PRODUCT MONOGRAPH

[Pr] NTP-RISEDRONATE

Risedronate sodium (as the monohydrate)

5 mg, 30 mg and 35 mg Tablets

Bone Metabolism Regulator

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Date of Revision:
July 26, 2012

Submission Control No: 156479

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Risedronate Sodium (as the monohydrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 5 mg, 30 mg and 35 mg	Lactose monohydrate *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section*

INDICATIONS AND CLINICAL USE

NTP-RISEDRONATE (risedronate sodium) is indicated for:
- the treatment and prevention of osteoporosis in postmenopausal women
- the treatment and prevention of glucocorticoid-induced osteoporosis in men and women
- Paget's disease of bone.

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

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

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

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

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

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

Paget's Disease of Bone: NTP-RISEDRONATE is indicated for patients with Paget's disease of bone (osteitis deformans) having alkaline phosphatase levels at least two times the upper limit of normal, or who are symptomatic, or who are at risk for future complications from their disease, to induce remission (normalization of serum alkaline phosphatase).

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) in the above osteoporosis studies. (See CLINICAL TRIALS section).

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

General

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

Adequate intake of calcium and vitamin D is important in all patients, especially in patients with Paget's disease in whom bone turnover is significantly elevated (see DRUG INTERACTIONS).

Osteonecrosis of the Jaw: In post-marketing reporting, osteonecrosis of the jaw has been reported in patients treated with bisphosphonates. The majority of reports occurred following dental procedures, such as tooth extractions, and have involved cancer patients treated with intravenous bisphosphonates, but some occurred in patients receiving oral treatment for postmenopausal osteoporosis and other diagnoses. Many had signs of local infection, including osteomyelitis. Osteonecrosis has other well documented multiple risk factors. It is not possible to determine if these events are related to bisphosphonates, to concomitant drugs or other therapies, to the patient's underlying disease or to other co-morbid risk factors (e.g., anemia, infection, pre-existing oral disease). A dental examination with appropriate preventative dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g., cancer, immune suppression, head and neck radiotherapy or poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures, if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of

bisphosphonate treatment prior to the procedure reduces the risk of osteonecrosis of the jaw. Clinical judgment, based on individual risk assessment, should guide the management of patients undergoing dental procedures.

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

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

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

Musculoskeletal: 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.

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

Ophthalmologic:
Ocular disturbances including conjunctivitis, uveitis, episcleritis, iritis, and scleritis have been reported with risedronate sodium therapy. Patients with ocular events other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. If ocular inflammatory symptoms are observed, treatment may have to be discontinued.

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

Special Populations

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

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

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

ADVERSE REACTIONS

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

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

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

In Paget's disease studies with risedronate sodium, the most commonly reported adverse reactions were diarrhea, nausea, abdominal pain and headache.

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

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

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

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

In the 1-year, double-blind, multicentre study comparing risedronate sodium 35 mg Once-a-Week to placebo for the prevention of osteoporosis in postmenopausal women, the overall safety

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

Glucocorticoid-Induced Osteoporosis: Risedronate sodium 5 mg daily has been studied in two Phase III glucocorticoid-induced osteoporosis trials enrolling more than 500 patients. The adverse event profile of this population was similar to that seen in postmenopausal osteoporosis trials.

The overall incidence of adverse events was found to be comparable between the risedronate sodium 5 mg daily and placebo treatment groups with the exception of back and joint pain. Back pain was reported in 8.8% of placebo-treated patients and 17.8% of risedronate sodium-treated patients; joint pain occurred in 14.7% of placebo patients and 24.7% of risedronate sodium patients. Most adverse experiences reported were either mild or moderate in severity and did not lead to discontinuation from the study. Discontinuation of therapy due to serious clinical adverse events occurred in 2.9% of risedronate sodium 5 mg daily-treated patients and 5.3% of patients treated with placebo. The occurrence of adverse events does not appear to be related to patient age, gender or race.

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

Table 2
Drug-Related* Adverse Events Reported in ≥1% of Risedronate sodium 5 mg Daily-Treated Patients in the Phase III Glucocorticoid-Induced Osteoporosis Trials

Adverse Event	Risedronate sodium 5 mg N = 174 (%)	Placebo Control N = 170 (%)
Body as a Whole		
Abdominal Pain	4.0	4.7
Headache	1.1	1.2
Digestive System		
Dyspepsia	5.7	2.9
Nausea	5.7	5.3
Constipation	2.9	3.5
Diarrhea	2.9	3.5
Dry Mouth	1.1	0.6
Duodenitis	1.1	0.0
Esophagitis	1.1	0.0
Flatulence	1.1	1.8
Gastrointestinal Disorder	1.1	0.0
Nervous System		
Dizziness	1.1	1.2
Skin and Appendages		
Rash	1.1	2.4
Skin Disorder	1.1	0.0

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

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 non-steroidal anti-inflammatory drug (NSAIDs) or acetylsalicylic acid (ASA). Investigators were encouraged to perform endoscopies in any patients with moderate-to-severe gastrointestinal complaints while maintaining the blind. These endoscopies were ultimately performed on equal numbers of patients between the treated and placebo groups (75 risedronate sodium; 75 placebo).

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

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

Paget's Disease of Bone: Risedronate sodium has been studied in over 390 patients with Paget's disease of bone. The adverse experiences reported have usually been mild or moderate and generally have not required discontinuation of treatment. The occurrence of adverse experiences does not appear to be related to patient age, gender or race.

In a Phase III clinical study, risedronate sodium and Didronel® (etidronate disodium tablets) showed similar adverse event profiles: 6.6% (4/61) of the patients treated with risedronate sodium 30 mg daily for 2 months discontinued treatment due to adverse experiences, compared with 8.2% (5/61) of the patients treated with Didronel 400 mg daily for 6 months.

Table 3 lists adverse events considered possibly or probably drug-related, reported in ≥1% of risedronate sodium 30 mg daily-treated patients, in the Phase III Paget's trial.

Table 3 Drug-Related* Adverse Events Reported in ≥1% of Risedronate sodium 30mg Daily-Treated Patients in the Phase III Paget's Trial		
Adverse Event	Risedronate sodium 30 mg/day x 2 months N = 61 (%)	Didronel 400 mg/day x 6 months N = 61 (%)
Body as a Whole		
Abdominal Pain	6.6	3.3
Headache	4.9	6.6
Infection	3.3	6.6
Flu Syndrome	1.6	0.0
Neck Rigidity	1.6	1.6
Neoplasm	1.6	0.0
Pain	1.6	8.2
Chest Pain	1.6	0.0
Digestive System		
Diarrhea	13.1	9.8
Nausea	8.2	4.9
Constipation	3.3	1.6
Flatulence	3.3	4.9
Colitis	1.6	0.0
Metabolic and Nutritional		
Peripheral Edema	1.6	0.0
Hypocalcemia	1.6	0.0
Weight Decreased	1.6	0.0
Musculoskeletal System		
Arthralgia	9.8	8.2
Leg Cramps	1.6	0.0
Myasthenia	1.6	0.0
Bone Pain	1.6	0.0
Nervous System		
Dizziness	1.6	0.0
Respiratory System		
Apnea	1.6	0.0
Bronchitis	1.6	0.0
Sinusitis	1.6	0.0
Skin		
Rash	1.6	0.0
Special Senses		
Amblyopia	1.6	0.0
Corneal Lesion	1.6	0.0
Dry Eyes	1.6	0.0
Ear Pain	1.6	1.6
Tinnitus	1.6	0.0
Urogenital System		
Nocturia	1.6	0.0
* Considered to be possibly or probably causally related by clinical study investigators.		

In the Phase III comparative study versus Didronel, patients with a history of upper GI disease or abnormalities were not excluded. Patients were also not excluded based on NSAID or ASA use. The proportion of risedronate sodium 30 mg daily-treated patients with mild or moderate upper

GI experiences was similar to that in the Didronel-treated group, with no severe upper GI experiences observed in either treatment group.

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

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

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

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

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

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

Patients in the clinical trials were exposed to a wide variety of commonly used concomitant medications (including NSAIDs, H_2-blockers, proton pump inhibitors, antacids, calcium channel blockers, beta-blockers, thiazides, glucocorticoids, anticoagulants, anticonvulsants, cardiac glycosides) without evidence of clinically relevant interactions.

The drugs listed in Table 4 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 4
Established or Predicted Drug-Drug Interactions with Risedronate Sodium

Risedronate sodium	Reference	Effect	Clinical Comment
Antacids and calcium supplements which contain polyvalent cations (e.g., calcium, magnesium, aluminum, and iron)	CT/T	Interference with the absorption of risedronate sodium.	Such medications should be administered at a different time of the day from risedronate sodium (see DOSAGE AND ADMINISTRATION).
Hormone replacement therapy (HRT)	CT	No clinically significant effect for risedronate sodium.	If considered appropriate, risedronate sodium may be used concomitantly with HRT (see CLINICAL TRIALS, Study 8).
H_2-blockers and proton pump inhibitors (PPIs)	CT	Among H_2-blockers and PPIs users, the incidence of upper gastrointestinal adverse events was similar between the risedronate sodium-treated patients and placebo-treated patients.	Of over 5700 patients enrolled in the risedronate sodium 5 mg daily Phase III osteoporosis studies, 21% used H_2-blockers and/or PPIs.
		Among H_2-blockers and PPIs users, the incidence of upper gastrointestinal adverse experiences was found to be similar between the weekly- and daily-treated groups	In the 1-year study comparing risedronate sodium Once-a-Week and daily dosing regimens in postmenopausal women with osteoporosis, at least 9% of patients in the risedronate sodium 35 mg Once-a-Week and 5 mg daily groups used H_2-blockers and/or PPIs.

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 sodium-treated patients and placebo-treated patients.

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

Drug-Food Interactions
Clinical benefits may be compromised by failure to take NTP-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

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

- Risedronate sodium 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 risedronate sodium. (See Recommended Dose and Dosage Adjustment).

- Each risedronate sodium tablet should be swallowed whole while the patient is in an upright position and with sufficient plain water (≥ 120 mL) to facilitate delivery to the stomach.

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

- Risedronate sodium tablets should not be chewed, cut, or crushed (see WARNINGS AND PRECAUTIONS, General).

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

Recommended Dose and Dosage Adjustment
For all indications and doses: The patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to instructions.

Treatment of Postmenopausal Osteoporosis: The recommended regimen are daily (5 mg) or weekly (35 mg Once-a-Week), taken orally.

Prevention of Postmenopausal Osteoporosis: The recommended regimens are daily (5 mg daily) or weekly (35 mg Once-a-Week), taken orally.

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis: The recommended regimen is 5 mg daily, taken orally.

Treatment of Paget's Disease of Bone: The recommended regimen is 30 mg daily for 2 months, taken orally. Re-treatment may be considered (following post-treatment observation of at least 2 months) if relapse has occurred, or if treatment fails to normalize serum alkaline phosphatase. For re-treatment, the dose and duration of therapy are the same as for initial treatment. There are no data available on more than one course of re-treatment.

Renal Impairment: No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min or in the elderly. Not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min).

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

Missed Dose

Daily: Patients should be instructed that if they miss a dose of NTP-RISEDRONATE 5 mg or 30 mg, they should take 1 tablet of NTP-RISEDRONATE as they normally would for their next dose. Patients should not double their next dose or take 2 tablets on the same day.

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

OVERDOSAGE

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

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

Milk or antacids containing calcium, magnesium, and aluminum may be given to bind risedronate sodium and reduce absorption of the drug. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug if performed within 30 minutes of ingestion. Standard procedures that are effective for treating hypocalcemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

Treatment and Prevention of Osteoporosis in Postmenopausal Women: Osteoporosis is a degenerative and debilitating bone disease characterized by decreased bone mass and increased fracture risk at the spine, hip and wrist. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. Osteoporosis occurs in both men and women but is more common among women following menopause.

In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly-formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of bone fracture. After menopause, the risk of fractures of the spine and hip increases dramatically; approximately 40% of 50-year-old women will experience an osteoporosis-related fracture of the spine, hip, or wrist during their remaining lifetimes. After experiencing one osteoporosis-related fracture, the risk of future fracture increases 5-fold compared to the risk among a non-fractured population. One in five men older than 50 years will have an osteoporotic fracture, most commonly at the spine, hip and wrist.

Risedronate sodium treatment decreases the elevated rate of bone turnover and corrects the imbalance of bone resorption relative to bone formation that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of risedronate sodium to postmenopausal women resulted in dose-dependent decreases in biochemical markers of bone turnover, including urinary markers of bone resorption and serum markers of bone formation, at doses as low as 2.5 mg daily. At the 5 mg daily dose, decreases in resorption markers were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone formation and bone resorption; decreases in bone formation of about 20% were evident within 3 months of treatment. Bone turnover markers (BTMs) reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years.

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

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

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

In two 1-year studies for the treatment of osteoporosis in postmenopausal women comparing risedronate sodium 35 mg Once-a-Week to risedronate sodium 5 mg daily, similar mean changes from baseline in serum calcium, phosphate and PTH were found for the intermittent regimen when compared to the daily dosage regimen.

Consistent with the effects of risedronate sodium on biochemical markers of bone turnover, daily oral doses as low as 2.5 mg produced dose dependent, significant increases in lumbar spine bone mineral density (BMD) (risedronate sodium 2.5 mg, 3% to 3.7%; risedronate sodium 5 mg, 4% to 4.5%) after 12 months of treatment in large-scale postmenopausal osteoporosis trials. A dose-dependent response to treatment was also observed in the BMD of the femoral neck over the same time (risedronate sodium 2.5 mg, 0.7% to 0.9%; risedronate sodium 5 mg, 1.5% to 2%). (see CLINICAL TRIALS, Treatment of Osteoporosis in Postmenopausal Women).

Glucocorticoid-Induced Osteoporosis: Chronic exposure to glucocorticoids (≥7.5 mg/day prednisone or its equivalent) induces rapid bone loss by decreasing bone formation and increasing bone resorption. The bone loss occurs most rapidly during the first 6 months of therapy with persistent but slowing bone loss for as long as glucocorticoid therapy continues.

Glucocorticoid-induced osteoporosis is characterized by low bone mass that leads to an increased risk of fracture (especially vertebral, hip and rib). It occurs in both men and women, and approximately 50% of patients on chronic glucocorticoid treatment will experience fractures. The relative risk of a hip fracture in patients on >7.5 mg/day prednisone is more than doubled (RR = 2.27); the relative risk of vertebral fracture is increased five-fold (RR = 5.18).

Risedronate sodium treatment decreases bone resorption without directly inhibiting bone formation. In 1-year clinical trials in the treatment and prevention of glucocorticoid-induced osteoporosis, risedronate sodium 5 mg daily produced rapid and statistically significant reductions in biochemical markers of bone turnover, similar to those seen in postmenopausal osteoporosis. Urinary collagen cross-linked N-telopeptide (a marker of bone resorption) and serum bone specific alkaline phosphatase (a marker of bone formation) were decreased by 50%

to 55% and 25% to 30%, respectively, within 3 to 6 months after initiation of therapy. The reduction was evident within 14 days and BTMs remained decreased throughout the duration of risedronate sodium treatment.

Consistent with the changes in biochemical markers of bone turnover, risedronate sodium 5 mg daily provides a beneficial effect on bone mineral density and reduces the risk of vertebral fractures by approximately 70% when compared to placebo (see CLINICAL TRIALS, Glucocorticoid-Induced Osteoporosis).

Paget's Disease of Bone: Paget's disease of bone is a chronic focal skeletal disorder characterized by greatly increased and disordered bone remodelling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged and weakened bone structure.

Clinical manifestations of Paget' s disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical marker of disease activity, provides an objective measure of disease severity and response to therapy.

Risedronate sodium is a bisphosphonate that acts primarily to inhibit bone resorption. This effect is related to its inhibitory effect on osteoclasts. In the Phase III clinical trial, risedronate sodium 30 mg daily for 2 months produced significant ($p < 0.001$) reductions of 81% to 88% in serum alkaline phosphatase excess, as well as significant reductions in bone-specific serum alkaline phosphatase (Ostase, 67% to 70%) and urinary deoxypyridinoline/creatinine (47% to 51%). Reductions were evident as early as 1 month after the start of treatment, and progressively increased in magnitude (following completion of the 2 month treatment) when measured at monthly intervals over a 6 month period. Clinically meaningful reductions in serum alkaline phosphatase were observed starting at 1 month with levels maintained through 12 months.

Asymptomatic and mild decreases in serum calcium and phosphorus levels have been observed in some patients. These decreases in calcium are associated with increases in serum intact PTH and 1,25-dihydroxy vitamin D, resulting in an increase in tubular reabsorption of calcium.

Markers of bone resorption (such as urinary deoxypyridinoline/creatinine or hydroxyproline/creatinine) usually decrease before markers of bone formation (such as serum alkaline phosphatase). This difference is indicative of the primary antiresorptive effect of risedronate sodium.

Bone turnover marker levels continue to decrease when risedronate sodium treatment is stopped. Therefore, to assess the full effect of response, patients should be followed for at least 2 months following the 2-month treatment period.

Pharmacokinetics

Table 5
Summary of Pharmacokinetic Parameters of Risedronate

	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$, z (h)	$AUC_{0-\infty}$ (ng•h/mL)	Clearance (L/h/kg)	V_z (L/kg)
5 mg tablet; single dose	0.85	0.93[a]	206.1	3.45	19.94	5542

30 mg tablet; single dose	4.2	0.87[a]	226.1	17.1	23.60	7542
35 mg tablet; multiple dose[b], steady-state	10.6	0.49	nd	53.3	12.9	nd

a Arithmetic mean
b administered weekly
$t_{½}$, z is the half-life of the terminal exponential phase
V_z is the terminal volume of distribution uncorrected for bioavailability
nd not determined

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

Distribution: The mean steady-state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was found to be minimal (in the range of 0.001% to 0.01%), with drug levels quickly decreasing after the final dose.

Metabolism: There is no evidence that risedronate is systemically metabolized.

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

Special Populations and Conditions

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

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

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

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency: No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in rat, dog, and human liver preparations. Insignificant amounts (<0.1% of intravenous dose) of drug are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.

Renal Insufficiency: Risedronate is excreted intact primarily via the kidney. Patients with mild-to-moderate renal impairment (creatinine clearance >30 mL/min) do not require a dosage adjustment. Exposure to risedronate was estimated to increase by 44% in patients with creatinine clearance of 20 mL/min. Risedronate sodium is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of a lack of clinical experience.

Genetic Polymorphism: No data are available.

STORAGE AND STABILITY

Store at controlled room temperature (15°C - 30°C). Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DOSAGE FORMS and COMPOSITION:

NTP-RISEDRONATE is supplied as:
5 mg: Yellow, oval-shaped, film-coated tablet, debossed with "R5" on one side and plain on the other.
30 mg: White, oval-shaped, film-coated tablet, debossed with "R30" on one side and plain on the other.
35 mg: Orange, oval-shaped, film-coated tablet, debossed with "R35" on one side and plain on the other.

Each tablet contains either 5 mg, 30 mg or 35 mg risedronate sodium (as the monohydrate) as the active ingredient. Each tablet also contains the following nonmedicinal ingredients: Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, pregelatinized starch, sodium stearyl fumarate, starch and film-coating containing the following:

5 mg: D&C yellow #10 lake, hydroxypropyl methylcellulose, iron oxide yellow, polyethylene glycol, polysorbate and titanium dioxide.

30 mg: hydroxypropyl methylcellulose, polyethylene glycol, polysorbate and titanium dioxide.

35 mg: FD&C yellow #6/sunset yellow FCF aluminium lake, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, polyethylene glycol, polysorbate and titanium dioxide.

PACKAGING:
5 mg: Available in bottles of 30 and 100 tablets and blisters of 30 tablets.
30 mg: Available in bottles of 30 tablets.
35 mg: Available in bottles of 30 tablets and blisters of 4 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

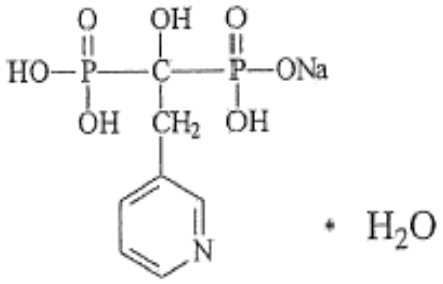
Common name: Risedronate sodium (as monohydrate)

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

Molecular formula: $C_7H_{10}NO_7P_2Na \cdot H_2O$

Molecular mass: 323 g/mol

Structural formula:



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

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY STUDIES

A blinded, randomized, single-dose, two-period, two-sequence, two-treatment, comparative bioavailability study under fasting conditions between NTP-RISEDRONATE 5mg Tablets (NT Pharma Canada Ltd.) and ACTONEL® 5mg Tablets (Procter & Gamble Pharmaceuticals Inc., Canada) was conducted in healthy male volunteers (N=64) aged 19-54 years. The pharmacokinetic data calculated for the two risedronate sodium formulations are tabulated below:

Risedronic Acid (3 x 5 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	NTP-RISEDRONATE *	Actonel® †	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	12.662 14.746 (59)	13.014 14.890 (55)	97.30	86.32 – 109.67
AUC_I (ng*h/mL)	13.197 15.299 (59)	13.546 15.442 (54)	97.42	86.70 – 109.47
C_{max} (ng/mL)	4.15172 4.84728 (60)	4.46472 5.03693 (50)	92.99	82.35 – 105.00
T_{max} § (h)	1.13 (35)	1.06 (37)		
$T_{½}$ § (h)	2.39 (29)	2.31 (25)		

* NTP-RISEDRONATE 5 mg tablets (NT Pharma Canada Ltd.).

† Actonel® 5 mg tablets. (Procter and Gamble Pharmaceuticals Canada, Inc.). Purchased in Canada

§ Expressed as the arithmetic mean (CV%) only

A blinded, randomized, single-dose, two-period, two-sequence, two-treatment, comparative bioavailability study under fasting conditions between NTP-RISEDRONATE 35mg Tablets (NT Pharma Canada Ltd.) and ACTONEL® 35mg 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	NTP-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)		

* NTP-RISEDRONATE 35 mg tablets (NT Pharma Canada Ltd.).

† 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 6
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 Study Supplement** Vitamin D
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 Placebo	2 years	543	45-80 (64.7)	-
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*	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 elemental calcium/day

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

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

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

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

Study Results
Results of Studies 1 and 2:

The pivotal studies of risedronate sodium in the treatment of postmenopausal osteoporosis clearly demonstrate that risedronate sodium 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 fractures is lower with risedronate sodium compared with placebo at all time points, consistent with the positive effect of risedronate sodium on bone strength.

Table 7
Effect of Risdedronate sodium on Fracture, Height and Bone Mineral Density in the Treatment of Osteoporosis in Postmenopausal Women

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

Mean increase in BMD	(%)					
6 months	Lumbar Spine	2.7	0.4	2.2		<0.001
36 months	Lumbar Spine	5.4	1.1	4.3		<0.001
	Femoral Neck	1.6	-1.2	2.8		<0.001
	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 nonvertebral fracture[b] over 3 years	(% of patients)	7.1	11.0		36	0.005

[a] Measured by stadiometer

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

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

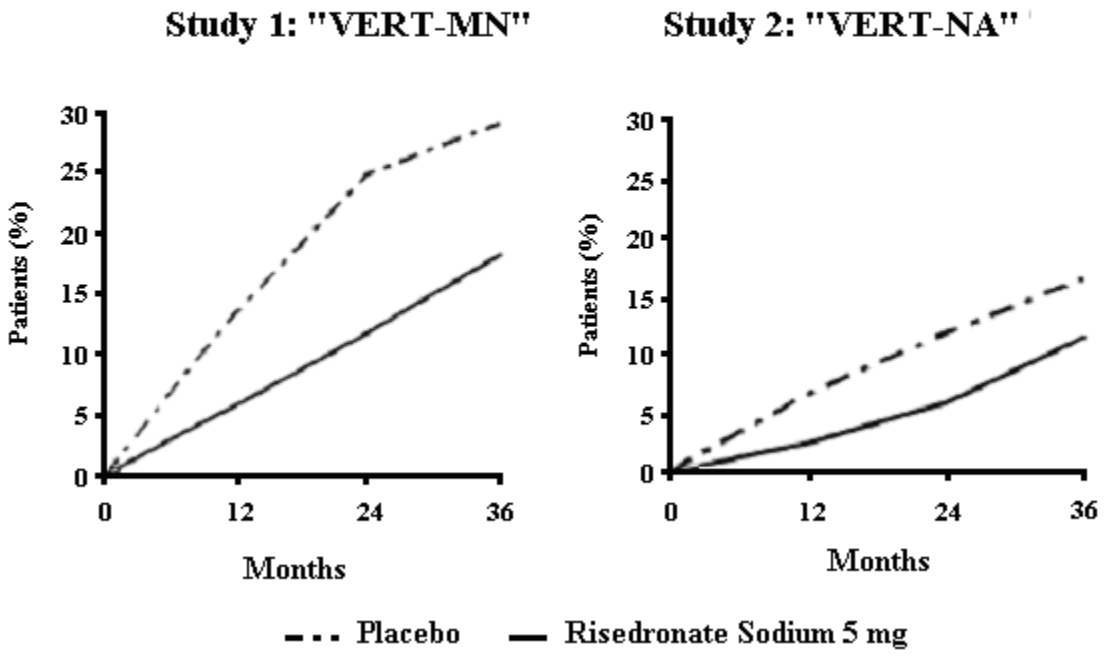
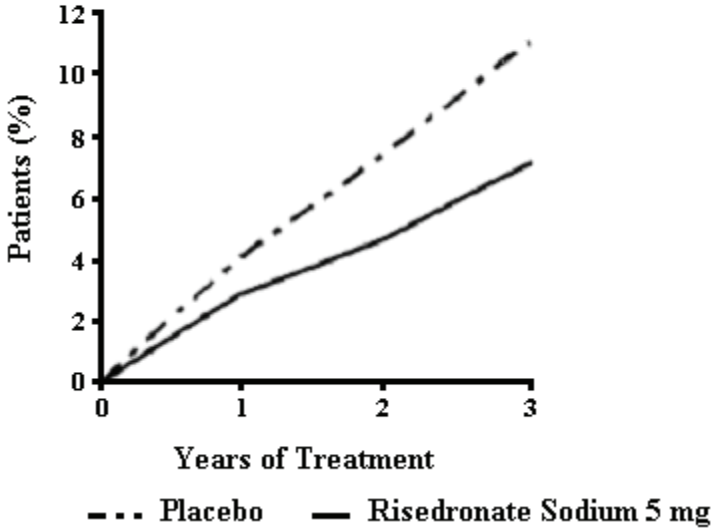


Figure 2
Cumulative Incidence of Osteoporosis-Related Non-vertebral Fractures
Studies 1 and 2 Combined



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

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

Results of Studies Number 3 and 4

Table 8
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	Lumbar spine	4.1	0.0	4.1**
	Femoral Neck	1.3	-1.0	2.3*
	Trochanter	2.7	-0.6	3.3**
Study 4				
6 months	Lumbar spine	3.3	0.7	2.6**
18 months	Lumbar spine	5.2	0.3	5.0**
	Femoral Neck	3.1	0.2	2.8**
	Trochanter	4.8	1.4	3.3**
vs placebo: *p<0.01; **p<0.001				

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

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

Results of Study Number 5

Table 9
Comparison of Risedronate sodium Once-a-Week vs. Daily Dosing in the Treatment of Osteoporosis in Postmenopausal Women - Primary Efficacy Analysis of Completers

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

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

In trials with risedronate sodium 5 mg daily, changes in BMD of this magnitude were associated with a significant decrease in fracture incidence relative to placebo (see Table 7). This is further supported by the fact that within the 1-year study comparing risedronate sodium 35 mg Once-a-Week to risedronate sodium 5 mg daily, no statistically significant differences amongst these treatment groups were seen with respect to the number of patients with at least 1 new fractured vertebra at 1 year. Risedronate sodium 35 mg taken once a week is similar in safety and efficacy to risedronate sodium 5 mg daily for the treatment of postmenopausal osteoporosis.

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

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

Prevention of Osteoporosis in Postmenopausal Women

Study Demographics and Trial Design

Table 10
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 years postmenopausal without osteoporosis. All patients were supplemented with 1000 mg elemental calcium and 400 IU vitamin D per day.

Results of Study 6

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

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

* vs placebo: $p<0.001$

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

Results of Study 7

Table 12 Effect of Risedronate sodium 35 mg Once-a-Week on Bone Mineral Density in Postmenopausal Women without Osteoporosis				
Endpoints		Risedronate sodium 35 mg Once-a-Week Mean Increase in BMD %	Placebo Mean Increase in BMD %	Mean Difference From Placebo %
6 months	Lumbar Spine	1.7	-0.5	2.2*
	Trochanter	1.0	-0.4	1.3*
	Femoral Neck	0.4	-1.0	1.4*
12 months	Lumbar Spine	1.9	-1.1	3.0*
	Trochanter	1.0	-0.7	1.7*
	Femoral Neck	0.3	-1.0	1.3**
vs placebo: *p≤0.0001; ** p = 0.0041				

Combined Administration with Hormone Replacement Therapy

Study Demographics and Trial Design

Table 13 Summary of Patient Demographics for Clinical Trials of Risedronate sodium in Combined Administration with Hormone Replacement Therapy						
Study Number	Trial Design	Dosage	Duration	Patients N = number	Age Range (Age Mean)	Gender
8	R, PC, DB, MC, PG, Stratified	Risedronate sodium 5 mg/day and conjugated estrogen 0.625 mg/day Placebo and conjugated estrogen 0.625 mg/day	1 year	524	37 – 82 (58.9)	Postmenopausal female
R: randomized; PC: placebo-controlled; DB: double-blind; MC: multicentre; PG: parallel-group						

For inclusion in Study 8 women had a mean lumbar spine BMD 1.3 SD below the pre menopausal mean and had recently initiated conjugated estrogen treatment (i.e., not taken estrogen for more than 1 month in the past year).

Results of Study 8

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

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

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

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

Glucocorticoid-Induced Osteoporosis

Study Demographics and Trial Design

Table 15
Summary of Patient Demographics for Clinical Trials of Risedronate sodium in the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Study Number	Trial Design	Dosage	Duration	Patients N=number	Age Range (Age Mean)	Gender
9 Recent GC	DB, PC	5 mg/day Placebo	1 year	228	18-85 (59.5)	Men and Women
10 Long-term GC	DB, PC	5 mg/day Placebo	1 year	290	19-85 (58.4)	Men and Women
GC: glucocorticoid; DB: double-blind; PC: placebo-controlled						

In Study 9, each patient had initiated glucocorticoid therapy (>7.5 mg/day of prednisone or equivalent) within the previous 3 months for rheumatic, skin and pulmonary diseases. The mean lumbar spine BMD was normal at baseline. All patients in this study received supplemental calcium 500 mg/day.

Long-term use in Study 10 was defined as >6 months of glucocorticoids for rheumatic, skin and pulmonary diseases. The baseline mean lumbar spine BMD was low (1.63 SD below the young healthy population mean), with 28% of the patients more than 2.5 SD below the mean. All patients in this study received supplemental calcium 1000 mg/day and supplemental vitamin D 400 IU/day.

Results of Studies 9 and 10

Table 16
Change in Bone Mineral Density at 12 months from Baseline in Patients taking Glucocorticoid Therapy

Endpoint	Risedronate sodium 5 mg Mean Change in BMD %	Placebo Mean Change in BMD %	Least Squares Mean Difference from Placebo %
Study 9: Recent GC			
	N = 58-60	N = 56-57	
Lumbar Spine	0.6	-2.8	3.8**
Femoral Neck	0.8	-3.1	4.1**
Trochanter	1.4	-3.1	4.6**
Study 10: Long-term GC			
	N = 77-79	N = 66-67	
Lumbar Spine	2.9	0.4	2.7**
Femoral Neck	1.8	-0.3	1.9*
Trochanter	2.4***	1.0	1.4*

GC: glucocorticoid; * $p \leq 0.01$ vs placebo; ** $p \leq 0.001$ vs placebo; *** $p \leq 0.05$ vs baseline

By the third month of treatment, and continuing through treatment, the placebo group experienced losses in BMD at the lumbar spine, femoral neck and trochanter, while BMD was maintained or increased in the risedronate sodium 5 mg group. At each skeletal site there were statistically significant differences between the risedronate sodium 5 mg group and the placebo group at all time points (Months 3, 6, 9, 12). The treatment differences increased with continued treatment. The results at these skeletal sites were also statistically significant when the subgroups of men and postmenopausal women were analyzed separately.

Risedronate sodium was effective and prevented bone loss regardless of underlying disease, age, gender, glucocorticoid dose or baseline BMD.

Vertebral Fractures: Vertebral fractures were monitored for safety in the two placebo-controlled studies.

Table 17 Incidence of Vertebral Fracture in Patients Initiating or Continuing G1ucocorticoid Therapy				
	Risedronate sodium 5 mg		Placebo	
Endpoints	N	% of patients	N	% of patients
Study 9: Recent GC	53	6	52	17
Study 10: Long-term GC	58	5	59	15
Combined Studies 9 and 10	111	5*	111	16
vs. placebo: *$p \leq 0.05$				

The statistically significant reduction in vertebral fracture incidence in the analysis of the combined studies corresponded to a relative risk reduction of 70%.

Histology/Histomorphometry: Histomorphometric evaluation of 70 bone biopsy samples from 48 patients on glucocorticoid therapy who received either placebo or risedronate sodium 5 mg daily for 1 year (including 22 pairs of biopsies, 16 from risedronate sodium -treated patients) indicated that risedronate sodium reduces bone resorption and produces a mild-to-moderate decrease in the rate of bone turnover. The rate of bone formation was preserved or increased and there was no evidence of impaired mineralization. The structure of the cortical bone (cortical thickness and porosity) was maintained in the risedronate sodium -treated patients; cortical porosity increased, however, in the placebo group. These findings indicate that bone formed during risedronate sodium treatment is of normal quality.

Bone histology demonstrated that bone formed during treatment with risedronate sodium was of normal lamellar structure and normal mineralization, with no bone or marrow abnormalities observed.

Paget's Disease of Bone

Study Demographics and Trial Design

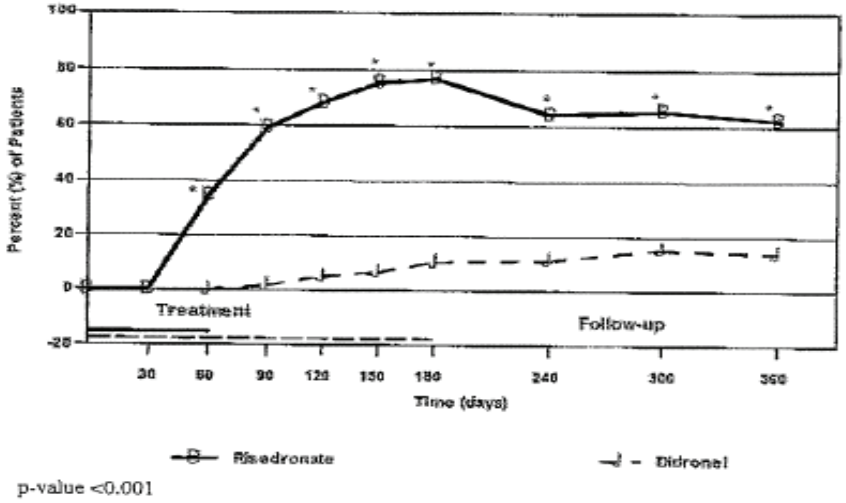
Table 18 Summary of Patient Demographics for Clinical Trials in the Treatment of Paget's Disease of Bone					
Study Number	**Trial Design**	**Dosage and Duration**	**Patients N = number**	**Age Range (Age Mean)**	**Gender**
11	DB, AC	Risedronate sodium 30 mg for 2 months Didronel 400 mg for 6 months	123	34-85 (66.8)	Men and women
12	AC	Risedronate 10, 20 or 30 mg for 28 days	62	(67.7)	Men and women
13	OL	Risedronate 30 mg	162	(68.4)	Men and women
14	OL	Risedronate 30 mg	13	(68.2)	Men and women
15	OL	Risedronate 30 mg	20	(74.0)	Men and women
16	OL	Risedronate 30 mg	73	(69)	Men and women
DB: double-blind; AC: active-controlled; OL: open-label					

Patients in Study 11 had moderate-to-severe Paget's disease (i.e., serum alkaline phosphatase levels of at least two times the upper limit of normal). The efficacy of risedronate sodium 30 mg daily was demonstrated in six clinical studies involving over 390 male and female patients.

Results of Study 11

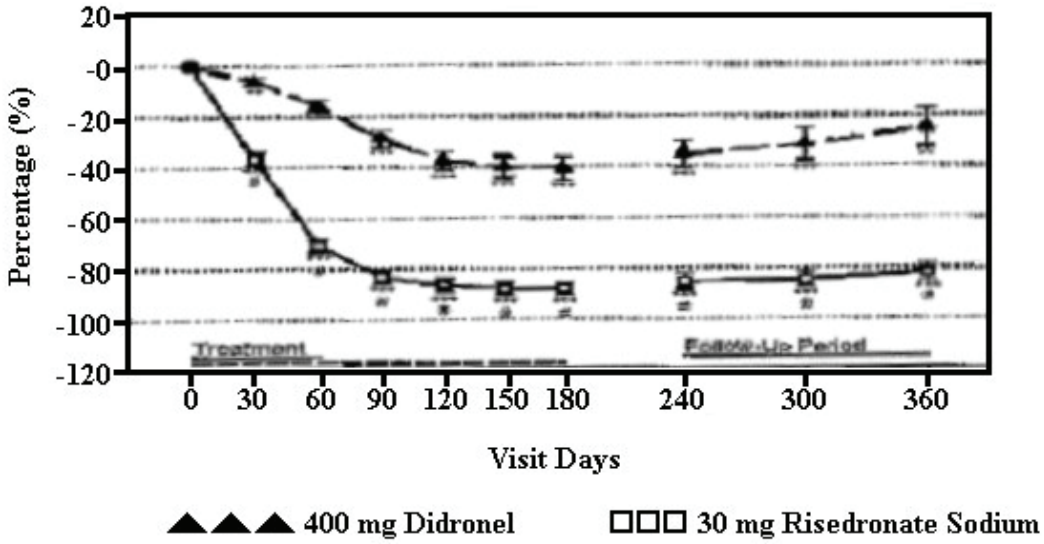
Figure 3 below shows that at Day 180, 77% (43/56) of risedronate sodium -treated patients achieved normalization of serum alkaline phosphatase levels compared to 10.5% of patients treated with Didronel ($p<0.001$), For 33 of these 43 patients (77%), the remission (i.e., normalization of serum alkaline phosphatase) induced by risedronate sodium treatment was maintained through at least 300 days of post-treatment observation.

Figure 3
Percent of Patients with Normalized Serum Alkaline Phosphatase vs. Time



During the first 180 days of the active-controlled study, 85% (51/60) of risedronate sodium -treated patients demonstrated a ≥75% reduction from baseline in serum alkaline phosphatase excess (difference between measured level and midpoint of the normal range) with 2 months of treatment compared to 20% (12/60) in the Didronel-treated group with 6 months of treatment ($p<0.001$). Changes in serum alkaline phosphatase excess over time (shown in Figure 4 below) reveal that the onset of the effect of risedronate sodium is significant following only 30 days of treatment, with a 36% reduction in serum alkaline phosphatase excess at that time compared to only 6% seen with Didronel treatment at the same time point ($p<0.001$).

Figure 4
Mean Percent from Baseline in Serum Alkaline Phosphatase Excess by Visit Study RPD-001694



p-value <0.05, significant difference between treatments based on a three-way ANOVA model
*, **, *** Significant change from baseline (p<0.050, 0.010, 0.001, respectively), based on a one-sample t-test

Response to risedronate sodium therapy was independent of age, gender, or race and was similar in patients with mild to very severe Paget's disease. Table 19 below shows the maximum mean percent reduction from baseline in excess serum alkaline phosphatase in patients with mild moderate, or severe disease.

Table 19
Maximum Percent Reduction from Baseline in Total Serum Alkaline Phosphatase (AP) Excess by Disease Severity - 30 mg Risedronate sodium

Subgroup: Baseline Disease Severity (AP)	N	Baseline Serum AP (U/L)*	Mean Maximum % Reduction
>2, <3x ULN	32	271.6 ± 5.3	-90.2
≥3, <7x ULN	14	475.3 ± 28.8	-90.4
≥7x ULN	17	1611.3 ± 231.5	-80.9
* values shown are mean ± SEM; ULN: upper limit of normal			

Results of Study 12:

Response to risedronate sodium was similar between patients who had previously received anti-pagetic therapy and those who had not. In the active-controlled study, four out of five patients (80%) previously non-responsive to complete courses of anti-pagetic therapy (calcitonin, Didronel, clodronate) responded to treatment with risedronate sodium 30 mg daily (defined by at least a 30% change from baseline). Of these four patients, all achieved at least 90% reduction from baseline in serum alkaline phosphatase excess with three patients achieving normalization of serum alkaline phosphatase levels. Risedronate sodium does not impair mineralization.

Histology data showed that the bone formed during risedronate sodium treatment was lamellar and of normal quality.

Radiographs taken at baseline and after 6 months from patients treated with risedronate sodium 30 mg daily demonstrate that risedronate sodium is highly effective in decreasing the extent of osteolysis across all anatomical sites including the appendicular and axial skeleton. Importantly, osteolytic lesions in the lower extremities improved or were unchanged in 15/16 (94%) of assessed patients; 9/15 (60%) patients showed clear improvement in osteolytic lesions. No evidence of new fractures was observed.

DETAILED PHARMACOLOGY

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

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

TOXICOLOGY

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

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

32 mg/kg (640 mg/m^2) and consisted of liver, testicular, and renal toxicities. Gastric lesions were observed at 16 mg/kg (320 mg/m^2). These doses are equivalent to approximately 3.5 and 7 times the human 150 mg dose based on surface area, mg/m^2.

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

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

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

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

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

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

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

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

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38. Actonel® Product Monograph by Warner Chilcott Canada Co. Control Number 133857. Date of Revision: July 15, 2011.

PART III: CONSUMER INFORMATION

Pr NTP-RISEDRONATE
risedronate sodium (as monohydrate)

This leaflet is Part III of a three part "Product Monograph" published when NTP-RISEDRONATE was approved for sale in Canada. It is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NTP-RISEDRONATE. 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 osteoporosis in postmenopausal women.
- Treatment and prevention of osteoporosis caused by treatment with steroid medication such as prednisone.
- Treatment of Paget's disease of bone.

What it does:

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

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

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

When it should not be used:

- If you have low blood calcium levels (hypocalcemia),
- If you are allergic to risedronate sodium or any other ingredients in NTP-RISEDRONATE.

What the medicinal ingredient is:
Risedronate sodium

What the nonmedicinal ingredients are:

Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, pregelatinized starch, sodium stearyl fumarate, starch and film-coating containing the following:

5 mg: D&C yellow #10 lake, hydroxypropyl methylcellulose, iron oxide yellow, polyethylene glycol, polysorbate and titanium dioxide.

30 mg: hydroxypropyl methylcellulose, polyethylene glycol, polysorbate and titanium dioxide.

35 mg: FD&C yellow #6/sunset yellow FCF aluminium lake, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, polyethylene glycol, polysorbate and titanium dioxide.

What dosage forms it comes in:

NTP-RISEDRONATE is available as tablets. Each tablet contains: risedronate sodium 5 mg (yellow), 30 mg (white) or 35 mg (orange).

WARNINGS AND PRECAUTIONS

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

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

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

INTERACTIONS WITH THIS MEDICATION

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

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

Vitamins, mineral supplements, antacids and other medications may contain substances (e.g., calcium, magnesium, aluminum, and iron) which can stop your body from absorbing or using NTP-RISEDRONATE.
These medications should be taken at a different time of day than NTP-RISEDRONATE.

If you are taking this drug for Paget's disease, talk to your doctor before taking acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs used for pain management because the risk of stomach upset may be increased.

PROPER USE OF THE MEDICATION

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

Usual Dose:

Treatment of postmenopausal osteoporosis:

- 1 tablet (5 mg) per day or
- 1 tablet (35 mg) per week

Prevention of postmenopausal osteoporosis:

- 1 tablet (5 mg) per day or
- 1 tablet (35 mg) per week

Treatment and prevention of glucocorticoid-induced osteoporosis:

- 1 tablet (5 mg) per day

Paget's disease of the bone:

- 1 tablet (30 mg) per day

DOSING INSTRUCTIONS

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

These recommendations help NTP-RISEDRONATE work correctly and help you avoid possible irritation of the esophagus (the tube connecting the mouth and the stomach).

Once daily dosing (5 mg or 30 mg per day):

- Take 1 NTP-RISEDRONATE tablet first thing in the morning with plain water before you have anything to eat or drink.

Once weekly dosing (35 mg per week):

- Choose a day of the week to take your tablet.
- On your chosen day, take 1 ACTONEL tablet first thing in the morning with plain water before you have anything to eat or drink.

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

Missed Dose:

Daily dose (5 mg or 30 mg tablet): If you forget to take your dose, do not double your next dose (i.e., do not take 2 tablets on the same day). Simply take 1 tablet at your next scheduled time.

Weekly dose (35 mg tablet): 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. Then resume your schedule by taking 1 tablet on the originally chosen day of the week. If you've missed your dose by exactly one 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 usual weekly schedule.

Overdose:

If you take too many tablets on any given day, contact your doctor, or a Poison Control Centre, or an emergency room of the nearest hospital immediately.

For NTP-RISEDRONATE overdose, drink a full glass of milk. Do not induce vomiting.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Drugs like NTP-RISEDRONATE may cause problems in your esophagus (the tube that connects 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 NTP-RISEDRONATE and tell your doctor right away. Remember to take NTP-RISEDRONATE as directed.

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

NTP-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 NTP-RISEDRONATE.

Very rarely patients have reported non-healing jaw wounds while receiving risedronate sodium 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 seek immediate emergency medical attention
	Only if severe	In all cases	
Common (more than 1 in 100)			
Pain in bones, joints or muscles	✓		
Abdominal pain	✓		
Uncommon (less than 1 in 100)			
Eye pain, redness or inflammation; sensitivity to light, decreased vision			✓
Rare (less than 1 in 1,000)			
Painful tongue		✓	
Very rare (less than 1 in 10,000)			
Allergic and skin reactions such as: hives; rash (with or without blisters); swelling of face, lips, tongue, or throat; difficult or painful swallowing; trouble breathing.			✓
Jaw problems associated with delayed healing and infection, often following tooth extraction.		✓	
Symptoms of low blood calcium level, such as numbness, tingling, muscle spasms.		✓	
New or unusual pain in hip, groin or thigh		✓	

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

HOW TO STORE IT

- Keep NTP-RISEDRONATE and all other medications out of the reach of children.
- Keep the tablets in their original package and store at controlled room temperature (15°C - 30°C). Protect from light.
- 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 0701E
  Ottawa, ON 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 found by contacting Teva Canada Limited at:
1-800-268-4127 ext. 5005 (English);
1-877-777-9117 (French)
or druginfo@tevacanada.com

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Last revised: July 26, 2012