PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**pms-RISEDRONATE**

Risedronate Sodium Tablets

Tablets, 35 mg and 150 mg risedronate sodium (as the hemi-pentahydrate), Oral

USP

Bisphosphonates

PHARMASCIENCE INC.
6111 Ave. Royalmount
Montréal, Québec
H4P 2T4

www.pharmascience.com

Date of Initial Authorization
JUL 27, 2010

Date of Revision:
FEB 01, 2023

Submission Control Number: 269451

RECENT MAJOR LABEL CHANGES

N/A	

TABLE OF CONTENTS

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pms-RISEDRONATE (risedronate sodium) is indicated for:

- the treatment and prevention of osteoporosis in postmenopausal women
- the treatment of osteoporosis in men, to improve bone mineral density

Postmenopausal Osteoporosis: In the treatment of osteoporosis in postmenopausal women at risk of fracture, risedronate sodium 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).

For the prevention of osteoporosis in postmenopausal women who are at risk of developing osteoporosis, risedronate sodium preserves or increases BMD at sites of clinical importance.

pms-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.

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 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 14 CLINICAL TRIALS.

2 CONTRAINDICATIONS

pms-RISEDRONATE is 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 regimens are weekly (35 mg once-a-week) or monthly (1 tablet of 150 mg once-a-month on the same calendar day each month), taken orally.

- **Prevention of Postmenopausal Osteoporosis:** The recommended regimen is 35 mg once-a-week, taken orally.

- **Treatment of Osteoporosis in Men, to Improve Bone Mineral Density:** The recommended regimen is 35 mg once-a-week, 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

- pms-RISEDRONATE should be taken 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

pms-RISEDRONATE. See 4.2 Recommended Dose and Dosage Adjustment; and 9 DRUG INTERACTIONS).

- Each pms-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 pms-RISEDRONATE should not lie down for at least 30 minutes after taking the medication. See 7 WARNINGS AND PRECAUTIONS).
- pms-RISEDRONATE tablets should not be chewed, cut, or crushed. See 7 WARNINGS AND PRECAUTIONS).
- Medications containing polyvalent cations (e.g., calcium, magnesium, aluminum, and iron) can interfere with the absorption of pms-RISEDRONATE. These medications should be administered at a different time of the day than pms-RISEDRONATE.
- 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 pms-RISEDRONATE on an individual patient basis.

4.5 Missed Dose

Weekly: Patients should be instructed that if they miss a dose of pms-RISEDRONATE 35 mg Once-a-Week on their regularly scheduled day, they should take 1 tablet of pms-RISEDRONATE 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.

Once-a-Month: Patients should be instructed that if they miss a 150 mg dose of pms-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 pms-RISEDRONATE 150 mg as originally scheduled.

If a dose of pms-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 pms-RISEDRONATE 150 mg. Patients should not take more than 150 mg of pms-RISEDRONATE within 7 days.

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 pms-RISEDRONATE 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.

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	Tablet / 35 mg & 150 mg	**35 mg:** Colloidal Silicon Dioxide, Iron Oxide Red, Iron Oxide Yellow, Maltodextrin, Mannitol, Polyethylene Glycol/Magrocol, Polyvinyl Alcohol, Povidone, Pregelatinized Starch, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Talc, Titanium Dioxide. **150 mg:** Crospovidone, FD&C Blue #2 Indigo Carmine Aluminium Lake, Hydroxypropyl Cellulose, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol/Macrogol, Silica, Titanium Dioxide.

35 mg: pms-RISEDRONATE is supplied as 35 mg strength orange, modified capsule-shape, coated tablet, debossed with “RS” on one side and “35” on the other side.

35 mg: pms-RISEDRONATE tablets 35 mg are available in HDPE bottles of 30 tablets and blister package of 4 tablets.

150 mg: pms-RISEDRONATE is supplied as 150 mg strength blue, modified capsule-shape, coated tablet, debossed with “RS” on one side and “150” on the other side.

150 mg: pms-RISEDRONATE tablets 150 mg are available in HDPE bottles of 30 tablets and blister package of 1 tablet.

Medicinal Ingredients:
35 mg: Each coated pms-RISEDRONATE tablet for oral administration contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemipentahydrate with small amounts of monohydrate.

150 mg: Each coated pms-RISEDRONATE tablet for oral administration contains the equivalent of 150 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate.

7 WARNINGS AND PRECAUTIONS

General

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

Adequate intake of calcium and vitamin D is important in all patients.
pms-RISEDRONATE should be taken on an empty stomach at least 30 minutes before first food of the day. Detailed dosing instructions (see 4.2 Recommended Dose and Dosage Adjustment; and 4.4 Administration) are provided to ensure correct dosing of each pms-RISEDRONATE 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 pms-RISEDRONATE 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 pms-RISEDRONATE, 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 pms-RISEDRONATE. Patients should receive routine dental check-ups while taking pms-RISEDRONATE.

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 pms-RISEDRONATE, 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 pms-RISEDRONATE.

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., anemia, 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 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 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 for all indications.

In risedronate sodium 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 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 and Prevention of Postmenopausal Osteoporosis: Risedronate sodium 5 mg daily has been studied for up to 3 years in over 5,000 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 and placebo-treated patients.

Table 2 lists adverse events considered possibly or probably drug-related, reported in ≥ 1% of risedronate sodium 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 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 5 mg Daily-Treated Patients in Combined Phase III Postmenopausal Osteoporosis Trials

	Risedronate Sodium 5 mg n = 1742 (%)	Placebo n = 1,744 (%)
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

	Risedronate Sodium 5 mg n = 1742 (%)	Placebo n = 1,744 (%)
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.

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

In the 1-year, double-blind, multicentre study comparing risedronate sodium 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 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 5 mg daily versus risedronate sodium 35 mg Once-a-Week treatment study.

Monthly Dosing: (Once-a-Month): In a 1-year, double-blind, multicentre study for the treatment of osteoporosis in postmenopausal women comparing risedronate sodium 150 mg Once-a-Month to risedronate sodium 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 150 mg Once-a-Month and the risedronate sodium 5 mg daily treated groups. In addition to the previously described adverse reactions diarrhea (risedronate sodium 150 mg, 3.1%; risedronate sodium 5 mg, 0.5%), vomiting (risedronate sodium 150 mg, 1.5%; risedronate sodium 5 mg, 0.6%), arthralgia (risedronate sodium 150 mg, 1.5%; risedronate sodium 5 mg, 0.9%) and myalgia (risedronate sodium 150 mg, 1.1%; risedronate sodium 5 mg, 0.3%) were reported in ≥1% of patients and in more risedronate sodium 150 mg treated patients than in risedronate sodium 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 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 150 mg once-a-month group and 1.1% in the risedronate sodium 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 150 mg Once-a-Month group and 0.2% of patients in the risedronate sodium 5 mg daily group.

Treatment of Osteoporosis in Men, to Improve Bone Mineral Density: In a 2-year, double-blind, multicentre study using risedronate sodium 35 mg Once-a-Week (n=191) and placebo (n=93) in men with osteoporosis, the overall safety and tolerability profiles of the two treatment groups were similar.

The proportion of patients who experienced an upper gastrointestinal adverse event and the pattern of those events were higher in placebo (18%) than in risedronate sodium 35 mg Once-a-Week treated patients (8%).

In addition to the previously described adverse events, the following adverse events were reported in ≥ 2% of patients and in more risedronate sodium-treated patients than placebo-treated patients in the male osteoporosis study (events are included without attribution of causality): hypoaesthesia (risedronate sodium 35 mg, 2%; placebo, 1%), nephrolithiasis (risedronate sodium 35 mg, 3%; placebo, 0%), benign prostatic hyperplasia (risedronate sodium 35 mg, 5%; placebo, 3%) and arrhythmia (risedronate sodium 35 mg, 2%; placebo, 0%).

Endoscopic Findings: Risedronate sodium 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; 75 placebo).

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

At the 1-year time point in studies, comparing risedronate sodium 35 mg Once-a-Week to risedronate sodium 5 mg daily and risedronate sodium delayed-release 35 mg weekly to risedronate sodium 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.

In a 1-year study for the treatment of osteoporosis in postmenopausal women comparing risedronate sodium 150 mg Once-a-Month to risedronate sodium 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 150 mg, 3.4%; risedronate sodium 5 mg, 4.2%).

8.3 Less Common Clinical Trial Adverse Reactions

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

- Eye Disorders: iritis (0.1-1.0%)
- Gastrointestinal Disorders: duodenitis (0.1-1.0%), 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.

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 3 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.	Such medications should be administered at a different time of the day from pms-RISEDRONATE (see 4.4 Administration).
Hormone replacement therapy (HRT)	CT	No clinically significant effect for risedronate sodium.	If considered appropriate, pms-RISEDRONATE may be used concomitantly with HRT (see Combined Administration with Hormone Replacement Therapy).

Proper/Common Name	Source of Evidence	Effect	Clinical Comment
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 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 adverse experiences was found to be similar between the weekly- and daily-treated groups.	In the 1-year study comparing risedronate sodium Once-a-Week and daily dosing regimens in postmenopausal women with osteoporosis, at least 9% of patients in the risedronate sodium 35 mg Once-a-Week and 5 mg daily groups used H_2-blockers and/or PPIs.
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 pms-RISEDRONATE (see Musculoskeletal).

Legend: CT = Clinical Trial; T = Theoretical

Of over 5,700 patients enrolled in the risedronate sodium 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 -treated patients and placebo-treated patients.

In the 1-year study comparing risedronate sodium 35 mg Once-a-Week to risedronate sodium 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 weekly- and daily-treated groups.

In a 1-year study comparing risedronate sodium 150 mg once-a-month to risedronate sodium 5 mg daily in postmenopausal women, 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 monthly-treated groups when compared to the daily-treated groups respectively.

9.5 Drug-Food Interactions

Clinical benefits may be compromised by failure to take pms-RISEDRONATE on an empty stomach. 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 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 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 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 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 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 parathyroid hormone (PTH) levels were observed within 6 months in risedronate sodium 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 35 mg Once-a-Week and risedronate sodium 150 mg Once-a-Month respectively to risedronate sodium 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.

Consistent with the effects of risedronate sodium 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 2.5 mg, 3% to 3.7%; risedronate sodium 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 2.5 mg, 0.7% to 0.9%; risedronate sodium 5 mg, 1.5% to 2%). In

two, 1-year weekly and monthly dosing studies for the treatment of osteoporosis in postmenopausal women, comparing risedronate sodium 35 mg Once-a-Week and risedronate sodium 150 mg Once-a-Month respectively to risedronate sodium 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 Treatment of Osteoporosis in Postmenopausal Women).

Treatment of Osteoporosis in Men, to Improve Bone Mineral Density: In a 2-year clinical trial in the treatment of osteoporosis in men, risedronate sodium 35 mg once-a-week decreased urinary collagen cross-linked N-telopeptide (NTX) (a marker of bone resorption), and serum bone specific alkaline phosphatase (BAP) (a marker of bone formation) by approximately 40% and 30%, below baseline values, respectively, within 12 months. The BTMs all had statistically significant decreases in bone turnover from baseline compared to placebo at all time points. The decreases in bone turnover were observed within 3 months after initiation of therapy and maintained throughout the 2-year study.

10.3 Pharmacokinetics

Table 4: Summary of Pharmacokinetic Parameters of Risedronate

	C_{max} (ng/mL)	T_{max} (h)	$t_{½, z}$ (h)	AUC $_{0-\infty}$ (ng·h/mL)	Clearance (L/h/kg)	V_z (L/kg)
35 mg tablet; multiple dose[a], steady state	10.6	0.49	nd	53.3	12.9	nd
150 mg tablet; single dose	74.8[b]	0.66[b]	349.6[b]	332.4[b]	6.94[b]	3118[b]

a administered weekly
b 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

Absorption
Absorption after an oral dose is relatively rapid (t_{max} ~ 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.

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. pms-RISEDRONATE is 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 between 15°C and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

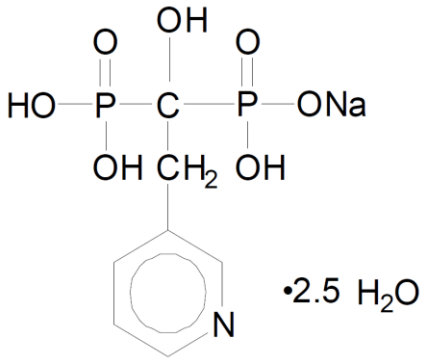
Proper name: Risedronate sodium hemi-pentahydrate

Chemical name: pms-RISEDRONATE 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.

Molecular formula and molecular mass: $C_7H_{10}NO_7P_2Na \cdot 2.5H_2O$

Anhydrous:	305.10 g/mol
Hemi-pentahydrate:	350.13 g/mol

Structural formula:



Physicochemical Properties

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 pKa 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.

Description: Risedronate sodium is a fine white to off-white crystalline powder.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Osteoporosis in Postmenopausal Women

Study Demographics and Trial Design

Table 5: Summary of Patient Demographics for Clinical Trials of Risedronate Sodium 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	1,226	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	2,458	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	1,456	67.9 (48-95)	≤500 IU
6	R, AC, DB, MC, PG	5 mg/day or 150 mg once/month* Oral administration 12 months	1,292	64.9 (50-88)	400-500 to 1000 IU

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

* Placebo on other days of treatment

** 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 and 4, 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 and 6, 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 daily, weekly or monthly 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 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 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 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 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 5 mg daily also significantly reduced the proportion of patients experiencing new and worsening vertebral fractures in each of the studies. Figure 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 compared with placebo at all time points, consistent with the positive effect of risedronate sodium on bone strength.

Table 6: Effect of risedronate sodium on Fracture, Height and Bone Mineral Density in the Treatment of Osteoporosis in Postmenopausal Women

Endpoints		Risedronate sodium 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/y)	-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
	Trochanter	3.3	-0.7	3.9		<0.001
36 months	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

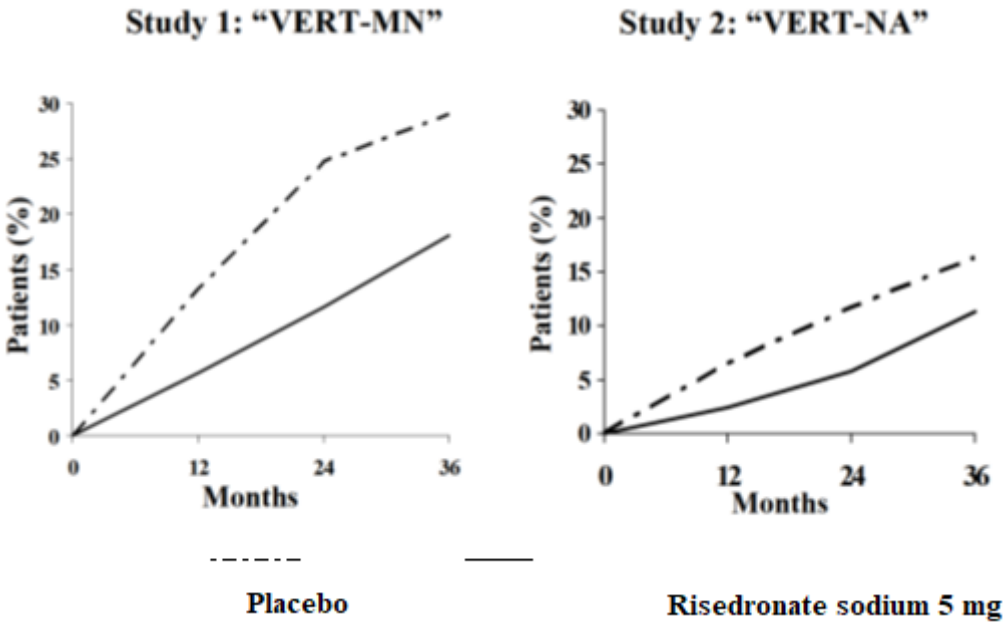
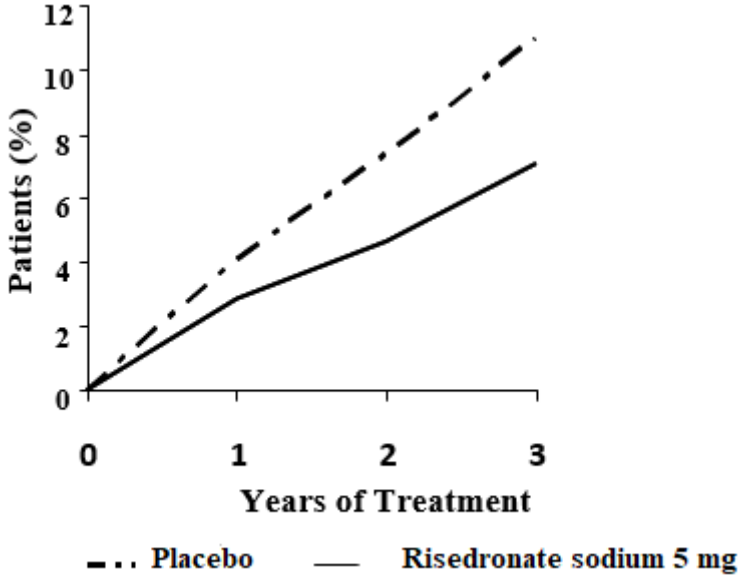


Figure 2: Cumulative Incidence of Osteoporosis-Related Non-vertebral Fractures Studies 1 and 2 Combined



Risedronate sodium 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 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 on Bone Mineral Density in the Treatment of Osteoporosis in Postmenopausal Women

Endpoints		Risedronate Sodium 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	Lumber 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	Lumber Spine	5.2	0.3	5.0**
	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 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 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 Once-a-Week vs. Daily Dosing in the Treatment of Osteoporosis in Postmenopausal Women - Primary Efficacy Analysis of Completers

Endpoints		Risedronate Sodium 5 mg Daily Mean Increase in BMD % (95% Confidence Interval)	Risedronate Sodium 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 35 mg Once-a-Week was concluded to be non-inferior to risedronate sodium 5 mg daily.

In trials with risedronate sodium 5 mg daily, changes in BMD of this magnitude were associated with a significant decrease in fracture incidence relative to placebo (see Table 6). This is further supported by the fact that within the 1-year study comparing risedronate sodium 35 mg Once-a-Week to risedronate sodium 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 35 mg taken once a week is similar in safety and efficacy to risedronate sodium 5 mg daily for the treatment of postmenopausal osteoporosis.

Results of Study 7

Table 9: Comparison of Risedronate Sodium Once-a-Month vs. Daily Dosing in the Treatment of Osteoporosis in Postmenopausal Women - Primary Efficacy Analysis

Endpoints	**Risedronate Sodium 5 mg Daily Mean Increase in BMD % (95% Confidence Interval)**	**Risedronate Sodium 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 150 mg Once-a-Month was shown to be non-inferior to risedronate sodium 5 mg daily. risedronate sodium 150 mg Once-a-Month was statistically shown to be non-inferior to the risedronate sodium 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 150 mg Once-a-Month is similar in safety and efficacy to risedronate sodium 5 mg daily for the treatment of postmenopausal osteoporosis. The safety and efficacy of risedronate sodium 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 5 mg or placebo once daily for 2 to 3 years (including 74 pairs of biopsies, 43 from risedronate sodium-treated patients) showed a moderate and expected decrease in bone turnover in risedronate sodium-treated women.

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

Prevention of Osteoporosis in Postmenopausal Women

Table 10: Summary of Patient Demographics for Clinical Trials of risedronate sodium in the Prevention of Osteoporosis in Postmenopausal Women

Study #	Study Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Daily Supplement	
					Elemental Calcium	Vitamin D
8	R, PC, DB, MC, PG	2.5 mg/day or 5 mg/day Oral administration 2 years	383	52.7 (42-63)	1,000 mg	-
9	R, PC, DB, MC, PG	35 mg/week Oral administration 1 year	280	53.6 (44-64)	1,000 mg	400 IU

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

Women in Study 7 were within 3 years of menopause and all patients in this study received supplemental calcium 1000 mg/day. Study 8 included women who were 0.5 to 5 years postmenopausal without osteoporosis. All patients were supplemented with 1000 mg elemental calcium and 400 IU vitamin D per day.

Results of Study 8

Table 11: Effect of Risedronate Sodium 5 mg Daily on Bone Mineral Density in Postmenopausal Women without Osteoporosis

Endpoints		Risedronate sodium 5 mg Mean Increase in BMD %	Placebo Mean Increase in BMD %	Mean Difference from Placebo %
24 months	Lumbar Spine	2.0	-2.5	4.5*
	Femoral Neck	1.0	-2.3	3.3*
	Trochanter	2.3	-2.0	4.3*

*vs. placebo: p<0.001

Increases in BMD were observed as early as 3 months following initiation of risedronate sodium treatment. Prevention of spinal bone loss was observed in the vast majority of women who received risedronate sodium treatment. In contrast, most placebo-treated women experienced significant and progressive bone loss, despite receiving supplemental calcium 1000 mg/day. Risedronate sodium 5 mg daily was similarly effective in patients with lower baseline BMD (i.e., more than 1 SD below the premenopausal mean) and in those with higher BMD.

Results of Study 9

Table 12: Effect of risedronate sodium 35 mg Once-a-Week on Bone Mineral Density in Postmenopausal Women without Osteoporosis

Endpoints		Risedronate sodium 35 mg Once-a-Week Mean Increase in BMD %	Placebo Mean Increase in BMD %	Mean Difference from Placebo %
6 months	Lumbar Spine	1.7	-0.5	2.2*
	Trochanter	1.0	-0.4	1.3*
	Femoral Neck	0.4	-1.0	1.4*
12 months	Lumbar Spine	1.9	-1.1	3.0*
	Trochanter	1.0	-0.7	1.7*
	Femoral Neck	0.3	-1.0	1.3**

*vs. placebo: p≤0.0001; ** p=0.0041

Combined Administration with Hormone Replacement Therapy

Table 13: 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	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 10

Table 14: Effect of risedronate sodium on Bone Mineral Density in Combination Therapy with Conjugated Estrogen

Endpoints		Risedronate sodium 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 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 5 mg daily for 1 year (including 32 pairs of biopsies, 16 from risedronate sodium-treated patients) found decreases in bone turnover in the risedronate sodium-treated patients that were consistent with the changes in bone turnover markers (BTMs). Bone histology demonstrated that the bone of patients treated with risedronate sodium plus estrogen was of normal lamellar structure and normal mineralization.

Treatment of Osteoporosis in Men, to Improve Bone Mineral Density

Table 15: Summary of Patient Demographics for Clinical Trial of risedronate sodium in Treatment of Osteoporosis in Men, to Improve Bone Mineral Density

Study #	Study Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Daily Supplement	
					Elemental Calcium	Vitamin D
11	R, PC, DB, MC, PG	35 mg/week Placebo Oral administration 2 years	191 93	60.8 (36-84)	1000 mg	400-500 IU

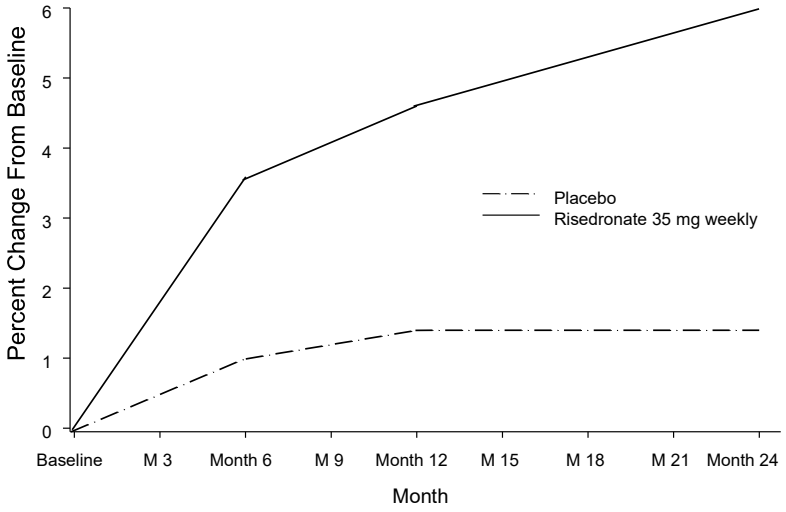
R = randomized; PC =placebo-controlled; DB = double-blind; MC = multicenter; PG = parallel-group

Patients with active or a history of upper gastrointestinal disorders at baseline and those taking ASA, NSAIDs, or drugs traditionally used for the treatment of peptic ulcers were not specifically excluded from participating in the 2-year male osteoporosis study.

Results of Study 11

Risedronate sodium 35-mg Once-a-week demonstrated efficacy in men with osteoporosis, as measured by change in BMD. All patients in this study received supplemental calcium 1000 mg/day and vitamin D 400-500 IU/day. Risedronate sodium 35 mg produced significant mean increases in BMD at the lumbar spine, femoral neck, trochanter and total hip compared to placebo in a 2-year study (lumbar spine, 4.5%; femoral neck, 1.1%; trochanter, 2.2%; total hip, 1.5%). Statistically significant increases in lumbar spine BMD were observed within 6 months following initiation of risedronate sodium treatment. Lumbar spine BMD percent change from baseline at Months 6, 12 and 24 showed that the risedronate sodium 35 mg Once-a-week group had a statistically significant increase in mean percent change from baseline versus placebo at all time points (see Figure 3).

Figure 3: Mean Percent Change from Baseline in Lumbar Spine BMD at all Time Points (Intent-to-Treat Population)



14.2 Comparative Bioavailability Studies

A blind, randomized, 2-way crossover, bioequivalence study of pms-RISEDRONATE 35 mg tablet was performed versus "Warner Chilcott Canada Co." Pharmaceuticals ACTONEL®, administered as 1 X 35 mg tablet in 70 healthy adult male volunteers under fasting conditions. 64 healthy male volunteers were included in the calculation of presented pharmacokinetic parameters.

Bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Risedronate (1 x 35 mg tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_T (pg·h/mL)	24182.8 28494.5 (67.9)	23015.1 27491.8 (66.7)	105.07	91.71 – 120.39
AUC_I (pg·h/mL)	25122.9 29558.7 (67.4)	23869.0 28467.1 (66.4)	105.25	91.91 – 120.53
C_{max} (pg/mL)	8113.8 9909.8 (81.1)	7881.4 10164.6 (88.8)	102.95	88.71 – 119.48
T_{max}§ (h)	1.00 (0.25 – 4.00)	1.00 (0.25 – 2.50)		
$T_{½}$€ (h)	3.25 (29.9)	3.19 (37.4)		

*pms-RISEDRONATE 35 mg tablets

†ACTONEL® 35 mg tablets, Warner Chilcott Canada Co., purchased in Canada

§ Expressed as the median (range)

€ Expressed as the arithmetic mean (CV %)

Comparative Bioavailability Study

A double blind, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioequivalence study of pms-RISEDRONATE 150 mg Tablets was performed versus "Warner Chilcott Canada Co." Pharmaceuticals ACTONEL®, administered as 1 x 150 mg tablet in 100 normal, healthy, adult, human male subjects under fasting conditions. 97 healthy male volunteers were included in the calculation of presented pharmacokinetic parameters.

Bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Risedronate (1 × 150 mg tablet Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng.h/mL)	415.2 467.8 (48.1)	427.4 484.3 (51.1)	97.1	90.9 - 103.8
AUC_I (ng.h/mL)	441.5 496.8 (47.6)	452.6 513.0 (50.7)	97.5	91.3 - 104.2
C_{max} (ng/mL)	117.0 133.0 (51.0)	119.7 137.4 (54.7)	97.7	90.1 - 106.1
T_{max} (h)§	1.250 (0.500-3.000)	1.033 (0.500-4.000)		
$T_{½}$€ (h)	6.18 (35.9)	5.66 (42.4)		

* pms-RISEDRONATE 150 mg Tablets; Manufactured by Pharmascience Inc., Canada.

†PrACTONEL® (Risedronate Sodium Tablets, USP 150 mg); manufactured by Warner Chilcott, Canada.

§ Expressed as the median (range) value

€ Expressed as the arithmetic mean (CV %)

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 (5,826 mg/m^2) and male rats at 1,703 mg/kg (10,967 mg/m^2). The minimum lethal dose in mice, rabbits, and dogs was 4,000 mg/kg (10,909 mg/m^2), 1,000 mg/kg (10,870 mg/m^2), and 128 mg/kg (2,560 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® (risedronate sodium tablets, 35 mg and 150 mg), submission control 261847, Product Monograph, Allergan Inc (July 5, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-RISEDRONATE
Risedronate Sodium Tablets

Read this carefully before you start taking **pms-RISEDRONATE** 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 **pms-RISEDRONATE**.

What is pms-RISEDRONATE used for?
pms-RISEDRONATE is used in adults to:
- treat or prevent osteoporosis in postmenopausal women.
- increase bone density in men with osteoporosis.

How does pms-RISEDRONATE work?
pms-RISEDRONATE 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. pms-RISEDRONATE 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 pms-RISEDRONATE helps to increase bone density.

What are the ingredients in pms-RISEDRONATE?
Medicinal ingredients: Risedronate Sodium (as risedronate sodium hemi-pentahydrate)

Non-medicinal ingredients: *35 mg:* Colloidal Silicon Dioxide, Iron Oxide Yellow, Iron Oxide Red, Maltodextrin, Mannitol, Polyvinyl Alcohol, Polyethylene Glycol/Macrogrol, Povidone, Pregelatinized Starch, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Talc, Titanium Dioxide. *150 mg:* Crospovidone, FD&C Blue #2 Indigo Carmine Aluminium Lake, Hydroxypropyl Cellulose, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol/Macrogol, Silica, Titanium Dioxide.

pms-RISEDRONATE comes in the following dosage forms:
Tablets: 35 mg and 150 mg

Do not use pms-RISEDRONATE if:
- you have low levels of calcium in your blood (hypocalcemia).
- you are allergic to risedronate sodium or any of the other ingredients in pms-RISEDRONATE (see **What are the ingredients in pms-RISEDRONATE?)**.

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

- have or have had problems swallowing or have 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 pms-RISEDRONATE**)
- 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 pms-RISEDRONATE 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 pms-RISEDRONATE incorrectly may cause you to experience problems with your esophagus. Stop taking pms-RISEDRONATE 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 pms-RISEDRONATE with a full glass of water.
- do NOT chew or suck the tablet.
- do NOT lie down for at least 30 minutes after taking pms-RISEDRONATE or until you have had your first meal of the day.
- do NOT take pms-RISEDRONATE at bedtime or before starting your day.

Eye Problems: Drugs like pms-RISEDRONATE 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 pms-RISEDRONATE. Dental work should be done before you start treatment with pms-RISEDRONATE. 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 pms-RISEDRONATE.

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 pms-RISEDRONATE.

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 pms-RISEDRONATE:

- Vitamins, mineral supplements and antacids may contain substances that can stop your body from absorbing pms-RISEDRONATE. They include calcium, magnesium, aluminum and iron. Take these medicines at a different time of day than pms-RISEDRONATE. Talk to your healthcare professional about how and when to take these medications.

- Taking pms-RISEDRONATE 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 pms-RISEDRONATE:

- Take pms-RISEDRONATE exactly as your healthcare professional tells you to.
- Take pms-RISEDRONATE in the morning on an empty stomach, at least 30 minutes before you eat, drink or take other medicines.
- Swallow each pms-RISEDRONATE tablet whole, while you are sitting or standing in an upright position. Drink enough **plain water** (at least 120 mL or ½ cup) to make sure the tablet gets to your stomach. Do not chew, cut or crush the tablets.
- Do not lie down for at least 30 minutes after taking pms-RISEDRONATE.

Usual dose:

To treat osteoporosis in women after menopause:

- 35 mg per week of pms-RISEDRONATE
- 150 mg per month of pms-RISEDRONATE

To prevent osteoporosis in women after menopause:

- 35 mg per week of pms-RISEDRONATE

To increase bone density in men with osteoporosis:

- 35 mg per week of pms-RISEDRONATE

Overdose:
If you take too much pms-RISEDRONATE, drink a full glass of milk, and tell your healthcare professional immediately. Do not make yourself vomit. Do not lie down.

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

Missed Dose:
Weekly dose (35 mg):
If you missed your dose on your usual day, take one tablet 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 one week, do not take 2 tablets on the same day. Skip your missed dose and go back to your regular schedule.

Monthly dose (150 mg):
If you forget to take your monthly dose of pms-RISEDRONATE, take it next in the morning if your next dose is more than 7 days away. Take your next dose on the regularly scheduled day.

If your next dose is less than 7 days away, wait until your next scheduled dose. Do not take more than 150 mg of pms-RISEDRONATE within 7 days.

What are possible side effects from using pms-RISEDRONATE?
These are not all the possible side effects you may have when taking pms-RISEDRONATE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:
- abdominal pain, heartburn, nausea
- diarrhea
- constipation
- flatulence (gas)
- headache
- lack of energy

When you take pms-RISEDRONATE once a month, it may cause short-lasting, mild flu-like symptoms. These symptoms usually decrease as you keep taking doses.

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 or breastbone pain, black or bloody stool			✓
UNCOMMON			
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 fractures: 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 between 15°C and 30°C.
- Keep out of reach and sight of children.

If you want more information about pms-RISEDRONATE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), or by contacting the sponsor 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

Last revised: February 1, 2023