hormone Replacement Therapy). No data are available on the concomitant use of risedronate sodium delayed-release tablets and HRT
H_2-blockers and proton pump inhibitors (PPIs)	CT	Among H_2-blockers and PPIs users, the incidence of upper gastrointestinal adverse events was similar between the risedronate sodium tablets-treated patients and placebo-treated patients. Among H_2-blockers and PPIs users, the incidence of upper gastrointestinal adverse experiences was found to be similar between the weekly-	Of over 5700 patients enrolled in the risedronate sodium tablets 5 mg daily Phase III osteoporosis studies, 21% used H_2- blockers and/or PPIs. In the 1-year study comparing risedronate sodium tablets Once-a-Week and daily dosing regimens in postmenopausal women with osteoporosis, at

Proper/Common name	Source of Evidence	Effect	Clinical Comment
		and daily-treated groups. Concomitant administration of PPIs and risedronate sodium delayed-release tablets has been shown to affect the bioavailability of risedronate sodium delayed-release tablets (see 10.3 Pharmacokinetics). The effects of concomitant administration of H_2-blockers on bioavailability of risedronate sodium delayed-release tablets have not been evaluated.	least 9% of patients in the risedronate sodium tablets 35 mg Once-a-Week and 5 mg daily groups used H_2-blockers and/or PPIs. In the 2-year study comparing risedronate sodium delayed-release tablets and daily dosing regimens in postmenopausal women with osteoporosis, at least 8% and 14% of patients in the risedronate sodium delayed-release tablets and 5 mg daily groups used H_2- blockers and/or PPIs respectively. Concomitant administration of AA-RISEDRONATE DR and H_2 blockers or PPIs is not recommended.
Angiogenesis inhibitors	T	Osteonecrosis of the jaw (ONJ)	Concomitant administration of risedronate sodium and angiogenesis inhibitors may increase the risk of developing ONJ. Caution should be exercised. Patients taking angiogenesis inhibitors should have a dental examination prior to treatment with risedronate sodium tablets and AA-RISEDRONATE DR. (see Musculoskeletal).
Legend : CT: Clinical Trial; T: Theoretical			

In the Phase 3 study comparing risedronate sodium delayed release tablets 35 mg weekly immediately following breakfast and risedronate sodium tablets 5 mg daily, 22% of NSAID/ASA users in both groups developed upper gastrointestinal adverse reactions. Among non-users, 16% of patients taking risedronate sodium delayed release tablets 35 mg weekly immediately following breakfast developed upper gastrointestinal adverse reactions, compared to 13% taking risedronate sodium tablets 5 mg daily.

9.5 Drug-Food Interactions

AA-RISEDRONATE DR should be taken with food. When compared with risedronate sodium tablets 5 mg, treatment with risedronate sodium delayed release tablets resulted in a higher incidence of upper abdominal pain when administered before breakfast under fasting conditions. For dosing information see 4.4 Administration.

9.6 Drug-Herb Interactions

Interactions with herbs have not been studied.

9.7 Drug-Laboratory Test Interactions

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with risedronate sodium tablets and risedronate sodium delayed release tablets have not been performed.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Risedronate sodium, a pyridinyl-bisphosphonate in the form of hemi-pentahydrate with small amounts of monohydrate, inhibits osteoclast bone resorption and modulates bone metabolism. Risedronate has a high affinity for hydroxyapatite crystals in bone and is a potent antiresorptive agent. At the cellular level, risedronate inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (e.g., lack of ruffled border). Histomorphometry in rats, dogs, minipigs and humans showed that risedronate treatment reduces bone turnover (i.e., activation frequency, the rate at which bone remodelling sites are activated) and bone resorption at remodelling site.

10.2 Pharmacodynamics

Treatment of Osteoporosis in Postmenopausal Women: Osteoporosis is a degenerative and debilitating bone disease characterized by decreased bone mass and increased fracture risk at the spine, hip, and wrist. 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 men and women but is more common among women following menopause.

In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly-formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of bone fracture. After menopause, the risk of fractures of the spine and hip increases dramatically; approximately 40% of 50-year-old

women will experience an osteoporosis-related fracture of the spine, hip, or wrist during their remaining lifetimes. After experiencing one osteoporosis-related fracture, the risk of future fracture increases 5-fold compared to the risk among a non-fractured population. One in five men older than 50 years will have an osteoporotic fracture, most commonly at the spine, hip and wrist.

Risedronate sodium treatment decreases the elevated rate of bone turnover and corrects the imbalance of bone resorption relative to bone formation that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of risedronate sodium tablets to postmenopausal women resulted in dose-dependent decreases in biochemical markers of bone turnover, including urinary markers of bone resorption and serum markers of bone formation, at doses as low as 2.5 mg daily.

In a 2-year study for the treatment of osteoporosis in postmenopausal women comparing risedronate sodium delayed release tablets 35 mg weekly to risedronate sodium tablets 5 mg daily, similar mean percent changes from baseline to 2 years were found between the 2 oral dosing regimens in serum calcium and phosphate. The effect of risedronate sodium delayed release tablets 35 mg weekly and risedronate sodium tablets 5 mg daily on PTH was evaluated in postmenopausal women with osteoporosis. At 2 years, in subjects with normal levels at baseline, PTH levels greater than 65 ng/L (upper limit of normal) were noted in 12% of subjects receiving risedronate sodium delayed release tablets 35 mg weekly immediately following breakfast and 6% of subjects receiving risedronate sodium tablets 5 mg daily. In subjects with normal levels at baseline, PTH levels greater than 97 ng/L (1.5 times the upper limit of normal) at 2 years were seen in 3% of subjects receiving risedronate sodium delayed release tablets 35 mg weekly immediately following breakfast and 0 subjects receiving risedronate sodium tablets 5 mg daily. There were no clinically significant differences between treatment groups for levels of calcium, phosphorus and magnesium.

In the two year study of risedronate sodium delayed release tablets 35 mg weekly, it was shown that at 1 year and 2 years, risedronate sodium delayed release tablets 35 mg weekly was non-inferior to the risedronate sodium tablets 5 mg daily regimen for the primary efficacy variable of percent change from baseline of lumbar spine BMD. The two treatment groups were also similar with regard to percent change from baseline BMD at the total proximal femur, greater trochanter and femoral neck. Non-inferiority was observed with risedronate sodium delayed release tablets relative to risedronate sodium tablets 5 mg. At 2 years, the mean percent change from baseline in lumbar spine BMD was 4.1% for risedronate sodium 5 mg and 5.2% for the risedronate sodium delayed release tablets 35 mg (upper limit CI = -0.355%). See Treatment of Osteoporosis in Postmenopausal Women.

The AA-RISEDRONATE DR tablet has an enteric coating, which delays the release of risedronate until the small intestine. The other formulations of risedronate sodium tablets are film coated.

10.3 Pharmacokinetics

Table 4 - Summary of Pharmacokinetic Parameters of Risedronate

	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$,z (h)	$AUC_{0-\infty}$ (ng.h/mL)	Clearance (L/h/kg)	V_z (L/kg)
35 mg DR tablet; single dose	14.1	3.0[a]	nd	34.2[b]	nd	nd
[a] = geometric mean; $t_{1/2}$, z = the half-life of the terminal exponential phase; V_z = is the terminal volume of distribution uncorrected for bioavailability; nd = not determined; [b] = AUC_{tlast}						

Absorption

Risedronate sodium delayed-release tablets 35 mg achieved a peak serum concentration at approximately 3 hours. Urinary excretion data showed that the fraction of the dose absorbed from Risedronate sodium delayed-release tablets is independent of the dose over the range studied (single dose, from 20 mg to 100 mg).

In a crossover pharmacokinetic study that evaluated food effect, the bioavailability of risedronate sodium delayed-release tablets 35 mg decreased by ~30% when administered immediately after a high-fat breakfast compared to administration 4 hours before a meal. The bioavailability of the 35 mg risedronate sodium delayed release tablet administered after a high fat breakfast was ~2 to 4-fold greater than the 35 mg risedronate film-coated tablet administered 30 minutes prior to a high-fat breakfast. Across different studies, the bioavailability of risedronate sodium delayed-release tablets was not affected by breakfast meals with varying amount of fat and calories.

In a separate study, risedronate sodium delayed-release tablets administered after dinner exhibited approximately 87% increase in exposure compared to administration following a breakfast. The safety and efficacy of dosing risedronate sodium delayed-release tablets after dinner has not been evaluated see 4.4 Administration.

A post-approval cross-over pharmacokinetic study evaluated the impact of co-administered esomeprazole on the bioavailability of risedronate sodium delayed-release tablets. Esomeprazole was administered 1 hour prior to breakfast for 6 days prior to one dose of risedronate sodium delayed-release tablets administered after breakfast on day 6. The resulting median t_{max} values were shorter (3.5 vs 5.0 hours), and the C_{max} and AUC values of risedronate sodium delayed-release tablets increased 60% and 22%, respectively. A 47% increase in the amount of risedronate excreted was also observed.

Distribution

The mean steady-state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with

single doses of [^{14}C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was found to be minimal (in the range of 0.001% to 0.01%), with drug levels quickly decreasing after the final dose.

Metabolism

There is no evidence that risedronate is systemically metabolized.

Elimination

Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine over 28 days. The mean renal clearance is 105 mL/min (CV = 34%) and mean total clearance is 122 mL/min (CV = 19%), with the difference primarily reflecting non-renal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. Once risedronate is absorbed, the serum concentration-time profile is multi-phasic with an initial half- life of about 1.5 hours and a terminal exponential half-life of 480 hours. Although the elimination rate of bisphosphonates from human bone is unknown, the 480 hour half-life is hypothesized to represent the dissociation of risedronate from the surface of bone.

Special Populations and Conditions

- **Pediatrics:** Risedronate pharmacokinetics have not been studied in patients < 18 years of age.
- **Geriatrics:** Bioavailability and disposition are similar in elderly (> 65 years of age) and younger subjects. No dosage adjustment is necessary.
- **Sex:** Bioavailability and disposition following oral administration are similar in men and women.
- **Genetic Polymorphism:** No data are available.
- **Ethnic Origin:** Pharmacokinetic differences due to race have not been studied.
- **Hepatic Insufficiency:** No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in rat, dog, and human liver preparations. Insignificant amounts (< 0.1% of intravenous dose) of drug are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.
- **Renal Insufficiency:** Risedronate is excreted intact primarily via the kidney. Patients with mild-to-moderate renal impairment (creatinine clearance > 30 mL/min) do not require a dosage adjustment. Exposure to risedronate was estimated to increase by 44% in patients with creatinine clearance of 20 mL/min. AA-RISEDRONATE DR are not

recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min) because of a lack of clinical experience.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

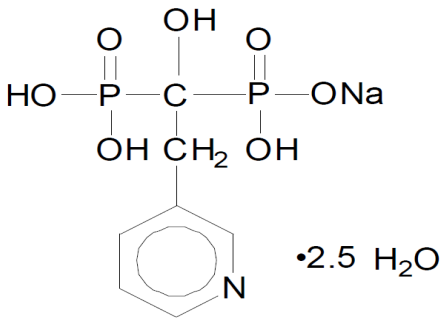
Drug Substance

Proper name: risedronate sodium hemi-pentahydrate

Chemical name: Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt.

Molecular formula and molecular mass: $C_7H_{10}NO_7P_2Na \cdot 2.5H_2O$
Anhydrous molecular weight: 305.10 g/mol
Hemi-pentahydrate molecular weight: 350.13 g/mol

Structural formula:



Physicochemical properties: Risedronate sodium is a fine white to off-white crystalline powder. Risedronate sodium is present in the form of hemi-pentahydrate with small amounts of monohydrate.

- Solubility: Risedronate sodium is soluble in pH 7.0 potassium phosphate dibasic solution, 0.1 N sodium hydroxide, and water; very slightly soluble in 0.1 N hydrochloric acid, practically insoluble in ethanol, and insoluble in isopropanol.
- Solution pH: The pH of a 1.0% aqueous solution of risedronate sodium is 4.15.
- Dissociation Constants: The five pK_a values for risedronate sodium are as follows: pK_1 = 1.6 ± 0.2, pK_2 = 2.2 ± 0.2, pK_3 = 5.9 ± 0.1, pK_4 = 7.1 ± 0.1 and pK_5 = 11.7 ± 0.3.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Osteoporosis in Postmenopausal Women

Table 5 Summary of Patient Demographics for Clinical Trials of risedronate sodium tablets or risedronate sodium delayed-release tablets in the Treatment of Osteoporosis in Postmenopausal Women

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Daily Supplement**
					Vitamin D
1 VERT-MN	R, PC, DB, MC, PG	2.5 mg/day – 2 years 5 mg/day – 3 years Placebo – 3 years Oral administration	1226	71.0 (48-85)	≤ 500 IU
2 VERT-NA	R, PC, DB, MC, PG	2.5 mg/day – 1 year 5 mg/day – 3 years Placebo – 3 years Oral administration	2458	68.6 (28-85)	≤ 500 IU
3	R, PC, DB, MC, PG	2.5 mg/day, 5 mg/day or Placebo Oral administration 2 years	543	64.7 (45-80)	-
4	R, PC, DB, MC, PG	2.5 mg/day, 5 mg/day or Placebo Oral administration 12-18 months	648	62.5 (39-80)	-
5	R, AC, DB, MC, PG	5 mg/day, 35 mg/week* or 50 mg/week* Oral administration 12 months	1456	67.9 (48-95)	≤ 500 IU
6	R, AC, DB, MC, PG	5 mg/day or 35 mg/week*†	922	65.7 (50-87)	800 – 1000 IU

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Daily Supplement**
					Vitamin D
		Oral administration 24 months			
7	R, AC, DB, MC, PG	5 mg/day or 150 mg once/month* Oral administration 12 months	1292	64.9 (50-88)	400-500 to 1000 IU

R=randomized; AC = active-controlled; PC=placebo-controlled; DB = double-blind; MC = multicentre; PG = parallel-group

* Placebo on other days of treatment; † 35 mg enteric-coated following breakfast and before breakfast;

** patients in these studies were supplemented with 1000 mg elemental calcium/day

In Studies 1 and 2, patients were selected on the basis of radiographic evidence of previous vertebral fracture, and had established disease. The average number of prevalent vertebral fractures per patient at study entry was 4 in Study 1, and 2.5 in Study 2, with a broad range of baseline BMD levels. All fractures (symptomatic/painful/clinical vertebral fractures and asymptomatic/nonpainful/silent vertebral fractures) were systematically captured and measured by annual radiographs.

In Studies 3 to 5 postmenopausal women were recruited on the basis of low lumbar spine bone mass (i.e., more than 2 SD below the premenopausal mean) rather than a history of vertebral fracture.

In Studies 5 to 7, patients had either lumbar spine bone mass more than 2.5 SD below the premenopausal mean, or lumbar spine bone mass more than 2.0 SD below, and a prevalent vertebral fracture.

Patients with active or a history of upper gastrointestinal disorders at baseline and those taking ASA, NSAIDs or drugs usually used for the treatment of peptic ulcers were not specifically excluded from participating in the risedronate sodium tablets daily, weekly or monthly or risedronate sodium delayed-release tablets weekly dosing osteoporosis studies.

Study Results

Results of Studies 1 and 2:

The pivotal studies of risedronate sodium in the treatment of postmenopausal osteoporosis clearly demonstrate that risedronate sodium tablets 5 mg daily reduces vertebral fracture incidence in patients with low bone mass and vertebral fractures, regardless of age, years since menopause or disease severity at baseline. Risedronate sodium tablets 5 mg daily significantly

reduced the risk of new vertebral fractures in each of the two large treatment studies. When measured by annual radiographs, the effect of risedronate sodium tablets 5 mg daily on vertebral fracture incidence was seen at the first year of treatment in each study. In the North American study, treatment with risedronate sodium tablets 5 mg daily for 1 year significantly reduced the risk of new vertebral fractures by 65% compared to treatment with placebo ($p < 0.001$). In the Multinational study, a similar significant reduction of 61% was seen ($p = 0.001$). Treatment with risedronate sodium tablets 5 mg daily also significantly reduced the proportion of patients experiencing new and worsening vertebral fractures in each of the studies. Figures 1 and Figure 2 below display the cumulative incidence of vertebral and nonvertebral fractures (i.e., hip, wrist, humerus, clavicle, pelvis and leg). In both figures, the cumulative incidence of these types of fractures is lower with risedronate sodium tablets compared with placebo at all time points, consistent with the positive effect of risedronate sodium tablets on bone strength.

Table 6 Effect of Risedronate Sodium Tablets on Fracture, Height and Bone Mineral Density in the Treatment of Osteoporosis in Postmenopausal Women

Endpoints		Risedronate sodium tablets 5 mg	Placebo	Mean Difference from Placebo	Relative Risk Reduction %	p-value
Study 1: VERT-MN						
Cumulative incidence of new vertebral fracture over 3 years (% of patients)		18.1	29.0		49	<0.001
Median annual height change[a] (mm/yr)		-1.33	-2.4			0.003
Mean increase in BMD (%)						
6 months	Lumbar Spine	3.3	-0.1	3.4		<0.001
36 months	Lumbar Spine	7.1	1.3	5.9		<0.001
	Femoral Neck	2.0	-1.0	3.1		<0.001
	Trochanter	5.1	-1.3	6.4		<0.001
36 months	Midshaft Radius	0.5	-1.9	2.4		<0.001
Study 2: VERT-NA						
Cumulative incidence of new vertebral Fracture over 3 years (% of patients)		11.3	16.3		41	0.003
Median annual height change[a] (mm/yr)		-0.67	-1.14			0.001
Mean increase in BMD (%)						
6 months	Lumbar Spine	2.7	0.4	2.2		<0.001
36 months	Lumbar Spine	5.4	1.1	4.3		<0.001
	Femoral Neck	1.6	-1.2	2.8		<0.001

Endpoints		Risedronate sodium tablets 5 mg	Placebo	Mean Difference from Placebo	Relative Risk Reduction %	p-value
36 months	Trochanter	3.3	-0.7	3.9		<0.001
	Midshaft Radius	0.2	-1.4	1.6		<0.001
Prospectively Combined Studies 1 and 2: VERT-MN and VERT-NA						
Cumulative incidence of non-vertebral fracture[b] over 3 years (% of patients)		7.1	11.0		36	0.005

[a] Measured by stadiometer

[b] Osteoporosis-related non-vertebral fractures (hip, wrist, humerus, clavicle, pelvis, and leg)

Figure 1 - Cumulative New Vertebral Fracture Incidence in Postmenopausal Women with Osteoporosis

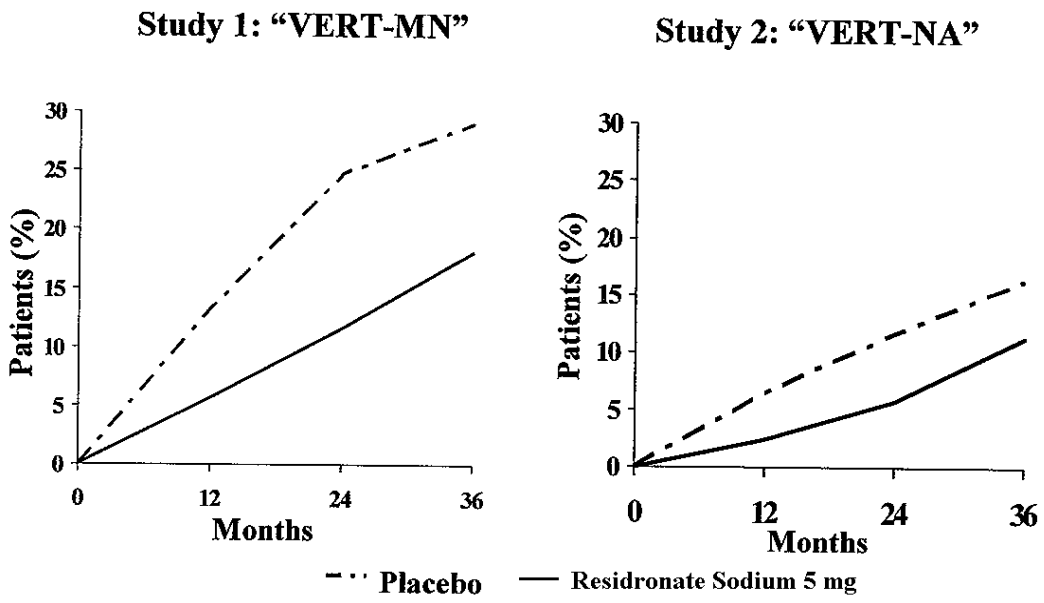
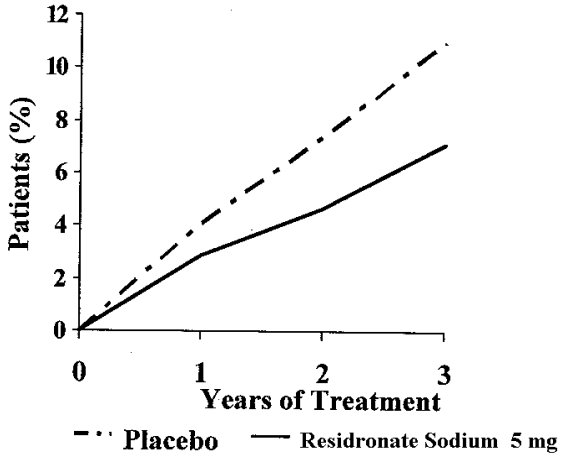


Figure 2 - Cumulative Incidence of Osteoporosis-Related Non-vertebral Fractures

Studies 1 and 2 Combined



Risedronate sodium tablets 5 mg daily was associated with a significant reduction of about 50% in the annual rate of height loss compared to treatment with placebo.

Risedronate sodium tablets 5 mg daily produced increases in lumbar spine BMD which were progressive over the 3 years of treatment, and were statistically significant relative to baseline and to placebo at 6 months and at all later time points (12, 18, 24 and 36 months).

Results of Studies 3 and 4:

Table 7 Effect of Risedronate Sodium Tablets on Bone Mineral Density in the Treatment of Osteoporosis in Postmenopausal Women

Endpoints		Risedronate sodium tablets 5 mg Daily Mean Increase in BMD %	Placebo Mean Increase in BMD %	Mean Difference from Placebo %
Study 3				
6 months	Lumbar Spine	3.3	0.4	2.8**
24 months	Lumbar Spine	4.1	0.0	4.1**
	Femoral Neck	1.3	-1.0	2.3*
	Trochanter	2.7	-0.6	3.3**
Study 4				
6 months	Lumbar Spine	3.3	0.7	2.6**
18 months	Lumbar Spine	5.2	0.3	5.0**

Endpoints	Risedronate sodium tablets 5 mg Daily Mean Increase in BMD %	Placebo Mean Increase in BMD %	Mean Difference from Placebo %
Femoral Neck	3.1	0.2	2.8**
Trochanter	4.8	1.4	3.3**
vs. placebo: *p<0.01; **p<0.001			

In Studies 3 and 4, risedronate sodium tablets 5 mg daily produced significant mean increases in BMD of the lumbar spine compared to placebo at 6 months in women with low bone mass. Compared to placebo after 1.5 to 2 years, further significant mean increases in BMD were seen at the lumbar spine, femoral neck and trochanter.

The results of four large, randomized, placebo-controlled trials (Studies 1 to 4) in women with postmenopausal osteoporosis separately and together demonstrate that risedronate sodium tablets 5 mg daily reverses the progression of disease, increasing BMD at the spine, hip and wrist compared to the effects seen with placebo.

Results of Study 5:

Table 8 Comparison of risedronate sodium tablets Once–a-Week vs. Daily Dosing in the Treatment of Osteoporosis in Postmenopausal Women – Primary Efficacy Analysis of Completers

Endpoints		Risedronate sodium tablets 5 mg Daily Mean Increase in BMD % (95% Confidence Interval)	Risedronate sodium tablets 35 mg Once-a-Week Mean Increase in BMD % (95% Confidence Interval)
		n = 391	n = 387
12 months	Lumbar Spine	4.0 (3.7, 4.3)	3.9 (3.6, 4.3)

The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. There were also no statistically significant differences between the two treatment groups at 1 year in regards to BMD increases from baseline at other skeletal sites (total proximal femur, femoral neck and femoral trochanter). Based on these BMD outcomes, risedronate sodium tablets 35 mg Once-a-Week was concluded to be non- inferior to risedronate sodium tablets 5 mg daily.

In trials with risedronate sodium tablets 5 mg daily, changes in BMD of this magnitude were associated with a significant decrease in fracture incidence relative to placebo (see Table 8). This is further supported by the fact that within the 1-year study comparing risedronate sodium tablets 35 mg Once-a-Week to risedronate sodium tablets 5 mg daily, no statistically significant differences amongst these treatment groups were seen with respect to the number of patients with at least 1 new fractured vertebra at 1 year. Risedronate sodium tablets 35 mg taken once a week is similar in safety and efficacy to risedronate sodium tablets 5 mg daily for the treatment of postmenopausal osteoporosis.

Results of Study 6:

Table 9 Comparison of risedronate sodium delayed-release tablets Weekly vs. risedronate sodium tablets Daily Dosing in the Treatment of Osteoporosis in Postmenopausal Women – Primary Efficacy Analysis

Endpoints	Risedronate sodium tablets 5 mg Daily Mean Increase in BMD % (95% Confidence Interval)	Risedronate sodium delayed-release tablets 35 mg Weekly following breakfast Mean increase in BMD % (95% Confidence Interval)
	n=307	n=307
12 months* Lumbar Spine	3.1** (2.7, 3.5)	3.3** (2.9, 3.7)
24 months† Lumbar Spine	4.1** (3.7, 4.6)	5.2** (4.7, 5.7)
*Last available observation on or prior to month 12, †Last available observation on or prior to month 24 ** Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons.		

In a 2-year, double-blind, multicentre study of postmenopausal women with osteoporosis, risedronate sodium delayed-release tablets 35 mg weekly was statistically shown to be non-inferior to risedronate sodium tablets 5 mg administered daily. At all time points, increases in BMD were statistically significant ($p<0.05$) compared to baseline for all sites measured.

At 1 year, risedronate sodium delayed-release tablets 35 mg weekly was shown to be non-inferior to the risedronate sodium tablets 5 mg daily regimen for the primary efficacy variable of percent change from baseline of lumbar spine BMD. The two treatment groups were also similar with regard to percent change from baseline BMD at the total proximal femur, greater trochanter and femoral neck.

At 2 years, there were statistically significant greater increases ($p<0.05$; unadjusted for multiple comparisons) in mean percent change from baseline BMD at the total proximal femur for risedronate sodium delayed-release tablets 35 mg weekly following breakfast (2.8) compared to risedronate sodium tablets 5 mg daily (2.2). This statistically significant difference at 2 years was also observed at the lumbar spine (see Table 9). The treatment groups were similar with regard to percent change from baseline BMD at the femoral neck.

At 2 years, a statistically significant greater ($p<0.05$) percentage of patients in the risedronate sodium delayed-release tablets 35 mg weekly group (89%) were considered responders (i.e., change from baseline in lumbar spine >0%) compared to the risedronate sodium tablets 5 mg group (82%).

Results of Study 7:

Table 10 Comparison of Risedronate sodium tablets Once-a-Month vs. Daily Dosing in the Treatment of Osteoporosis in Postmenopausal Women – Primary Efficacy Analysis

Endpoints	Risedronate sodium tablets 5 mg Daily Mean Increase in BMD % (95% Confidence Interval)	Risedronate sodium tablets 150 mg Once-a-Month Mean Increase in BMD % (95% Confidence Interval)
	n = 561	n = 578
12 months (using LOCF*) Lumbar Spine	3.4 (3.0, 3.8)	3.5 (3.1, 3.9)
* LOCF: last observation carried forward		

In the first year of a 2-year, double-blind, multicentre study of postmenopausal women with osteoporosis, risedronate sodium tablets 150 mg Once-a-Month was shown to be non-inferior to risedronate sodium tablets 5 mg daily. risedronate sodium tablets 150 mg Once-a-Month was statistically shown to be non-inferior to the risedronate sodium tablets 5 mg daily regimen for the primary efficacy variable of percent change from baseline to 1 year in increasing lumbar spine BMD. The two treatment groups were similar with regard to BMD increases at the lumbar spine, total proximal femur, femoral neck and femoral trochanter. The incidence of vertebral and non-vertebral fractures, reported as adverse events, was similar in the two treatment groups. risedronate sodium tablets 150 mg Once-a-Month is similar in safety and efficacy to risedronate sodium tablets 5 mg daily for the treatment of postmenopausal osteoporosis. The safety and efficacy of risedronate sodium tablets 150 mg Once-a-Month is currently being assessed beyond one year of treatment.

Histology/Histomorphometry: Histomorphometric evaluation of 278 bone biopsy samples from 204 postmenopausal women who received risedronate sodium tablets 5 mg or placebo

once daily for 2 to 3 years (including 74 pairs of biopsies, 43 from risedronate sodium tablets-treated patients) showed a moderate and expected decrease in bone turnover in risedronate sodium tablets-treated women.

Histologic assessment showed no osteomalacia, impaired bone mineralization, or other adverse effects on bone in risedronate sodium tablets-treated women. These findings demonstrate that the bone formed during risedronate sodium tablets administration is of normal quality.

Results of Study 8:

Combined Administration with Hormone Replacement Therapy

Table 11 Summary of Patient Demographics for Clinical Trials of risedronate sodium in Combined Administration with Hormone Replacement Therapy

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender
10	R, PC, DB, MC, PG stratified	5 mg/day and oral conjugated estrogen 0.625 mg/day Placebo and conjugated estrogen 0.625 mg/day Oral administration 1 year	524	58.9 (37-82)	Postmenopausal female
R: randomized; PC: placebo-controlled; DB: double-blind; MC: multicentre; PG: parallel-group					

For inclusion in Study 9 women had a mean lumbar spine BMD 1.3 SD below the pre-menopausal mean and had recently initiated conjugated estrogen treatment (i.e., not taken estrogen for more than 1 month in the past year).

Results of Study 9:

Table 12 Effect of risedronate sodium tablets on Bone Mineral Density in Combination Therapy with Conjugated Estrogen

Endpoints		Risedronate sodium tablets 5 mg Daily and Conjugated Estrogen Mean increase in BMD (%)	Conjugated Estrogen Mean increase in BMD (%)
12 months	Lumbar Spine	5.2	4.6
	Femoral Neck	2.7*	1.8
	Trochanter	3.7	3.2
	Midshaft Radius	0.7*	0.4
All values represent significant ($p \leq 0.05$) change vs. baseline. vs. conjugated estrogen alone: *$p \leq 0.05$			

Consistent with the changes in BMD, the reduction in bone turnover, as measured by urinary deoxypyridinoline/creatinine, was significantly greater in the combined risedronate sodium tablets 5 mg daily plus estrogen group compared to the estrogen alone group (45-50% vs. 40%) and remained within the premenopausal range.

Histomorphometric evaluation of 93 bone biopsy samples from 61 women on estrogen therapy who received either placebo or risedronate sodium tablets 5 mg daily for 1 year (including 32 pairs of biopsies, 16 from risedronate sodium tablets-treated patients) found decreases in bone turnover in the risedronate sodium tablets-treated patients that were consistent with the changes in BTMs. Bone histology demonstrated that the bone of patients treated with risedronate sodium tablets plus estrogen was of normal lamellar structure and normal mineralization.

14.2 Comparative Bioavailability Studies

A randomized, single-dose, blinded, 3-way, reference replicated crossover comparative bioavailability study of AA-RISEDRONATE DR 35 mg tablets (AA Pharma Inc.) and ACTONEL DR® 35 mg tablets (Warner Chilcott Canada Co.,) was conducted in healthy adult male subjects under fed conditions. The results obtained from 72 subjects that were included in the statistical analysis are presented in the following table.

Summary Table of the Comparative Bioavailability Data

Risedronate (1 x 35 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (pg•h/mL)	29229.5 44817.6 (96.0)	31060.3 44991.3 (82.4)	94.1	76.7 - 115.4
AUC_I (pg•h/mL)	32150.3 48165.2 (95.1)	36490.3 50788.1 (78.3)	88.1	72.3- 107.4
C_{max} (pg/mL)	9879.1 15971.4 (101.1)	9963.9 15546.0 (90.0)	99.1	79.4- 123.8
T_{max}[3] (h)	6.0 (2.0 – 24.0)	7.5 (2.0 – 24.0)		
$T_{1/2}$[4] (h)	32.51 (44.2)	37.00 (58.5)		

[1] AA-RISEDRONATE DR (risedronate as risedronate sodium) delayed-release tablet, 35 mg (AA Pharma Inc.)

[2] ACTONEL DR® (risedronate as risedronate sodium) delayed-release tablet, 35 mg (Warner Chilcott Canada Co.,)

[3] Expressed as the median (range)

[4] Expressed as arithmetic means (CV%) only

Bioequivalence acceptance limits were scaled to the within-subject reference variability for AUC_{0-72}

15 MICROBIOLOGY

No microbial information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

***Acute Toxicity*:** Lethality after single oral doses was seen in female rats at 903 mg/kg (5826 mg/m^2) and male rats at 1703 mg/kg (10967 mg/m^2). The minimum lethal dose in mice, rabbits, and dogs was 4000 mg/kg (10909 mg/m^2), 1000 mg/kg (10870 mg/m^2), and 128 mg/kg (2560 mg/m^2), respectively. These values represent 140 to 620 times the human 30 mg dose based on

surface area, mg/m^2.

***Chronic Toxicity*:** In a 1-year daily repeat dose toxicity study in dogs, the limiting toxicity of risedronate was observed at 8 mg/kg/day (160 mg/m^2) and consisted of liver, testicular, renal, and gastrointestinal changes. Gastrointestinal effects at 16 mg/kg (111 mg/m^2) were the first limiting toxicity in rats in a 26-week study. These doses are equivalent to approximately 6.25 to 9 times the human 30 mg dose based on surface area, mg/m^2. In 6 month and 1-year monthly repeat dose toxicity studies in dogs, the limiting systemic toxicity of risedronate was observed at 32 mg/kg (640 mg/m^2) and consisted of liver, testicular, and renal toxicities. Gastric lesions were observed at 16 mg/kg (320 mg/m^2). These doses are equivalent to approximately 3.5 and 7 times the human 150 mg dose based on surface area, mg/m^2.

A 13-week oral dog study was performed to evaluate the gastric and lower gastrointestinal toxicity and toxicokinetics of risedronate (8 and 16 mg/kg) when dosed with or without EDTA (2.5 and 12.5 mg/kg) following 14 once-weekly oral doses. No additional GI toxicity was observed with the addition of either dose of EDTA to either dose of risedronate. No new organs of toxicity were identified when dogs were treated with risedronate in combination with EDTA (*vs* risedronate alone). Treatment with EDTA alone was not associated with any treatment- related changes.

Co-administration of EDTA with 8 and/or 16 mg/kg risedronate was associated with potentiation of risedronate-mediated histologic alterations in the liver, kidneys, and testes (incidence and/or severity). Potentiation of toxicity was more evident at 12.5 mg/kg EDTA when compared with 2.5 mg/kg EDTA. With respect to expected pharmacological effects (e.g. increased bone), 12.5 mg/kg EDTA potentiated the severity of rib hypertrophy and the incidence of increased bone in nasal turbinates when administered in combination with 8 and 16 mg/kg risedronate (*vs* risedronate alone). These findings may be related to the observed increase in exposure noted when risedronate was administered in combination with EDTA.

Carcinogenicity: Three carcinogenicity studies in two species (mouse and rat) have been completed. All studies clearly showed dose-dependent bone pharmacologic effects. Risedronate was not carcinogenic in male or female rats dosed daily by gavage for 104 weeks at doses up to 24 mg/kg/day (12 times the human 30 mg dose based on surface area, mg/m^2). Similarly, there was no evidence of a carcinogenic potential in male or female mice dosed daily by gavage for 80 weeks at doses up to 32 mg/kg/day (5 times the human 30 mg dose based on surface area, mg/m^2).

Genotoxicity: In a series of seven *in vitro* and *in vivo* mutagenicity assays, risedronate was not genotoxic. An *in vitro* chromosomal aberration assay in Chinese hamster ovary cells was weakly positive at highly cytotoxic doses (> 675 mcg/mL). However, when the assay was repeated at doses exhibiting increased cell survival (300 mcg/mL), risedronate was negative.

Reproductive and Developmental Toxicology: In female rats, ovulation was inhibited at an

oral dose of 16 mg/kg/day (approximately 5.2 times the 30 mg/day human dose based on surface area, mg/m^2). Decreased implantation was noted in female rats treated with doses ≥ 7 mg/kg/day (approximately 2.3 times the 30 mg/day human dose based on surface area, mg/m^2). In male rats, testicular and epididymal atrophy and inflammation were noted at 40 mg/kg/day (approximately 13 times the 30 mg/day human dose based on surface area, mg/m^2). Testicular atrophy was also noted in male rats after 13 weeks of treatment at oral doses of 16 mg/kg/day (approximately 5.2 times the 30 mg/day human dose based on surface area, mg/m^2). There was moderate-to-severe spermatid maturation block after 13 weeks in male dogs at an oral dose of 8 mg/kg/day (approximately 8 times the 30 mg/day human dose based on surface area, mg/m^2). These findings tended to increase in severity with increased dose and exposure time.

Survival of neonates was decreased in rats treated during gestation with oral doses ≥ 16 mg/kg/day (approximately 5.2 times the 30 mg/day human dose based on surface area, mg/m^2). Body weight was decreased in neonates from dams treated with 80 mg/kg (approximately 26 times the 30 mg/day human dose based on surface area, mg/m^2). In rats treated during gestation, the number of fetuses exhibiting incomplete ossification of sternebrae or skull was statistically significantly increased at 7.1 mg/kg/day (approximately 2.3 times the 30 mg/day human dose based on surface area, mg/m^2). Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses ≥ 16 mg/kg/day (approximately 5.2 times the 30 mg/day human dose based on surface area, mg/m^2). A low incidence of cleft palate was observed in fetuses from female rats treated with oral doses ≥ 3.2 mg/kg/day (approximately 1 time the 30 mg/day human dose based on surface area, mg/m^2). The relevance of this finding to human use of risedronate sodium is unclear. No significant fetal ossification effects were seen in rabbits treated with oral doses up to 10 mg/kg/day during gestation (approximately 6.7 times the 30 mg/day human dose based on surface area, mg/m^2). However, in rabbits treated with 10 mg/kg/day, 1 of 14 litters were aborted and 1 of 14 litters were delivered prematurely.

Similar to other bisphosphonates, treatment during mating and gestation with doses as low as 3.2 mg/kg/day (approximately 1 time the 30 mg/day human dose based on surface area, mg/m^2) has resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over periods of weeks to years. The amount of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been studied.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Actonel DR®**,** Delayed-Release Tablets 35 mg**,** submission control: 267898, Product Monograph, AbbVie Corporation. (NOV 03, 2022)**.**

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]AA-RISEDRONATE DR

Risedronate Sodium Delayed-Release Tablets

Read this carefully before you start taking **AA-RISEDRONATE DR** 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 **AA-RISEDRONATE DR**.

What is AA-RISEDRONATE DR used for?

- AA-RISEDRONATE DR is used to treat osteoporosis in postmenopausal women.

How does AA-RISEDRONATE DR work?

AA-RISEDRONATE DR contains the medicinal ingredient risedronate sodium. Risedronate sodium belongs to a class of non-hormonal drugs called bisphosphonates. Bisphosphonates are similar to a molecule naturally made in your body that breaks down bone tissue. AA-RISEDRONATE DR binds to the receptors in your body to prevent the bone from breaking down. This slows down bone loss which can help to reduce the risk of fractures. In many people AA-RISEDRONATE DR helps to increase bone density.

What are the ingredients in AA-RISEDRONATE DR?

Medicinal ingredients: Risedronate sodium hemi-pentahydrate

Non-medicinal ingredients: colloidal silicon dioxide, disodium edetate, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polysorbate 80, sodium starch glycolate, stearic acid, talc, triethyl citrate, yellow ferric oxide

AA-RISEDRONATE DR comes in the following dosage form:

Enteric-coated tablets: 35 mg (yellow).

The AA-RISEDRONATE DR tablet has an enteric coating which delays the release of risedronate until it reaches the small intestine.

Do not use AA-RISEDRONATE DR if:

- you have low levels of calcium in your blood (hypocalcemia)

- you are allergic to risedronate sodium or any of the other ingredients in AA-RISEDRONATE DR (see **What are the ingredients in AA-RISEDRONATE DR?**)

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

- have or have had problems swallowing or have/had problems with your esophagus (the tube that connects your mouth to your stomach)
- have or have had stomach or digestive problems
- have or have had kidney problems
- cannot stand or sit upright for at least 30 minutes (see **How to take AA-RISEDRONATE DR**)
- are pregnant or breastfeeding
- have one of the following risk factors for developing osteonecrosis (bone damage in the jaw):
  - have cancer and/or are currently receiving chemotherapy
  - are currently having or have had radiotherapy of the head or neck
  - have an infection or a lowered immune system (immunosuppression)
  - are taking corticosteroids (used to treat inflammation) or cancer drugs such as angiogenesis inhibitors (used to slow down the growth of new blood vessels)
  - have diabetes (high blood sugar)
  - have poor oral hygiene or dentures that do not fit well
  - have or have had pain, swelling or numbness of the jaw or loosening of a tooth
  - have sores in your mouth. Your healthcare professional may tell you not to take AA-RISEDRONATE DR until all the sores in your mouth have healed.
  - are or have been a smoker
  - have or have had poor dental health, teeth or gum disease
  - have anemia (low red blood cell count)
  - have a blood disorder where your blood cannot form clots in the normal way

Other warnings you should know about:

Gastrointestinal Problems: Taking AA-RISEDRONATE DR incorrectly may cause you to experience problems with your esophagus. Stop taking AA-RISEDRONATE DR and talk 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 to allow the drug to reach the stomach, consider the following instructions:

- swallow each tablet of AA-RISEDRONATE DR with a full glass of water.
- do NOT chew or suck the tablet.
- do NOT lie down for at least 30 minutes after taking AA-RISEDRONATE DR.
- do NOT take AA-RISEDRONATE DR at bedtime or before starting your day.

Eye Problems: Drugs like AA-RISEDRONATE DR 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 see symptoms of inflammation.

Oral Health: Your healthcare professional should check your mouth and may ask you to see your dentist before you start taking AA-RISEDRONATE DR. Dental work should be done before you start treatment with AA-RISEDRONATE DR. Tell your healthcare professional if you recently had any major dental procedures like an extraction or a root canal. Take good care of your teeth and gums and see the dentist for regular checkups while taking AA-RISEDRONATE DR.

Calcium and Vitamin D: Calcium and vitamin D are also important for strong bones. Your healthcare professional may ask you to take calcium and vitamin D while you are on AA-RISEDRONATE DR.

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 AA-RISEDRONATE DR:

- Vitamins, mineral supplements and antacids may contain substances that can stop your body from absorbing AA-RISEDRONATE DR. They include calcium, magnesium, aluminum and iron. Take these medicines at a different time of day than AA-RISEDRONATE DR. Talk to your health care professional about how and when to take these medications.
- Taking AA-RISEDRONATE DR with corticosteroids or cancer drugs like angiogenesis inhibitors may increase your chance of jaw bone problems (osteonecrosis of the jaw).
- Talk to your healthcare professional before taking pain medication like ASA or other non-steroidal anti-inflammatory drugs (NSAIDs) because they may upset your stomach.

How to take AA-RISEDRONATE DR:

- Take AA-RISEDRONATE DR exactly as your healthcare professional tells you to.
- On the same day each week, take AA-RISEDRONATE DR in the morning with breakfast (including high fat foods, coffee, tea, milk, orange juice etc.). Do not take AA-RISEDRONATE DR before food or on an empty stomach as it may cause abdominal pain.
- Swallow each AA-RISEDRONATE DR tablet whole, while you are sitting or standing in an upright position. Do not chew, cut or crush the tablets or break the outer coating. Drink enough plain water (at least 120 mL or ½ cup) to make sure the tablet gets to your stomach.
- Do not lie down for at least 30 minutes after taking AA-RISEDRONATE DR.

Usual dose:

- 1 AA-RISEDRONATE DR 35 mg tablet per week

Overdose:

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

Missed Dose:

If you forget to take your AA-RISEDRONATE DR on your usual day take it in the morning after you remember. You can go back to your regular schedule for the next dose. If you have missed your dose by 1 week do not take two tablets on the same day. Skip your missed dose and go back to your regular schedule.

What are possible side effects from using AA-RISEDRONATE DR?

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

Side effects may include:

- abdominal pain, heartburn, nausea, vomiting
- diarrhea, constipation
- stuffy nose, sore throat

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**	
COMMON			
Pain in bones, joints or muscles	√		
Esophagus and stomach problems: abdominal pain, pain or trouble swallowing, vomiting blood, heartburn, chest/breastbone pain, black or bloody stool			√
UNCOMMON			

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**	
Eye problems: eye pain, redness or swelling, sensitivity to light, decreased vision			√
RARE			
Pain in your tongue		√	
Jaw bone problems (osteonecrosis): numbness or a feeling of heaviness in the jaw; poor healing of gums; loose teeth; exposed bone in the mouth; sores in the mouth; discharge; dry mouth; swelling gums; infections; bad breath; pain in the mouth, teeth or jaw		√	
VERY RARE			
Allergic reactions: hives, rash (with or without blisters); swelling of the face, lips, tongue or throat; difficult or painful swallowing; trouble breathing			√
Hypocalcemia (low levels of calcium in the blood): numbness, tingling or muscle spasms		√	
Atypical femur fracture: new or unusual pain in the hip, groin or thigh		√	

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 to 30°C).

Keep out of reach and sight of children.

If you want more information about AA-RISEDRONATE DR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc., 1165 Creditstone Road Unit #1, Vaughan, Ontario, L4K 4N7.

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