PRODUCT MONOGRAPH

PR APO-RISEDRONATE

Risedronate Sodium (as the hemi-pentahydrate)

Tablets USP, 150 mg

Bone Metabolism Regulator

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Control No.: 127259

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PR **APO-RISEDRONATE**
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 150 mg	anhydrous lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

APO-RISEDRONATE (risedronate sodium hemi-pentahydrate) is indicated for:
- the treatment of osteoporosis in postmenopausal women

Postmenopausal Osteoporosis: In the treatment of osteoporosis in postmenopausal women at risk of fracture, APO-RISEDRONATE prevents vertebral and nonvertebral osteoporosis-related (fragility) fractures and increases 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 (for example, at least 2 standard deviation [SD] below the premenopausal mean).

APO-RISEDRONATE 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 fracture.

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.

The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.

Geriatrics: In risedronate sodium tablets osteoporosis studies, 26-46% of patients were between 65 and 75 years of age and 10-23% 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 CLINICAL TRIALS section).

Pediatrics: Safety and efficacy in children and growing adolescents have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

- Hypocalcemia (see WARNINGS AND PRECAUTIONS, General).

WARNINGS AND PRECAUTIONS

General

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting APO-RISEDRONATE (risedronate sodium) therapy.

Adequate intake of calcium and vitamin D is important in all patients, especially in patients with Paget's disease in whom bone turnover is significantly elevated (see DRUG INTERACTIONS). Detailed dosing instructions (see DOSAGE AND ADMINISTRATION) is provided to ensure correct dosing of APO-RISEDRONATE therapy.

Osteonecrosis of the Jaw: In post-marketing reporting, osteonecrosis of the jaw has been reported in patients treated with bisphosphonates. The majority of reports occurred following dental procedures such as tooth extractions and have involved cancer patients treated with intravenous bisphosphonates, but some occurred in patients receiving oral treatment for postmenopausal osteoporosis and other diagnoses. Many had signs of local infection, including osteomyelitis. Osteonecrosis has other well documented multiple risk factors. It is not possible to determine if these events are related to bisphosphonates, to concomitant drugs or other therapies, to the patient’s underlying disease or to other co-morbid risk factors (e.g. anemia, infection, pre-existing oral disease). A dental examination with appropriate preventative dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, immune suppression, head and neck radiotherapy or poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. 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 osteonecrosis of the jaw. Clinical judgment, based on individual risk assessment, should guide the management of patients undergoing dental procedures.

Atypical Subtrochanteric and Diaphyseal Femoral Features:
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: In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates (see ADVERSE REACTIONS). 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.

Gastrointestinal

Bisphosphonates may cause upper gastrointestinal (GI) disorders such as dysphagia, esophagitis, esophageal ulcer, and gastric ulcer (see ADVERSE REACTIONS). 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 Risedronate Sodium Tablets USP 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).

Ophthalmologic:

Ocular disturbances including conjunctivitis, uveitis, episcleritis, iritis, and scleritis have been reported with Risedronate Sodium Tablets USP 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).

Special Populations

Pediatrics: The safety and efficacy of Risedronate Sodium Tablets USP in children and growing adolescents have not been established.

Pregnant Women: Risedronate Sodium Tablets USP are not intended for use during pregnancy. There are no studies of Risedronate Sodium Tablets USP in pregnant women.

Nursing Women: Risedronate Sodium Tablets USP are 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.

ADVERSE REACTIONS

Adverse Drug 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 DOSAGE AND ADMINISTRATION).

Musculoskeletal pain, rarely severe, has been reported as a common adverse event in patients who received Risedronate Sodium Tablets USP.

In Risedronate Sodium Tablets USP osteoporosis studies, the most commonly reported adverse reactions were abdominal pain, dyspepsia and nausea. In addition, diarrhea was the most commonly reported adverse reactions for the highest Risedronate Sodium Tablets USP monthly dose.

Clinical Trial Adverse Drug Reactions

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

Treatment and Prevention of Postmenopausal Osteoporosis: Risedronate Sodium Tablets USP 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 event (AEs) was found to be comparable amongst Risedronate Sodium Tablets USP and placebo-treated patients.

Table 1 lists adverse events considered possibly or probably drug related, reported in ≥ 1% of Risedronate Sodium Tablets USP 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 USP 5 mg daily-treated patients and 6.0% of patients treated with placebo.

Table 1 Drug-Related* Adverse Events Reported in ≥ 1% of Risedronate Sodium Tablets USP 5 mg Daily-Treated Patients in Combined Phase III Postmenopausal Osteoporosis Trials		
Adverse Event	Risedronate Sodium Tablets USP 5 mg N = 1742 (%)	Placebo Control 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
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.		

Once-a-Week Dosing: In the 1-year, double-blind, multicentre study comparing Risedronate Sodium Tablets USP 35 mg Once-a-Week to Risedronate Sodium Tablets USP 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 USP 35 mg Once-a-Week and Risedronate Sodium Tablets USP 5 mg daily-treated groups. In addition to the previously described adverse reactions reported in Risedronate Sodium Tablets USP osteoporosis clinical trials, arthralgia (Risedronate Sodium Tablets USP 35 mg, 2.1%; Risedronate Sodium Tablets USP 5 mg, 1.3%) was reported in ≥ 1% of patients and in more Risedronate Sodium Tablets USP 35 mg weekly treated patients than Risedronate Sodium Tablets USP 5 mg daily treated patients.

In the 1-year, double-blind, multicentre study comparing Risedronate Sodium Tablets USP 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 USP 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 USP 5 mg daily versus Risedronate Sodium Tablets USP 35 mg Once-a-Week treatment study.

Monthly Dosing: (Two Consecutive Days per Month) – In a 1-year, double-blind, multicentre study for the treatment of osteoporosis in postmenopausal women comparing Risedronate Sodium Tablets USP 75 mg on two consecutive days per month to Risedronate Sodium Tablets USP 5 mg daily, the overall safety profiles of the 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 USP 75 mg two consecutive days per month and the Risedronate Sodium Tablets USP 5 mg daily treated groups. In addition to the previously described adverse reactions, arthralgia (Risedronate Sodium Tablets USP 75 mg, 1.5%; Risedronate Sodium Tablets USP 5 mg, 1.0%), vomiting (Risedronate Sodium Tablets USP 75 mg, 1.1%; Risedronate Sodium Tablets USP 5 mg, 1.0%) and gastritis erosive (Risedronate Sodium Tablets USP 75 mg, 1.0%; Risedronate Sodium Tablets USP 5 mg, 0.3%) was reported in ≥ 1% of patients and in more Risedronate Sodium Tablets USP 75 mg treated patients than in Risedronate Sodium Tablets USP 5 mg daily treated patients.

Symptoms consistent with acute phase reactions have been reported. Based on reporting of any 33 acute phase reaction-like symptoms (without regard to causality) within the first 5 days of first dose, the overall incidence of acute phase reaction was 7.6% of patients on Risedronate Sodium Tablets USP 75 mg two consecutive days per month and 3.6% of patients on Risedronate Sodium Tablets USP 5 mg daily. Fever or influenza-like illness (without regard to causality) occurring within the first 5 days of first dose were reported by 0.6% of patients in the Risedronate Sodium Tablets USP 75 mg two consecutive days per month and 0.0% in the Risedronate Sodium Tablets USP 5 mg daily groups.

(Once-a-Month) - In a 1-year, double-blind, multicentre study for the treatment of osteoporosis in postmenopausal women comparing Risedronate Sodium Tablets USP 150 mg Once-a-Month to Risedronate Sodium Tablets USP 5 mg daily, the overall safety profiles of the 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 USP 150 mg Once-a-Month and the Risedronate Sodium Tablets USP 5 mg daily treated groups. In addition to the previously described adverse reactions diarrhea (Risedronate Sodium Tablets USP 150 mg, 3.1%; Risedronate Sodium Tablets USP 5 mg, 0.5%), vomiting (Risedronate Sodium Tablets USP 150 mg, 1.5%; Risedronate Sodium Tablets USP 5 mg, 0.6%), arthralgia (Risedronate Sodium Tablets USP 150 mg, 1.5%; Risedronate Sodium Tablets USP 5 mg, 0.9%) and myalgia (Risedronate Sodium Tablets USP 150 mg, 1.1%; Risedronate Sodium Tablets USP 5 mg, 0.3%) were reported in ≥1% of patients and in more Risedronate Sodium Tablets USP 150 mg treated patients than Risedronate Sodium Tablets USP 5 mg daily.

Symptoms consistent with acute phase reactions have been reported. Based on reporting of any 33 acute phase reaction-like symptoms (without regard to causality) within the first 3 days of first dose and lasting less than 7 days, the overall incidence of acute phase reaction was 5.2 % of patients in the Risedronate Sodium Tablets USP 150 mg once-a-month group and 1.1% in the Risedronate Sodium Tablets USP 5 mg daily group. Fever or influenza-like illness (without regard to causality) occurring within the first 3 days of first dose and lasting less than 7 days was reported by 1.4% of patients in the Risedronate Sodium Tablets USP 150 mg Once-a-Month group and 0.2% of patients in the Risedronate Sodium Tablets USP 5 mg daily group.

Endoscopic Findings: Risedronate Sodium Tablets USP 5 mg daily clinical studies enrolled over 5700 patients for the treatment and prevention of postmenopausal and glucocorticoid-induced osteoporosis, many with pre-existing gastrointestinal disease and concomitant use of NSAIDs or ASA. Investigators were encouraged to perform endoscopies in any patients with moderate-to-severe gastrointestinal complaints while maintaining the blind. These endoscopies were ultimately performed on equal numbers of patients between the treated and placebo groups (75 Risedronate Sodium Tablets USP; 75 placebo).

Across treatment groups, the percentage of patients with normal esophageal, gastric, and duodenal mucosa on endoscopy was similar (21% Risedronate Sodium Tablets USP; 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 USP 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 USP; 51% placebo).

At the 1-year time point in studies, comparing Risedronate Sodium Tablets USP 35 mg Once-a-Week to Risedronate Sodium Tablets USP 5 mg daily in the treatment of postmenopausal osteoporosis, endoscopies performed during the study 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.

In two, 1-year studies for the treatment of osteoporosis in postmenopausal women comparing Risedronate Sodium Tablets USP 75 mg on two consecutive days per month and Risedronate Sodium Tablets USP 150 mg Once-a-Month respectively to Risedronate Sodium Tablets USP 5 mg daily, a similar percentage of patients for each of the intermittent regimens had at least one abnormal endoscopic finding when compared to the daily regimen (Risedronate Sodium Tablets USP 75 mg, 3.2%; Risedronate Sodium Tablets USP 5 mg, 3.1% and Risedronate Sodium Tablets USP 150 mg, 3.4%; Risedronate Sodium Tablets USP 5 mg, 4.2%).

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

The following adverse drug reactions were reported in ≤1% of patients who received Risedronate Sodium Tablets USP for all indications:

- Uncommon (0.1-1.0%): duodenitis, iritis
- Rare (<0.1%): abnormal liver function tests, glossitis

Abnormal Hematologic and Clinical Chemistry Findings

Asymptomatic mild decreases in serum calcium and phosphorus levels have been observed in some patients (see ACTION AND CLINICAL PHARMACOLOGY, 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.

Post-Market Adverse Drug Reactions

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

Musculoskeletal and Connective tissue: Reported very rarely, low-energy femoral shaft fractures (see WARNINGS AND PRECAUTIONS)

Osteonecrosis of the Jaw: Osteonecrosis of the jaw has been reported rarely (see WARNINGS AND PRECAUTIONS).

Ophthalmologic: Reported rarely, conjunctivitis, episcleritis, iritis, scleritis and uveitis (see WARNINGS AND PRECAUTIONS).

DRUG INTERACTIONS

Overview

No specific drug-drug interaction studies were performed with Risedronate Sodium Tablets USP. 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 Tablets USP is therefore not expected to interact with other drugs based on the effects of protein binding displacement, enzyme induction or metabolism of other drugs.

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) without evidence of clinically relevant interactions.

The drugs listed in Table 2 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 2
Established or Predicted Drug-Drug Interactions with Risedronate Sodium Tablets USP

	Reference	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 USP.	Such medications should be administered at a different time of the day from Risedronate Sodium Tablets USP (see DOSAGE AND ADMINISTRATION).
Hormone replacement therapy (HRT)	CT	No clinically significant effect for risedronate sodium tablets USP.	If considered appropriate, Risedronate Sodium Tablets USP may be used concomitantly with HRT (see CLINICAL TRIALS, Study 11).
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-treated patients and placebo-treated patients.	Of over 5700 patients enrolled in the Risedronate Sodium Tablets USP 5 mg daily Phase III osteoporosis studies, 21% used H_2-blockers and/or PPIs.
		Among H_2-blockers and PPIs users, the incidence of upper gastrointestinal	In the 1-year study comparing Risedronate Sodium Tablets USP

Table 2 Established or Predicted Drug-Drug Interactions with Risedronate Sodium Tablets USP			
	Reference	**Effect**	**Clinical Comment**
		adverse experiences was found to be similar between the weekly- and daily-treated groups.	Once-a-Week and daily dosing regimens in postmenopausal women with osteoporosis, at least 9% of patients in the Risedronate Sodium Tablets USP 35 mg Once-a-Week and 5 mg daily groups used H_2-blockers and/or PPIs.
Legend: CT = Clinical Trial; T = Theoretical			

Of over 5700 patients enrolled in the Risedronate Sodium Tablets USP 5 mg daily Phase III osteoporosis studies, ASA use was reported by 31% of patients and NSAID use by 48%. Among these ASA or NSAID users, the incidence of upper gastrointestinal adverse events was similar between the Risedronate Sodium Tablets USP-treated patients and placebo-treated patients.

In the 1-year study comparing Risedronate Sodium Tablets USP 35 mg Once-a-Week to Risedronate Sodium Tablets USP 5 mg daily, ASA use was reported by 56% and NSAID use by 41%. The incidence of upper gastrointestinal adverse events was similar between the Risedronate Sodium Tablets USP weekly- and daily-treated groups.

In two, 1-year studies comparing Risedronate Sodium Tablets USP 75 mg two consecutive days per month or Risedronate Sodium Tablets USP 150 mg once-a-month to Risedronate Sodium Tablets USP 5 mg daily in postmenopausal women, 55% (75 mg) and 46% (150 mg) of patients reported the use of ASA and/or NSAIDs. Among these ASA or NSAID users, the incidence of upper gastrointestinal adverse events was similar in the Risedronate Sodium Tablets USP monthly-treated groups when compared to the daily-treated groups respectively.

Drug-Food Interactions
Clinical benefits may be compromised by failure to take Risedronate Sodium Tablets USP on an empty stomach. For dosing information see DOSAGE AND ADMINISTRATION.

Drug-Herb Interactions
Interactions with herbs have not been studied.

Drug-Laboratory Interactions
Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with Risedronate Sodium Tablets USP have not been performed.

DOSAGE AND ADMINISTRATION

Dosing Considerations
- Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see WARNINGS AND PRECAUTIONS, General).

Risedronate Sodium Tablets USP

- APO-RISEDRONATE should be taken on an empty stomach at least 30 minutes before consuming the first food, drink (other than plain water) and/or other medication of the day. Food, medication or drink other than plain water can interfere with the absorption of APO-RISEDRONATE. (See Recommended Dose and Dosage Adjustment).

- Each APO-RISEDRONATE 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 APO-RISEDRONATE should not lie down for at least 30 minutes after taking the medication (see WARNINGS AND PRECAUTIONS, General).

- APO-RISEDRONATE tablet should not be chewed, cut, or crushed (see WARNINGS AND PRECAUTIONS, General).

- Medications containing polyvalent cations (e.g. calcium, magnesium, aluminum, and iron) can interfere with the absorption of APO-RISEDRONATE. These medications should be administered at a different time of the day than APO-RISEDRONATE.

Recommended Dose and Dosage Adjustment

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 1 tablet of 150 mg once-a-month on the same calendar day each month, 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).

Geriatrics: No dosage adjustment is necessary in elderly patients (see INDICATIONS AND CLINICAL USE, Geriatrics).

Missed Dose

Patients should be instructed that if they miss a 150 mg dose of APO-RISEDRONATE (1 tablet of 150 mg), and the next month's scheduled dose is more than 7 days away, they should take the missed tablet in the morning after the day it is remembered. Patients should then return to taking their APO-RISEDRONATE 150 mg as originally scheduled.

If a dose of APO-RISEDRONATE 150 mg is missed, and the next month's scheduled dose is within 7 days, patients should be instructed to wait until their next month's scheduled dose and then continue taking APO-RISEDRONATE 150 mg. Patients should not take more than 150 mg of APO-RISEDRONATE within 7 days.

OVERDOSAGE

For management of a suspected overdose, the patient should be instructed to contact the regional Poison Control Centre.

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 USP and reduce absorption of the drug. 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.

ACTION AND CLINICAL PHARMACOLOGY

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 sites.

Pharmacodynamics

Treatment and Prevention 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 USP 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. At the 5 mg daily dose, decreases in resorption markers were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone formation and bone resorption; decreases in bone formation of about 20% were evident within 3 months of

treatment. Bone turnover markers (BTMs) reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years.

These data demonstrate that Risedronate Sodium Tablets USP 5 mg administered daily to postmenopausal women produces a rapid reduction in bone resorption without over-suppression of bone formation. Bone turnover is decreased as early as 2 weeks and maximally within about 6 months of treatment, with achievement of a new steady-state which more nearly approximates the rate of bone turnover seen in premenopausal women.

In weekly and monthly Risedronate Sodium Tablets USP postmenopausal osteoporosis dosing studies, consistent decreases in bone resorption (50-60%) and bone formation (30-40%) markers were observed at Month 12.

As a result of the inhibition of bone resorption, asymptomatic and usually transient decreases from baseline in serum calcium (about 2%) and serum phosphate levels (about 5%) and compensatory increases in serum parthyroid hormone (PTH) levels were observed within 6 months in Risedronate Sodium Tablets USP 5 mg daily-treated patients in postmenopausal osteoporosis trials. No further decreases in serum calcium or phosphate, or increases in PTH were observed in postmenopausal women treated for up to 3 years.

In two 1-year studies for the treatment of osteoporosis in postmenopausal women comparing Risedronate Sodium Tablets USP 35 mg Once-a-Week Week and Risedronate Sodium Tablets USP 150 mg Once-a-Month respectively to Risedronate Sodium Tablets USP 5 mg daily, similar mean changes from baseline in serum calcium, phosphate and PTH were found for each of the intermittent regimens when compared to the daily dosage regimen. In the 1-year study comparing Risedronate Sodium Tablets USP 75 mg on two consecutive days per month to Risedronate Sodium Tablets USP 5 mg daily, the mean percent changes from baseline were for serum calcium (0.8% and 0.2%), phosphate (-1.1% and -1.9%) and PTH (-11.7% and -3.0%), respectively.

Consistent with the effects of Risedronate Sodium Tablets USP on biochemical markers of bone turnover, daily oral doses as low as 2.5 mg produced dose dependent, significant increases in lumbar spine bone mineral density (BMD) (Risedronate Sodium Tablets USP 2.5 mg, 3% to 3.7%; Risedronate Sodium Tablets USP 5 mg, 4% to 4.5%) after 12 months of treatment in large-scale postmenopausal osteoporosis trials. A dose-dependent response to treatment was also observed in the BMD of the femoral neck over the same time (Risedronate Sodium Tablets USP 2.5 mg, 0.7% to 0.9%; Risedronate Sodium Tablets USP 5 mg, 1.5% to 2%). In three 1-year weekly and monthly dosing studies for the treatment of osteoporosis in postmenopausal women, comparing Risedronate Sodium Tablets USP 35 mg Once-a-Week, Risedronate Sodium Tablets USP 75 mg on two consecutive days per month and Risedronate Sodium Tablets USP 150 mg Once-a-Month respectively to Risedronate Sodium Tablets USP 5 mg daily, similar mean changes from baseline in BMD of the lumbar spine, total proximal femur, femoral neck and femoral trochanter were found for each of the intermittent regimens when compared to the daily regimen (see CLINICAL TRIALS, Treatment of Osteoporosis in Postmenopausal Women).

Risedronate Sodium Tablets USP are film-coated.

Pharmacokinetics

Table 3
Summary of Pharmacokinetic Parameters of Risedronate

	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$,z (h)	AUC_0 - ∞ (ng.h/mL)	Clearance (L/h/kg)	V_z (L/kg)
5 mg tablet; single dose	0.85	0.93[a]	206.1	3.45	19.94	5542
30 mg tablet; single dose	4.2	0.87[a]	226.1	17.1	23.60	7542
35 mg tablet; multiple dose[b], steady state	10.6	0.49	nd	53.3	12.9	nd
75 mg tablet, multiple dose[c], steady state	19.3[d]	0.66[a]	299.7[d]	180.7[d]	14.8[a]	nd
150 mg tablet, single dose	74.8[d]	0.66[d]	349.6[d]	332.4[d]	6.94[d]	3118[d]

[a] Arithmetic mean
[b] administered weekly
[c] administered on two consecutive days per month (150 mg total monthly dose)
d geometric mean
$t_{1/2}$, z is the half-life of the terminal exponential phase.
V_Z is the terminal volume of distribution uncorrected for bioavailability.
nd not determined

Absorption: Absorption after an oral dose is relatively rapid (tmax ~ 1 hour) for the film-coated tablet and occurs throughout the upper gastrointestinal tract. Absorption is independent of dose up to 75 mg two consecutive days per month); systemic exposure increases disproportionally at 150 mg (about 2 fold greater than expected based on dose). Steady-state conditions in the serum are observed within 57 days of daily dosing. The mean oral bioavailability of the 30 mg film-coated tablet is 0.63% and is bioequivalent to a solution. Extent of absorption when administered 30 minutes before breakfast is reduced by 55% compared to dosing in the fasting state (i.e., no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces extent of absorption by 30% compared to dosing in the fasting state. Dosing either 30 minutes prior to breakfast or 2 hours after a meal results in a similar extent of absorption.

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.

Excretion: 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.

Gender: Bioavailability and disposition following oral administration are similar in men and women.

Race: 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. Risedronate Sodium Tablets USP is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min) because of a lack of clinical experience.

Genetic Polymorphism: No data are available.

STORAGE AND STABILITY

Store at controlled room temperature (15^{o}C – 30^{o}C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-RISEDRONATE SODIUM 150 MG TABLETS USP: Each light blue, oval, biconvex coated tablet, engraved “APO” on one side, “RIS150” on the other side contains risedronate sodium hemi-pentahydrate equivalent to 150 mg risedronate sodium. Available in bottles of 30 or 100 tablets and blister packs of 1 tablet.

In addition to the active ingredient risedronate sodium hemi-pentahydrate, each tablet also contains the non-medicinal ingredients colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose 2910 E5, hydroxypropyl cellulose type LF, anhydrous lactose, magnesium stearate, polyethylene glycol 8000, indigotine AL Lake 12-14% (Blue #2), sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

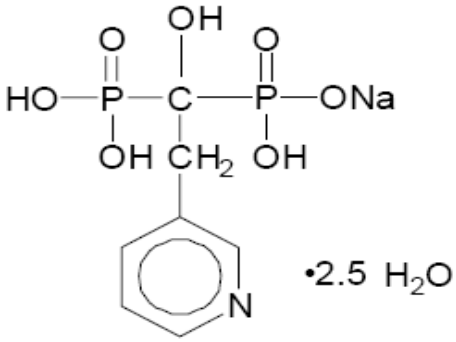
Drug Substance

Proper Name: Risedronate sodium hemi-pentahydrate

Chemical Name: Risedronate sodium tablets contain risedronate sodium in the form of hemi-pentahydrate with small amounts of monohydrate. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt hemipentahydrate.

Molecular formula and molecular weight: $C_7H_{10}NO_7P_2Na \cdot 2.5\ H_2O$.
Anhydrous: 305.09
Hemi-pentahydrate: 350.03

Structural Formula:



Physicochemical properties:

Solubility: Risedronate Sodium is soluble in water and essentially insoluble in common organic solvents. Risedronate Sodium, in terms of Biopharmaceutical Pharmaceutics Classification System (BCS), is considered a low soluble drug (BCS Class 4 established based on the 75 mg dose).

Solution pH: 4.2

Dissociation Constants: pKa: pKa1= 13.81, pKa2= 11.03, pKa3= 5.99, pKa4= 5.02, pKa5= 2.52, pKa6= 1.24 (Risedronic Acid, calculated values)
Partition Coefficient: 0.55 + 0.44 (Risedronic Acid, calculated value)

Description: Risedronate sodium is a white powder.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male and female volunteers (n=36). The rate and extent of absorption of risedronate was measured and compared following a single oral dose of Apo-Risedronate (risedronate sodium, Apotex Inc.) or Actonel® (risedronate sodium, Procter & Gamble Pharmaceuticals Canada Inc.) 150 mg tablets. The results from measured data are summarized in the following table:

Table 4: Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data Risedronate (A single 150 mg dose: 1 x 150 mg) From Measured Data/Fasting Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	Apo–Risedronate (Apotex Inc.) (Canada)	Actonel®† (Procter & Gamble Pharmaceuticals Canada, Inc.) (Canada)	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_{72} (ng·h/mL)	333.261 385.658 (59.7)	310.797 353.016 (53.6)	107	93-123
AUC_{∞} (ng·h/mL)	356.552 412.668 (59.6)	332.701 377.913 (53.8)	107	93-123
C_{max} (ng/mL)	82.562 99.602 (83.5)	73.810 85.958 (56.4)	112	96-130
Tmax§ (h)	1.00 (0.50-4.00)	1.00 (0.50-5.00)		
$T_{1/2}$* (h)	37.04 (21.3)	37.10 (17.2)		

§ Expressed as the median (range)

* Expressed as the arithmetic mean (CV%) only

† Actonel® is manufactured by Procter & Gamble Pharmaceuticals Canada, Inc. and was purchased in Canada.

Treatment of Osteoporosis in Postmenopausal Women

Study Demographics and Trial Design

Table 5
Summary of Patient Demographics for Clinical Trials of Risedronate Sodium Tablets USP in the Treatment of Osteoporosis in Postmenopausal Women

Study Number	Trial Design[a]	Dosage	Duration	Patients N = number	Age Range (Age Mean)	Gender	Daily Supplement**
1	R, AC, DB, MC, PG	5 mg/day 150 mg once/month*	12 months	1292	50-88 (64.9)	Postmenopausal female	400-500 to 1000 IU

[a] R: randomized; AC: active-controlled; PC: placebo-controlled; DB: double-blind; MC: multicentre; PG: parallel-group
* Placebo other days of treatment
** Patients in these studies were supplemented with 1000 mg elemental calcium/day

Results of Study 1:

Table 6
Comparison of Risedronate Sodium Tablets USP Once-a-Month vs. Daily Dosing in the Treatment of Osteoporosis in Postmenopausal Women – Primary Efficacy Analysis

Endpoints	Risedronate Sodium Tablets USP 5 mg Daily Mean Increase in BMD % (95% Confidence Interval)	Risedronate Sodium Tablets USP 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)

** Last observation carried forward (LOCF).

In the first year of a 2-year, double-blind, multicentre study of postmenopausal women with osteoporosis, Risedronate Sodium Tablets USP 150 mg Once-a-Month was shown to be non-inferior to Risedronate Sodium Tablets USP 5 mg daily. Risedronate Sodium Tablets USP 150 mg Once-a-Month was statistically shown to be non-inferior to the Risedronate Sodium Tablets USP 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 USP 150 mg Once-a-Month is similar in safety and efficacy to Risedronate Sodium Tablets USP 5 mg daily for the treatment of postmenopausal osteoporosis. The safety and efficacy of Risedronate Sodium Tablets USP 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 USP 5 mg or placebo once daily for 2 to 3 years (including 74 pairs of biopsies, 43 from Risedronate Sodium Tablets USP-treated patients) showed a moderate and expected decrease in bone turnover in Risedronate Sodium Tablets USP-treated women.

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

DETAILED PHARMACOLOGY

There are extensive preclinical data to support that bone produced during risedronate sodium treatment at therapeutic doses is of normal quality, consistent with clinical experience. Risedronate demonstrated potent anti-osteoclast, antiresorptive activity in ovariectomized animals, increasing bone mass and biomechanical strength dose-dependently. Risedronate treatment maintained the positive correlation between BMD and bone strength. In intact dogs, risedronate induced positive bone balance at the level of the basic multicellular unit.

Long-term oral administration of risedronate to ovariectomized rats (up to 2.5 mg/kg/day for 12 months) and ovariectomized minipigs (up to 2.5 mg/kg/day for 18 months) did not impair bone structure, mineralization, or biomechanical strength. These doses were 5 times the optimal antiresorptive dose for these species. Normal lamellar bone was formed in these animals. Risedronate treatment did not impair the normal healing of radial fractures in adult dogs. The Schenk rat assay, based on histologic examination of the epiphyses of growing rats after drug treatment, demonstrated that risedronate did not interfere with bone mineralization even at the highest dose tested (5 mg/kg/day, subcutaneously), which was > 3000 times the lowest antiresorptive dose (1.5 µg/kg/day).

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).

Mutagenesis: 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 µg/mL). However, when the assay was repeated at doses exhibiting increased cell survival (300 µg/mL), risedronate was negative.

Reproduction: 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 Tablets USP 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.

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PART III: CONSUMER INFORMATION

[Pr]APO-RISEDRONATE
Risedronate Sodium Tablets USP

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

ABOUT THIS MEDICATION

What the medication is used for:

- Treatment of osteoporosis in postmenopausal women

What it does:
APO-RISEDRONATE is a bisphosphonate that helps to slow bone loss. In many people, APO-RISEDRONATE helps to increase bone density. In osteoporosis, the body removes more bone than it replaces. This causes bones to get weaker and more likely to break or fracture (usually at the spine, wrist or hip). Spine fractures may result in a curved back, height loss or back pain. APO-RISEDRONATE corrects this imbalance by decreasing the elevated rate of bone removal. APO-RISEDRONATE can therefore help reduce the risk of spine and non-spine fractures.

Your doctor may measure the thickness (i.e., density) of your bone through a bone mineral density (BMD) test or x-ray to check your progress against further bone loss or fracture.

APO-RISEDRONATE is not a pain reliever. Your doctor may prescribe or recommend another medicine specifically for pain relief.

When it should not be used:
- If you have low blood calcium levels (hypocalcemia).
- If you are allergic to risedronate sodium or any other ingredients in APO-RISEDRONATE.

What the medicinal ingredient is:
Risedronate Sodium

What the nonmedicinal ingredients are:
APO-RISEDRONATE contains the following non-medicinal ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose 2910 E5, hydroxypropyl cellulose type LF, anhydrous lactose, magnesium stearate, polyethylene glycol 8000, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, indigotine Al Lake and titanium dioxide.

What dosage forms it comes in:
APO-RISEDRONATE 150 mg is available as tablets. Each blue tablet contains risedronate sodium 150 mg.

WARNINGS AND PRECAUTIONS

Before you use APO-RISEDRONATE, talk to your doctor or pharmacist if:

- You have had problems or disease in your kidneys, esophagus (i.e., the tube connecting the mouth and the stomach), stomach, or intestines.
- You cannot carry out dosing instructions (see PROPER USE OF THIS MEDICATION).
- You are pregnant or nursing.
- You have one of the following risk factors: cancer, chemotherapy, radiotherapy of the head or neck, treatment with corticosteroids, or dental problems or dental infections. If so, a dental examination and any necessary dental procedures should be considered before you start treatment with APO-RISEDRONATE.

Calcium and vitamin D are also important for strong bones. Your doctor may ask you to take calcium and vitamin D while you are on APO-RISEDRONATE therapy (see INTERACTIONS WITH THIS MEDICATION section).

INTERACTIONS WITH THIS MEDICATION

If taken with some other medicines, the effects of APO-RISEDRONATE or the effects of other medicines may be changed. It is important to tell your health care providers, including doctors and dentists, about all medications you are taking, even if the medicine does not require a prescription (including vitamins and herbal supplements).

You should not take APO-RISEDRONATE with food, as it may prevent your body from absorbing or using APO-RISEDRONATE. You should take APO-RISEDRONATE on an empty stomach. (See PROPER USE OF THIS MEDICATION for instruction).

Vitamin and mineral supplements, as well as antacids, may contain substances (e.g. calcium, magnesium, aluminum, and iron) which can stop your body from

absorbing or using APO-RISEDRONATE. These should be taken at a different time of day.

PROPER USE OF THIS MEDICATION

As with all medications, it is important to take APO-RISEDRONATE as directed by your doctor.

Usual dose:

Treatment of postmenopausal osteoporosis:

- Choose a day of the month that you will remember and that best fits your schedule to take your APO-RISEDRONATE dose (1 tablet of 150 mg) once per month.
- On your chosen day each month, take 1 APO-RISEDRONATE 150 mg tablet first thing in the morning with plain water before you have anything to eat or drink.

Dosing Instructions

- APO-RISEDRONATE should be taken in the morning on an empty stomach at least 30 minutes before consuming the first food, drink (other than plain water) and/or any other medication of the day. Food, medication or drink other than plain water can interfere with the absorption of APO-RISEDRONATE.
- Each APO-RISEDRONATE tablet should be swallowed whole while you are in the upright position and with sufficient plain water (>120 mL or ½ cup) to facilitate delivery to the stomach.
- You should not lie down for at least 30 minutes after taking the medication. You may sit, stand or do normal activities like read the newspaper, take a walk, etc.
- APO-RISEDRONATE tablet should not be chewed, cut, or crushed.
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These recommendations help APO-RISEDRONATE work correctly and help you avoid possible irritation of the esophagus (the tube connecting the mouth and the stomach).

You should take APO-RISEDRONATE for as long as your doctor recommends, to continue to prevent bone loss and protect your bones from fractures.

Missed Dose:

If you miss a dose of APO-RISEDRONATE 150 mg in the morning, do not take it later in the day. If the next month's scheduled dose is more than 7 days away, take the missed tablet on the morning after the day it is remembered. You should then return to your usual schedule of APO-RISEDRONATE 150 mg.

If the next month's scheduled dose is 1 to 7 days away, you should wait until next month's scheduled dose and then resume taking APO-RISEDRONATE 150 mg as originally scheduled. Do not take more than 150 mg of APO-RISEDRONATE within 7 days.

Overdose:

If you take too many tablets on any given day, contact your doctor, or a Poison Control Centre immediately. Drink a full glass of milk. Do not induce vomiting.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Drugs like APO-RISEDRONATE may cause problems in your esophagus (the tube connecting the mouth and the stomach), stomach and intestines, including ulcers. If you have trouble or pain upon swallowing, heartburn, chest pain and black or bloody stools, stop taking APO-RISEDRONATE and tell your doctor right away. Remember to take APO-RISEDRONATE as directed.

In clinical studies of osteoporosis with APO-RISEDRONATE, the most commonly reported side effects were abdominal pain, heartburn and nausea. In studies of Paget's disease, diarrhea, and headache were also commonly reported.

APO-RISEDRONATE may cause pain in bones, joints or muscles, rarely severe. Pain may start as soon as one day or up to several months after starting APO-RISEDRONATE.

APO-RISEDRONATE at monthly doses may cause short-lasting, mild flu-like symptoms. These symptoms usually decrease after subsequent doses.

Very rarely patients have reported non-healing jaw wounds while receiving APO-RISEDRONATE or other drugs in this class. Consult your doctor if you experience persistent pain in your mouth, teeth or jaw, or if your gums or mouth heal poorly.

Very rarely patients have reported unusual fractures in their thigh bone while receiving drugs in this class. Consult your doctor if you experience new or unusual pain in your hip, groin, or thigh.

IMPORTANT SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common (more than 1 in 100)			
Pain in bones, joints, or muscles	√		
Abdominal pain	√		
Uncommon (less than 1 in 100)			
Eye pain, redness or inflammation; sensitivity to light, decreased vision			√
Rare (less than 1 in 1,000)			
Painful tongue		√	
Very rare (less than 1 in 10,000)			
Allergic and skin reactions such as: hives; rash (with or without blisters); swelling of face, lips, tongue, or throat; difficult or painful swallowing; trouble breathing			√
Jaw problems associated with delayed healing and infection, often following tooth extraction.		√	
Symptoms of low blood calcium level such as numbness, tingling, muscle spasms		√	
New or unusual pain in hip, groin or thigh		√	

This is not a complete list of side effects. For any unexpected effects while taking APO-RISEDRONATE, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep APO-RISEDRONATE and all other medications out of the reach of children.
- Keep the tablets in their original package and store at controlled room temperature (15°-30°C).
- Do not keep medicine that is out of date or that you no longer need.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at:
http://www.apotex.ca/products.

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

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