PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICIATION INFORMATION

PrTEVA-RISEDRONATE/CALCIUM

Risedronate Sodium (as the monohydrate) 35 mg Tablets

Bone Metabolism Regulator

and

Calcium Carbonate 1250 mg Tablets, Teva Standard
500 mg elemental calcium

Mineral Supplement

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PrTEVA-RISEDRONATE / CALCIUM

Risedronate Sodium (as the monohydrate) 35 mg tablets and
Calcium Carbonate 1250 mg tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Component of Combination Pack	Dosage Form/ Strength	All Nonmedicinal Ingredients
Oral	TEVA-RISEDRONATE Once-a-Week (risedronate sodium)	Tablet, 35 mg	Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, pregelatinized starch, sodium stearyl fumarate, starch and film-coating containing FD&C yellow #6/sunset yellow FCF aluminium lake, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, polyethylene glycol, polysorbate and titanium dioxide.
Oral	Calcium carbonate	Tablet, 1250 mg; elemental calcium 500 mg	Microcrystalline cellulose, croscarmellose sodium, vegetable stearic acid, vegetable magnesium stearate, silicon dioxide, titanium dioxide, polyethylene glycol, FD&C Blue #2, sorbitol, talc, polyvinyl alcohol.

INDICATIONS AND CLINICAL USE

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

Treatment of Postmenopausal Osteoporosis: In postmenopausal women with osteoporosis, TEVA-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 (for example, at least 2 SD below the premenopausal mean).

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

TEVA-RISEDRONATE may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

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

The calcium component of TEVA-RISEDRONATE / 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 sodium 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 sodium in postmenopausal women, 41% of patients receiving risedronate sodium 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 TEVA-RISEDRONATE / CALCIUM or to any ingredients in the formulation. For a complete listing, see **DOSAGE FORMS**, **COMPOSITION AND PACKAGING**.

TEVA-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 TEVA-RISEDRONATE / 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 TEVA-RISEDRONATE / 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 TEVA-RISEDRONATE / CALCIUM combination pack therapy.

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 risedronate sodium 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

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 **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

Prior to treatment with TEVA-RISEDRONATE / CALCIUM, 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 TEVA-RISEDRONATE / CALCIUM.

During treatment with risedronate sodium, patients should maintain good oral hygiene, undergo routine dental check-ups and immediately report any oral symptoms. While on treatment, these patients should avoid invasive dental procedures if possible but should continue with regular dental cleaning and oral hygiene. For patients requiring dental procedures, there are no data

available to suggest whether discontinuation of bisphosphonate treatment prior to the procedure reduces the risk of ONJ. In patients who develop ONJ while on bisphosphonate therapy, surgery at the affected area may exacerbate the condition. Clinical judgment of the treating physician should guide the management of patients undergoing dental procedures, based on individual benefit/risk assessment.

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

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

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

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

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

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.

Musculoskeletal Pain:
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 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

The TEVA-RISEDRONATE component of TEVA-RISEDRONATE / 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 tablets 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 TEVA-RISEDRONATE in children and growing adolescents have not been established.

Pregnant Women: TEVA-RISEDRONATE / CALCIUM is not intended for use during pregnancy. There are no studies of TEVA-RISEDRONATE / CALCIUM in pregnant women.

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

Nursing Women: TEVA-RISEDRONATE / 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.

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 trials (see **CLINICAL TRIALS**).

Monitoring and Laboratory Tests

Osteonecrosis of the jaw: Prior to treatment with TEVA-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 TEVA-RISEDRONATE. Patients should receive routine dental check-ups while taking TEVA-RISEDRONATE.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Bisphosphonates may cause upper gastrointestinal disorders such as dysphagia, esophagitis, esophageal ulcer, and gastric ulcer. It is therefore important to follow the recommended dosing instructions (see **DOSAGE AND ADMINISTRATION**).

Musculoskeletal pain, rarely severe, has been reported as a common adverse event in patients who received the risedronate sodium component of risedronate/calcium.

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

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 sodium 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 sodium and placebo-treated patients.

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

Adverse Event	Risedronate sodium 5 mg N = 1742 (%)	Placebo Control N = 1744 (%)
Body as a Whole		
Abdominal Pain	4.1	3.3

Adverse Event	Risedronate sodium 5 mg N = 1742 (%)	Placebo Control N = 1744 (%)
Headache	2.5	2.3
Asthenia	1.0	0.7
Digestive System		
Dyspepsia	5.2	4.8
Nausea	4.8	5.0
Constipation	3.7	3.6
Diarrhea	2.9	2.5
Flatulence	2.1	1.8
Gastritis	1.1	0.9
Skin and Appendages		
Rash	1.4	0.9
Pruritus	1.0	0.5

* Considered to be possibly or probably causally related by clinical study Investigators.

Once a Week Dosing: In the 1-year, double-blind, multicentre study comparing risedronate sodium 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 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, 13.9% of patients taking risedronate sodium 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 sodium 5 mg daily versus risedronate sodium 35 mg Once-a-Week treatment study.

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).

In the 1-year study comparing risedronate sodium 35 mg Once-a-Week to risedronate sodium 5 mg daily in the treatment of postmenopausal osteoporosis, endoscopies performed during the study revealed no dose dependent pattern in the number of patients with positive endoscopic findings or in the anatomical location of abnormalities detected. Endoscopies were conducted only on consenting patients experiencing moderate to severe gastrointestinal complaints.

Less Common Clinical Trial Adverse Drug Reactions

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

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 **WARNINGS AND PRECAUTIONS**).

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

DRUG INTERACTIONS

Overview

No specific drug-drug interaction studies were performed with risedronate sodium. 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. TEVA-RISEDRONATE / 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). 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 this table are based on either drug interaction case reports, or predicted interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2: Established or Predicted Drug-Drug Interactions with Risedronate sodium

Drug	Reference	Effect	Clinical Comment
Antacids and calcium supplements which contain polyvalent cations (e.g., calcium, magnesium, aluminum and iron)	T	Interference with the absorption of risedronate sodium.	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 sodium 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 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, 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.
Non-steroidal anti-inflammatory drugs (NSAIDs)	CT	Among NSAIDs users, the incidence of upper gastrointestinal adverse events was similar between the risedronate sodium -treated patients and placebo-treated	Of over 5700 patients enrolled in the risedronate sodium 5 mg daily Phase III osteoporosis studies, 48% used Non-steroidal anti-inflammatory drugs NSAIDs.

Drug	Reference	Effect	Clinical Comment
		patients.	
		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 sodium 35 mg Once-a-Week to risedronate sodium 5 mg daily in postmenopausal women, 41% of patients in the risedronate sodium 35 mg Once-a-Week and 5 mg daily groups used NSAIDs.
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 TEVA-RISEDRONATE (see **WARNINGS AND PRECAUTIONS**).

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

Of over 5700 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-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.

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	Patients should be monitored with regard to electrocardiogram

Drug	Reference	Effect	Clinical Comment
		glycosides.	(ECG) and serum calcium levels.
Phenytoin	T	May form a non-absorbable 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.
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 TEVA-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 sodium 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 risedronate sodium. 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 TEVA-RISEDRONATE tablet 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 the TEVA-RISEDRONATE tablet (see Recommended Dose and Dosage Adjustment and **DRUG INTERACTIONS**).
- The TEVA-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).
- TEVA-RISEDRONATE Tablets should not be chewed, cut or crushed (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 TEVA-RISEDRONATE and to maximize TEVA-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. TEVA-RISEDRONATE / CALCIUM provides 500 mg calcium and does not contain any vitamin D.
- TEVA-RISEDRONATE / 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 TEVA-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 TEVA-RISEDRONATE / 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, TEVA-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 TEVA-RISEDRONATE tablet should be swallowed whole – do not chew.

The calcium tablet 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) tablet, 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 TEVA-RISEDRONATE tablet dose is missed, patients should be instructed that the TEVA-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 tablet on the following day. Patients should be instructed that the TEVA-RISEDRONATE tablet and the calcium tablet should be taken on different days.

If the calcium tablet 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 tablets at the end of the weekly cycle should be discarded.

OVERDOSAGE

TEVA-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, magnesium or aluminium may be helpful to chelate risedronate sodium 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

TEVA-RISEDRONATE: Risedronate sodium, a pyridinyl-bisphosphonate in the form 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 remodeling sites are activated) and bone resorption at remodeling 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

Risedronate sodium: 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 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 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 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 the 1-year study comparing risedronate sodium 35 mg Once-a-Week to risedronate sodium 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 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) (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 sodium 35 mg Once-a-Week to risedronate sodium 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 Sodium:

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)	Vz (L/kg)
5 mg tablet; single dose	0.85	0.93[a]	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.
V_Z 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 have 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. Risedronate sodium is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min) because of a lack of clinical experience.

Genetic Polymorphism: No data are available.

STORAGE AND STABILITY

Store at room temperature between 15ºC and 30ºC. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-RISEDRONATE / CALCIUM is supplied as a monthly (28 days) course of therapy. Each carton contains 4 strips of calcium tablets (4 x 6) and 1 strip of TEVA-RISEDRONATE Tablets (1 x 4) blister packaged.

- TEVA-RISEDRONATE: Orange, oval shaped, film-coated tablet, debossed with "R35" on one side and plain on the other.
- Calcium Tablets: blue capsule-shaped coated tablets, engraved with "**N**" on one side and "**500**" on the other side.

Medicinal Ingredients:
Each TEVA-RISEDRONATE tablet for oral administration contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the monohydrate. Each calcium tablet contains 500 mg elemental calcium as 1250 mg calcium carbonate.

Nonmedicinal Ingredients:
TEVA-RISEDRONATE: Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, pregelatinized starch, sodium stearyl fumarate, starch and film-coating containing FD&C yellow #6/sunset yellow FCF aluminium lake, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, polyethylene glycol, polysorbate and titanium dioxide.

Calcium: croscarmellose sodium, FD&C blue #2 aluminum lake, microcrystalline cellulose, polyethylene glycol, silicon dioxide, vegetable stearic acid, titanium dioxide, vegetable magnesium stearate, sorbitol, talc and polyvinyl alcohol.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Risedronate sodium (as monohydrate)
Calcium carbonate

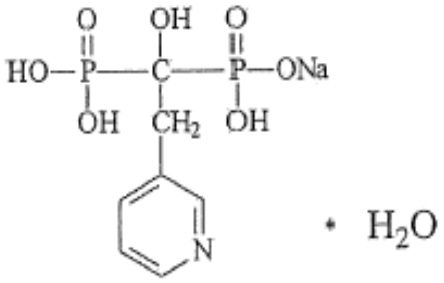
Chemical Name: [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt (as monohydrate)
&
Calcium carbonate

Molecular Formula: Risedronate sodium - $C_7H_{10}NO_7P_2Na \cdot H_2O$
Calcium carbonate - $CaCO_3$

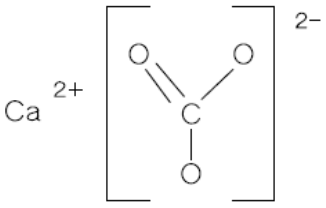
Molecular Weight: Risedronate sodium - Monohydrate: 323 g/mol
Calcium carbonate - 100 g/mol

Structural Formula:

Risedronate sodium



Calcium Carbonate



Description: Risedronate sodium is a white to pale yellow (or off-white) solid which is soluble in water.

Calcium carbonate is a white, odourless, tasteless, microcrystalline powder. It is practically insoluble in water but soluble in dilute acids.

CLINICAL TRIALS

A blinded, randomized, single-dose, two-period, two-sequence, two-treatment, comparative bioavailability study under fasting conditions between TEVA-RISEDRONATE 35 mg Tablets (Teva Canada Limited) and ACTONEL® 35 mg Tablets (Procter & Gamble Pharmaceuticals Inc., Canada) was conducted in healthy male volunteers (N=61) aged 18-55 years. The pharmacokinetic data calculated for the two risedronate sodium formulations are tabulated below:

Risedronic Acid (1 x 35 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	TEVA-RISEDRONATE*	Actonel®†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	41.737 49.851 (58)	39.468 46.818 (61)	105.75	93.34 - 119.80
AUC_I (ng*h/mL)	43.802 52.099 (58)	41.104 49.658 (59)	106.56	93.94 - 120.89
C_{max} (ng/mL)	12.459 14.923 (62)	12.183 14.407 (59)	102.27	89.51 - 116.85
T_{max}§ (h)	1.32 (44)	1.19 (56)		
$T_{½}$§ (h)	6.27 (46)	6.05 (47)		

* TEVA-RISEDRONATE 35 mg Tablets (Teva Canada Limited).
† Actonel® 35 mg Tablets (Procter and Gamble Pharmaceuticals Canada, Inc.). Purchased in Canada
§ Expressed as the arithmetic mean (CV%) only

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 Number	Trial Design[a]	Dosage	Duration	Patients N = number	Age Range (Age Mean)	Daily Supplement**
1 VERT-MN	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day Placebo	2 years 3 years 3 years	1226	48-85 (71.0)	≤ 500 IU
2 VERT-NA	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day Placebo	1 year 3 years 3 years	2458	28-85 (68.6)	≤ 500 IU
3	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day	2 years	543	45-80 (64.7)	-

Study Number	Trial Design[a]	Dosage	Duration	Patients N = number	Age Range (Age Mean)	Daily Supplement**
		Placebo				
4	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day Placebo	12 – 18 months	648	39-80 (62.5)	-
5	R, AC, DB, MC, PG	5 mg/day 35 mg/week* 50 mg/week* *Placebo other 6 days	12 months	1456	48-95 (67.9)	≤ 500 IU

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

* Placebo other days of treatment

** Patients in these studies were supplemented with 1000 mg of 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 bone mineral density (BMD) levels. All fractures (symptomatic/painful/clinical vertebral fractures and asymptomatic/ non-painful/silent vertebral fractures) were systematically captured and measured by annual radiographs.

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

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 sodium once-a-week dosing study.

Study Results

Results of Studies Number 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. 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 sodium compared with placebo at all time points, consistent with risedronate sodium's positive effect 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[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[a] 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

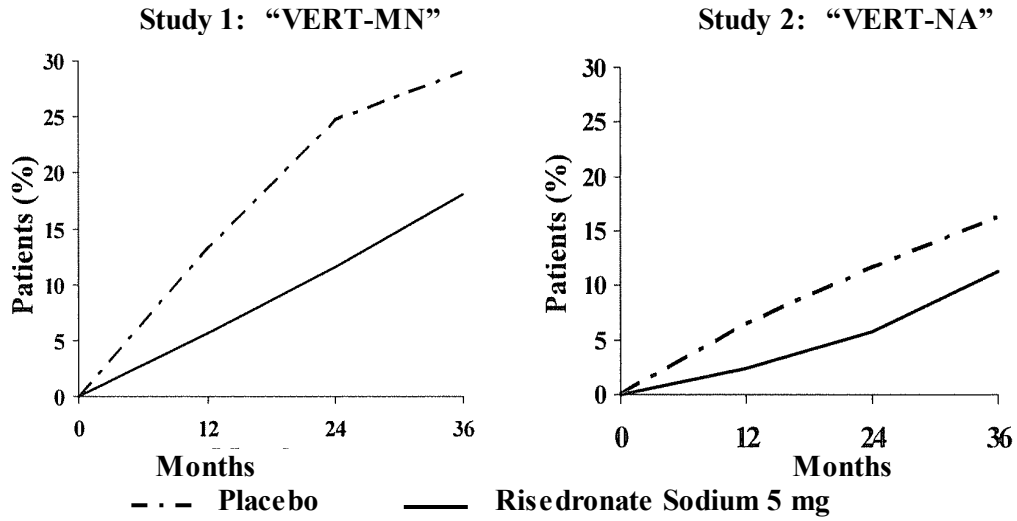
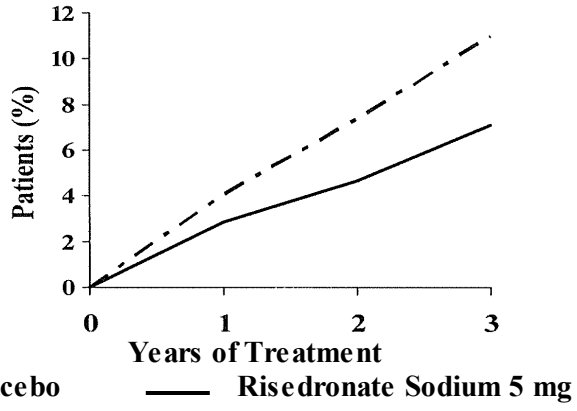


Figure 2: Cumulative Incidence of Osteoporosis-Related Non-vertebral Fractures Studies 1 and 2 Combined



Risedronate 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 Number 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 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		0.0	
Lumber Spine	4.1		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. 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 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 Number 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 per day 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 as risedronate sodium 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 Sodium in the Prevention of Osteoporosis in Postmenopausal Women

Study Number	Trial Design	Dosage	Duration	Patients N = number	Age Range (Age Mean)	Daily Supplement	
						Elemental Calcium	Vitamin D
6	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day	2 years	383	42-63 (52.7)	1000 mg	-
7	R, DB, PC, MC, PG	35 mg/week Placebo	1 year	280	44-64 (53.6)	1000 mg	400 IU

R: randomized; PC: placebo-controlled; DB: double-blind; MC: multicentre; 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 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 Number 7

Table 11: 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

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.

DETAILED PHARMACOLOGY

Risedronate sodium:

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

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

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 sodium:

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

Chronic Toxicity: In a 1-year 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/m2.

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

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

Reproduction:
In female rats, ovulation was inhibited at an oral dose of 16 mg/kg/day (approximately 5.2 times the 30 mg/day human dose based on surface area, mg/m^2). Decreased implantation was noted in female rats treated with doses $\geq$ 7.1 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, predominately 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.

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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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrTEVA-RISEDRONATE/CALCIUM
Risedronate Sodium 35 mg tablets and
Calcium Carbonate 1250 mg tablets (equivalent to 500 mg elemental calcium)
Film-coated tablets

Read this carefully before you start taking TEVA-RISEDRONATE/CALCIUM 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 TEVA-RISEDRONATE/CALCIUM.

What TEVA-RISEDRONATE/CALCIUM is used for:

- To treat or to prevent osteoporosis in postmenopausal women.

How does TEVA-RISEDRONATE/CALCIUM work?

TEVA-RISEDRONATE/CALCIUM is a combination of TEVA-RISEDRONATE (risedronate sodium monohydrate) tablets and calcium carbonate tablets.

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 and hip). Spine fractures may result in a curved back, height loss or back pain. TEVA-RISEDRONATE slows down bone loss which can help to reduce the risk of fractures. In many people, TEVA-RISEDRONATE helps to increase bone density.

TEVA-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.

It is not known how long TEVA-RISEDRONATE/CALCIUM should be used for treating osteoporosis. Keep talking to your doctor about whether TEVA-RISEDRONATE/CALCIUM is still right for you.

What are the ingredients in TEVA-RISEDRONATE/CALCIUM?

Medicinal ingredients:
Risedronate sodium, calcium (as calcium carbonate)

Nonmedicinal ingredients:
TEVA-RISEDRONATE: Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, pregelatinized starch, sodium stearyl fumarate, starch and film-coating containing: FD&C yellow #6/sunset yellow FCF, aluminium lake, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, polyethylene glycol, polysorbate and titanium dioxide.

Calcium: microcrystalline cellulose, croscarmellose sodium, vegetable stearic acid, vegetable magnesium stearate, silicon dioxide, titanium dioxide, polyethylene glycol, FD&C Blue #2, sorbitol, talc, polyvinyl alcohol.

TEVA-RISEDRONATE/CALCIUM comes in the following dosage forms:

TEVA-RISEDRONATE/CALCIUM is a combination pack containing TEVA-RISEDRONATE tablets and calcium carbonate tablets. It is supplied as a monthly (28 days) course of therapy. Each carton contains 4 strips of calcium 500 mg tablets (4 x 6) and 1 strip of TEVA-RISEDRONATE 35 mg tablets (1 x 4) blister packaged.

Do not use TEVA-RISEDRONATE/CALCIUM if:

- If you have low blood calcium levels (hypocalcemia).
- If you have high blood calcium levels (hypercalcemia)
- If you are allergic to TEVA-RISEDRONATE/CALCIUM or any of its ingredients (see below).

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

- Have/had problems swallowing or have problems with your esophagus (the tube that connects your mouth to your stomach)
- Have/had stomach or digestive problems
- Have/had kidney problems
- Cannot stand or sit upright for at least 30 minutes (see How to take TEVA-RISEDRONATE/CALCIUM)
- You are pregnant or breastfeeding
- Have one of the following risk factors: cancer, diabetes, chemotherapy, radiotherapy of the head or neck, lowered immune system (immunosuppression), poor oral hygiene, treatment with corticosteroids or cancer drugs such as angiogenesis inhibitors (drugs that slow down the growth of new blood vessels)
- Had/have pain, swelling or numbness of the jaw or loosening of a tooth or any other oral symptoms
- Have sores in the mouth. This can lead to osteonecrosis of the jaw

Your doctor may check if you:

- Smoke
- Have or have had tooth and/or gum disease
- Have dentures that do not fit well
- Have other relevant medical conditions at the same time, such as; low red blood cell count (called anemia) or if your blood cannot form clots in the normal way.

Your doctor may tell you to stop taking TEVA-RISEDRONATE/CALCIUM until all sores in your mouth are healed.

Other warnings you should know about:

Your doctor should check your mouth and may ask you to see your dentist before you start taking TEVA-RISEDRONATE. Dental work should be done before you start TEVA-RISEDRONATE treatment Take good care of your teeth and gums and see the dentist for regular checkups while taking TEVA-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 TEVA-RISEDRONATE/CALCIUM:
Vitamins, mineral supplements and antacids may contain substances that can stop your body from absorbing the TEVA-RISEDRONATE in TEVA-RISEDRONATE/CALCIUM. They contain calcium, magnesium, aluminium and iron. Take these medicines at a different time of day than TEVA-RISEDRONATE/CALCIUM. Talk to your healthcare provider about how and when to take these medicines.

Taking TEVA-RISEDRONATE with corticosteroids or cancer drugs may increase your chance of jaw bone problems (osteonecrosis of the jaw).

Talk to your doctor before taking pain medication like ASA or other non-steroidal anti-inflammatory drugs because they may upset your stomach.

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

Usual Dose:
- 1 TEVA-RISEDRONATE 35 mg tablet (orange) one day per week, taken orally on an empty stomach and
- 1 calcium tablet (blue) daily on the other 6 days per week, taken orally with food.

TEVA-RISEDRONATE/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 TEVA-RISEDRONATE tablet.

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

How to take TEVA-RISEDRONATE/CALCIUM:

TEVA-RISEDRONATE tablets (orange)
Choose a day of the week to take the orange TEVA-RISEDRONATE tablet. On your chosen day take one TEVA-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 TEVA-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 TEVA-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 tablets (blue)

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

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

Overdose:

If you think you have taken too many orange TEVA-RISEDRONATE tablets, drink a full glass of milk. Do not make yourself vomit. Contact your healthcare professional, hospital emergency room or regional Poison Control Centre immediately, even if there are no symptoms.
If you took a large number of blue calcium tablets, discontinue use and seek medical attention.

Missed Dose:

TEVA-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 tablet 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 tablets (blue): If you forget to take your dose, simply continue to take 1 tablet on the next day. Do not double your next dose (i.e., do not take more than 1 tablet on the same day). If the day that you remember is your regularly scheduled TEVA-RISEDRONATE day, do not take the missed calcium tablet.

Discard any unused calcium tablets at the end of week.

What are possible side effects from using TEVA-RISEDRONATE/ CALCIUM?

These are not all the possible side effects you may feel when taking TEVA-RISEDRONATE/ CALCIUM. If you experience any side effects not listed here, contact your healthcare professional.

Drugs like TEVA-RISEDRONATE may cause problems in your esophagus (the tube connecting the mouth and the stomach), stomach and intestines, including ulcers. If you have trouble or pain

upon swallowing, heartburn, chest pain and black or bloody stools, stop taking TEVA-RISEDRONATE and tell your doctor right away. Remember to take TEVA-RISEDRONATE/ CALCIUM as directed.

The most common side effects reported with TEVA-RISEDRONATE are abdominal pain, heartburn and nausea.

TEVA-RISEDRONATE may cause pain in bones, joints or muscles, rarely severe.
Calcium carbonate may cause constipation, flatulence, nausea, abdominal pain and bloating.

Patients receiving TEVA-RISEDRONATE or other drugs in this class have reported:

- Rarely, non-healing jaw wounds
- Very rarely, unusual fractures in their thigh bone. Consult your doctor in you experience new or unusual pain in your hip, groin, or thigh.
- Consult your doctor if you experience persistent pain in your mouth, teeth or jaw, or if your gums or mouth heal poorly.

Serious Side Effects And What To Do About Them			
Symptom / Effect	Talk with your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Common			
Pain in bones, joints, or muscles	√		
Abdominal pain	√		
Uncommon			
Eye pain, redness or swelling; sensitivity to light, decreased vision			√
Rare			
Painful 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 and skin reactions such as hives; rash (with or without blisters); swelling of the face, lips, tongue, or throat; difficult or painful swallowing; trouble breathing			√
New or unusual pain in hip, groin or thigh		√	
Symptoms of low levels of calcium in the blood such as numbness, tingling or muscle spasms		√	

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

- Keep TEVA-RISEDRONATE/CALCIUM and all other medications out of the reach and sight of children.
- Keep the tablets in their original package and store at room temperature between 15ºC and 30ºC. Protect from light. Do not keep medicine that is out of date or that you no longer need.

If you want more information about TEVA-RISEDRONATE/ CALCIUM:

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

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