Risedro Once A Week

PRODUCT INFORMATION

Name of the medicine

Risedronate sodium. The chemical name for risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis(phosphonic acid) monosodium salt. Its structural formula is:

![Structural formula of risedronate sodium](image)

C₇H₁₀NO₇P₂Na  Molecular weight: 305.10  Cas No.: 115436-72-1

Description

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

Risedro Once A Week tablets contains 35 mg of risedronate sodium. The tablets also contain the following excipients: microcrystalline cellulose, sorbitol, colloidal anhydrous silica, croscarmellose sodium and sodium stearyl fumarate. The tablets are gluten free.

Pharmacology

Pharmacodynamics

Risedronate is a potent pyridinyl bisphosphate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. Risedronate is a third generation bisphosphonate. In preclinical studies risedronate demonstrated potent anti-osteoclast and anti-resorptive 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.

Pharmacokinetics

Absorption
Risedronate is relatively rapidly absorbed ($T_{\text{max}} \approx 1$ 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 ~ 19/group), a comparison of the average serum concentration ($C_{\text{avg}}$) for 35 mg/week and 5 mg/day was not statistically significantly different. The 95% confidence interval for $C_{\text{avg}}$ 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.

In a crossover, randomised comparative bioavailability study, 60 healthy male and female volunteers were enrolled for treatment. Volunteers were administered a single dose of 35 mg Risedro Once A Week risedronate tablet or the Australian reference risedronate tablet. Results demonstrated bioequivalence of Risedro Once A Week with the Australian reference risedronate (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Risedro Once A Week 35 mg tablets (mean)</th>
<th>Australian reference risedronate 35 mg tablets (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risedronate</td>
<td>$C_{\text{max}} \text{ (ng/mL)*}$</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-\infty} \text{ (ng<em>hl/mL)</em>}$</td>
<td>32.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36.57</td>
</tr>
</tbody>
</table>

*The 90% confidence interval for $AUC_{0-\infty}$ and $C_{\text{max}}$ for the test preparation vs. the Australian reference preparation was each within the acceptance range (range of 0.75 -1.33 for $AUC_{0-\infty}$ and 0.80 – 1.25 for $C_{\text{max}}$) required to conclude bioequivalence.

Distribution
The mean steady-state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of risedronate is about 24%. Predinical 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/min and mean total clearance is 122 mL/min. The difference primarily reflects 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. 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.

Special groups
Paediatric: Safety and efficacy of risedronate have not been established in patients under 18 years of age.

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/min) to that observed in young subjects (age 18 to 45 years). No dosage adjustment is necessary (see Dosage and 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/min) and, therefore, risedronate is not recommended for this patient group.

No dosage adjustment is necessary in patients with a creatinine clearance ≥ 30 mL/min.

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.

Clinical Trials

Treatment of 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 H2-blockers.

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.

Figure 1: Cumulative Incidence of New Vertebral Fractures

![Figure 1: Cumulative Incidence of New Vertebral Fractures](image-url)
Effect on nonvertebral 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 nonvertebral fractures (wrist, humerus, clavicle, pelvis, hip and leg) over three years by 36% (p = 0.005). See Figure 2.

**Figure 2: Cumulative incidence of Osteoporosis-Related Non-Vertebral Fractures - Treatment Studies**

The incidence of nonvertebral 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 nonvertebral 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 nonvertebral, osteoporosis related fractures.
Table 2: Cumulative Non-Vertebral Osteoporosis-Related Fracture Incidence Year 0 – 3, RVN008993 and RVE009093 Combined Intent-to-Treat

<table>
<thead>
<tr>
<th>Skeletal site</th>
<th>Patients with Incident Fracture</th>
<th>% a</th>
<th>Relative Risk b</th>
<th>95% CI b</th>
<th>P value c</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Placebo</td>
<td>103</td>
<td>11.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5 mg risedronate</td>
<td>69</td>
<td>7.11</td>
<td>0.643</td>
<td>(0.474, 0.874)</td>
</tr>
<tr>
<td>Hip</td>
<td>Placebo</td>
<td>19</td>
<td>2.12</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>5 mg risedronate</td>
<td>20</td>
<td>1.99</td>
<td>1.029</td>
<td>(0.549, 1.930)</td>
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<tr>
<td>Wrist</td>
<td>Placebo</td>
<td>43</td>
<td>4.66</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5 mg risedronate</td>
<td>29</td>
<td>3.05</td>
<td>0.653</td>
<td>(0.408, 1.047)</td>
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<tr>
<td>Humerus</td>
<td>Placebo</td>
<td>24</td>
<td>2.55</td>
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<td>-</td>
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<td></td>
<td>5 mg risedronate</td>
<td>11</td>
<td>1.13</td>
<td>0.447</td>
<td>(0.219, 0.913)</td>
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<tr>
<td>Pelvis</td>
<td>Placebo</td>
<td>15</td>
<td>1.64</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>5 mg risedronate</td>
<td>6</td>
<td>0.59</td>
<td>0.391</td>
<td>(0.152, 1.008)</td>
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<td>Clavicle</td>
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<td>1</td>
<td>0.08</td>
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<td>4.892</td>
<td>(0.571, 41.877)</td>
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<tr>
<td>Leg</td>
<td>Placebo</td>
<td>13</td>
<td>1.34</td>
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<td>5 mg risedronate</td>
<td>11</td>
<td>1.18</td>
<td>0.823</td>
<td>(0.369, 1.838)</td>
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</table>

Number of patients with baseline and at least one non-follow-up visit during the 3-year studies: placebo = 1551, 5 mg risedronate = 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 5 mg risedronate groups using stratified (by study) long-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.

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 oversuppression 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.

35 mg once a week dose
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.

Table 3: Study HMR 4003E/3001 Bone Mineral Density by Visit – Mean Percent Change from Baseline (Intent-to-treat Population)

<table>
<thead>
<tr>
<th>Analysis Visit</th>
<th>5 mg Daily Risedronate</th>
<th>35 mg once a week risedronate</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>N</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td>402</td>
<td>3.12a</td>
<td>389</td>
</tr>
<tr>
<td>Month 12</td>
<td>391</td>
<td>4.00a</td>
<td>387</td>
</tr>
</tbody>
</table>

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 once a week 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 BMD 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.

Figure 4: Change in BMD from Baseline Patients Recently Initiating Corticosteroid Therapy 1 Year Study

![Figure 4: Change in BMD from Baseline Patients Recently Initiating Corticosteroid Therapy 1 Year Study](image)

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.
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.

Indications
Risedro Once A Week 35 mg tablets are indicated for the:
- Treatment of osteoporosis.
- Treatment of glucocorticoid-induced osteoporosis.
- Preservation of bone mineral density in patients on long-term corticosteroid therapy.
Contraindications

Known hypersensitivity to the drug.

Hypocalcaemia (see Precautions).

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

Precautions

Food, certain medication and beverages (except plain water) can interfere with the absorption of risedronate sodium. Therefore, for patients to gain maximum benefit, doctors must stress the importance of taking Risedro Once A Week as per the dosage instructions (see Dosage and Administration). This is especially important in the case of patients with a history of oesophageal disorders.

Hypocalcaemia must be corrected before starting risedronate sodium therapy.

Bone and mineral metabolism dysfunction (e.g. vitamin D deficiency and parathyroid abnormalities) should be effectively treated before starting risedronate therapy.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

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

Risedronate sodium, like other bisphosphonates, may cause local irritation of the upper GI mucosa. Since some bisphosphonates have been associated with oesophagitis and oesophageal ulcerations, 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. Doctors should be particularly careful to emphasise the importance of taking Risedronate sodium as per the dosage instructions to patients who have a history of oesophageal disorders.

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

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 and 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.
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 µg/kg/day). These data indicate that risedronate administered at therapeutic doses is unlikely to induce osteomalacia.

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 0-24 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.

Mutagenicity
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).

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 0-24 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)
Risedronate has not been studied in pregnant women. It should only be used during pregnancy if the potential benefit justifies the potential risk to mother and fetus. If administration during pregnancy is contemplated, serum calcium levels should be monitored and calcium supplementation (with vitamin D to aid calcium absorption) 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 0-24 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.
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/m². 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.

**Interactions with Other Medicines**

No specific drug interactions studies have been performed. However risedronate 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 and should be taken at a different time of the day.

Risedronate 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, H2-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 IIII postmenopausal trials with 5 mg daily dosing, 29 and 37% of patients used aspirin and NSAIDs respectively. The incidence of upper GI adverse reactions 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 Once-a-Week study, 57 and 40% of patients used aspirin and NSAIDs respectively.

**Effect 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.

**Adverse Effects**

**Osteoporosis - 5 mg daily dosing**
The phase IIIA clinical trials were designed to include patients with a history of upper gastrointestinal (GI) disorder. Patients were permitted concomitant use of NSAIDs and aspirin. In these patients the incidence of upper GI adverse reactions in the risedronate group was similar to that in the placebo control group.

Abdominal and musculoskeletal pain were commonly reported (1 to 10%). Glossitis, iritis and duodenitis were reported uncommonly (0.1% to 1%). There were rare reports (< 0.1%) of abnormal liver function tests.

Laboratory test findings. Asymptomatic, small decreases in serum calcium and phosphorus levels have been observed in some patients.
Risedronate has been studied for up to three years in over 5,000 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 incidence of serious adverse events in the placebo group was 24.9% and in the risedronate group 26.3%. The percentage of patients who withdrew from the study due to adverse events was 14.4 and 13.5% for the placebo and risedronate groups respectively.

Table 4 lists adverse events reported in ≥5% of risedronate treated patients and at an incidence higher than in the placebo group in phase III postmenopausal osteoporosis trials. Adverse events are shown without attribution of causality.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Placebo % (N = 1744)</th>
<th>Risedronate 5 mg % (N = 1742)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9.4</td>
<td>10.6</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>9.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint Disorder</td>
<td>5.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>4.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>4.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>5.3</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Endoscopic findings: Risedronate clinical studies enrolled over 5,000 postmenopausal women and included patients with pre-existing gastrointestinal disease and concomitant use of NSAIDs or aspirin. 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 (11.9%) risedronate; 75 (14.5%) placebo). Across treatment groups, the percentage of patients with normal oesophageal, gastric and duodenal mucosa on endoscopy was similar (20% placebo and 21% risedronate). Positive findings on endoscopy were also generally comparable across treatment groups (58 (82.9%) placebo and 57 (81.4%) risedronate).

There was a higher number of reports of mild duodenitis in the risedronate group (11 (15.7%); placebo 7 (10%)), however, there were more duodenal ulcers in the placebo group (33 (47.1%); risedronate 26 (37.1%)). The number of patients who had positive findings and withdrew from the studies was similar across treatment groups (placebo 26 (37.1%) and risedronate 27 (38.6%)) and there was no evidence of treatment related oesophageal, gastric or duodenal ulcers/ erosions.

Risedronate has been studied in phase III corticosteroid induced osteoporosis trials enrolling more than 500 patients. The adverse event profile in this population was similar to that seen in postmenopausal osteoporosis trials, except for musculoskeletal events, which were reported by > 10% of patients and occurred at a greater frequency in the risedronate 5 mg treatment group (75 (43.1%)) compared to the placebo group (57 (33.5%)). The adverse experiences reported (165 placebo and 167 risedronate) have usually been mild or moderate and generally have not required discontinuation of treatment. The occurrence of adverse events does not appear to be related to patient age, gender or race.
Osteoporosis - 35 mg once a week dosing
In a one year, double blind multicentre study comparing 5 mg risedronate daily and 35 mg risedronate once a week in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar. Table 5 lists the adverse events in greater than or equal to 5% of patients from this trial. Events are shown without attribution of causality.

| Table 5: Adverse Events Occurring in ≥5% of Either Treatment Group in the Daily vs 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                                   | 5.8                              | 4.9                             |
| Dizziness                                        |                                  |                                 |

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 very rarely reported during postmarketing use.
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 and bulbous skin reactions, some severe.

Dosage and Administration
Risedro Once A Week must only be taken with plain water. Please note that some mineral waters or water from regional areas may have a higher concentration of calcium and therefore should not be used.
Risedro Once A Week must be taken 30 minutes before the first food or drink other than water. To facilitate delivery to the stomach, it 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.

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

**Use in the elderly**
No dose adjustment is necessary.

**Renal impairment**
No dose adjustment is necessary in patients with mild to moderate renal insufficiency (creatinine clearance 30 to 60 mL/minute). Risedronate is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/minute) due to limited clinical data.

**Use in children**
Safety and efficacy of risedronate has not been established in patients under 18 years of age.

**Compatibility with other drugs**
Calcium, antacids, aluminium and some oral medications will interfere with the absorption of risedronate and therefore should be taken at a different time of the day.

**Overdosage**
No specific information is available on the treatment of overdose with risedronate. 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. Administration of milk or antacids (containing magnesium, calcium or aluminium) to chelate risedronate 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.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on management of overdose.

**Presentation and storage conditions**

**Risedro Once A Week**
Each tablet contains 35 mg of risedronate sodium. White to off-white capsule shaped tablet, embossed with RE 35 on one side and plain on the other; blister packs (PVC/PVDC/Al) of 4 tablets.

Store the tablets below 25°C.

**Name and address of the sponsor**

Arrow Pharma Pty Ltd
15 – 17 Chapel Street
Cremorne VIC 3121
Poison schedule of the medicine

S4 – Prescription Only Medicine

Date of first inclusion on the Australia Register of Therapeutic Goods (ARTG)

24 February 2011

Date of most recent amendment

30 June 2017