

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take Risedronate Sodium?

- Take Risedronate Sodium exactly as your doctor tells you. Your doctor may change your dose of Risedronate Sodium if needed.
 - Risedronate Sodium works only if taken on an empty stomach.
 - Take 1 Risedronate Sodium, after you get up for the day and before taking your first food, drink, or other medicine.
 - Take Risedronate Sodium while you are sitting or standing.
 - Do not chew or suck on a tablet of Risedronate Sodium.
 - Swallow Risedronate Sodium with a full glass (6 to 8 ounces) of plain water only.
 - Do not take Risedronate Sodium with mineral water, coffee, tea, soda, or juice.
- After swallowing Risedronate Sodium, wait at least 30 minutes:
- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
 - Before you take your first food or drink except for plain water.
 - Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take Risedronate Sodium and after you eat your first food of the day. If you miss a dose of Risedronate Sodium, do not take it later in the day. Take your missed dose the next morning and then return to your normal schedule. Do not take 2 doses at the same time.

If you miss more than 2 doses of Risedronate Sodium in a month, call your doctor for instructions. If you take too much Risedronate Sodium, call your doctor. Do not try to vomit. Do not lie down.

What are the possible side effects of Risedronate Sodium?

- Risedronate Sodium may cause serious side effects:
- See "What is the most important information I should know about Risedronate Sodium?"
- The most common side effects of Risedronate Sodium are:
- pain, including back and joint pain
 - stomach area (abdominal) pain
 - heartburn

You may get allergic reactions, such as hives, swelling of your face, lips, tongue, or throat. Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Risedronate Sodium. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Risedronate Sodium?

- Store Risedronate Sodium at room temperature, 68° F to 77° F (20° C to 25° C).

Safely throw away medicine that is out of date or no longer needed.

Keep Risedronate Sodium and all medicines out of the reach of children.

General information about the safe and effective use of Risedronate Sodium.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Risedronate Sodium for a condition for which it was not prescribed. Do not give Risedronate Sodium to other people, even if they have the same symptoms you have. It may harm them. This Medication Guide summarizes the most important information about Risedronate Sodium. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Risedronate Sodium that is written for health professionals.

What are the ingredients in Risedronate Sodium?

Active ingredient: Risedronate Sodium
Inactive ingredients in all dose strengths: crospovidone, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

Inactive ingredients specific to a dose strength:
30 mg—ferric oxide yellow, lactose monohydrate, ferric oxide yellow, lactose monohydrate; 75 mg—ferric oxide red, 150 mg—FD&C blue #2 aluminum lake.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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No overall differences in safety between geriatric and younger patients were observed in the Risedronate Sodium trials, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Risedronate Sodium is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 30 mL/min.

8.7 Hepatic Impairment

No studies have been performed to assess Risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in human liver preparations. Dosage adjustment is unlikely to be needed in patients with hepatic impairment.

OVERDOSEAGE

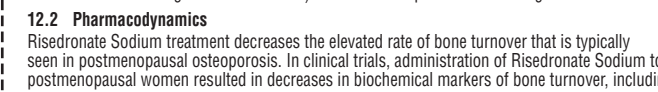
Increases in serum calcium and phosphorus following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients. Milk or antacids containing calcium should be given to bind Risedronate Sodium and reduce absorption of the drug.

In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug. 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.

Lethality after single oral doses was seen in female rats at 903 mg/kg and male rats at 1703 mg/kg. The minimum lethal dose in mice and rabbits was 4000 mg/kg and 1000 mg/kg, respectively. These values represent 220 to 620 times the 30 mg human dose based on surface area (mg/m²).

11 DESCRIPTION

Risedronate Sodium is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Each Risedronate Sodium oral administration contains the equivalent of 5, 30, 35, 75, or 150 mg of anhydrous Risedronate Sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. The empirical formula for Risedronate Sodium hemi-pentahydrate is C₁₂H₁₀N₂O₇P₂·2.5 H₂O. The chemical name of Risedronate Sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis(phosphonic acid) sodium salt. The chemical structure of Risedronate Sodium hemi-pentahydrate is the following:



Risedronate Sodium is a fine, white to off-white, odorless, crystalline powder. It is soluble in water and in aqueous solutions, and essentially insoluble in common organic solvents.

Inactive Ingredients

All dose strengths contain: crospovidone, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide. Dose strength-specific ingredients include: 5 mg—ferric oxide yellow, lactose monohydrate; 30 mg—lactose monohydrate; 35 mg—ferric oxide red, ferric oxide yellow, lactose monohydrate; 75 mg—ferric oxide red; 150 mg—FD&C blue #2 aluminum lake.

12 CLINICAL PHARMACOLOGY

Risedronate Sodium has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, Risedronate Sodium inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (for example, lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that Risedronate Sodium treatment reduces bone turnover (activation frequency), that is, the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

12.2 Pharmacokinetics

Risedronate Sodium treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of Risedronate Sodium to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxyribonucleoside/creatinine and urinary collagen cross-linked N-telopeptide (markers of bone resorption) and serum bone-specific alkaline phosphatase (a marker of bone formation). At the 5 mg dose, decreases in deoxyribonucleoside/creatinine 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 resorption and bone formation.

Decreases in bone-specific alkaline phosphatase 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. Bone turnover as measured as early as 14 days and maximally within about 6 months of treatment, with achievement of a new steady-state that more nearly approximates the rate of bone turnover seen in premenopausal women. In a 1-year study comparing daily versus weekly oral dosing regimens of Risedronate Sodium for the treatment of osteoporosis in postmenopausal women, Risedronate Sodium 5 mg daily and Risedronate Sodium 35 mg once-a-week decreased urinary collagen cross-linked N-telopeptide by 60% and 61%, respectively. In addition, serum bone-specific alkaline phosphatase was also reduced by 42% and 41% in the Risedronate Sodium 5 mg daily and Risedronate Sodium 35 mg once-a-week groups, respectively.

When postmenopausal women with osteoporosis were treated for 1 year with Risedronate Sodium 5 mg daily or Risedronate Sodium 35 mg two consecutive days per month, urinary collagen cross-linked N-telopeptide was decreased by 54% and 52%, respectively, and serum bone-specific alkaline phosphatase was reduced by 36% and 35%, respectively. In a 1-year study comparing Risedronate Sodium 5 mg daily versus Risedronate Sodium 150 mg once-a-month in women with postmenopausal osteoporosis, urinary collagen cross-linked N-telopeptide was decreased by 52% and 49%, respectively, and serum bone-specific alkaline phosphatase was reduced by 31% and 32%, respectively.

Osteoporosis in Men

In a 2-year study of men with osteoporosis, treatment with Risedronate Sodium 35 mg once-a-week resulted in a mean decrease from baseline compared to placebo of 16% (placebo 20%, Risedronate Sodium 35 mg 37%) for the bone resorption marker urinary collagen cross-linked N-telopeptide, 45% (placebo 25%, Risedronate Sodium 35 mg 39%) for the bone resorption marker serum C-telopeptide, and 27% (placebo -2%, Risedronate Sodium 35 mg 25%) for the bone formation marker serum bone-specific alkaline phosphatase.

Glucocorticoid-Induced Osteoporosis

Osteoporosis with glucocorticoid use occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Risedronate Sodium decreases bone resorption without directly inhibiting bone formation.

In two 1-year clinical trials in the treatment and prevention of glucocorticoid-induced osteoporosis, Risedronate Sodium 5 mg decreased urinary collagen cross-linked N-telopeptide (a marker of bone resorption) and serum bone-specific alkaline phosphatase (a marker of bone formation) by 50% to 55% and 25% to 30%, respectively, within 3 to 6 months after initiation of therapy.

Page's Disease

Page's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorganized bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

In pagetic patients treated with Risedronate Sodium 30 mg daily for 2 months, bone turnover returned to normal in a majority of patients as evidenced by reductions in serum calcium, serum alkaline phosphatase (a marker of bone formation), and in urinary hydroxyproline/creatinine and deoxyribonucleoside/creatinine (markers of bone resorption).

12.3 Pharmacokinetics

Absorption: Based on simultaneous modeling of serum and urine data, peak absorption after an oral dose is achieved at approximately 1 hour (T_{max}) and occurs throughout the upper gastrointestinal tract. The fraction of the dose absorbed is independent of dose over the range studied (single dose, from 2.5 mg to 30 mg; multiple dose, from 2.5 mg to 5 mg). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean absolute oral bioavailability of the 30 mg tablet is 0.63% (90% CI: 0.54% to 0.75%) and is comparable to a solution.

Food Effect

The extent of absorption of a 30 mg dose (three 10 mg tablets) when administered 0.5 hours before breakfast is reduced by 55% compared to dosing in the fasting state (no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces the extent of absorption by 30% compared to dosing in the fasting state. Dosing either 0.5 hours prior to breakfast or 2 hours after dinner (evening meal) results in a similar extent of absorption. Risedronate Sodium is effective when administered at least 30 minutes before breakfast.

Distribution

The mean steady-state volume of distribution for Risedronate is 13.8 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 [¹⁴C] 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 in the range of 0.001% to 0.01%.

Metabolism

There is no evidence of systemic metabolism of Risedronate.

Excretion

In young healthy subjects, approximately half of the absorbed dose of Risedronate was excreted in urine within 24 hours, and 85% of an intravenous dose was recovered in the urine over 28 days. Based on simultaneous modeling of serum and urine data, mean renal clearance was 105 mL/min (CV = 34%) and mean total clearance was 122 mL/min (CV = 19%), with the difference primarily reflecting nonrenal 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. In osteoporotic postmenopausal women, the terminal elimination half-life was 561 hours, mean renal clearance was 92 mL/min (CV = 25%), and mean total clearance was 73 mL/min (CV = 15%).

Specific Populations

Pediatric: Risedronate Sodium is not indicated for use in pediatric patients [see *Pediatric Use* (8.4)].

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

Geriatric: Bioavailability and disposition are similar in elderly (greater than 60 years of age) and younger subjects. No dosage adjustment is necessary.

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

Renal Impairment: Risedronate is excreted unchanged primarily via the kidney. As compared to persons with normal renal function, the renal clearance of Risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 mL/min. Risedronate Sodium is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 30 mL/min.

Hepatic Impairment: 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 (less than 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.

Drug Interactions: No specific drug-drug interaction studies were performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (Cytochrome P450) [see *Drug Interactions* (7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In a 104-week carcinogenicity study, rats were administered daily oral doses up to approximately 12 times the maximum recommended human daily dose. There were no significant drug-induced tumor findings in male or female rats. The high dose male study was terminated early in the study (Week 53) due to excessive toxicity, and data from this group were not included in the standard evaluation of the study results. In an 80-week carcinogenicity study, mice were administered daily oral doses approximately 6.5 times the human dose. There were no significant drug-induced tumor findings in male or female mice.

Mutagenesis

Risedronate did not exhibit genetic toxicity in the following assays: in vitro chromosomal mutagenesis in *Salmonella* and *E. coli* (Ames assay), mammalian cell mutagenesis in CHO/HGPRT assay, unscheduled DNA synthesis in rat hepatocytes and an assessment of chromosomal aberrations in vivo in bone marrow. Risedronate was negative in a chromosome aberration assay in CHO cells at high cytotoxic concentrations (greater than 675 mcg/mL survival of 6% to 7%). When the assay was repeated at doses exhibiting appropriate cell survival (29%), there was no evidence of chromosomal damage.

Impairment of Fertility

In female rats, ovulation was inhibited at an oral dose approximately 5 times the human dose. Decreased implantation was noted in female rats treated with doses approximately 2.5 times the human dose. In male rats, testicular and epididymal atrophy and inflammation were noted at approximately 13 times the human dose. Testicular atrophy was also noted in male rats after 13 weeks of treatment at oral doses approximately 5 times the human dose. There was moderate to severe spermatid maturation block after 13 weeks in male rats given an oral dose approximately 8 times the human dose. These findings tended to increase in severity with increased dose and exposure time.

Dosing multiples provided above are based on the recommended human dose of 30 mg/day and normalized using body surface area (m²). Actual doses were 24 mg/kg/day in rats, 32 mg/kg/day in mice, and 8, 16 and 40 mg/kg/day in dogs.

13.2 Animal Toxicology and/or Pharmacology

Risedronate demonstrated potent anti-osteoclast, antiresorptive activity in ovariectomized rats and minipigs. Bone mass and biomechanical strength were increased dose-dependently at daily oral doses up to 4 and 25 times the human recommended oral dose of 5 mg for rats and minipigs, respectively. Risedronate treatment maintained the positive correlation between BMD and bone strength and did not have a negative effect on bone structure or mineralization. In intact dogs, Risedronate induced positive bone remodeling at the level of the bone remodeling unit at oral doses ranging from 0.5 to 1.5 times the 5 mg/day human daily dose.

In dogs treated with an oral dose approximately 5 times the human daily dose, Risedronate caused a delay in fracture healing of the tibia. The observed delay in fracture healing is similar to other bisphosphonates. This effect did not occur at a dose approximately 0.5 times the human daily dose.

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, which was approximately 2,500 times the lowest antiresorptive dose in this model (1.5 mcg/kg/day) and approximately 800 times the human daily dose of 5 mg. This indicates that Risedronate Sodium administered at the therapeutic dose is unlikely to induce osteomalacia.

Dosing multiples provided above are based on the recommended human dose of 5 mg/day and normalized using body surface area (m²/m²).

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women

The fracture efficacy of Risedronate Sodium 5 mg daily in the treatment of postmenopausal osteoporosis was demonstrated in a large, randomized, placebo-controlled, double-blind study that enrolled a total of almost 4,000 postmenopausal women under similar protocols. The Multinational Study (VERT MM) (Risedronate Sodium 5 mg, N = 408) was conducted primarily in Europe and Australia; a second study was conducted in North America (VERT NA) (Risedronate Sodium 5 mg, N = 821). All patients were selected on the basis of radiographic evidence of previous vertebral fracture, and therefore, had established disease. The average number of prevalent vertebral fractures per patient at study entry was 4 in VERT MM, and 2.5 in VERT NA, with a broad range of baseline BMD levels. All patients in these studies received supplemental calcium 1000 mg/day. Patients with low 25-hydroxyvitamin D levels (approximately 40 nmol/L or less) also received supplemental vitamin D 500 international units/day.

Effect on Osteoporosis-Related Fractures (new fractures) and worsening of pre-existing vertebral fractures that were diagnosed radiographically, some of these fractures were also associated with symptoms (that is, clinical fractures). Spinal radiographs were scheduled annually and prospectively planned analyses were based on the time to a patient's first diagnosed fracture. The primary endpoint for these studies was the incidence of new and worsening vertebral fractures across the period of 0 to 3 years. Risedronate Sodium 5 mg daily significantly reduced the incidence of new and worsening vertebral fractures and of new vertebral fractures in both VERT NA and VERT MM at all time points (Table 3). The reduction in risk seen in the subgroup of patients who had 2 or more vertebral fractures at study entry was similar to that seen in the overall study population.

| | Placebo N = 678 | Risedronate Sodium 5 mg N = 696 | Absolute Risk Reduction (%) | Relative Risk Reduction (%) |
|--------------------------|------------------------------------|------------------------------------|-----------------------------|-----------------------------|
| New and Worsening | | | | |
| 0 - 1 Year | 7.2 | 3.9 | 3.3 | 49 |
| 0 - 2 Years | 12.8 | 6.0 | 6.8 | 42 |
| 0 - 3 Years | 18.5 | 13.9 | 4.6 | 33 |
| New | | | | |
| 0 - 1 Year | 6.4 | 2.4 | 4.0 | 63 |
| 0 - 2 Years | 11.7 | 5.8 | 5.9 | 51 |
| 0 - 3 Years | 16.3 | 11.3 | 5.0 | 45 |
| VERT MM | | | | |
| Placebo N = 346 | Risedronate Sodium 5 mg N = 344 | Absolute Risk Reduction (%) | Relative Risk Reduction (%) | |
| New and Worsening | | | | |
| 0 - 1 Year | 15.3 | 8.2 | 7.1 | 50 |
| 0 - 2 Years | 28.3 | 13.9 | 14.4 | 56 |
| 0 - 3 Years | 34.0 | 21.8 | 12.2 | 46 |
| New | | | | |
| 0 - 1 Year | 13.3 | 5.6 | 7.7 | 61 |
| 0 - 2 Years | 24.7 | 11.6 | 13.1 | 59 |
| 0 - 3 Years | 29.0 | 18.1 | 10.9 | 49 |

*Calculated by Kaplan-Meier methodology.

Effect on Osteoporosis-Related Nonvertebral Fractures

In VERT MM and VERT NA, a prospectively planned efficacy endpoint was defined consisting of all radiographically confirmed fractures of skeletal sites accepted as associated with osteoporosis. Fractures at these sites were collectively referred to as osteoporosis-related nonvertebral fractures. Risedronate Sodium 5 mg daily significantly reduced the incidence of nonvertebral osteoporosis-related fractures over 3 years in VERT NA (81% versus 5%; relative risk reduction 39%) and reduced the fracture incidence in VERT MM from 16% to 11%. There was a significant reduction from 11% to 7% when the studies were combined, with a corresponding 38% reduction in relative risk. Figure 1 shows the overall results as well as the results at the individual skeletal sites for the combined studies.

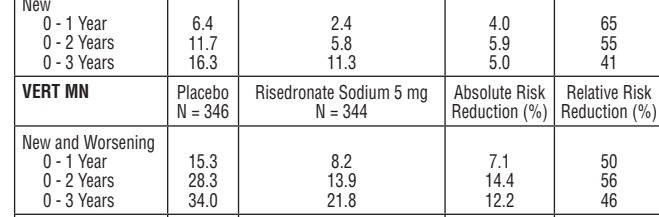


Figure 1
Nonvertebral Osteoporosis-Related Fractures
Combined VERT NA and VERT MM

| | VERT MM | VERT NA | BMD† | BMD NA† |
|-----------------|-------------------------|-------------------------|-------------------------|-------------------------|
| | Placebo 5 mg N = 323 | Placebo 5 mg N = 599 | Placebo 5 mg N = 161 | Placebo 5 mg N = 191 |
| Lumbar Spine | 1.0 | 6.6 | 0.8 | 5.0 |
| Femoral Neck | -1.4 | 1.6 | -1.0 | 1.4 |
| Trochanter | -1.9 | 3.9 | -0.5 | 3.0 |
| Midshaft Radius | -1.5* | 0.2* | -1.2* | 0.1* |
| | ND | ND | ND | ND |

* The endpoint value is the value at the study's last time point for all patients who had BMD measured at that time; otherwise the last post-baseline BMD value prior to the study's last time point is used.

† The duration of the studies was 3 years.

‡ The duration of the studies was 1.5 to 2 years.

§ BMD of the midshaft radius was measured in a subset of centers in VERT MM (Placebo, N = 222; 5 mg, N = 214) and VERT NA (Placebo, N = 310; 5 mg, N = 306). ND = analysis not done.

Risedronate Sodium 35 mg once-a-week (N = 405) was shown to be non-inferior to Risedronate Sodium 5 mg daily (N = 480) in a 1-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 4.0% (3.7, 4.3; 95% confidence interval [CI]) in the 5 mg daily group (N = 391) and 3.9% (3.6, 4.3; 95% CI) in the 35 mg once-a-week group (N = 387) and the mean difference between 5 mg daily and 35 mg once-a-week was 0.1% (-0.4, 0.6; 95% CI). The results of the intent-to-treat analysis with the last observation carried forward were similar with regard to BMD increases at other skeletal sites.

In a double-blind, multicenter study of postmenopausal women with osteoporosis, treatment with Risedronate Sodium 75 mg two consecutive days per month (N = 616) was shown to be non-inferior to Risedronate Sodium 5 mg daily (N = 613). In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 3.6% (3.3, 3.9; 95% CI) in the 5 mg daily group (N = 527) and 3.4% (3.1, 3.7; 95% CI) in the 75 mg two days per month group (N = 524) with a mean difference between groups being 0.2% (-0.2, 0.6; 95% CI). The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites.

Risedronate Sodium 150 mg once-a-month (N = 650) was shown to be non-inferior to Risedronate Sodium 5 mg daily (N = 642) in a 1-year, double-blind, multicenter study of postmenopausal women with osteoporosis. The primary efficacy analysis was conducted in all randomized patients with baseline and post-baseline lumbar spine BMD values (modified intent-to-treat population) using last observation carried forward. The mean increases from baseline in lumbar spine BMD at 1 year were 3.4% (3.0, 3.8; 95% CI) in the 5 mg daily group (N = 561), and 3.5% (3.1, 3.9; 95% CI) in the 150 mg once-a-month group (N = 576) with a mean difference between groups being 0.1% (0.5, 0.3; 95% CI). The results of the completers analysis were consistent with the primary efficacy analysis. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites.

Histology/Histomorphometry

Bone biopsies from 110 postmenopausal women were obtained at endpoint. Patients had received placebo or daily Risedronate Sodium (2.5 mg or 5 mg) for 2 to 3 years. Histologic evaluation (N = 103) showed no osteomalacia, impaired bone mineralization, or other adverse effects on bone in Risedronate Sodium-treated women. These findings demonstrate that bone formed during Risedronate Sodium administration is of normal quality. The histomorphometric parameter mineralizing surface, an index of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 21 treated with placebo and 23 patients treated with Risedronate Sodium 5 mg daily. The mineralizing surface was similar in both groups. Osteoporosis-treated patients (median percent change, placebo, -21%; Risedronate Sodium 5 mg, -74%), consistent with the known effects of treatment on bone turnover.

Effect on Height

Height and osteoporosis treatment studies, standing height was measured yearly by stadiometer. Both Risedronate Sodium and placebo-treated groups lost height during the studies. Patients who received Risedronate Sodium had a statistically significantly smaller loss of height than those who received placebo. In VERT MM, the median annual height change was -2.4 mm/yr in the placebo group compared to -1.3 mm/yr in the Risedronate Sodium 5 mg daily group. In VERT NA, the median annual height change was -1.1 mm/yr in the placebo group compared to -0.7 mm/yr in the Risedronate Sodium 5 mg daily group.

14.2 Prevention of Osteoporosis in Postmenopausal Women

The safety and effectiveness of Risedronate Sodium 5 mg daily for the prevention of postmenopausal osteoporosis were demonstrated in a 2-year, double-blind, placebo-controlled study of 383 postmenopausal women (age range 42 to 63 years) within three years of menopause (Risedronate Sodium 5 mg, N = 192). All patients were selected on the basis of radiographic evidence of previous vertebral fracture, and therefore, had established disease. The average number of prevalent vertebral fractures per patient at study entry was 4 in VERT MM, and 2.5 in VERT NA, with a broad range of baseline BMD levels. All patients in these studies received supplemental calcium 1000 mg/day. Increases in BMD were observed as early as 3 months following initiation of Risedronate Sodium treatment. Risedronate Sodium 5 mg daily produced significant mean increases in BMD at the lumbar spine, femoral neck, and trochanter compared to placebo at the end of the study (Figure 2). Risedronate Sodium 5 mg daily was also effective in patients with lower baseline lumbar spine BMD (more than 1 SD below the premenopausal mean) and in those with normal baseline lumbar spine BMD. Bone mineral density at the distal radius decreased in both Risedronate Sodium and placebo-treated women following 1 year of treatment.

Figure 2 Change in BMD from Baseline in Patients Taking Risedronate Sodium 5 mg or Placebo at Endpoints*

