# PRODUCT MONOGRAPH

## [Pr] pms-RISEDRONATE PLUS CALCIUM

Risedronate Sodium (as the hemi-pentahydrate) 35 mg Tablets, House Standard

**Bone Metabolism Regulator**

and

Calcium Carbonate 1250 mg Caplets, House Standard
(Equivalent to 500 mg elemental calcium)

**Mineral Supplement**

**PHARMASCIENCE INC.**
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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Component of Combination Pack | Dosage Form/ Strength | All Non-medicinal Ingredients |
|---|---|---|---|
| Oral | pms-RISEDRONATE (Risedronate sodium) | Tablets, 35 mg | Colloidal Silicon Dioxide, Iron Oxide Yellow, Maltodexterin, Mannitol, Polyvinyl Alcohol-Polyethylene Glycol Graft Copolymer, Povidone, Pregelatinized Starch, Red Iron Oxide, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Sucrose, Talc, Titanium Dioxide and Triethyl Citrate. |
| Oral | Calcium carbonate | Caplet, 1 250 mg (elemental calcium 500 mg) | Carnauba wax, Crospovidone, FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 5 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, Hydroxypropyl Methylcellulose, Maltodextrin, Microcrystalline Cellulose, Mineral Oil, Polysorbate 80, Stearic Acid, Titanium Dioxide, Triethyl Citrate, Vegetable Magnesium Stearate. |

### INDICATIONS AND CLINICAL USE

The pms-RISEDRONATE (risedronate sodium) component of pms-RISEDRONATE PLUS CALCIUM is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

**Treatment of Postmenopausal Osteoporosis:** In postmenopausal women with osteoporosis, pms-RISEDRONATE prevents vertebral and nonvertebral osteoporosis-related 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 (e.g., at least 2 SD below the premenopausal mean).

**Prevention of Postmenopausal Osteoporosis:** In postmenopausal patients at risk of developing osteoporosis, pms-RISEDRONATE preserves or increases BMD at sites of clinical importance for osteoporosis.

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), 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 calcium component of pms-RISEDRONATE PLUS CALCIUM contains calcium carbonate which is a calcium supplement to dietary intake of calcium.

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

**Geriatrics:** Of the patients receiving risedronate 5 mg daily in postmenopausal osteoporosis studies (see CLINICAL TRIALS), 43% were between 65 and 75 years of age, and 20% were over 75. In the 1-year study comparing daily versus weekly oral dosing regimens of risedronate in postmenopausal women, 41% of patients receiving risedronate 35 mg once-a-week were between 65 and 75 years of age and 23% were over 75.

Based upon the above study populations, no overall differences in efficacy or safety were observed between these patients and younger patients (< 65 years).

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

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

## CONTRAINDICATIONS

- Patients who are hypersensitive to pms-RISEDRONATE PLUS CALCIUM or to any ingredients in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

**pms-RISEDRONATE**

- Hypocalcemia (see WARNINGS AND PRECAUTIONS, General)

**Calcium**

- Hypercalcemia from any cause including, but not limited to, hyperparathyroidism, hypercalcemia of malignancy, or sarcoidosis.

## WARNINGS AND PRECAUTIONS

### General

Before commencing pms-RISEDRONATE PLUS CALCIUM, patients' calcium requirements should be assessed. It is recommended that patients receive at least 1200-1500 mg per day of calcium from all sources, as well as a daily vitamin D intake of at least 400-800 IU. The calcium carbonate tablet in pms-RISEDRONATE PLUS CALCIUM provides 500 mg elemental calcium per day and does not contain vitamin D.

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting pms-RISEDRONATE PLUS CALCIUM combination pack 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 has 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 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

Concomitant use of calcium-containing antacids should be monitored to avoid excessive intake of calcium. Total daily intake of calcium above 1500 mg has not demonstrated additional bone benefits, however daily intake above 2000 mg has been associated with increased risk of adverse effects, including hypercalcemia and kidney stones.

**Gastrointestinal**

Bisphosphonates may cause upper gastrointestinal 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 the pms-RISEDRONATE tablet 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).

Patients with achlorhydria may have decreased absorption of calcium that may be attenuated by taking calcium with food. Taking calcium with food enhances absorption (see DOSAGE AND ADMINISTRATION).

**Musculoskeletal**

In post marketing 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.

**Ophthalmologic**

Ocular disturbances including conjunctivitis, uveitis, episcleritis, iritis, and scleritis have been reported with risedronate 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

The pms-RISEDRONATE component of pms-RISEDRONATE PLUS CALCIUM is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).

Administration of calcium has been associated with a slight increase in the risk of kidney stones. In patients with a history of kidney stones or hypercalciuria, metabolic assessment to seek treatable causes of these conditions is warranted. If administration of calcium caplets should be needed in these patients, urinary calcium excretion and other appropriate testing should be monitored periodically.

## Special Populations

**Pediatrics:** The safety and efficacy of risedronate in children and growing adolescents have not been established.

**Pregnant Women:** pms-RISEDRONATE PLUS CALCIUM is not intended for use during pregnancy. There are no studies of risedronate and calcium in pregnant women.

Calcium crosses the placenta, reaching higher levels in fetal blood than in maternal blood.

**Nursing Women:** pms-RISEDRONATE PLUS CALCIUM 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.

Calcium is excreted in breast milk.

# 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 side effect in patients who received the risedronate component of pms-RISEDRONATE PLUS CALCIUM.

In osteoporosis studies with risedronate, the most commonly reported adverse reactions were abdominal pain, dyspepsia and nausea.

Most adverse events (AEs) reported in the Phase III trials with risedronate were mild or moderate in severity and did not generally lead to discontinuation of risedronate.

Calcium carbonate may cause gastrointestinal adverse effects such as constipation, flatulence, nausea, abdominal pain, and bloating.

## 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 of Postmenopausal Osteoporosis:** Risedronate 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 AEs was found to be comparable amongst risedronate and placebo-treated patients.

Table 1 list adverse events considered possibly or probably drug related, reported in ≥ 1% of risedronate 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 5 mg daily-treated patients and 6.0% of patients treated with placebo.

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

| Adverse Event | Risedronate 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, multicenter study comparing risedronate 35 mg once-a-week (the same formulation as the risedronate in risedronate plus calcium) to risedronate 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.

Patients with active or a history of upper gastrointestinal disorders at baseline and those taking ASA, non-steroidal anti-inflammatory drugs (NSAIDs) or drugs traditionally used for the treatment of peptic ulcers were not specifically excluded from participating in the risedronate once-a-week dosing study. 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 35 mg once-a-week and risedronate 5 mg daily-treated groups.

In the 1-year, double-blind, multicenter study comparing risedronate 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, 13.9% of patients taking risedronate 35 mg once-a-week experienced arthralgia compared to 7.8% of placebo patients. The overall safety profile observed in this study showed no substantive difference from that observed in the risedronate 5 mg daily versus risedronate 35 mg once-a-week treatment study.

**Endoscopic Findings:** Risedronate 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; 75 placebos).

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

In the 1-year study comparing risedronate 35 mg once-a-week to risedronate 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.

## Less Common Clinical Trial Adverse Drug Reactions

The following adverse drug reactions were reported in ≤1% of patients who received risedronate 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**

**Risedronate:**
**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. 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 is not systemically metabolized, does not induce cytochrome $P_{450}$ enzymes and has low protein binding. pms-RISEDRONATE PLUS CALCIUM 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 risedronate 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 this table are based on either drug interaction case reports or studies, 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**

| Drug | Reference | Effect | Clinical Comment |
|---|---|---|---|
| Acetylsalicylic acid (ASA) | CT | Among ASA users, the incidence of upper gastrointestinal adverse events was similar between the risedronate-treated patients and placebo-treated patients. | Of over 5700 patients enrolled in the risedronate 5 mg daily Phase III osteoporosis studies, ASA use was reported by 31 % of patients. |
| | | Among ASA 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 35 mg once-a-week to risedronate 5 mg daily in postmenopausal women, ASA use was reported by 56% of patients in the risedronate 35 mg once-a- week and 5 mg daily groups. |
| Antacids/supplements which contain polyvalent cations (e.g., calcium, magnesium, aluminum and iron) | T | Interference with the absorption of risedronate. | Such medications should be administered at a different time of the day (see DOSAGE AND ADMINISTRATION). |
| Hormone replacement therapy | CT | No clinically significant effect. | If considered appropriate, risedronate may be used concomitantly with hormone replacement therapy. |
| $H_2$-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 - treated patients and placebo-treated patients. | Of over 5700 patients enrolled in the risedronate 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 once-a-week and daily dosing regimens in postmenopausal women, at least 9% of patients in the risedronate 35 mg once-a- week and 5 mg daily groups used $H_2$-blockers and/or PPIs. |

| Drug | Reference | Effect | Clinical Comment |
|---|---|---|---|
| Non-steroidal anti-inflammatory drugs (NSAIDs) | CT | Among NSAIDs users, the incidence of upper gastrointestinal adverse events was similar between the risedronate-treated patients and placebo-treated patients. | Of over 5700 patients enrolled in the risedronate 5 mg daily Phase III osteoporosis studies, 48% used NSAIDs. |
| | | Among NSAIDs 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 35 mg once-a-week to risedronate 5 mg daily in postmenopausal women, 41 =% of patients in the risedronate 35 mg once-a-week and 5 mg daily groups used NSAIDs |

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

**Table 3: Established or Predicted Drug-Drug Interactions with Calcium**

| Drug | Reference | Effect | Clinical Comment |
|---|---|---|---|
| Iron | T | Calcium may interfere with the absorption of iron. | Iron and calcium should be taken at different times of the day. |
| Bisphosphonates | T | Decreased absorption of the bisphosphonate may occur. | Such medications should be administered at a different time of the day (see DOSAGE AND ADMINISTRATION). |
| Tetracyclines | CT | Calcium carbonate may interfere with the absorption of concomitantly administered tetracycline preparations. | Tetracycline preparations should be administered at least two hours before or four to six hours after oral intake of calcium carbonate. |
| Digoxin | T | Hypercalcemia may increase the toxicity of cardiac glycosides. | Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels. |
| Phenytoin | T | May form a nonabsorbable complex with calcium. | Administration times of these medications should be separated by at least 3 hours. |
| Thyroid hormones: Levothyroxine | CT | Concomitant intake of levothyroxine and calcium carbonate was found to reduce levothyroxine absorption and increase serum thyrotropin levels. Levothyroxine may adsorb to calcium carbonate in an acidic environment, which may block its absorption. | Levothyroxine should be administered on an empty stomach and calcium should be taken with food. Monitor serum TSH in patients taking calcium and adjust dose accordingly. |
| Fluoroquinolones (e.g. ciprofloxacin, moxifloxacin, ofloxacin) | CT | Concomitant administration of a fluoroquinolone and calcium may decrease the absorption of the fluoroquinolone. | Administration times of these medications should be separated by several hours. |
| $H_2$-blockers (e.g. cimetidine, famotidine, ranitidine) | T | Concomitant intake can cause decreased absorption of calcium. | Calcium should be taken with food to maximize absorption. |

| Drug | Reference | Effect | Clinical Comment |
|---|---|---|---|
| Proton Pump Inhibitors (e.g. lansoprazole, omeprazole, rabeprazole sodium) | T | Concomitant intake can cause decreased absorption of calcium. | Calcium should be taken with food to maximize absorption. |
| Systemic Glucocorticoids | T | Calcium absorption may be reduced and excretion increased when calcium is taken concomitantly with systemic glucocorticoids. | Additional calcium supplementation may be considered in patients taking long-term systemic glucocorticoids. |
| Vitamin D (e.g. calcitriol ergocalciferol, doxercalciferol) | CT | Absorption of calcium may be increased when given concomitantly with vitamin D analogues. | Ensure adequate Vitamin D intake through diet or supplements for optimal calcium absorption. |
| Thiazide Diuretics | C | Reduced urinary excretion of calcium has been reported during concomitant use of calcium carbonate and thiazide diuretics. | Serum calcium should be monitored during concomitant use with thiazide diuretics, particularly in hyperparathyroid patients. |

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

### Drug-Food Interactions

Clinical benefits may be compromised by failure to take pms-RISEDRONATE 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 have not been performed.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

- Food and medications containing polyvalent cations (e.g., calcium, magnesium, aluminum, and iron) can interfere with the absorption of pms-RISEDRONATE. Therefore, food and other medications should be administered at a different time of the day (see RECOMMENDED DOSE AND DOSAGE ADJUSTMENT AND DRUG INTERACTIONS, DRUG-DRUG INTERACTIONS).

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

- Other calcium-containing medications (e.g., multivitamins, antacids) should be administered at a different time of the day to prevent an interaction with pms-RISEDRONATE and to maximize pms-RISEDRONATE absorption.
- It is recommended that patients receive at least 1200 -1500 mg calcium per day from all sources, as well as, a vitamin D intake of at least 400-800 IU. pms-RISEDRONATE PLUS CALCIUM provides 500 mg calcium and does not contain any vitamin D.

- pms-RISEDRONATE PLUS CALCIUM is appropriate for additional supplementation of 500 mg of calcium for 6 out of 7 days, in conjunction with dietary and multivitamin intake, in patients whose calcium intake is 700-1000 mg/day. In patients who have a low daily calcium intake (i.e. less than 700-1000 mg/day) or who require vitamin D supplementation, it may be advisable to prescribe pms-RISEDRONATE 35 mg and a higher dose of calcium and/or vitamin D.

- 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 PLUS CALCIUM on an individual patient basis.

**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. Specifically, pms-RISEDRONATE should be taken on an empty stomach at least 30 minutes before the first food or drink (other than plain water) and/or any other medication of the day. The pms-RISEDRONATE tablet should be swallowed whole – do not chew.

The calcium caplet should be taken with food.

The recommended regimen is one 35 mg risedronate tablet, taken orally once a week (Day 1 of the 7-day treatment cycle) followed by one 1250 mg calcium carbonate (500 mg elemental calcium) caplet, taken orally daily on each of the remaining six days (Days 2 through 7) of the 7-day treatment cycle.

**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).

**Achlorhydria:** Absorption of calcium from calcium carbonate is poor in patients with achlorhydria unless taken with food.

**Missed Dose**

In case the pms-RISEDRONATE tablet dose is missed, patients should be instructed that the pms-RISEDRONATE tablet should be taken on the next day in the morning according to the dosing instructions. In this particular instance, patients should then take their calcium caplet on the following day. Patients should be instructed that the pms-RISEDRONATE tablet and the calcium caplet should be taken on different days.

If the calcium caplet is missed, the patient should be instructed to take it as soon as she remembers. She should not take more than 1 tablet from the package on the same day. Any remaining calcium caplets at the end of the weekly cycle should be discarded.

## OVERDOSAGE

pms-RISEDRONATE: 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.

Administration of milk or antacids containing calcium may be helpful to chelate 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.

**Calcium**: Because of its limited intestinal absorption, overdosage with calcium carbonate is unlikely. However, prolonged use of very high doses can lead to hypercalcemia associated with milk alkali syndrome. Clinical manifestations of hypercalcemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias.

**Treatment**:

Calcium should be discontinued. Other therapies that may be contributing to the condition, such as thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides should also be discontinued. Gastric emptying of any residual calcium should be considered. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should also be considered. Serum electrolytes, renal function and vital signs must be monitored. In severe cases, ECG and central venous pressure should be followed.

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

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

pms-RISEDRONATE: 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.

Calcium: Calcium is an important nutrient that must be ingested in sufficient quantities to promote bone health. A total intake of 1200 to 1500 mg per day of elemental calcium from both dietary and supplemental sources is recommended. Inadequate intake of calcium may result in reduced bone mass and increased risk of fractures. Calcium is a major substrate for mineralization and has an antiresorptive effect on bone. Calcium suppresses parathyroid hormone (PTH) secretion and decreases bone turnover. Increased levels of PTH are known to contribute to age-related bone loss, especially at cortical sites, while increased bone turnover is an independent risk factor of fractures.

### Pharmacodynamics

pms-RISEDRONATE: 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.

Risedronate 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 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 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 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 a 1-year study comparing risedronate 35 mg once-a-week to risedronate 5 mg daily for the treatment of osteoporosis in postmenopausal women, similar decreases in bone resorption (about 60%) and formation markers (about 40%) were observed for both dosage regimens.

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 PTH levels were observed within 6 months in risedronate 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 the 1-year study comparing risedronate 35 mg once-a-week to risedronate 5 mg daily for the treatment of osteoporosis in postmenopausal women, similar mean changes from baseline in serum calcium, phosphate and PTH were found for both dosage regimes.

Consistent with the effects of risedronate 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) (2.5 mg, 3% to 3.7%; 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 (2.5 mg, 0.7% to 0.9%; 5 mg, 1.5% to 2 %). In the 1-year study comparing risedronate 35 mg once-a-week to risedronate 5 mg daily for the treatment of osteoporosis in postmenopausal women, similar mean changes from baseline in BMD of the lumbar spine, total proximal femur, femoral neck and femoral trochanter were found for both dosage regimens (see CLINICAL TRIALS, *Treatment of Osteoporosis in Postmenopausal Women*).

Calcium: Calcium administration decreases the elevated rate of bone turnover typically seen in postmenopausal women with osteoporosis. In randomized, placebo controlled studies in postmenopausal women, calcium administration (500 mg to 1600 mg) decreased biochemical markers of bone turnover, including urine N-telopeptide, urine free pyridinoline (markers of bone resorption), alkaline phosphatase and osteocalcin (markers of bone formation) relative to placebo treated women.

Calcium administration may transiently increase levels of serum calcium with compensatory reductions in serum PTH and an increase in urinary calcium. However, urinary and serum calcium levels usually remain within the normal reference range.

## Pharmacokinetics

### Risedronate:

**Table 4: Summary of Pharmacokinetic Parameters of Risedronate**

| | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$,z (h) | $AUC_{0-\infty}$ (ng·h/mL) | Clearance (L/h/kg) | $V_z$ (L/kg) |
|---|---|---|---|---|---|---|
| 5 mg tablet; single dose | 0.85 | 0.93a | 206.1 | 3.45 | 19.94 | 5542 |
| 35 mg tablet; multiple dose, steady state | 10.6 | 0.49 | nd | 53.3 | 12.9 | nd |

a: Arithmetic mean
$t_{1/2}$, z: is the half-life of the terminal exponential phase.
VZ: is the terminal volume of distribution for IV doses and is uncorrected for bioavailability for oral doses.
nd: not determined

**Absorption:** Absorption after an oral dose is relatively rapid ($t_{max}$ ~ 1 hour) and occurs throughout the upper gastrointestinal tract. Absorption is independent of dose over the range studied (single dose, 2.5 to 30 mg; multiple dose, 2.5 to 5 mg daily; and multiple dose, 35 and 50 mg weekly). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean oral bioavailability of the 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. 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.

**Calcium:**

**Absorption:** Calcium is released from calcium complexes during digestion in a soluble, ionized form, for absorption from the small intestine. Absorption can be by both passive and active mechanisms. As calcium intake increases, the active transfer mechanism becomes saturated and an increasing proportion of calcium is absorbed via passive diffusion. Absorption of calcium carbonate is dose-dependent, with fractional absorption being highest when taken at doses up to 500 mg and when taken with food.

**Distribution:** Approximately 50% of calcium in the plasma is in the physiologically active ionized form; about 10% is complexed to phosphate, citrate or other anions, while the remaining 40% is bound to proteins, primarily albumin.

**Elimination:** Unabsorbed calcium from the small intestine is excreted in the feces. Renal excretion depends largely on glomerular filtration and calcium tubular reabsorption with more than 98% of calcium reabsorbed from the glomerular filtrate.

**Special Populations and Conditions**

**Pediatrics:** Risedronate pharmacokinetics has not been studied in patients < 18 years of age.

**Geriatrics:** Bioavailability and disposition of risedronate are similar in elderly (> 65 years of age) and younger subjects. No dosage adjustment is necessary.

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

**Race:** Pharmacokinetic differences of risedronate 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.

**Genetic Polymorphism:** No data are available.

## STORAGE AND STABILITY

Store between 15°C to 30°C.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-RISEDRONATE PLUS CALCIUM is supplied in a kit as a monthly (28 days) course of therapy. All risedronate tablets are packed in one blister and calcium caplets in another one blister. These two blisters are inserted in one folded carton; one blisters in each side of the carton.

- 4 risedronate tablets: Orange, modified capsule-shape, coated tablet debossed with "RS" on one side and "35" on the other side.
- 24 calcium caplets: Capsule shaped, green coated tablet.

Medicinal Ingredients:

Each pms-RISEDRONATE tablet for oral administration contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate.

Each calcium caplet contains 500 mg Elemental Calcium (as calcium carbonate from oyster shell).

Nonmedicinal Ingredients:

pms-RISEDRONATE:
Colloidal Silicon Dioxide, Iron Oxide Yellow, Maltodexterin, Mannitol, Polyvinyl Alcohol-Polyethylene Glycol Graft Copolymer, Povidone, Pregelatinized Starch, Red Iron Oxide, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Sucrose, Talc, Titanium Dioxide and Triethyl Citrate.

Calcium:
Carnauba Wax, Crospovidone, FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 5 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, Hydroxypropyl Methylcellulose, Maltodextrin, Microcrystalline Cellulose, Mineral Oil, Polysorbate 80, Stearic Acid, Titanium Dioxide, Triethyl Citrate, Vegetable Magnesium Stearate.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

**Drug Substance**

**Proper Name:** Risedronate sodium hemi-pentahydrate

Calcium carbonate

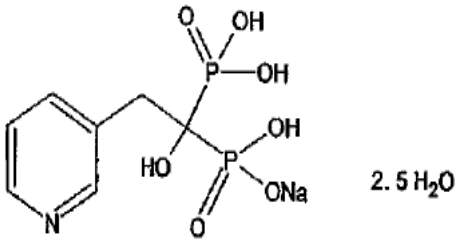
**Chemical Name:** pms-RISEDRONATE tablets contain risedronate sodium in the form of hemipentahydrate with small amounts of monohydrate. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl) ethylidene] bis [phosphonic acid] monosodium salt.

Calcium caplets contain calcium carbonate.

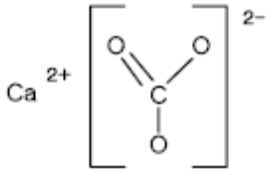
**Molecular Formula:** Risedronate sodium - $C_7H_{10}NNaO_7P_2 .2.5H_2O$
Calcium carbonate - $CaCO_3$

**Structural Formula:**

**Risedronate sodium**




**Calcium carbonate**



**Molecular Weight:** Risedronate sodium - 350.13 g/mol (Hemipentahydrate)
305.13 g/mol (anhydrous)
Calcium carbonate - 100.09 g/mol

**Solubility:** Risedronate sodium is soluble in pH 7.0 potassium phosphate dibasic solution, 0.1 N sodium hydroxide, and water; very slightly soluble in 0.1N hydrochloric acid, practically insoluble in ethanol, and insoluble in isopropanol.

Calcium carbonate is practically insoluble in water; soluble in dilute acids.

**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:
$pK_1 = 1.6 \pm 0.2$, pK2 = 2.2 ± 0.2, pK3 = 5.9 ± 0.1,
$pK_4 = 7.1 \pm 0.1$ and pK5 = 11.7 ± 0.3.

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

Precipitated calcium carbonate is a fine, white, odorless powder. It is stable and non-hygroscopic.

## CLINICAL TRIALS

### Comparative Bioavailability Study

A blind, randomized, 2-way crossover, bioequivalence study of pms-RISEDRONATE 35 mg tablet was performed versus "Warner Chilcott Canada Co." 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<br>(1 x 35 mg tablet)<br>From measured data<br>Geometric Mean<br>Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| **Parameter** | **Test*** | **Reference†** | **% Ratio of Geometric Means** | **Confidence Interval 90%** |
| $AUC_T$<br>(pg·h/mL) | 24182.8<br>28494.5 (67.9) | 23015.1<br>27491.8 (66.7) | 105.07 | 91.71 – 120.39 |
| $AUC_I$<br>(pg·h/mL) | 25122.9<br>29558.7 (67.4) | 23869.0<br>28467.1 (66.4) | 105.25 | 91.91 – 120.53 |
| $C_{max}$<br>(pg/mL) | 8113.8<br>9909.8 (81.1) | 7881.4<br>10164.6 (88.8) | 102.95 | 88.71 – 119.48 |
| $T_{max}$§<br>(h) | 1.00<br>(0.25 – 4.00) | 1.00<br>(0.25 – 2.50) | | |
| $T_{½}$€<br>(h) | 3.25 (29.9) | 3.19 (37.4) | | |

*pms-RISEDRONATE 35 mg tablets, Pharmascience Inc.
†ACTONEL® 35 mg tablets, Warner Chilcott Canada Co., purchased in Canada
§ Expressed as the median (range)
€ Expressed as the arithmetic mean (CV %)

## Treatment of Osteoporosis in Postmenopausal Women

### Study Demographics and Trial Design

**Table 5: Summary of Patient Demographics for Clinical Trials of Risedronate in the Treatment of Osteoporosis in Postmenopausal Women**

| Study Number | Trial Design[a] | Dosage | Duration | Patients N = number | Age Range (Age Mean) | Gender |
|---|---|---|---|---|---|---|
| 1<br>VERT-MN | R, PC, DB, MC, PG | 2.5 mg/day<br>5 mg/day<br>Placebo | 2 years<br>3 years<br>3 years | 1226 | 48-85<br>(71.0) | Postmenopausal female |
| 2<br>VERT-NA | R, PC, DB, MC, PG | 2.5 mg/day<br>5 mg/day<br>Placebo | 1 year<br>3 years<br>3 years | 2458 | 28-85<br>(68.6) | Postmenopausal female |
| 3 | R, PC, DB, MC, PG | 2.5 mg/day<br>5 mg/day<br>Placebo | 2 years | 543 | 45-80<br>(64.7) | Postmenopausal female |
| 4 | R, PC, DB, MC, PG | 2.5 mg/day<br>5 mg/day<br>Placebo | 12 – 18 months | 648 | 39-80<br>(62.5) | Postmenopausal female |
| 5 | R, AC, DB, MC, PG | 5 mg/day<br>35 mg/week*<br>50 mg/week*<br>*Placebo other 6 days | 12 months | 1456 | 48-95<br>(67.9) | Postmenopausal female |

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

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 bone mineral density (BMD) levels. All patients in these studies received supplemental calcium 1000 mg/day. Patients with low vitamin D levels also received supplemental vitamin D 500 IU/day. 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.

## Study Results

### Results of Studies Number 1 and 2:

The pivotal studies of risedronate in the treatment of postmenopausal osteoporosis clearly demonstrate that risedronate 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 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 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 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 5 mg daily also significantly reduced the proportion of patients experiencing new and worsening vertebral fractures in each of the studies. Figures 1 and 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 fracture is lower with risedronate compared with placebo at all-time points, consistent with risedronate's positive effect on bone strength.

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

| Endpoints | | Risedronate 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 [b] | (mm/yr) | -1.33 | -2.4 | | | 0.003 |
| Mean increase in BMD | (%) | | | | | |
| 6 months | Lumbar spine | 3.3 | -0.1 | 3.4 | | <0.001 |
| 36 months | Lumbar spine | 7.1 | 1.3 | 5.9 | | <0.001 |
| | Femoral neck | 2.0 | -1.0 | 3.1 | | <0.001 |
| | Trochanter | 5.1 | -1.3 | 6.4 | | <0.001 |
| 36 months | Midshaft radius | 0.5 | -1.9 | 2.4 | | <0.001 |
| **Study 2: VERT-NA** | | | | | | |
| Cumulative incidence of new vertebral Fracture over 3 years | (% of patients) | 11.3 | 16.3 | | 41 | 0.003 |
| Median annual height change [b] | (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 over 3 years (% of patients) | | 7.1 | 11.0 | | 36 | 0.005 |

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

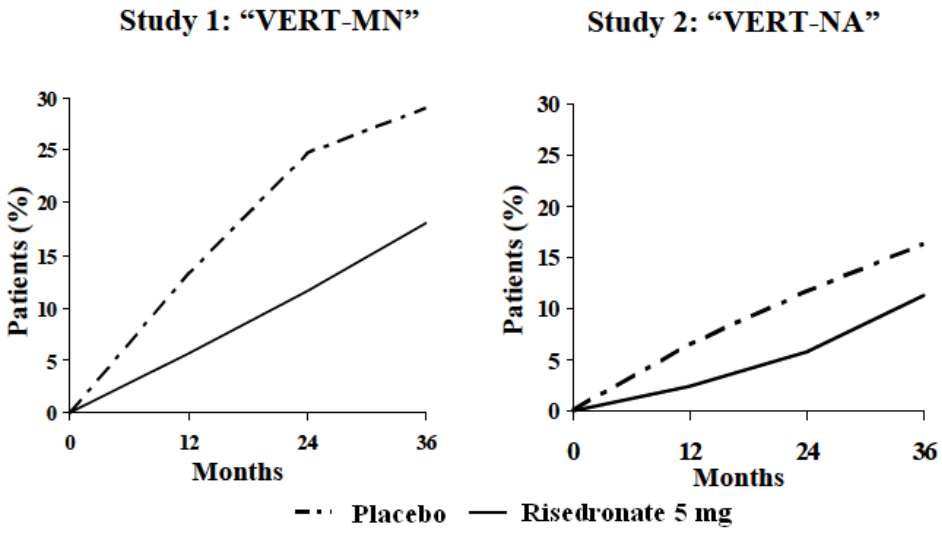



**Figure 1:Cumulative New Vertebral Fracture Incidence in Postmenopausal Women with Osteoporosis**

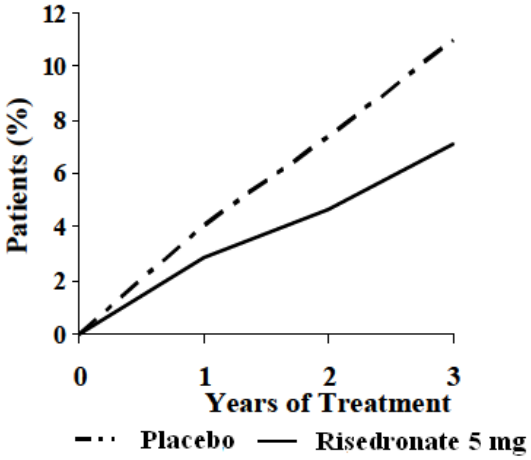



**Figure 2: Cumulative Incidence of Osteoporosis-Related Non-vertebral Fractures Studies 1 and 2 Combined**

Risedronate 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 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 Number 3 and 4

**Table 7: Effect of Risedronate on Bone Mineral Density in the Treatment of Osteoporosis in Postmenopausal Women**

| Endpoints | | Risedronate 5 mg 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, in these women with low bone mass, risedronate 5 mg daily produced significant mean increases in BMD of the lumbar spine compared to placebo at 6 months.
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 - 4) in women with postmenopausal osteoporosis separately and together demonstrate that risedronate 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 Number 5

**Table 8: Comparison of Risedronate Once–a-week vs. Daily Dosing in the Treatment of Osteoporosis in Postmenopausal Women – Primary Efficacy Analysis of Completers**

| Endpoints | | Risedronate 5 mg per day Mean Increase in BMD % (95% Confidence Interval) | Risedronate 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 35 mg once-a-week was concluded to be therapeutically equivalent to risedronate 5 mg daily.

In trials with risedronate 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 35 mg once-a-week to risedronate 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 35 mg taken once a week is as safe and effective as risedronate 5 mg daily for the treatment of postmenopausal osteoporosis.

## Prevention of Osteoporosis in Postmenopausal Women

### Study Demographics and Trial Design

**Table 9: Summary of Patient Demographics for Clinical Trials of Risedronate in the Prevention of Osteoporosis in Postmenopausal Women**

| Study Number | Trial Design | Dosage | Duration | Patients N = number | Age Range (Age Mean) | Gender |
|---|---|---|---|---|---|---|
| 6 | R, PC, DB, MC, PG | 2.5 mg/day<br>5 mg/day | 2 years | 383 | 42-63<br>(52.7) | Postmenopausal female |
| 7 | R, DB, PC, MC, PG | 35 mg/week<br>Placebo | 1 year | 280 | 44-64<br>(53.6) | Postmenopausal female |

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

Women in Study 6 were within 3 years of menopause and all patients in this study received supplemental calcium 1000 mg/day.

Study 7 included women who were 0.5 to 5 year postmenopausal without osteoporosis. All patients were supplemented with 1000 mg elemental calcium and 400 IU vitamin D per day.

### Study Results

### Results of Study Number 6

**Table 10: Effect of Risedronate 5 mg Daily on Bone Mineral Density in Postmenopausal Women without Osteoporosis**

| Endpoints | | Risedronate 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 treatment. Prevention of spinal bone loss was observed in the vast majority of women who received risedronate treatment. In contrast, most placebo-treated women experienced significant and

progressive bone loss, despite receiving supplemental calcium 1000 mg/day. Risedronate 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 Number 7

**Table 11: Effect of Risedronate sodium 35 mg Once-a-Week on Bone Mineral Density in Postmenopausal Women without Osteoporosis**

| Endpoints | | Risedronate 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: $p<0.0001$; ** $p=0.0041$

**Histology/Histomorphometry:** Histomorphometric evaluation of 278 bone biopsy samples from 204 postmenopausal women who received risedronate 5 mg or placebo once daily for 2 to 3 years (including 74 pairs of biopsies, 43 from risedronate-treated patients) showed a moderate and expected decrease in bone turnover in risedronate-treated women.

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

## DETAILED PHARMACOLOGY

### Risedronate:

There are extensive preclinical data to support that bone produced during risedronate 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 mcg/kg/day).

**Calcium:**
Published studies have demonstrated that changes in the dietary intake of calcium affect bone growth and skeletal development in intact animals, as well as bone loss in animal models of estrogen-depletion/ovariectomy and aging.

In young female rats, tibial BMD and trabecular bone volume were directly related to dietary calcium intake. The lower BMD and bone volume in the low calcium group were associated with higher bone resorption and lower bone formation. Peak bone mass remained low in the adult (8-month old) rats which had been fed low calcium diet from 1 to 3-months of age even if they were fed normal or high calcium diet from 3-months through 8-months.

In adult female rats (5-6 months), a low calcium diet for up to 9 months induced loss of BMD and bone volume, and potentiated the ovariectomy-induced loss of bone and bone strength in long bones and vertebra. In female dogs, a low calcium diet for 18 months induced loss of BMD in trabecular (vertebra) and cortical (forearm) bone but did not potentiate the ovariectomy induced bone loss. Bone loss with low calcium dietary intake was associated in both studies with increased bone turnover as measured by bone histomorphometry or turnover markers.

In rats fed a high calcium diet from 2-months through 24-months of age, the age-related loss of vertebral BMD and bone volume was reduced. This effect was associated with reduced bone turnover in the high calcium group.

## TOXICOLOGY

**Risedronate:**

**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 1703 mg/kg (10 967 mg/$m^2$). The minimum lethal dose in mice and rabbits was 4 000 mg/kg (10 909 mg/$m^2$) and 1000 mg/kg (10870 mg/$m^2$), respectively. These values represent 320 to 620 times the human 30 mg dose based on surface area (mg/$m^2$). There was no lethality in dogs at a dose of 100 mg/kg (2 000 mg/$m^2$), the highest dose tested.

**Chronic Toxicity:** In a 1-year 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/$m^2$.

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

**Reproduction:** Risedronate had no effect on fertility (male or female) in rats at doses up to 16 mg/kg/day (6.25 times the human 30 mg dose based on surface area, $mg/m^2$).

Reproduction studies in rats showed decreased implantation at 7.1 mg/kg/day and increased body weights of neonates at 7.1 and 16 mg/kg/day. Sites of incomplete fetal ossification of sternebrae were statistically significantly decreased in rats at 3.2 mg/kg/day and increased in rats at 7.1 mg/kg/day. Unossified fetal sternebrae were statistically significantly decreased in rats at 3.2 mg/kg/day and 7.1 mg/kg/day. The above doses ranged from 1.25 times (3.2 mg/kg) to 6.25 times (16 mg/kg) the human 30 mg dose based on surface area, $mg/m^2$. No significant fetal ossification effects were seen when rabbits were treated at doses up to 10 mg/kg/day (6 times the human 30 mg dose based on surface area, $mg/m^2$).

Similar to other bisphosphonates, treatment throughout mating and gestation with doses as low as 3.2 mg/kg/day has resulted in acute periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

**Calcium:**

**Acute Toxicity:** The $LD_{50}$ in rats for calcium (as calcium gluconate) was found to be 930 mg calcium/kg.

**Chronic Toxicity:** Rats fed about 5 mg Ca/g as dibasic calcium phosphate for 20 days had significantly enlarged kidneys.

An elevated calcium diet can have deleterious effects on development and growth and in the adult animal.

**Carcinogenicity:** No carcinogenesis studies have been identified for calcium.

**Mutagenesis:** In a published report, calcium carbonate was negative in a *Salmonella typhimurium* (TA97 & TA102) assay for mutagenesis.

**Reproduction:** Combinations of calcium salts have been used widely and extensively in clinical practice worldwide for many years. Human experience generally supersedes previously documented nonclinical data in these situations.

In one published study, moderate increases in dietary calcium given to rats for six weeks prior to pregnancy, and during gestation had no deleterious impact on fertility, maintenance of pregnancy, nor was there any fetal toxicity or teratogenicity.

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31. PrACTONEL PLUS CALCIUM® Product Monograph, Warner Chilcott Canada Co., Revision date: February 19, 2013, Control No.: 160238

**PART III: CONSUMER INFORMATION**

**[Pr]pms-RISEDRONATE PLUS CALCIUM**
Risedronate Sodium 35 mg tablets and
Calcium Carbonate 1250 mg caplets
(Equivalent to 500 mg elemental calcium)

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

## ABOUT THIS MEDICATION

**What the medication is used for:**
Treatment and prevention of postmenopausal osteoporosis.

**What it does:**
pms-RISEDRONATE PLUS CALCIUM is a combination of pms-RISEDRONATE (risedronate sodium hemi-pentahydrate) tablets and calcium carbonate caplets.

pms-RISEDRONATE is a non-hormonal drug (i.e., not an estrogen) that builds and strengthens bones. In many people, pms-RISEDRONATE actually rebuilds some of the bone that has already been lost. 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. pms-RISEDRONATE corrects this imbalance by decreasing the elevated rate of bone removal. pms-RISEDRONATE can therefore help reduce the risk of spine and non-spine fractures.

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

Calcium carbonate helps to provide the calcium that your body may need to harden new bone.

Since it is not known how long pms-RISEDRONATE PLUS CALCIUM should be continued, you should discuss the need to stay on this medication with your doctor regularly to determine if pms-RISEDRONATE PLUS CALCIUM is still right for you.

**When it should not be used:**
- If you have low blood calcium levels (hypocalcemia).
- If you have high blood calcium levels (hypercalcemia)
- If you are allergic to pms-RISEDRONATE PLUS CALCIUM or any of its ingredients (see below).

**What the medicinal ingredient is:**
Risedronate sodium, Calcium (as calcium carbonate).

**What the nonmedicinal ingredients are:**
pms-RISEDRONATE: Colloidal Silicon Dioxide, Iron Oxide Yellow, Maltodexterin, Mannitol, Polyvinyl Alcohol-Polyethylene Glycol Graft Copolymer, Povidone, Pregelatinized Starch, Red Iron Oxide, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Sucrose, Talc, Titanium Dioxide and Triethyl Citrate.

Calcium: Carnauba Wax, Crospovidone, FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 5 Aluminum lake, FD&C Yellow No. 6 Aluminum Lake, Hydroxypropyl Methylcellulose, Maltodextrin, Microcrystalline Cellulose, Mineral Oil, Polysorbate 80, Stearic Acid, Titanium Dioxide, Triethyl Citrate, Vegetable Magnesium Stearate.

**What dosage form it comes in:**
pms-RISEDRONATE PLUS CALCIUM is a combination pack containing:
- 4 pms-RISEDRONATE 35 mg orange tablets
- 24 calcium carbonate green film-coated caplets.

for a monthly (28 days) course of therapy.

## WARNINGS AND PRECAUTIONS

Before you use pms-RISEDRONATE PLUS CALCIUM, 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 are pregnant or nursing.
- You cannot carry out the dosing instructions (see PROPER USE OF THIS MEDICATION).
- 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 pms-RISEDRONATE.

Be sure to tell your health care providers, including doctors and dentists, about all medicines you are taking, including pms-RISEDRONATE PLUS CALCIUM.

## INTERACTIONS WITH THIS MEDICATION

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 the pms-RISEDRONATE in pms-RISEDRONATE PLUS CALCIUM. These should be taken at a different time of day.

If taken with some other medicines, the effects of pms-RISEDRONATE PLUS CALCIUM or the effects of other medicines may be changed. It is important to tell your doctor what other medications you are taking, even if the medicine does not require a prescription (including vitamins and herbal supplements).

Calcium products may interact with medications such as digoxin, certain antibiotics, iron supplements, phenytoin, thyroid hormones, steroid medications and thiazide diuretics.

Food, if taken with pms-RISEDRONATE, may prevent your body from absorbing pms-RISEDRONATE. Take pms-RISEDRONATE on an empty stomach. (See "PROPER USE OF THIS MEDICATION" for instruction).

## PROPER USE OF THIS MEDICATION

**Recommended Dose:**

- 1 pms-RISEDRONATE 35 mg tablet (orange) one day per week, taken orally on an empty stomach and
- 1 calcium caplet (green) daily on the other 6 days per week, taken orally with food.

pms-RISEDRONATE PLUS CALCIUM provides 500 mg of elemental calcium for 6 days per week. It is intended to increase your calcium intake towards the recommended daily intake of 1200-1500 mg in elemental calcium from diet and supplementation. The amount of calcium in this product is not enough by itself to provide you with your daily requirements. Talk to your doctor about whether you are getting enough calcium from your diet and supplements.
Other medications which may also contain calcium (e.g., multivitamins, antacids) should be taken at separate times of the day with food. All medications containing calcium should be taken at a different time of the day than your pms-RISEDRONATE tablet.

pms-RISEDRONATE PLUS CALCIUM does not contain vitamin D . Talk to your doctor or pharmacist about taking a vitamin D supplement.

***pms-RISEDRONATE tablets (orange)***
Choose a day of the week to take the orange pms-RISEDRONATE tablet. On your chosen day take one pms-RISEDRONATE tablet first thing in the morning with plain water before you have anything to eat or drink. Aside from plain water, do not eat or drink for at least 30 minutes after taking pms-RISEDRONATE. Plain water is allowed at all times.

***Instructions for all dosing options***

- Take with at least ½ cup (120 mL) of plain water. Do not take with coffee, tea, milk, or juice; they may prevent your body from absorbing pms-RISEDRONATE.
- Swallow whole – do not chew or wait for it to dissolve.
- Do not lie down for at least 30 minutes after taking a dose. You may sit, stand or do normal activities like read the newspaper, take a walk, etc.

***Calcium caplets (green)***

- Take 1 green caplet on each of the other 6 days per week that you don't take the orange pms-RISEDRONATE tablets. Calcium caplets should be taken with food.

These recommendations help pms-RISEDRONATE PLUS CALCIUM work correctly and help you avoid possible irritation of the esophagus (i.e., the tube connecting the mouth and the stomach).

**Missed Dose**:

***pms-RISEDRONATE tablet (orange):*** If you forget to take your dose on the regularly scheduled day, simply take 1 tablet on the day you first remember having missed your dose. Do not take a calcium caplet on that day. Then resume your schedule by taking 1 tablet on the originally chosen day of the week, do not take 2 tablets on the same day. Simply take 1 tablet as you normally would have on this day and resume your weekly schedule.

***Calcium caplets (green):*** If you forget to take your dose, simply continue to take 1 caplet on the next day. Do not double your next dose (i.e., do not take more than 1 caplet on the same day). If the day that you remember is your regularly scheduled pms-RISEDRONATE day, do not take the missed calcium caplet.

Discard any unused calcium caplets at the end of week.

**Overdose:**

If you took too many orange **pms-RISEDRONATE** tablets, drink a full glass of milk and contact your doctor or Poison Control Centre immediately. Do not induce vomiting. If you took a large number of green calcium caplets, discontinue use and seek medical attention.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Drugs like pms-RISEDRONATE may cause problems in your stomach and 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 pms-RISEDRONATE and tell your doctor right away. Remember to take pms-RISEDRONATE PLUS CALCIUM as directed.

In clinical studies of osteoporosis with pms-RISEDRONATE, the most commonly reported side effects were abdominal pain, heartburn and nausea.

pms-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 pms-RISEDRONATE.

Calcium carbonate may cause constipation, flatulence, nausea, abdominal pain and bloating.

Very rarely patients have reported non-healing jaw wounds while receiving 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 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 | | ✓ | |
| New or unusual pain in hip, groin or thigh | | ✓ | |
| Symptoms of low blood calcium level such as numbness, tingling, muscle spasms | | ✓ | |

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

## HOW TO STORE IT

- Keep pms-RISEDRONATE PLUS CALCIUM and all other medications out of the reach of children.
- Keep the tablets & caplets in their original package and store at controlled room temperature (15°C – 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 the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    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.healthcanada.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

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Pharmascience Inc. at, 1-888-550-6060.

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