NEW ZEALAND DATA SHEET
RISEDRONATE SANDOZ (RISEDRONATE SODIUM) FILM-COATED TABLETS

1. PRODUCT NAME

Risedronate sodium

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Risedronate Sandoz 35 mg film-coated tablet contains 35 mg risedronate sodium equivalent to 32.5 mg risedronic acid.

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

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Risedronate Sandoz 35 mg - orange, oval, biconvex film-coated tablets marked 35 on one side and containing 35 mg risedronate sodium.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Treatment of Osteoporosis.
Prevention of Glucocorticoid-induced Osteoporosis.
Treatment of Postmenopausal Osteoporosis.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended dose is 35 mg once a week, taken on the same day each week.

Method of administration

Risedronate Sandoz must only be taken with plain water. Plain water is the only drink that should be taken with Risedronate Sandoz tablets. Please note that some mineral waters or water from regional areas may have a higher concentration of calcium and therefore should not be used.

Risedronate Sandoz must be taken 30 minutes before the first food or drink other than water. To facilitate delivery to the stomach, Risedronate Sandoz should be taken in an upright position and the patient should avoid lying down for 30 minutes.

Patients should not chew or suck on the tablet because of the potential for oropharyngeal irritation.

Dosage adjustment in:

- renal impairment

No dose adjustment is necessary in patients with mild to moderate renal insufficiency (creatinine clearance 30 to 60 mL/minute). Risedronate Sandoz is not recommended in patients

with severe renal impairment (creatinine clearance < 30 mL/minute) due to limited clinical data.

- Children

Risedronate sodium is not recommended for use in children below the age of 18 due to insufficient data on safety and efficacy.

- Men

The dosage is 35 mg/week.

- Elderly

No dose adjustment is necessary.

4.3. CONTRAINDICATIONS

Known hypersensitivity to the drug or any of the ingredients.

Hypocalcaemia (see Section 4.4 Special warnings and precautions for use).

Inability to stand or sit upright for at least 30 minutes.

Pregnancy and lactation.

Severe renal impairment (creatinine clearance < 30 mL/minute).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Food, certain medication and beverages (except plain water) can interfere with the absorption of Risedronate Sandoz. Therefore, for patients to gain maximum benefit from Risedronate Sandoz, doctors must stress the importance of taking Risedronate Sandoz as per the dosage instructions (see Section 4.2 Dose and method of administration). This is especially important in the case of patients with a history of oesophageal disorders.

Risedronate Sandoz, like other bisphosphonates, may cause local irritation of the upper GI mucosa. Bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations and gastro-duodenal ulcerations. Thus, caution should be used:

- in patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia.
- in patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet.
- in patients with active or recent oesophageal or upper GI problems (including known Barrett's oesophagus).
- Or in patients who are using NSAIDs or aspirin concomitantly.

Bisphosphates may cause hypocalcaemia and/or hypophosphatemia due to effects on bone. Risks of decreases in serum calcium and phosphate may be higher in those on parenteral bisphosphonate therapy, in elderly patients, and individuals with pre-existing conditions that affect calcium and phosphate levels, such as vitamin D deficiency, renal impairment, malabsorption and hyperparathyroidism.

Hypocalcaemia must be corrected before starting Risedronate Sandoz therapy. Bone and mineral metabolism dysfunction (e.g. vitamin D deficiency and parathyroid abnormalities) should be effectively treated before starting Risedronate Sandoz therapy. Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

Monitoring of calcium and phosphate may be needed throughout treatment, especially in individuals with risk factors.

High age or clinical risk factors for fracture alone are not sufficient reasons to initiate treatment of osteoporosis with a bisphosphonate.

Gastrointestinal

Risedronate like other bisphosphonates may cause local irritation of the upper GI mucosa. Since some bisphosphonates have been associated with oesophagitis and oesophageal ulcerations and gastroduodenal ulceration, doctors should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction, especially in patients with a history of upper GI disease or who are using NSAIDs or aspirin concomitantly. Prescribers should emphasise to patients the importance of taking Risedronate Sandoz as per the dosage instructions to patients who have a history of oesophageal disorders. The patient should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

There is very little experience with risedronate in patients with inflammatory bowel disease.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgment of the treating doctor should guide the management plan of each patient based on individual benefit/ risk assessment.

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Osteomalacia

The potential for risedronate to induce osteomalacia was investigated in the Schenk rat assay. This assay is based on histological examination of the epiphyses of the growing rats after drug treatment. Risedronate did not interfere with bone mineralisation even at the highest dose tested (5 mg/kg/day, subcutaneously) which was > 3,000 times the lowest antiresorptive dose (1.5 µ/kg/day). These data indicate that risedronate administered at therapeutic doses is unlikely to induce osteomalacia.

Atypical Stress Fractures

A small number of patients on long-term bisphosphonate therapy (usually longer than three years), mostly in connection with the use of alendronate have developed stress fractures of the proximal femoral shaft (also known as insufficiency or atypical fractures), some of which occurred in the absence of apparent trauma. Some of these patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred.

Approximately one third of these fractures were bilateral; therefore, the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. It is not known to what extent other agents of the aminobisphosphonate class, including risedronate, may be associated with this adverse event. Prior treatment with alendronate should be a cause for added vigilance. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (eg vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care.

During bisphosphonate, treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Discontinuation of bisphosphonate therapy in patients with stress fractures is advisable pending evaluation of the patient, based on an individual benefit risk assessment. Causality has not been excluded in regard to bisphosphonate use and stress fractures.

Use in renal impairment

See Section 4.2 Dose and method of administration.

Use in the elderly

No dose adjustment is necessary.

Paediatric use

See Section 4.2 Dose and method of administration.

Effects on laboratory tests

Bisphosphonates are known to interfere with the use of bone imaging agents. However, specific studies with risedronate have not been performed.

Small asymptomatic decreases in serum calcium and phosphorus levels have been observed in some patients.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No specific drug interactions studies have been performed. However, Risedronate Sandoz is not systemically metabolised, does not induce or inhibit hepatic microsomal drug metabolising enzymes (cytochrome P450) and has low protein binding.

Concomitant intake of medications containing polyvalent cations (e.g. calcium, magnesium, iron, aluminium, antacids) will interfere with the absorption of Risedronate Sandoz and should be taken at a different time of the day.

Risedronate Sandoz may be used concomitantly with hormone replacement therapy or the contraceptive pill.

During clinical trials, patients were exposed to a wide variety of commonly used concomitant medication while taking risedronate. No clinically relevant interactions were noted. The medications included NSAIDs, aspirin, H_2-blockers, proton pump inhibitors, antacids, calcium channel blockers, beta-blockers, thiazides, glucocorticoids, anticoagulants, anticonvulsants and cardiac glycosides. There are no clinical data concerning the concomitant medication with two or more bisphosphonates and such concomitant medication is not recommended.

In the phase III postmenopausal trials with 5 mg daily dosing, 29 and 37% of patients used aspirin and NSAIDs respectively. The incidence of upper GI adverse events in risedronate patients (aspirin/ NSAIDs taken greater than or equal to 3 days/week) was similar to that in placebo treated patients. In the phase III study using risedronate 35 mg once a week, 57 and 40% of patients used aspirin and NSAIDs respectively.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility study in male and female rats showed no adverse effects at oral doses up to 16 mg/kg/day, corresponding to systemic exposure (serum $AUC_{0\text{-}24\ hours}$) about 30 times higher than that in humans dosed at 30 mg/day. At higher dose levels, systemic toxicity, testicular atrophy and reduced fertility were seen in male rats, but these effects are unlikely to have clinical relevance.

Use in pregnancy

Category B3

[Category B3] – Drugs, which have been taken by only a limited number of pregnant women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There are no adequate data from the use of risedronate sodium in pregnant women. Studies in animals have shown reproductive toxicity.

The potential risk for humans is unknown.

Studies in animals indicate that a small amount of risedronate sodium pass into breast milk. Risedronate sodium must not be used during pregnancy or by breast-feeding women.

If administration during pregnancy is contemplated, serum calcium levels should be monitored and calcium supplementation provided in late gestation. Animal studies suggest that periparturient maternal hypocalcaemia and fetal ossification effects may occur.

Animal studies have shown that risedronate sodium crosses the placenta to a minimal extent in rats. The drug had no teratogenic activity in rats or rabbits at oral doses up to 80 and 10 mg/kg/day respectively. However, suppression of fetal growth and retardation of ossification were observed at the highest dose level in rats. When administered to rats during late gestation, maternal deaths and parturition failure were observed at oral dose levels greater than 2 mg/kg/day. These effects were probably secondary to maternal hypocalcaemia. Systemic exposure ($AUC_{0\text{-}24\ hours}$) at the no-effect level in rats was similar to that in patients with Paget's disease, and about six times higher than that in patients with corticosteroid induced osteoporosis. Systemic exposure in rabbits was not measured.

Use in lactation

There are no adequate data from the use of risedronate sodium in pregnant women. Studies in animals have shown reproductive toxicity.

The potential risk for humans is unknown.

Studies in animals indicate that a small amount of risedronate sodium pass into breast milk. Risedronate sodium must not be used during pregnancy or by breast-feeding women.

Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period post dosing, indicating a small degree of lacteal transfer. It is not known whether risedronate is excreted in human milk. Due to the potential for serious adverse reactions in breastfed infants from bisphosphonates, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

As with other bisphosphonates in preclinical models, fetuses from risedronate treated dams showed ossification changes in sternebrae and/or skull at doses as low as 3.2 mg/kg/day. This is equivalent to the human 30 mg dose and six times the human 5 mg dose based on surface area, mg/m^2. Treatment with risedronate during mating and gestation with doses of 3.2 mg/kg/day has resulted in periparturient hypocalcaemia and mortality in rats allowed to deliver.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person’s ability to drive and use machines were not assessed as part of its registration. However, when driving or operating machines, it should be taken into account that dizziness has been reported with Risedronate Sandoz (see Section 4.8 Undesirable effects)

4.8. UNDESIRABLE EFFECTS

In a one year, double blind multicentre study comparing risedronate 5 mg daily and risedronate 35 mg once a week in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar. Table 1 lists the adverse events in greater than or equal to 5% of patients from this trial. Events are shown without attribution of causality. Please refer to Table 1.

Table 1. Adverse events occurring in ≥ 5% of patients of either treatment group in the daily versus once a week osteoporosis treatment study in postmenopausal women

Body system	Risedronate 5 mg daily (n = 480) (%)	Risedronate 35 mg once a week (n = 485) (%)
Body as a whole		
Infection	19.0	20.6
Accidental injury	10.6	10.7
Pain	7.7	9.9
Back pain	9.2	8.7
Flu syndrome	7.1	8.5
Abdominal pain	7.3	7.6
Headache	7.3	7.2
Overdose	6.9	6.8
Asthenia	3.5	5.4
Cardiovascular system		
Hypertension	5.8	4.9
Digestive system		
Constipation	12.5	12.2
Dyspepsia	6.9	7.6
Nausea	8.5	6.2
Diarrhoea	6.3	4.9
Musculoskeletal system		
Arthralgia	11.5	14.2
Traumatic bone fracture	5.0	6.4
Myalgia	4.6	6.2
Nervous system		
Dizziness	5.8	4.9

In a two-year study in men with osteoporosis, the overall safety and tolerability were similar between the treatment and the placebo groups. Adverse experiences were consistent with those previously observed in women.

Risedronate postmarketing data.

The following additional adverse reactions have been reported during postmarketing use (frequency unknown).

Eye disorders:
Iritis, uveitis.

Musculoskeletal and connective tissue disorders:
Osteonecrosis of the jaw.

Skin and subcutaneous tissue disorders:
Hypersensitivity and skin reactions, including angioedema, generalised rash, urticaria and bulbous skin reactions, some severe including isolated reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, and leukocytoclastic vasculitis, hair loss.

Immune system disorders:
Anaphylactic reaction.

Hepatobiliary disorders:
Serious hepatic disorders. In most of the reported cases, the patients were also treated with other products known to cause hepatic disorders.

During post-marketing experience, the following reactions have been reported (frequency rare): Atipycal subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction). Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9. OVERDOSE

No specific information is available on the treatment of overdose with Risedronate Sandoz.

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

Treatment

In case of overdose, treatment should be supportive and symptomatic.

Administration of milk or antacids (containing magnesium, calcium or aluminium) to chelate Risedronate Sandoz may be helpful.

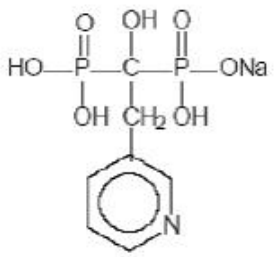
Standard procedures that are effective for treating hypocalcaemia, including the administration of calcium intravenously, would be expected to restore physiological amounts of ionised calcium and to relieve signs and symptoms of hypocalcaemia.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

The chemical name of Risedronate is Phosphonic acid, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis-, monosodium salt. Its Empirical formula is $C_7H_{10}NNaO_7P_2$ (MW: 305.10), CAS: 115436-72-1 and its chemical structure is:



Mechanism of action

Risedronate is a potent pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast mediated bone resorption. Risedronate is a third generation bisphosphonate.

In preclinical studies, risedronate demonstrated potent antiosteoclast and antiresorptive activity, increasing bone mass and biomechanical strength dose dependently. The activity of risedronate was confirmed by bone marker measurements during pharmacodynamic and clinical studies.

With risedronate 5 mg daily, decreases in biochemical markers of bone turnover were observed within one month of treatment and reached a maximum decrease in three to six months, remaining stable during the course of therapy. These data demonstrate that risedronate causes a moderate reduction in bone resorption and bone turnover. The new steady state approximates the rate of bone turnover seen in premenopausal women. Decreases in biochemical markers of bone turnover were similar with risedronate 35 mg once a week and risedronate 5 mg daily. In a study in men with osteoporosis, decreases in biochemical markers of bone turnover were observed at the earliest time point of three months and continued to be observed at 24 months.

Comparison of risedronate 5 mg daily dose and 35 mg once a week dose. Based on a lumbar spine bone mineral density (BMD), risedronate 35 mg once a week (n = 485) was shown to be therapeutically equivalent to risedronate 5 mg daily (n = 480) in a one year, double blind multicentre study of postmenopausal women with osteoporosis. The two treatment groups were also similar at one year with regard to BMD increases at the total proximal femur, femoral neck and trochanter.

Calcium carbonate/ cholecalciferol. In case of calcium deficiency, oral intake of calcium supplementation supports the remineralisation of the skeleton. Cholecalciferol increases the intestinal absorption of calcium. Administration of calcium and cholecalciferol counteracts the calcium deficiency induced increase in parathyroid hormone (PTH) and bone resorption. A meta-analysis of randomised controlled trials has suggested that oral vitamin D supplementation between 700 and 800 IU/day reduces the risk of hip and nonvertebral fractures in elderly patients. These results were complemented by a subsequent meta-analysis suggesting that oral vitamin D reduces the risk of hip fractures only when calcium supplementation is added.

Clinical trials

Treatment of postmenopausal osteoporosis. The clinical program involved a wide range of early and late postmenopausal women with and without fracture, including those with a history of GI disease and those using aspirin, NSAIDs, proton pump inhibitors and H_2-blockers.

Treatment of osteoporosis. The fracture efficacy of risedronate 5 mg daily in the treatment of postmenopausal osteoporosis was demonstrated in two large, randomised, placebo controlled, double blind studies, which enrolled a total of almost 4,000 women under similar protocols. The multinational study (RVE) was conducted primarily in Europe and Australia; a second study was conducted in North America (RVN). 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 the multinational study and 2.5 in the North American study, with a broad range of baseline BMD levels. All patients in these studies received supplemental calcium 1,000 mg/day. Patients with low vitamin D levels also received supplemental vitamin D 500 IU/day. The number of evaluable patients treated were:

RVN: risedronate 5 mg, n = 696; placebo, n = 678.
RVE: risedronate 5 mg, n = 344; placebo, n = 346.
RVN and RVE: n = 1,040; placebo, n = 1,024.

Effect on vertebral fracture. The pivotal studies of risedronate in the treatment of postmenopausal osteoporosis clearly demonstrate that risedronate 5 mg daily reduces vertebral fracture incidence in patients with low bone mass and vertebral fractures, regardless of age, years since menopause or disease severity at baseline. Risedronate 5 mg daily significantly reduced the risk of new vertebral fractures in each of the two large treatment studies. In the multinational study, treatment with risedronate 5 mg daily for three years significantly reduced the risk of new vertebral fractures by 49% compared to treatment with placebo ($p < 0.001$). (See Figure 1.) A similar, significant reduction of 41% was seen in the North American study ($p = 0.003$). The effect of risedronate 5 mg daily on vertebral fracture incidence was seen as early as the end of the first year of treatment in each study. In the multinational study, the incidence of new vertebral fractures after one year was reduced from 13.3 to 5.6%, an absolute risk reduction of 8% and a relative risk reduction of 61% ($p < 0.001$). In the North American study, the incidence of new vertebral fractures after one year was reduced from 6.4 to 2.4%, an absolute risk reduction of 4% and a relative risk reduction of 65% ($p < 0.001$). At both one and three years, the reduction in risk seen in the subgroup of patients who had two or more vertebral fractures at study entry was similar to that seen in the overall study population. Treatment with risedronate 5 mg daily also significantly reduced the proportion of patients experiencing new and worsening vertebral fractures in each of the studies. Please refer to Figure 1.

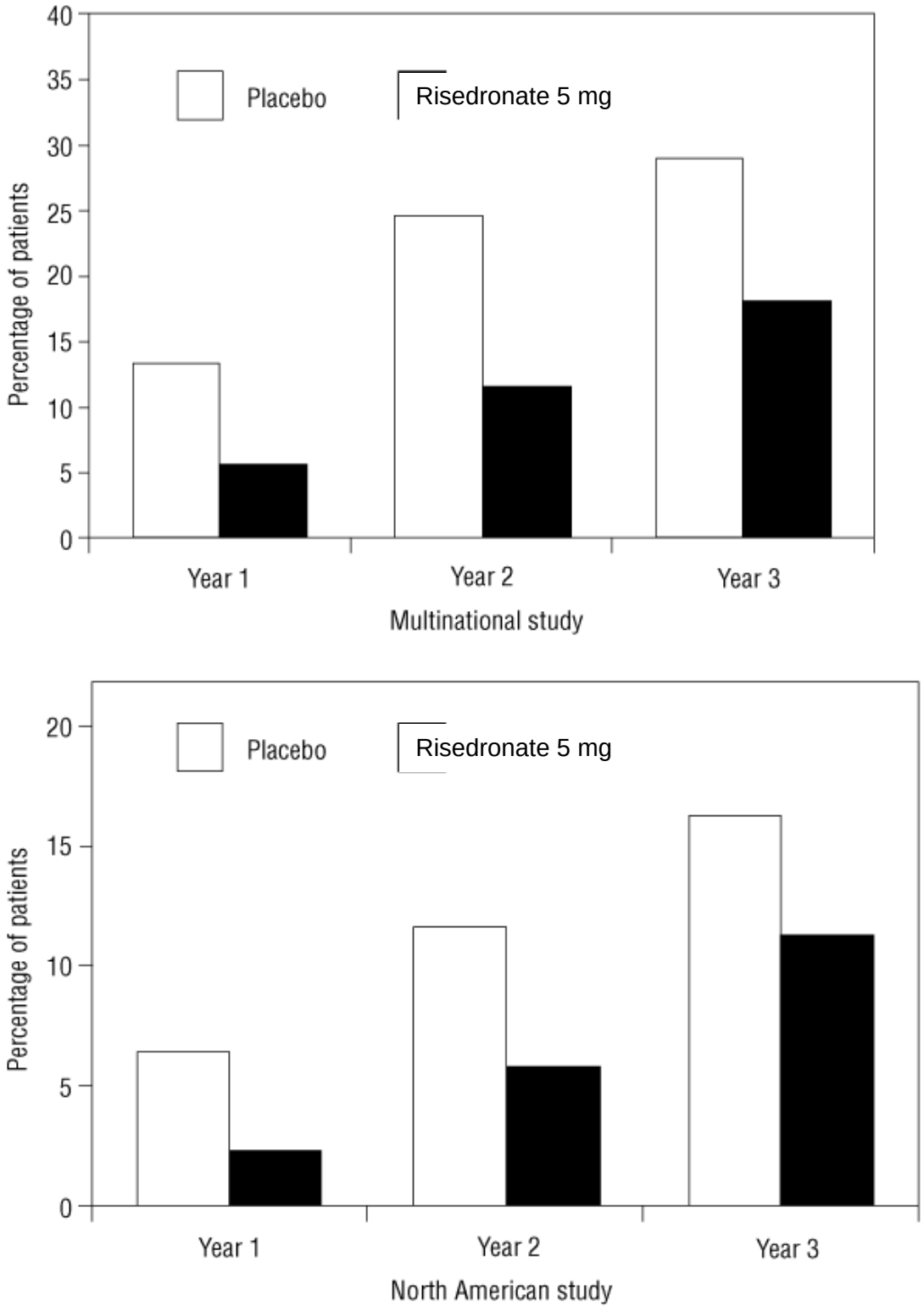


Figure 1. Cumulative incidence of new vertebral fractures

Effect on non-vertebral fractures. In a prospectively planned analysis of pooled data from the multinational and North American studies, risedronate 5 mg daily significantly reduced the cumulative incidence of patients experiencing osteoporosis related non-vertebral fractures

(wrist, humerus, clavicle, pelvis, hip and leg) over three years by 36% (p = 0.005). Please refer to Figure 2.

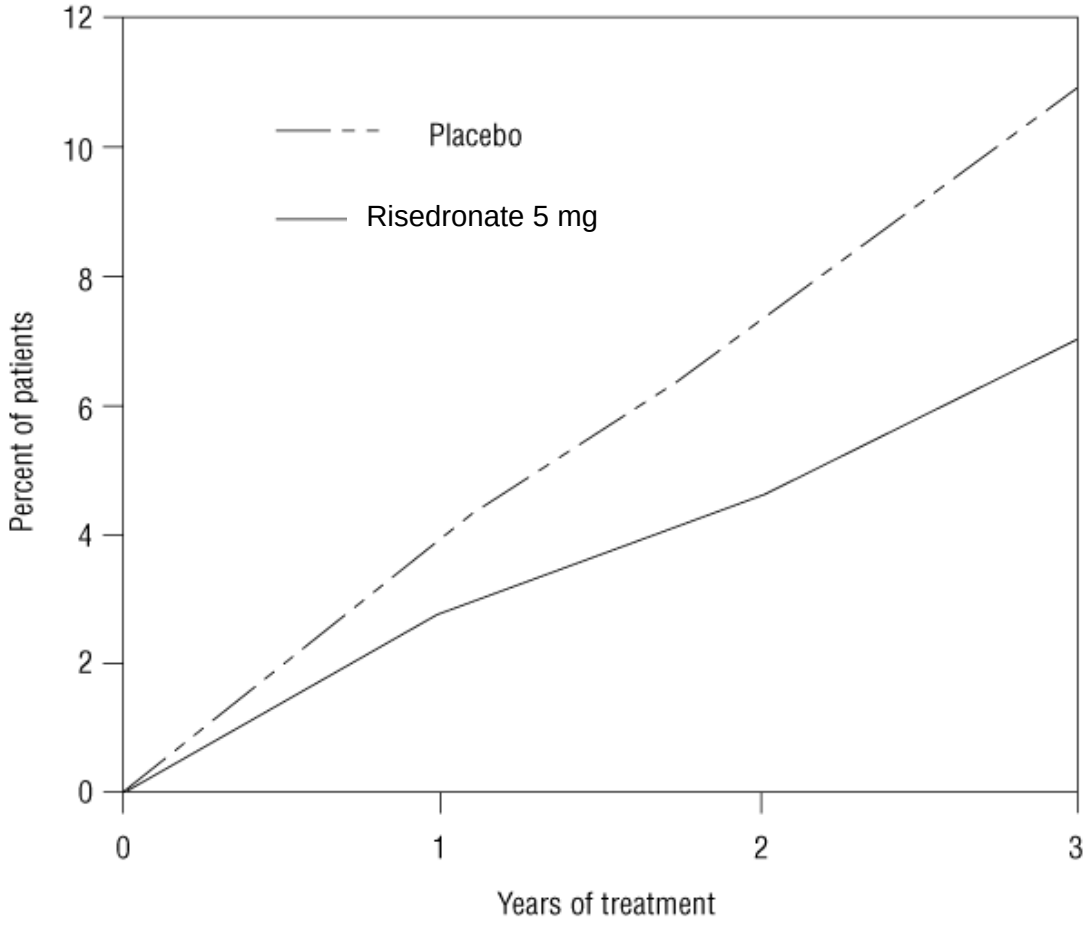


Figure 2. Cumulative incidence of osteoporosis related non-vertebral fractures: treatment studies

The incidence of non-vertebral fractures in the pooled analysis (RVN and RVE) was lower in the risedronate 5 mg group than in the placebo group for all fractures at these sites combined, as well as for the wrist, humerus, pelvis and leg separately. This difference was significant for all non-vertebral osteoporosis related fractures (p = 0.005), as well as for the humerus (p = 0.024) and pelvis (p = 0.044), while a trend was seen at the wrist (p = 0.075) (see Table 2).

These findings demonstrate a beneficial effect of risedronate in preventing non-vertebral, osteoporosis related fractures. Please refer to Table 2.

Table 2. Cumulative non-vertebral osteoporosis related fracture incidence Year 0 – 3: RVN008993 and RVE009093 combined intent to treat

Skeletal site	Patients with incident fracture	%[a]	Relative risk[b]	95% CI[b]	p value[c]
All					
Placebo	103	11.00	–	–	–
Risedronate 5 mg	69	7.11	0.643	(0.474, 0.874)	0.005
Hip					
Placebo	19	2.12	–	–	–
Risedronate 5 mg	20	1.99	1.029	(0.549, 1.930)	0.928
Wrist					
Placebo	43	4.66	–	–	–
Risedronate 5 mg	29	3.05	0.653	(0.408, 1.047)	0.075
Humerus					
Placebo	24	2.55	–	–	–
Risedronate 5 mg	11	1.13	0.447	(0.219, 0.913)	0.024
Pelvis					
Placebo	15	1.64	–	–	–
Risedronate 5 mg	6	0.59	0.391	(0.152, 1.008)	0.044
Clavicle					
Placebo	1	0.08	–	–	–
Risedronate 5 mg	5	0.55	4.892	(0.571, 41.877)	0.108
Leg					
Placebo	13	1.34	–	–	–
Risedronate 5 mg	11	1.18	0.823	(0.369, 1.838)	0.635

Number of patients with baseline and at least one non follow up visit during the 3-year studies: Placebo = 1221, Risedronate 5 mg = 1218.

[a] Cumulative proportion of patients with osteoporosis related fractures based on the Kaplan-Meier estimate of the survival function.

[b] Relative risk and 95% confidence interval based upon Cox regression model comprising terms for treatment group and study.

[c] p-value for testing the difference between the placebo and the risedronate 5 mg groups using stratified (by study) log-rank test.

– Not applicable.

Effect on height. In the two 3 year osteoporosis treatment studies, standing height was measured yearly by stadiometer. As shown in Figure 3, treatment with risedronate 5 mg daily was associated with a significant reduction of about 50% in the annual rate of height loss compared to treatment with placebo. Please refer to Figure 3.

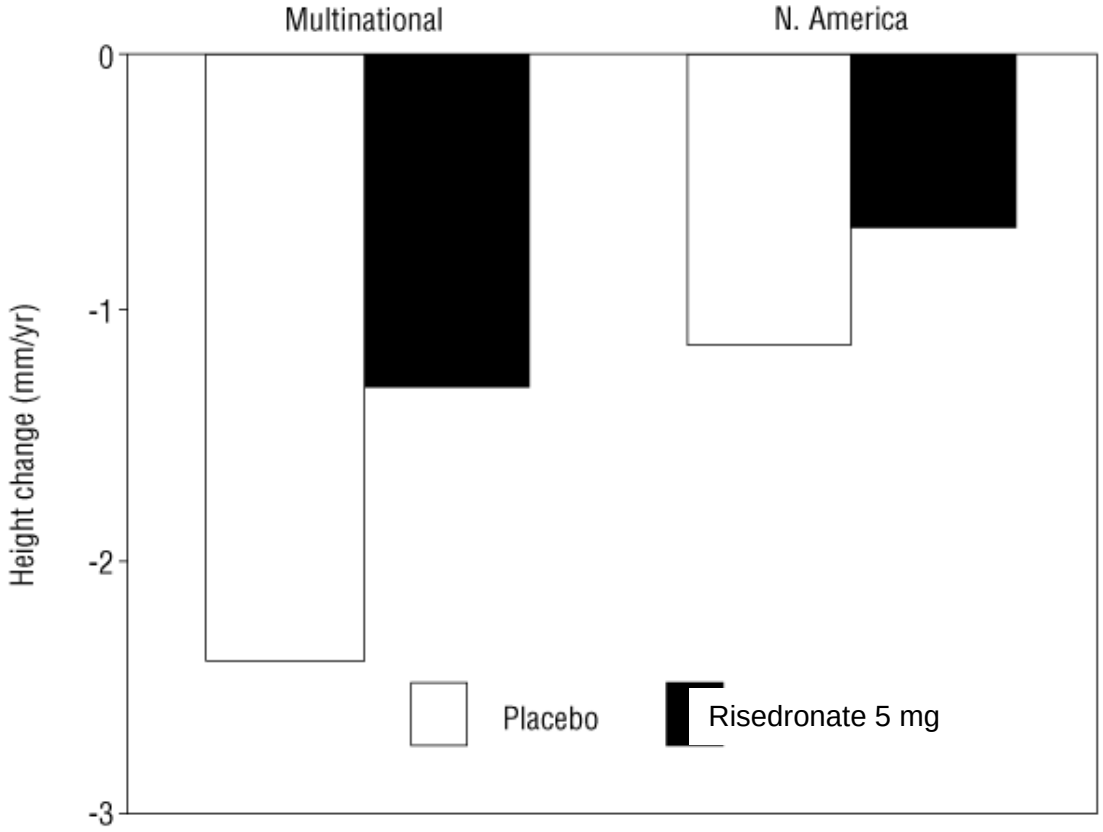


Figure 3. Median annual height change treatment studies

Effect on bone mineral density. The results of four large, randomised, placebo controlled trials in women with postmenopausal osteoporosis demonstrate that risedronate 5 mg daily reverses the progression of disease, increasing BMD at the spine, hip and wrist compared to the effects seen with placebo. In the large multinational vertebral fracture treatment study previously described, risedronate 5 mg daily produced increases in lumbar spine BMD, which were progressive over at least two years of treatment, and were statistically significant relative to baseline and to placebo at six months and at all later time points. The mean increase in BMD at the lumbar spine was 5.9%, compared to placebo at the end of three years. In the North American fracture trial, similarly, progressive and significant increases were seen; the mean increase was 4.3%, compared to placebo. Risedronate 5 mg also produced significant mean increases in BMD at the hip (femoral neck and trochanter) in each trial, compared to losses in BMD in the placebo group. The increases compared to placebo were 3.1% at the femoral neck and 6.4% at the trochanter in the multinational study, and 2.8 and 3.9%, respectively, in the North American study. Significant mean increases in the BMD of the midshaft radius, a skeletal site high in cortical bone, were also observed in each study in patients receiving risedronate treatment. These findings indicate that risedronate treatment produces positive effects at all measured skeletal sites of clinical importance for osteoporotic fractures.

Positive effects of risedronate treatment on BMD were also demonstrated in each of two large, randomised, placebo controlled trials in which almost 1,200 postmenopausal women were recruited on the basis of low lumbar spine bone mass (more than 2 SD below the premenopausal

mean) rather than a history of vertebral fracture. After 1.5 to 2 years, risedronate produced significant mean increases in BMD of the lumbar spine compared to placebo (5 and 4.1% in the two studies), femoral neck (2.8 and 2.3%) and trochanter (3.3 and 3.3%) in these women with low bone mass.

Histology/ histomorphometry. Histological evaluation of 278 bone biopsy samples from 204 postmenopausal women who received risedronate or placebo once daily for two to three years (including 74 pairs of biopsies, 43 from risedronate treated patients) showed a moderate decrease in bone turnover in risedronate treated women. Histological assessment showed no osteomalacia, impaired bone mineralisation or other adverse effects on bone in risedronate treated women. These findings demonstrate that the bone formed during risedronate administration is of normal quality.

Bone markers. In clinical studies, dose dependent decreases in biochemical markers of bone turnover were observed with risedronate 5 mg treatment. These effects were seen within one month of treatment and reached a plateau, with levels about 40% below baseline values, by the sixth month of treatment, which remained stable during continuous treatment for up to three years. These data demonstrate that risedronate 5 mg causes a moderate reduction in bone resorption without over-suppression of bone formation. This new steady state approximates the rate of bone turnover seen in premenopausal women.

Combined administration with hormone replacement therapy. The effects of combining risedronate 5 mg daily with conjugated oestrogen treatment (0.625 mg daily) were compared to the effects of conjugated oestrogen alone in a one year, randomised, double blind study in more than 500 postmenopausal women (mean lumbar spine BMD 1.3 SD below the premenopausal mean). Risedronate 5 mg daily in postmenopausal women taking oestrogen produced significant mean increases from baseline in BMD of the femoral neck (2.7%) and the midshaft radius (0.7%) at 12 months. These increases were greater than the increases observed in the oestrogen alone group, and reached statistical significance in favour of the combined treatment at the femoral neck and midshaft radius.

Consistent with the changes in BMD, the reduction in bone turnover was significantly greater in the combined risedronate plus oestrogen group compared to the oestrogen alone group (40 to 47% versus 35 to 40%) and remained within the premenopausal range. Histological evaluation of 93 bone biopsy samples from 61 women on oestrogen therapy who received either placebo or risedronate once daily for one year (including 32 pairs of biopsies, 16 from risedronate treated patients) found decreases in bone turnover in the risedronate treated patients that were consistent with the changes in bone turnover markers. Bone histology demonstrated that the bone of patients treated with risedronate plus oestrogen was of normal lamellar structure and normal mineralisation.

Endoscopic findings. Risedronate endoscopic findings from patients with moderate to severe GI complaints in both risedronate and control patients showed no evidence of treatment related gastric, duodenal or oesophageal ulcers. Duodenitis was rarely observed in the risedronate group. Four out of five patients with endoscopically diagnosed oesophageal strictures had been taking risedronate 5 mg for more than six months.

Risedronate 35 mg once a week (n = 485) was shown to be therapeutically equivalent to risedronate 5 mg daily (n = 480) in a one year double blind multicentre study of postmenopausal women with osteoporosis. In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 4.0% (3.7, 4.3; 95% CI) in the 5 mg group (n = 391) and 3.9% (3.6, 4.3; 95% CI) in the 35 mg group (n = 387) and the

mean difference between 5 mg daily and 35 mg once a week was 0.1% (-0.42, 0.55; 95% CI) (see Table 3). While once a week doses of risedronate resulted in slightly smaller increases in lumbar spine BMD compared to daily doses of 5 mg after six months, the two regimens are equivalent after 12 months. The clinical relevance of these six month BMD differences is unknown. The results of the intent to treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The two treatment groups were also similar with regard to BMD increases at other skeletal sites. This study is of two years' duration, the results of which will be included as soon as they are available. Please refer to Table 3.

Table 3. Study HMR 4003E/3001 bone mineral density by visit: mean percentage change from baseline (intent to treat population)

	Risedronate 5 mg daily		Risedronate 35 mg once-a-week		Mean difference (95% CI)
Analysis visit	n	Mean	n	Mean	5 mg daily vs 35 mg once-a-week
Lumbar spine					
Month 6	402	3.12[a]	389	2.68[a]	0.44[b] (0.01; 0.87) p = 0.045
Month 12	391	4.00[a]	387	3.94[a]	0.06 (-0.42; 0.55) p = 0.799

[a] Indicates statistically significant difference from baseline
[b] Indicates statistically significant difference between treatment groups

Very few patients in any treatment group had new fractured vertebrae at month 12 (5 mg daily: 1.5%; 35 mg once a week: 1.3%). No patient had more than one new fractured vertebra. There were no statistically significant differences in the percentage of patients with new vertebral fractures among the two treatment groups.

***Treatment of osteoporosis in men*.** Risedronate 35 mg once a week demonstrated efficacy in men with osteoporosis (age range 36 to 84 years) in a two year, double blind, placebo controlled study in 284 patients (risedronate sodium 35 mg n = 191). All patients received supplemental calcium and vitamin D. The primary efficacy endpoint was assessed by the percentage change from baseline in lumbar spine BMD at endpoint (month 24 or last post-baseline observation). Secondary efficacy measures included lumbar spine and proximal femur BMD at 6, 12 and 24 months; BMD responders (defined as patients who had a positive lumbar spine BMD change at month 24); bone turnover markers at 6, 12 and 24 months; body height; incidence of new vertebral fractures and incidence of clinical fractures. Increases in BMD were observed as early as six months following initiation of risedronate sodium treatment. The primary analysis showed a statistically significant difference between risedronate and placebo in least squares mean percent change from baseline to endpoint ($p < 0.0001$). The estimated difference at endpoint between risedronate and placebo in the intention to treat (ITT) population was 4.53% (95% CI: 3.46%, 5.60%). Risedronate 35 mg produced mean increases in BMD at the lumbar spine, femoral neck, trochanter and total hip compared to placebo after two years of treatment. The bone effect (BMD increase and bone turnover markers (BTM) decrease) of risedronate sodium is similar in males and females.

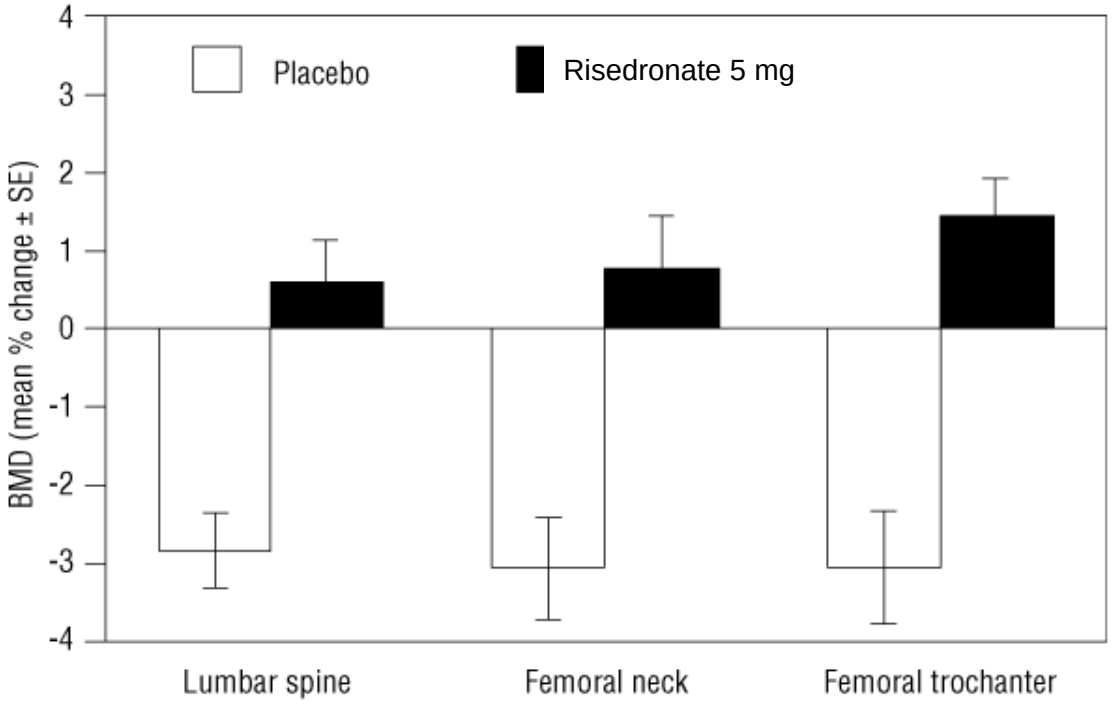
Corticosteroid induced osteoporosis.

Bone mineral density. Two one year, double blind, placebo controlled trials demonstrated that risedronate 5 mg once daily was effective in maintaining or increasing BMD in men and women initiating or continuing corticosteroid therapy.

The first study enrolled 228 patients, each of whom had initiated corticosteroid therapy (greater than or equal to 7.5 mg/day of prednisone or equivalent) within the previous three 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. After one year of treatment, the placebo group lost BMD at the lumbar spine, femoral neck and trochanter, as shown in Figure 4. Risedronate 5 mg once daily prevented this bone loss with a statistically significant difference from placebo of 3.8% at the lumbar spine, 4.1% at the femoral neck and 4.6% at the trochanter. The results at these three sites were also statistically significant when the subgroups of men or postmenopausal women were analysed separately. Risedronate prevented bone loss regardless of underlying disease, age, race, gender, corticosteroid dose or baseline BMD.

The effect of risedronate discontinuation on bone mineral density was studied in a double blind, placebo controlled study in postmenopausal women with glucocorticoid dependent rheumatoid arthritis. Women were treated for two years with risedronate 2.5 mg daily, cyclic risedronate (averaged 2.5 mg of risedronate per day over the 96 week active period), or placebo and then followed without treatment for one more year. Patients continued glucocorticoid treatment during the third year of the study. Risedronate discontinuation resulted in bone loss at all skeletal sites (proximal femur and lumbar spine) during the third year. The rate of bone loss, however, was similar to the placebo group indicating that bone loss was not accelerated after risedronate was discontinued. The study supports the use of continuous treatment with risedronate to prevent bone loss. Please refer to Table 4.

Table 4. Change in BMD from baseline in patients recently initiating corticosteroid therapy: 1-year study



A second study of similar design enrolled 290 patients with continuing, long-term use (greater than or equal to six months) of corticosteroids for rheumatic, skin and pulmonary diseases. The baseline mean lumbar spine BMD was low (1.64 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 1,000 mg/day. Patients also received supplemental vitamin D 400 IU/day. After one year of treatment, the BMD of the placebo group remained near baseline levels at the lumbar spine, femoral neck and trochanter. Risedronate 5 mg once daily improved bone mass with a statistically significant mean increase compared to placebo of 2.7% at the lumbar spine and 1.9% at the femoral neck as shown in Figure 5. At the trochanter, a statistically significant increase from baseline was demonstrated (2.4%). Risedronate was effective regardless of age, race, gender, underlying disease, corticosteroid dose or baseline BMD. Please refer to Figure 5.

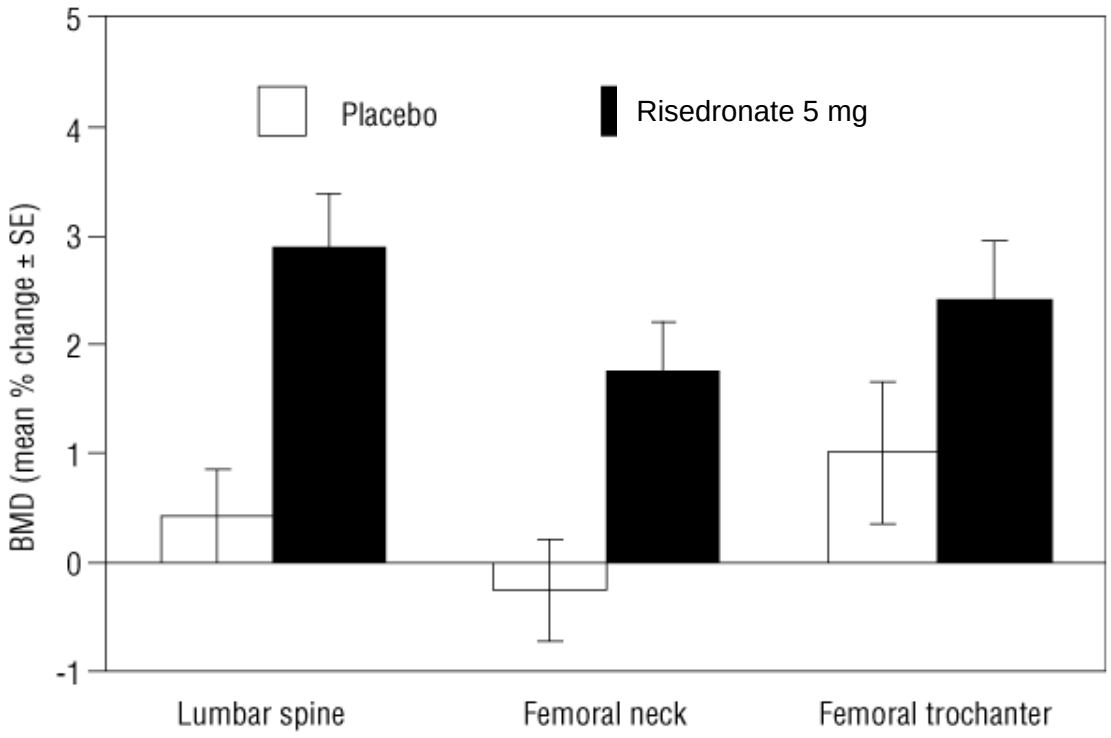


Figure 5. Change in BMD from baseline in patients on long-term corticosteroid therapy: 1-year study

Vertebral fractures. Vertebral fractures were monitored for safety in the two placebo controlled studies. The incidence of vertebral fractures in each study was 15 to 17% in the placebo patients. The risk of vertebral fractures was reduced approximately 70% in the patients treated with risedronate 5 mg compared to patients treated with placebo. This decrease reached statistical significance when the studies were pooled, but not when analysed individually.

Bone marker data. Risedronate 5 mg daily produced significant reductions in biochemical markers of bone turnover relative to placebo. Deoxypyridinoline/ creatinine and bone specific alkaline phosphatase (SAP) were significantly reduced by approximately 20% relative to placebo after one and three months of treatment, respectively, and remained reduced (maximum 35 and 26%, respectively) for the duration of the treatment period.

Histology/ histomorphometry. Histological evaluation of 70 bone biopsy samples from 48 women on corticosteroid therapy who received either placebo or risedronate once daily for one year (including 22 pairs of biopsies, 16 from risedronate treated patients) showed that bone formed during treatment with risedronate was of normal lamellar structure and normal mineralisation, with no bone or marrow abnormalities observed. Histomorphometric evaluation indicated that risedronate 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 mineralisation. The structure of the cortical bone (cortical thickness and porosity) was maintained in the risedronate treated patients; cortical porosity increased, however, in the placebo group. These findings indicate that bone formed during risedronate treatment is of normal quality.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Risedronate is relatively rapidly absorbed (T_{max} approx. 1 hour) throughout the upper gastrointestinal (GI) tract. Absorption is independent of dose over the range studied (single dose study, 2.5 to 30 mg; multiple dose studies, 2.5 to 5 mg daily and up to 50 mg dosed weekly). In a 13 week pharmacokinetic study with 5 mg daily and 35 mg weekly and 50 mg weekly dosing (n approx. 19 per group), a comparison of the average serum concentration (C_{avg}) for 35 mg/week and 5 mg/day was not statistically significantly different. The 95% confidence interval for C_{avg} was 57.1 to 101.2, with a point estimate of 76.0% for the 35 mg dose compared to the 5 mg dose. Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean oral bioavailability of the tablet is 0.63% and is decreased when risedronate is administered with food. Bioavailability was similar in men and women. Although administration of risedronate either 30 minutes prior to breakfast or two hours after dinner reduces absorption of risedronate by 55% compared to administration in the fasting state (i.e. no food or beverages for ten hours prior to, or four hours after dosing), and administration one hour prior to breakfast reduces absorption by 30%, risedronate has been shown to be effective in clinical trials when administered 30 minutes (or longer) before the first meal or beverage of the day (e.g. breakfast) and also when administered two hours (or longer) prior to and following food or beverages at other times of the day.

Distribution

The mean steady-state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of risedronate is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of ^{14}C-risedronate indicate that 40 to 45% of the dose was distributed in the bone after 72 hours. At the same time, risedronate levels in soft tissues of rats and dogs were at least 40 and 16 times lower than those in bone, respectively. The remainder of the dose was mainly excreted in the urine. This is likely to be considerably lower in humans who excrete 65% of an intravenously administered dose in the urine in 24 hours. After multiple oral dosing in rats, accumulation of risedronate was observed in bone but not in soft tissues.

Metabolism

There is no evidence of systemic metabolism of risedronate.

Excretion

Approximately half the absorbed dose is excreted in the urine within 24 hours. 85% of an intravenous dose is recovered in the urine over 28 days. Mean renal clearance is 105 mL/minute and mean total clearance is 122 mL/minute. The difference primarily reflects 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. In the same pharmacokinetic study mentioned (see Absorption), the percent of dose excreted in urine was measured. The point estimate for the 35 mg versus 5 mg doses was 66.8% (95% CI, 48.0 to 95.8). Although this was statistically significantly different, the clinical relevance is unknown.

Unabsorbed risedronate is eliminated unchanged in the faeces.

Following absorption, the serum concentration-time profile is multiphasic with an initial half-life of about 1.5 hours and a terminal exponential half-life of 480 hours. Although the

elimination rate from human bone is unknown, the 480 hour half-life is hypothesised to represent the dissociation of risedronate from the surface of the bone.

Following oral administration of a single-dose of Risedronate Sandoz 35 mg to healthy subjects under fasting conditions, a mean peak plasma concentration (C_{max}) of risedronate of approximately 9.47 ng/mL was achieved within approximately 1 hour (T_{max}).

Special groups

Paediatric. Risedronate sodium is not recommended for use in children below the age of 18 due to insufficient data on safety and efficacy.

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

Geriatric. Risedronate pharmacokinetics are similar in older subjects (age 45 to 76 years) with normal renal function (creatinine clearance 80 to 120 mL/minute) to that observed in young subjects (age 18 to 45 years). No dosage adjustment is necessary (see Section 4.2 Dose and method of administration).

Ethnicity. Pharmacokinetic differences due to ethnicity have not been studied.

Renal insufficiency. Risedronate is excreted intact primarily via the kidney. There is limited clinical data in patients with severe renal impairment (creatinine clearance < 30 mL/minute) and, therefore, risedronate is not recommended for this patient group.

No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 30 mL/minute.

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

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

Risedronate did not cause gene mutations in bacterial or mammalian cells *in vitro*, nor did it cause DNA damage in rat hepatocytes *in vitro*. In clastogenicity assays, risedronate was positive in an *in vitro* assay using Chinese hamster ovary cells at cytotoxic concentrations (7 to 18% cell survival), but there was no evidence of chromosomal damage when the assay was repeated at concentrations leading to 48 to 74% cell survival. Risedronate was negative at oral doses up to 1,336 mg/kg in an *in vivo* assay (chromosomal aberrations in rat bone marrow).

Carcinogenicity

No evidence of carcinogenicity was observed in either rats (treated for 104 weeks with up to 24 mg/kg/day) or mice (treated for 80 weeks with up to 32 mg/kg/day). Systemic exposure (serum $AUC_{0\text{-}24\ hours}$) at the high dose in rats was 160 times greater than that in humans dosed at 30 mg/day. Systemic exposure was not assessed in mice, but the highest dose in the carcinogenicity study was at least 30 times higher than the dose required for pharmacological effects on bone. Thus, risedronate sodium appears to have no carcinogenic potential at therapeutic dose levels.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Lactose monohydrate, crospovidone, microcrystalline cellulose, magnesium stearate, Opadry Orange (containing hypromellose, titanium dioxide, macrogol 400, iron oxide yellow, iron oxide red).

6.2. INCOMPATIBILITIES

Calcium, antacids, aluminium and some oral medications will interfere with the absorption of Risedronate Sandoz and therefore should be taken at a different time of the day.

6.3. SHELF LIFE

36 months from date of manufacture.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5. NATURE AND CONTENTS OF CONTAINER

Available in blisters packs of 4 tablets.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand
Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

05 May 2016

10. DATE OF REVISION OF THE TEXT

23 January 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of hypocalcaemia and hypophosphatemia warning
4.8	Update to ADR reporting URL