

## PRODUCT INFORMATION

# ACRIS COMBI

Risedronate sodium tablets and calcium carbonate tablets



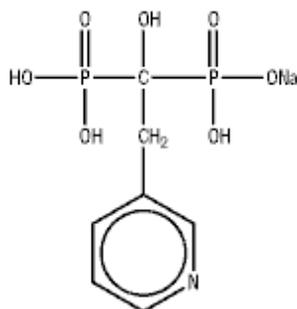
## NAME OF THE MEDICINE

### Risedronate sodium

Active ingredient : Risedronate sodium hemipentahydrate

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

Structural formula :



Molecular formula :  $C_7H_{10}NO_7P_2Na \cdot 2.5H_2O$

Molecular weight : 350.13

CAS Registry no. : 329003-65-8

### Calcium carbonate

Active ingredient : Calcium carbonate

Molecular formula :  $CaCO_3$

Molecular weight : 100.1

CAS Registry no. : 471-34-1

## DESCRIPTION

### Risedronate

Risedronate sodium (as hemipentahydrate) 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.

Each risedronate tablet contains 35 mg risedronate sodium (as hemipentahydrate) and the following inactive ingredients: Mannitol, microcrystalline cellulose, crospovidone, silicon dioxide, magnesium stearate, Opadry II beige 40L97490 (ARTG No. 107225) and Opadry clear YS-1-7006 (ARTG No. 12789).

### Calcium carbonate

Calcium carbonate is a white powder, practically insoluble in water.

Each calcium tablet contains 1250 mg calcium carbonate as a mixture of calcium carbonate and pregelatinised maize starch and the following inactive ingredients: Hydroxypropylcellulose, polysorbate 80, purified water, microcrystalline cellulose, croscarmellose sodium, Indigo carmine, Allura red AC, purified talc, magnesium stearate, Opadry Aqueous film coating Y-19-7483 (ARTG No. 3751).

## PHARMACOLOGY

### Pharmacodynamics

#### Risedronate

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 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 1 month of treatment and reached a maximum decrease in 3-6 months, remaining stable during the course of therapy. This data demonstrates that risedronate causes a moderate reduction in bone resorption and bone turnover. The new steady state approximates the rate of bone turnover seen in pre-menopausal women. Decreases in biochemical markers of bone turnover were similar with risedronate 35 mg Once-a-Week (Sanofi-Aventis) 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 3 months and continued to be observed at 24 months.

#### Comparison of 5 mg daily dose and 35 mg Once-a-Week dose (Sanofi-Aventis)

Based on a lumbar spine BMD (bone mineral density), 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.

#### Comparison of 5 mg daily dose and 150 mg Once-a-Month dose (Sanofi-Aventis)

Based on effects on mean percent change in lumbar spine BMD, risedronate sodium 150 mg (n = 561) once a month was shown to be equivalent to risedronate sodium 5 mg (n = 561) daily in a one-year, double-blind, multicentre study of postmenopausal women with osteoporosis. Both groups had statistically significant mean percent increases in lumbar spine BMD from baseline to Month 6, 12 and endpoint. The two treatment groups were also similar with regard to BMD increases at the total proximal femur and trochanter.

#### Calcium Carbonate

In case of calcium deficiency, oral intake of calcium supplementation supports the remineralisation of the skeleton. Administration of calcium 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 700-800 IU per 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.

### Pharmacokinetics

#### Risedronate

##### 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 150 mg monthly). 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 ( $C_{avg}$ ) for 35 mg/week and 5 mg/day was not statistically significantly different. The 95% confidence interval for  $C_{avg}$  was 57.1-101.2, 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 2 hours after dinner reduces absorption of risedronate by 55% compared to administration in the fasting state (i.e., no food or

beverages for 10 hours prior to, or 4 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 (eg., breakfast) and also when administered 2 hours (or longer) prior to and following food or beverages at other times of the day.

A bioavailability study was conducted comparing the generic Risedronate sodium 35 mg tablet against the originator Risedronate sodium 35 mg tablet. The generic and originator mean  $C_{max}$  for Risedronate was 14.00 ng/mL and 15.09 ng/mL respectively. The  $C_{max}$  point estimate for Risedronate was 0.98 with the 90% confidence interval between 0.91 and 1.06. The mean  $AUC_{\infty}$  point estimate for Risedronate was 0.96 with the 90% confidence interval between 0.89 and 1.04. The  $T_{max}$  for the generic tablet was 0.959 hours and for the originator tablet was 1.182 hours.

### 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 40-45% 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 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 in the “Absorption” section, 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, 48.0-95.8). 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 multi-phasic with an initial half-life of about 1.5 hours and a terminal exponential half-life of 480 hours. Although the elimination rate from human bone is unknown, the 480 hour half-life is hypothesised to represent the dissociation of risedronate from the surface of the bone.

### **Calcium carbonate**

Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

### **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  $\geq$  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 H<sub>2</sub> – blockers.

#### 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 1-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 1 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 2). While once a week doses of risedronate resulted in slightly smaller increases in lumbar spine BMD compared to daily doses of 5 mg after 6 months, the two regimens are equivalent after 12 months. The clinical relevance of these 6-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 2 treatment groups were also similar with regard to BMD increases at other skeletal sites. This study is of 2 years' duration, the results of which will be included as soon as they are available.

<b>Table 2: Study HMR 4003E/3001 Bone Mineral Density by Visit - Mean Percent Change from Baseline (Intent-to-treat Population)</b>					
Analysis Visit	5 mg Daily Risedronate		35 mg Once-a-Week Risedronate		Mean Difference (95% CI)
	N	Mean	N	Mean	5 mg Daily vs.35 mg Once-a-Week
Lumbar spine					
Month 6	402	3.12 <sup>a</sup>	389	2.68 <sup>a</sup>	0.44 <sup>b</sup> (0.01; 0.87) p=0.045
Month 12	391	4.00 <sup>a</sup>	387	3.94 <sup>a</sup>	0.06 (-0.42; 0.55) p=0.799

<sup>a</sup>Indicates statistically significant difference from baseline  
<sup>b</sup>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 2 treatment groups.

### **5 mg Daily Dose and 150 mg Once-a-Month Dose**

Information pertaining to the Clinical Trials of these tablet strengths can be found in the Actonel Combi PI.

### **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 2-year, double-blind, placebo-controlled study in 284 patients (risedronate sodium 35mg 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 6 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 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 2 years of treatment. The bone effect (BMD increase and BTM decrease) of risedronate sodium is similar in males and females.

### **Corticosteroid-Induced Osteoporosis**

#### **Histology/Histomorphometry**

Histologic evaluation of 70 bone biopsy samples from 48 women on corticosteroid therapy who received either placebo or risedronate once daily for 1 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**

- Treatment of osteoporosis.
- Treatment of glucocorticoid-induced osteoporosis.
- Preservation of bone mineral density in patients on long term corticosteroid therapy.

## **CONTRAINDICATIONS**

### **Risedronate**

- Known hypersensitivity to the drug or any of the ingredients.
- Hypocalcaemia (see **PRECAUTIONS**).
- Inability to stand or sit upright for at least 30 minutes.

### **Calcium carbonate**

- Known hypersensitivity to the drug or any of the ingredients
- Hypercalcaemia

- Hypercalciuria
- Nephrolithiasis

## PRECAUTIONS

### Risedronate

#### General

Food, certain medication containing polyvalent cations (such as calcium, magnesium, iron and aluminium) and beverages (except plain water) can interfere with the absorption of bisphosphonates and should not be taken at the same time as risedronate tablets.

Bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations and gastroduodenal 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
- If risedronate is given to patients with active or recent oesophageal or upper gastrointestinal problems (including known Barrett's oesophagus)

For patients to gain maximum benefit from risedronate, doctors must stress the importance of taking risedronate 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 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 is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).

#### 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, 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 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

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 physician should guide the management plan of each patient based on individual benefit/risk assessment.

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.

In patients with mild to moderate renal impairment or a history of absorptive or renal hypercalciuria, nephrocalcinosis, kidney stone formation, or hypophosphataemia, renal function, serum and urinary calcium and phosphate should be monitored regularly.

### **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. The number of reported cases of this condition is very low (some 40 reported cases worldwide in connection with alendronate as of 2009).

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 (e.g., 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 individual benefit/risk assessment. Causality has not been excluded in regard to bisphosphonate use and stress fractures.

### **Osteomalacia**

The potential for risedronate to induce osteomalacia was investigated in the Schenk rat assay. This assay is based on histologic 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 > 3000 times the lowest anti-resorptive dose (1.5 µg/kg/day). These data indicate that risedronate administered at therapeutic doses is unlikely to induce osteomalacia.

### **Calcium carbonate**

During long term treatment, serum and urinary calcium levels should be followed and renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics (see **INTERACTIONS WITH OTHER MEDICINES**) and in patients with a high tendency to calculus formation. Treatment must be reduced or suspended if urinary calcium exceeds 7.5 mmol/24 hours (300 mg/24 hours). In case of hypercalcaemia or signs of impaired renal function, treatment with calcium should be discontinued.

Calcium should be used with caution in patients suffering from sarcoidosis because of the increased risk of metabolism of vitamin D to its active metabolite. In these patients, serum calcium levels and urinary calcium excretion must be monitored.

Calcium should be used with caution in immobilised patients with osteoporosis due to the increased risk of hypercalcaemia. The calcium treatment might be discontinued in prolonged immobilisation and should only be resumed once the patient becomes mobile again.

## **Renal impairment**

### **Risedronate**

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

### **Calcium carbonate**

Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics and in patients with high tendency to calculus formation. In the case of hypercalcaemia or signs of impaired renal function, treatment with calcium should be discontinued.

## **Effects on Fertility**

### **Risedronate**

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 0-24h) 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)**

*Australian categorisation definition of Category B3:* Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

### **Risedronate**

Risedronate has not been studied in pregnant women. Risedronate should only be used during pregnancy if the potential benefit justifies the potential risk to mother and foetus. 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 foetal 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 foetal 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<sub>0-24 h</sub>) at the no-effect level in rats was similar to that in patients with Paget's disease, and about 6 times higher than that in patients with corticosteroid-induced osteoporosis. Systemic exposure in rabbits was not measured.

## Calcium carbonate

During pregnancy the daily intake should not exceed 1500 mg calcium. In pregnant women, overdoses of calcium should be avoided as permanent hypercalcemia has been related to adverse effect on the developing foetus.

## Use in Lactation

### Risedronate

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 nursing infants from bisphosphonates, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

As with other bisphosphonates in preclinical models, foetuses from risedronate treated dams showed ossification changes in sternbrae and/or skull at doses as low as 3.2 mg/kg/day. This is equivalent to the human 30 mg dose and 6 times the human 5 mg dose based on surface area, mg/m<sup>2</sup>. 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.

## Calcium carbonate

Calcium passes into breast milk.

## Paediatric Use

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

## Genotoxicity

### Risedronate

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 (7-18% cell survival), but there was no evidence of chromosomal damage when the assay was repeated at concentrations leading to 48-74% cell survival. Risedronate was negative at oral doses up to 1336 mg/kg in an in vivo assay (chromosomal aberrations in rat bone marrow).

## Carcinogenicity

### Risedronate

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 0-24h) 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.

## 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.

## INTERACTIONS WITH OTHER MEDICINES

### Risedronate

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, H<sub>2</sub> 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 2 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  $\geq 3$  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. In the Phase III study comparing 75 mg on 2 consecutive days a month and 5 mg daily in postmenopausal women, acetyl salicylic acid/NSAID use was reported by 54.8% of patients. Similar percentages of patients experienced upper gastrointestinal adverse events regardless of NSAIDs and aspirin use.

### Calcium carbonate

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of Calcium Carbonate.

Calcium carbonate may interfere with the absorption of concomitant administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least two hours before or four to six hours after oral intake of calcium.

Hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium. Such patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

If a bisphosphonate or sodium fluoride is used concomitantly, this preparation should be administered at least three hours before intake of calcium carbonate since gastrointestinal absorption may be reduced.

Oxalic acid (found in spinach and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through formation of insoluble compounds with calcium ions. The patient should not take calcium products within two hours of eating foods high in oxalic acid and phytic acid.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.

Concurrent administration of antacids containing aluminium hydroxide and cholecalciferol is not recommended in patients on haemodialysis as absorption of aluminium may be increased. Concurrent use should be avoided.

## ADVERSE EFFECTS

### Osteoporosis – Risedronate 5 mg daily dosing

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 3 years in over 5000 women enrolled in Phase 3 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 was 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  $\geq 5\%$  of risedronate treated patients and at an incidence higher than in the placebo group in Phase 3 postmenopausal osteoporosis trials. Adverse events are shown without attribution of causality.

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

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

Risedronate has been studied in Phase 3 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 – Risedronate 35 mg Once-a-Week dosing

In a one-year, double-blind, multicentre study comparing risedronate 5 mg daily and risedronate Once-a-Week 35 mg in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar. Table 5 lists the adverse events in >5% of patients from this trial. Events are shown without attribution of causality.

<b>Body System</b>	<b>5 mg Daily Risedronate % (N = 480)</b>	<b>35 mg Once-a-Week Risedronate % (N = 485)</b>
<b>Body as a Whole</b>		
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
<b>Cardiovascular System</b>		
Hypertension	5.8	4.9
<b>Digestive System</b>		
Constipation	12.5	12.2
Dyspepsia	6.9	7.6
Nausea	8.5	6.2
Diarrhoea	6.3	4.9
<b>Musculoskeletal System</b>		
Arthralgia	11.5	14.2
Traumatic Bone Fracture	5.0	6.4
Myalgia	4.6	6.2
<b>Nervous System</b>		
Dizziness	5.8	4.9

In a 2-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.

## Post-Marketing Data

### Risedronate

The following additional adverse reactions have been very rarely reported during post-marketing use:

Eye disorders: Iritis, uveitis

Musculoskeletal and connective tissues disorders: Osteonecrosis of the jaw

Skin and subcutaneous tissue disorders: Hypersensitivity and skin reactions, including angioedema, generalised rash, and bulbous skin reactions, some severe

### Calcium carbonate

The following additional adverse reactions have been described:

Uncommon: Hypercalcaemia and hypercalciuria

Rare: Constipation, flatulence, nausea, abdominal pain, diarrhoea, pruritis, rash and urticaria

## DOSAGE AND ADMINISTRATION

Risedronate must only be taken with plain water.

Plain water is the only drink that should be taken with risedronate 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 must be taken 30 minutes before the first food or drink other than water. To facilitate delivery to the stomach, risedronate 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.

### ACRIS Combi

ACRIS Combi is a two component therapy consisting of 7 tablets in a blister, 1 risedronate 35 mg film-coated tablet (light-orange tablet) and 6 Calcium Carbonate 1250 mg (equivalent to elemental calcium 500 mg) film-coated tablets (light lavender tablets). ACRIS Combi is intended for patients for whom the amount of calcium included is considered to provide adequate supplementation, based on individual assessment. Supplemental vitamin D should be considered if the dietary intake is inadequate.

The recommended dose in adults is 1 ACRIS 35 mg tablet on the first day, followed, beginning on the next day, by 1 Calcium Carbonate 1250 mg (equivalent to elemental calcium 500 mg) tablet daily for 6 days. This 7 day sequence is then repeated each week.

The ACRIS 35 mg tablet should always be taken on the same day each week, in accordance with the directions described above.

The calcium component should commence on the day after the ACRIS 35 mg tablet is taken, one calcium tablet should be taken each day for the next 6 days. The tablet should be swallowed whole. Calcium absorption is improved if taken with food. Therefore, patients should take the calcium tablet with a meal.

Patients should be instructed that if the ACRIS dose is missed, the ACRIS tablet should be taken on the next day in the morning according to the dosing instructions. On the following day they should take their next calcium tablet (light lavender tablet). Patients should not take more than 1 tablet from the blister strip per day.

If the calcium dose (light lavender tablet) is missed, the patient should be instructed to continue taking one tablet of calcium each day beginning on the day the missed dose is remembered. Any remaining calcium tablets in the blister at the end of the weekly cycle should be discarded.

Patients should be instructed to start a new blister strip every 7 days. They should begin the new strip by taking the ACRIS 35 mg tablet (light-orange tablet) on their originally chosen day of the 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.

### Paediatrics

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

### Risedronate

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 physiologic amounts of ionised calcium and to relieve signs and symptoms of hypocalcaemia.

### Calcium carbonate

Because of its limited intestinal absorption, overdose with calcium carbonate is not likely. However, overdose can lead to hypercalcaemia.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

## PRESENTATION AND STORAGE CONDITIONS

### ACRIS Combi

ACRIS Combi : Risedronate 35 mg tablets: A light orange film-coated, round, biconvex, beveled edge tablet debossed with “M” on one side of the tablet and “714” on the other side.

Calcium carbonate 1250 mg tablets: A light lavender, clear film-coated, modified oval shaped, biconvex, beveled edge tablet debossed with “M CC5” on one side of the tablet and plain on the other side.

Packed in PVC/Al blisters packs of:

7\* (1 Risedronate 35 mg tablet, 6 Calcium carbonate 1250 mg tablets)

14\* (2 Risedronate 35 mg tablets, 12 Calcium carbonate 1250 mg tablets)

28 (4 Risedronate 35 mg tablets, 24 Calcium carbonate 1250 mg tablets)

84\* (12 Risedronate 35 mg tablets, 72 Calcium carbonate 1250 mg tablets)

112\* (16 Risedronate 35 mg tablets, 96 Calcium carbonate 1250 mg tablets)

Store below 25°C.

\* Not marketed in Australia.

**NAME AND ADDRESS OF THE SPONSOR****Alphapharm Pty Limited**

Level 1, 30 The Bond

30 –34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

[www.alphapharm.com.au](http://www.alphapharm.com.au)

**POISON SCHEDULE OF THE MEDICINE**

S4 (Prescription Only Medicine)

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

01/04/2011

**DATE OF MOST RECENT AMENDMENT**

01/08/2016

**ACRIS Combi\_pi\01082016**