AUSTRALIAN PRODUCT INFORMATION- ACTONEL EC ONCE-A-WEEK (RISEDRONATE SODIUM) ENTERIC-COATED TABLET

1 NAME OF THE MEDICINE

Risedronate sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Actonel EC enteric-coated tablet contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. Actonel EC tablets have a pH-sensitive enteric coating and contain a chelating agent disodium edetate (EDTA). The formulation is designed to allow dosing with food, reducing the impact of food on risedronate absorption.

For the full list of excipients, see Section 6.1- List of excipients.

3 PHARMACEUTICAL FORM

Enteric-coated-tablet

Actonel EC tablets are oval, yellow enteric-coated tablets engraved with EC 35 on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Actonel EC should be taken in the morning, either with or without food. To facilitate delivery to the stomach, and thus reduce the potential for oesophageal irritation, enteric-coated Actonel 35 mg once-a-week should be swallowed whole while the patient is in an upright position with plain water. Patients should not chew, cut or crush the tablet because of a potential for oropharyngeal irritation, and because the tablet coating is an important part of the formulation. Patients should avoid lying down for 30 minutes after taking the medication.

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 insufficiency:

No dose adjustment is necessary in patients with mild to moderate renal insufficiency (creatinine clearance 30 to 60 mL/minute). Enteric-coated Actonel 35 mg once-a-week is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/minute) due to limited clinical data.

Hepatic insufficiency

Dose adjustments are unlikely to be needed in patients with hepatic impairment.

Paediatrics:

Safety and efficacy of enteric-coated Actonel 35 mg once-a-week has not been established in patients under 18 years of age.

Compatibility with other Drugs:

Calcium supplements and antacids will interfere with the absorption of risedronate and therefore should be taken at a different time of the day.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to the drug or any of the ingredients.
- Hypocalcaemia (see Section 4.4 Special warnings and precautions for use)
- Inability to stand or sit upright for at least 30 minutes.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Calcium supplements and antacids can interfere with the absorption of risedronate and should not be taken at the same time as Actonel EC.

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 Actonel EC 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 Actonel EC, doctors must stress the importance of taking Actonel EC as per the dosage instructions (see Section 4.2 Dose and method of

administration). This is especially important in the case of patients with a history of oesophageal disorders.

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

Gastrointestinal

Actonel EC like other bisphosphonates may cause local irritation of the upper GI mucosa. Since some bisphosphonates have been associated with oesophagitis and oesophageal ulcerations, and gastroduodenal ulceration doctors should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction, especially in patients with a history of upper GI disease or who are using NSAIDS or aspirin concomitantly. Doctors should be particularly careful to emphasise the importance of taking Actonel EC 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.

Atypical Stress Fractures

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

Approximately one third of these fractures were bilateral; therefore, the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture.

It is not known to what extent other agents of the aminobisphosphonate class, including ACTONEL, 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.

Use in hepatic impairment

No studies have been performed to assess the safety or efficacy of Actonel in patients with hepatic impairment.

Use in renal impairment

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

Use in the elderly

Of the patients receiving Actonel EC in postmenopausal osteoporosis studies, 59% were 65 and over, while 13% were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Paediatric Use

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

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Risedronate is not systemically metabolised, does not induce or inhibit hepatic microsomal drug metabolising enzymes (cytochrome P450) and has low protein binding.

The results of in-vitro studies indicated that the chelating agent (EDTA) in enteric-coated Actonel 35 mg once-weekly is not likely to result in changes in absorption of concomitant medications, including those with a narrow therapeutic index or antivirals.

A Phase 1 single-dose, cross-over study in 101 postmenopausal women evaluated the relative bioavailability of enteric-coated Actonel 35 mg once-a-week tablets taken after breakfast and following a 600 mg elemental calcium/400 IU vitamin D supplement, compared to enteric-coated Actonel 35 mg taken after breakfast alone. The addition of the calcium/vitamin D supplement following the meal resulted in an approximate 38% reduction in the amount of risedronate absorbed.

Although not specifically studied, if considered appropriate, enteric-coated Actonel 35 mg may be considered for concomitant use with hormone replacement therapy.

A Phase 1, single-dose, cross over study in 87 postmenopausal women evaluated the absorption of enteric-coated Actonel 35 mg following 5 days of esomeprazole 40 mg therapy compared to enteric-coated Actonel 35 mg alone. During concomitant use of esomeprazole, bioavailability of enteric-coated Actonel 35 mg is reduced by 32% to 48% depending on the time of esomeprazole administration (prior to the evening meal or prior to breakfast, respectively).

In the Phase 3 study evaluating enteric-coated Actonel 35 mg, efficacy as measured by mean percent change in BMD from baseline was not diminished in patients reporting concomitant use of H_2 blockers or Proton Pump Inhibitors (PPIs).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A fertility study in male and female rats showed no adverse effects at oral doses up to 16 mg/kg/day, corresponding to systemic exposure (serum $AUC_{0\text{-}24h}$) 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 – Pregnancy Category B3

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 ($AUC_{0\text{-}24\,h}$) 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.

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 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 sternebrae 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^2. Treatment with risedronate during mating and gestation with doses of 3.2 mg/kg/day has resulted in periparturient hypocalcaemia and mortality in rats allowed to deliver.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Osteoporosis – Actonel 5 mg daily dosing (immediate-release tablets)

The Phase IIIA clinical trials were designed to include patients with a history of upper GI disorder. Patients were permitted concomitant use of NSAIDs and aspirin. In these patients the incidence of upper GI adverse reactions in the Actonel 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.

Actonel 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 Actonel 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 Actonel groups respectively. Table 1 lists adverse events reported in ≥ 5% of Actonel 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.

Table 1: Adverse Events Reported in ≥5% of Actonel Treated Patients and Occurring at ≥1.1 Times the Placebo Rate in Phase 3 Postmenopausal Osteoporosis Trials

Body System	Placebo % (N = 1744)	Actonel 5 mg% (N = 1742)
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

Endoscopic Findings: Actonel clinical studies enrolled over 5000 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%) Actonel; 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% Actonel]. Positive findings on endoscopy were also generally comparable across treatment groups [58 (82.9%) placebo and 57 (81.4%) Actonel].

Gastrointestinal Adverse Events: There was a higher number of reports of mild duodenitis [11(15.7%)] in the Actonel group [7(10%) placebo], however there were more duodenal ulcers [33(47.1%)] in the placebo group [26(37.1%) Actonel]. 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%) Actonel] and there was no evidence of treatment-related oesophageal, gastric, or duodenal ulcers/erosions.

Actonel 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 Actonel 5 mg treatment group [75 (43.1%)] compared to the placebo group [57 (33.5%)]. The adverse experiences reported [165 placebo and 167 Actonel] 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 –Actonel EC Once-a-Week dosing

The safety of Actonel EC for the treatment of postmenopausal osteoporosis was assessed in a double-blind, multicentre study comparing Actonel 5 mg immediate-release daily (N = 307) and enteric-coated Actonel 35 mg once weekly administered either at least 30 minutes before (N = 308) or immediately following (N = 307) breakfast in postmenopausal women 50 years of age or older. The duration of the trial was 2 years, with 307 patients exposed to Actonel 5 mg immediate-release daily and 615 exposed to enteric-coated Actonel 35 mg once-a-week. Patients with pre-existing gastrointestinal disease (with the exception of those with a positive occult faecal blood test or history of inflammatory bowel disease, malabsorption or sprue) and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H_2 antagonists were included in this clinical trial. All women received daily supplementation with 1000 mg of elemental calcium plus 800-1000 IU vitamin D.

The overall safety and tolerability profiles were similar across the immediate-release and enteric-coated treatment groups. The incidence of all-cause mortality was 0.3% in the Actonel 5 mg immediate-release daily group and 0.2% in the combined enteric-coated Actonel 35 mg once-a-week group. The incidence of serious adverse events was 10.1% in the Actonel 5 mg daily group and 10.4% in the combined enteric-coated Actonel 35 mg once-a-week group. The percentage of patients who withdrew from the study due to adverse events was 9.1% in the Actonel 5 mg immediate-release daily group and 10.1% in the combined enteric-coated Actonel 35 mg once-a-week group. Table 2 lists adverse events reported in ≥2% of patients, combining before and after breakfast dosing of enteric-coated Actonel 35 mg once-a-week. Adverse events are shown without attribution of causality.

Table 2: Most Common (>=2% in Any Treatment Group) Treatment-emergent Adverse Events by MedDRA SOC and PT (Intent-to-treat)

System Organ Class Preferred Term	5 mg IRBB Daily (N=307) n(%) nAE	35 mg ECFB Weekly (N=307) n(%) nAE	35 mg ECBB Weekly (N=308) n(%) nAE
OVERALL	243 (79.2%) 1025	250 (81.4%) 1138	264 (85.7%) 1219
Infections and infestations	119 (38.8%) 193	135 (44.0%) 247	133 (43.2%) 241
Nasopharyngitis	24 (7.8%) 29	32 (10.4%) 38	38 (12.3%) 48
Influenza	23 (7.5%) 28	27 (8.8%) 33	25 (8.1%) 29
Urinary tract infection	20 (6.5%) 21	21 (6.8%) 27	22 (7.1%) 29
Bronchitis	20 (6.5%) 26	17 (5.5%) 25	21 (6.8%) 24
Upper respiratory tract infection	9 (2.9%) 9	13 (4.2%) 13	12 (3.9%) 17
Pharyngitis	7 (2.3%) 7	11 (3.6%) 12	12 (3.9%) 16
Cystitis	12 (3.9%) 13	9 (2.9%) 12	6 (1.9%) 6
Gastroenteritis	7 (2.3%) 7	9 (2.9%) 9	10 (3.2%) 10
Herpes zoster	3 (1.0%) 3	8 (2.6%) 8	3 (1.0%) 3
Sinusitis	8 (2.6%) 8	4 (1.3%) 6	3 (1.0%) 3
Gastrointestinal disorders	107 (34.9%) 193	119 (38.8%) 235	125 (40.6%) 270
Diarrhoea	19 (6.2%) 25	30 (9.8%) 32	21 (6.8%) 24
Abdominal pain	10 (3.3%) 11	19 (6.2%) 21	20 (6.5%) 23

Dyspepsia	16 (5.2%) 19	18 (5.9%) 24	12 (3.9%) 15
Constipation	11 (3.6%) 13	17 (5.5%) 17	17 (5.5%) 17
Vomiting	10 (3.3%) 10	15 (4.9%) 18	8 (2.6%) 12
Nausea	15 (4.9%) 17	12 (3.9%) 15	14 (4.5%) 16
Abdominal pain upper	8 (2.6%) 9	11 (3.6%) 15	26 (8.4%) 37
Haemorrhoids	4 (1.3%) 4	7 (2.3%) 7	4 (1.3%) 4
Gastrooesophageal reflux disease	9 (2.9%) 9	3 (1.0%) 3	11 (3.6%) 12
Hiatus hernia	4 (1.3%) 5	3 (1.0%) 3	10 (3.2%) 10
Musculoskeletal and connective tissue disorders	95 (30.9%) 157	103 (33.6%) 179	114 (37.0%) 174
Arthralgia	33 (10.7%) 38	29 (9.4%) 39	27 (8.8%) 33
Back pain	27 (8.8%) 31	29 (9.4%) 36	29 (9.4%) 31
Pain in extremity	13 (4.2%) 14	17 (5.5%) 18	14 (4.5%) 16
Musculoskeletal pain	13 (4.2%) 13	13 (4.2%) 14	11 (3.6%) 12
Osteoarthritis	10 (3.3%) 10	8 (2.6%) 8	5 (1.6%) 5
Tendonitis	6 (2.0%) 6	8 (2.6%) 8	3 (1.0%) 6
Muscle spasms	9 (2.9%) 9	5 (1.6%) 5	12 (3.9%) 16
Neck pain	6 (2.0%) 6	5 (1.6%) 5	8 (2.6%) 8
Injury, poisoning and procedural complications	50 (16.3%) 81	46 (15.0%) 68	46 (14.9%) 72
Fall	16 (5.2%) 18	18 (5.9%) 20	11 (3.6%) 11
Contusion	14 (4.6%) 15	11 (3.6%) 12	8 (2.6%) 12
Nervous system disorders	51 (16.6%) 76	42 (13.7%) 54	45 (14.6%) 49
Dizziness	10 (3.3%) 10	10 (3.3%) 10	11 (3.6%) 12
Headache	18 (5.9%) 18	9 (2.9%) 9	14 (4.5%) 14
Sciatica	7 (2.3%) 7	5 (1.6%) 6	2 (0.6%) 2
Vascular disorders	24 (7.8%) 30	32 (10.4%) 32	33 (10.7%) 39
Hypertension	20 (6.5%) 23	20 (6.5%) 20	21 (6.8%) 22
Skin and subcutaneous tissue disorders	19 (6.2%) 24	29 (9.4%) 36	33 (10.7%) 38
Dermatitis allergic	4 (1.3%) 4	5 (1.6%) 6	7 (2.3%) 7
General disorders and administration site conditions	27 (8.8%) 30	28 (9.1%) 41	41 (13.3%) 54
Fatigue	4 (1.3%) 4	7 (2.3%) 8	1 (0.3%) 1
Investigations	19 (6.2%) 28	26 (8.5%) 30	28 (9.1%) 33
Blood parathyroid hormone increased	3 (1.0%) 3	2 (0.7%) 3	7 (2.3%) 8
Cardiac disorders	20 (6.5%) 23	24 (7.8%) 35	31 (10.1%) 43
Respiratory, thoracic and mediastinal disorders	26 (8.5%) 35	23 (7.5%) 31	24 (7.8%) 28
Cough	10 (3.3%) 11	9 (2.9%) 9	6 (1.9%) 6
Metabolism and nutrition disorders	17 (5.5%) 18	21 (6.8%) 34	21 (6.8%) 22
Hypercholesterolaemia	6 (2.0%) 6	13 (4.2%) 13	9 (2.9%) 9
Blood and lymphatic system disorders	7 (2.3%) 7	15 (4.9%) 15	9 (2.9%) 9
Anaemia	3 (1.0%) 3	8 (2.6%) 8	3 (1.0%) 3
Psychiatric disorders	12 (3.9%) 14	15 (4.9%) 16	20 (6.5%) 25
Depression	5 (1.6%) 5	6 (2.0%) 6	7 (2.3%) 7
Eye disorders	22 (7.2%) 27	14 (4.6%) 17	16 (5.2%) 20
Cataract	7 (2.3%) 7	4 (1.3%) 6	6 (1.9%) 7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (3.6%) 11	13 (4.2%) 13	12 (3.9%) 13
Renal and urinary disorders	15 (4.9%) 17	13 (4.2%) 15	19 (6.2%) 25
Ear and labyrinth disorders	18 (5.9%) 21	11 (3.6%) 11	7 (2.3%) 8

Vertigo	7 (2.3%) 10	7 (2.3%) 7	3 (1.0%) 3
Endocrine disorders	12 (3.9%) 14	7 (2.3%) 7	13 (4.2%) 16
Reproductive system and breast disorders	13 (4.2%) 14	6 (2.0%) 8	9 (2.9%) 13
Hepatobiliary disorders	4 (1.3%) 4	5 (1.6%) 10	11 (3.6%) 12
Immune system disorders	6 (2.0%) 7	3 (1.0%) 3	10 (3.2%) 11
Treatment: IRBB = 5 mg/day risedronate immediate-release before breakfast, ECFB = 35 mg/week risedronate delayed-release following breakfast, ECBB = 35 mg/week risedronate delayed-release before breakfast. N = number of patients within specified treatment. n (%) = number (percent) of patients within specified category and treatment. nAE = number of adverse events within the specified category and treatment.			

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of symptoms consistent with acute phase reaction was 1.3% in the Actonel 5 mg immediate-release daily group, and 1.8% in the combined enteric-coated Actonel 35 mg once-a-week group. These incidence rates are based on reporting of one or more pre-specified acute phase reaction-like symptoms within 3 days of the first dose and for a duration of 7 days or less. Fever or influenza-like illness with onset within the same period were reported by 0.0% of patients on Actonel 5 mg immediate-release daily and 0.0% of patients on enteric-coated Actonel 35 mg once-a-week.

Gastrointestinal Adverse Events: The incidence of gastrointestinal adverse events in the Actonel 5 mg immediate-release daily group compared with the combined enteric-coated Actonel 35 mg once weekly group were: dyspepsia (5.2% vs. 4.9%), diarrhoea (6.2% vs. 8.3%), constipation (3.6% vs. 5.5%), abdominal pain (3.3% vs. 6.3%), abdominal pain upper (2.6% vs. 6.0%), gastro-oesophageal reflux disease (2.9% vs. 2.3%).

Musculoskeletal Adverse Events: The incidence of musculoskeletal adverse events in the Actonel 5 mg immediate-release daily group compared with the combined enteric-coated Actonel 35 mg once weekly group were: arthralgia (10.7% vs. 9.1%), back pain (8.8% vs. 9.4%), musculoskeletal pain (4.2% vs 3.9%).

Treatment discontinuations: The overall incidence of patients discontinuing treatment due to atreatmentemergent adverse event was similar across all groups (9.1% vs 10.1% for the immediate release and combined enteric coated groups, respectively). Study discontinuations in the Actonel 5 mg immediate-release daily group compared with the combined enteric-coated Actonel 35 mg once-a-week group included: diarrhoea (0.7% vs. 0.7%),abdominal pain (0.7% vs. 1.3%), abdominal pain upper (0.0% vs. 1.1%), abdominal pain lower (1% vs 0.0%), gastro-oesophageal reflux disease (0.7% vs. 0.2%), myalgia (0.3% vs 0.3%), arthralgia (0.0% vs 0.5%).

Laboratory Test Findings: The mean values for serum calcium, phosphorus, and magnesium were within the normal range at all time points and similar across treatment groups. The mean changes from baseline at each post-baseline time point were small for each parameter, with no clinically important differences across treatment groups.

The mean values for serum iPTH 1-84 were within the normal range at all time points and similar across treatment groups. Mean changes from baseline at each post-baseline time point were small and most prominent at Day 14.

In all treatment groups, small mean decreases in serum calcium and the expected reciprocal small mean increases in iPTH 1-84 were seen at Day 14; these changes were as would be expected upon initiation of antiresorptive therapy, and were not symptomatic or clinically meaningful. At week 104, the number of patients shifting from normal to high iPTH 1-84 was similar across the 3 groups.

Actonel Post-Marketing Data

The following additional adverse reactions have been very rarely reported during post-marketing use:
Eye disorders: Iritis, uveitis, orbital inflammation
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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 for Actonel immediate-release tablets and reduce absorption of the drug. The impact of this intervention for Actonel EC tablets has not been evaluated. The enteric-coated Actonel formulation is less sensitive to the binding effects of divalent cations. 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Risedronate is a potent pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. Risedronate is a third generation bisphosphonate. In preclinical studies risedronate demonstrated potent 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. In a 2 year study comparing Actonel 5 mg daily immediate-release versus enteric-coated Actonel 35 mg once-a-week oral dosing regimens (ie. taken either before or after breakfast) in postmenopausal women, there was no significant differences in mean percent change from baseline in urinary collagen cross-linked N- telopeptide (NTX/Cr) between the enteric-coated and the immediate-release groups. At 2 years, the mean reductions from baseline in urine NTX/Cr were 46% in the Actonel 5 mg daily group, 51% in the enteric-coated Actonel 35 mg once-a-week before breakfast group and 49% in the enteric-coated Actonel 35 mg once-a-week following breakfast group. In addition, serum bone-specific alkaline phosphatase at 2 years was reduced by 33% in the Actonel 5 mg daily group, 35% in the enteric-coated Actonel 35 mg once-a-week before breakfast group and 35% in the enteric-coated Actonel 35 mg once-a-week following breakfast group.

In a study with immediate-release Actonel 35 mg once-a-week 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.

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_2–blockers. The fracture efficacy of Actonel 5 mg daily (risedronate immediate-release formulation) in the treatment of postmenopausal osteoporosis was demonstrated in two large, randomised, placebo-controlled, double-blind studies which enrolled a total of almost 4000 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 1000 mg/day. Patients with low vitamin D levels also received supplemental vitamin D 500 IU/day. The number of evaluable patients treated were :

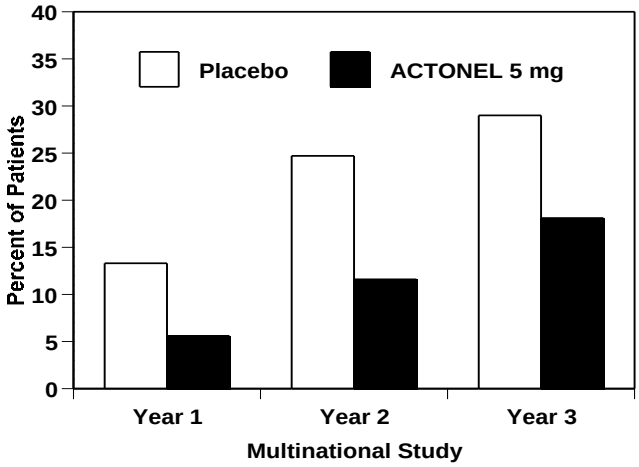
RVN – 5 mg risedronate n = 696; placebo n = 678

RVE – 5 mg risedronate n = 344; placebo n = 346

RVN and RVE: n = 1040; placebo n = 1024

Effect on Vertebral Fracture:

The pivotal studies of Actonel in the treatment of postmenopausal osteoporosis clearly demonstrate that Actonel 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. Actonel 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 Actonel 5 mg daily for 3 years significantly reduced the risk of new vertebral fractures by 49% compared to treatment with placebo ($p < 0.001$) (Figure 1). A similar, significant reduction of 41% was seen in the North American study ($p = 0.003$). The effect of Actonel 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 1 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 1 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 1 and 3 years, the reduction in risk seen in the subgroup of patients who had 2 or more vertebral fractures at study entry was similar to that seen in the overall study population. Treatment with Actonel 5 mg daily also significantly reduced the proportion of patients experiencing new and worsening vertebral fractures in each of the studies.



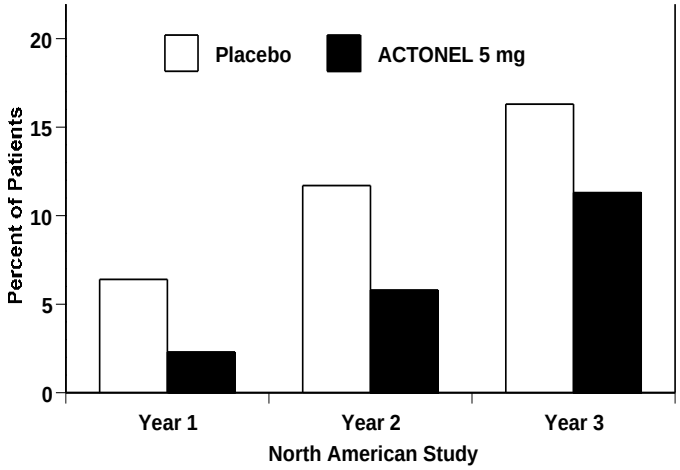


Figure 1: Cumulative Incidence of New Vertebral Fractures

Effect on Non-Vertebral Fractures:

In a prospectively-planned analysis of pooled data from the multinational and North American studies, Actonel 5 mg daily significantly reduced the cumulative incidence of patients experiencing osteoporosis-related non-vertebral fractures (wrist, humerus, clavicle, pelvis, hip, and leg) over 3 years by 36% (p = 0.005). See Figure 2.

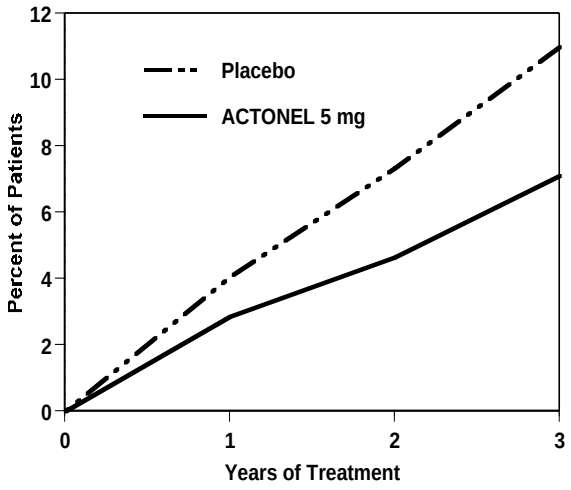


Figure 2: Cumulative Incidence of Osteoporosis-Related Non-Vertebral Fractures - Treatment Studies

The incidence of non-vertebral fractures in the pooled analysis (RVN and RVE) was lower in the 5 mg risedronate group than in the placebo group for all fractures at these sites combined, as well as for the wrist, humerus, pelvis, and leg separately. This difference was significant for all non-vertebral osteoporosis-related fractures (p=0.005), as well as for the humerus (p=0.024) and pelvis (p=0.044), while a trend was seen at the wrist (p=0.075) (Table 3).

These findings demonstrate a beneficial effect of risedronate in preventing non-vertebral, osteoporosis-related fractures.

Table 3: Cumulative Non-Vertebral Osteoporosis-Related Fracture Incidence Year 0-3, RVN008993 and RVE009093 Combined Intent-to-Treat

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

Number of patients with baseline and at least one non-follow-up visit during the 3-year studies: Placebo=1221, 5mg 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 5mg risedronate groups using stratified (by study) log-rank test.

-- Not applicable.

Effect on Height:

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

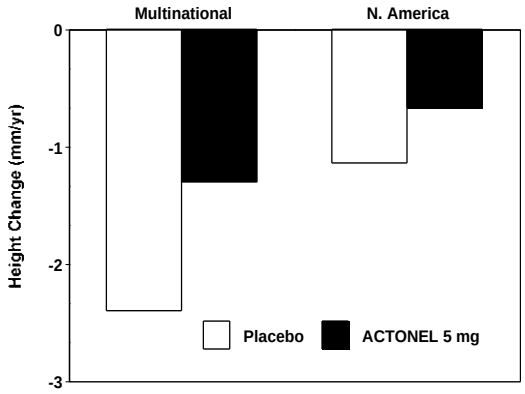


Figure 3: Median Annual Height Change Treatment Studies

Effect on Bone Mineral Density:

The results of four, large, randomised, placebo-controlled trials in women with postmenopausal osteoporosis demonstrate that Actonel 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, Actonel 5 mg daily produced increases in lumbar spine BMD which were progressive over at least 2 years of treatment, and were statistically significant relative to baseline and to placebo at 6 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 3 years. In the North American fracture trial, similarly progressive and significant increases were seen; the mean increase was 4.3%, compared to placebo. Actonel 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 Actonel treatment. These findings indicate that Actonel treatment produces positive effects at all measured skeletal sites of clinical importance for osteoporotic fractures.

Positive effects of Actonel treatment on BMD were also demonstrated in each of two large, randomised, placebo-controlled trials in which almost 1200 postmenopausal women were recruited on the basis of low lumbar spine bone mass (more than 2 SD below the pre-menopausal mean) rather than a history of vertebral fracture. After 1.5 to 2 years, Actonel 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 Actonel or placebo once daily for 2 to 3 years (including 74 pairs of biopsies, 43 from Actonel -treated patients) showed a moderate decrease in bone turnover in Actonel-treated

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

***Bone Markers**:*

In clinical studies, dose-dependent decreases in biochemical markers of bone turnover were observed with Actonel 5 mg treatment. These effects were seen within 1 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 3 years. These data demonstrate that 5 mg Actonel causes a moderate reduction in bone resorption without over-suppression of bone formation. This new steady-state approximates the rate of bone turnover seen in pre-menopausal women.

Combined Administration with Hormone Replacement Therapy:

The effects of combining Actonel 5 mg daily with conjugated oestrogen treatment (0.625 mg daily) were compared to the effects of conjugated oestrogen alone in a 1-year, randomised, double-blind study in more than 500 postmenopausal women (mean lumbar spine BMD 1.3 SD below the pre-menopausal mean). Actonel 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 Actonel plus oestrogen group compared to the oestrogen alone group (40% to 47% versus 35% to 40%) and remained within the pre-menopausal range. Histologic evaluation of 93 bone biopsy samples from 61 women on oestrogen therapy who received either placebo or Actonel once daily for 1 year (including 32 pairs of biopsies, 16 from Actonel treated patients) found decreases in bone turnover in the Actonel treated patients that were consistent with the changes in bone turnover markers. Bone histology demonstrated that the bone of patients treated with Actonel plus oestrogen was of normal lamellar structure and normal mineralisation.

Endoscopic findings:

Actonel Endoscopic findings from patients with moderate to severe GI complaints in both Actonel and control patients showed no evidence of treatment related gastric, duodenal or oesophageal ulcers. Duodenitis was rarely observed in the Actonel group. Four out of five patients with endoscopically-diagnosed oesophageal strictures had been taking risedronate 5 mg for more than 6 months.

Treatment of Osteoporosis in Men

Actonel 35 mg Once-a-Week (immediate-release) 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 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 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%). Actonel 35 mg Once-a-Week (immediate-release) 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.

Actonel EC

Enteric-coated Actonel 35 mg once-a-week administered either before or after breakfast was shown to be therapeutically equivalent to Actonel 5 mg daily (immediate-release formulation) in a 2-year, double-blind, multicentre study of postmenopausal women with osteoporosis. The primary efficacy endpoint of percent change from baseline in lumbar spine BMD at week 52 was met. Secondary efficacy endpoints included percent change from baseline in lumbar spine BMD at week 104; non-vertebral fractures at week 104 which were consistent with the primary outcome measure; and change in bone turnover markers. Table 4 presents the primary efficacy analysis of intent-to-treat patients with last observation carried forward (LOCF) at 1 year, as well as the 2-year results.

Table 4: Lumbar Spine BMD - Percent Change from Baseline at 1 yr and 2 yr Endpoints [a]

	Actonel 5 mg Daily immediate-release N=307	Actonel 35 mg Once a Week enteric-coated Following Breakfast N=307	Actonel 35 mg Once a Week enteric-coated Before Breakfast N=308
Primary Efficacy (LOCF), at 1 year			
n	270	261	271
LS Mean (95% CI)	3.1* (2.7, 3.5)	3.4* (2.9, 3.8)	3.4* (3.0, 3.8)
LS Mean Difference [b] (95% CI)		-0.2 (-0.8, 0.3)	-0.3 (-0.9, 0.3)
2 year-endpoint			
n	274	265	273
LS Mean (95% CI)	4.1 (3.7, 4.6)	5.2 (4.7, 5.7)	5.1 (4.6,5.6)
LS Mean Difference[b] (95% CI)		-1.0 (-1.8, -0.2)	-0.8 (1.6, 0.0)

N = number of intent-to-treat patients within specified treatment; n = number of patients with values at the visit.
* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons.
[a] at 1 year and 2 year LOCF
[b] LS Mean Difference is 5 mg daily minus 35 mg weekly treatment.

The mean percent change from baseline in lumbar spine BMD at week 104-endpoint was 4.1% for the 5 mg immediate-release before breakfast group, 5.2% for the 35 mg enteric-coated following breakfast group and 5.1% for the 35 mg enteric-coated before breakfast group. The 35 mg enteric-coated weekly regimen either before or following breakfast was determined to be non-inferior to the 5 mg immediate-release before breakfast regimen with respect to percent change in lumbar spine BMD at week 52 and week 104 endpoints.No clinically relevant differences in mean percent increases from baseline to week 104 for total proximal femur, femoral neck and trochanter BMD were seen in each of the 35 mg enteric-coated weekly groups compared to the 5 mg immediate-release daily group.

There were no clinically relevant differences in any of the bone turnover markers at any time point compared to 5mg IR daily dose.

There were no statistically significant differences in either of the 35 mg enteric-coated groups compared to the 5 mg immediate-release group in incidence of new morphometric vertebral fractures at week 52, or at week 104 endpoint.

Corticosteroid-Induced Osteoporosis

Bone Mineral Density:

Two 1-year, double-blind, placebo-controlled trials demonstrated that Actonel 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 (> 7.5 mg/day of prednisone or equivalent) within the previous 3 months

for rheumatic, skin, and pulmonary diseases. The mean lumbar spine BMD was normal at baseline. All patients in this study received supplemental calcium 500 mg/day. After 1 year of treatment, the placebo group lost BMD at the lumbar spine, femoral neck, and trochanter, as shown in Figure 4. Actonel 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. Actonel prevented bone loss regardless of underlying disease, age, race, gender, corticosteroid dose, or baseline BMD.

The effect of risedronate discontinuation on bone mineral density was studied in a double blind, placebo controlled study in postmenopausal women with glucocorticoid-dependent rheumatoid arthritis. Women were treated for 2 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.

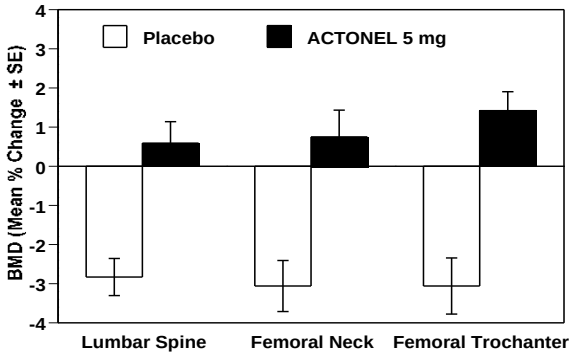


Figure 4: Change in BMD from Baseline Patients Recently Initiating Corticosteroid Therapy 1-Year Study

A second study of similar design enrolled 290 patients with continuing, long-term use (> 6 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 1000 mg/day. Patients also received supplemental vitamin D 400 IU/day. After 1 year of treatment, the BMD of the placebo group remained near baseline levels at the lumbar spine, femoral neck, and trochanter. Actonel 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%). Actonel was effective regardless of age, race, gender, underlying disease, corticosteroid dose, or baseline BMD.

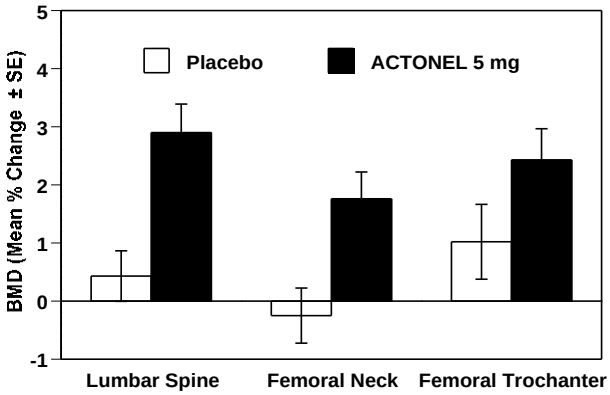


Figure 5: Change in BMD from Baseline Patients on Long-Term Corticosteroid Therapy (1-Year Study)

Vertebral Fractures:

Vertebral fractures were monitored for safety in the two placebo-controlled studies. The incidence of vertebral fractures in each study was 15% to 17% in the placebo patients. The risk of vertebral fractures was reduced approximately 70% in the patients treated with Actonel 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:

Actonel 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 1 and 3 months of treatment, respectively, and remained reduced (maximum 35% and 26%, respectively) for the duration of the treatment period.

Histology/Histomorphometry:

Histologic evaluation of 70 bone biopsy samples from 48 women on corticosteroid therapy who received either placebo or Actonel once daily for 1 year (including 22 pairs of biopsies, 16 from Actonel treated patients) showed that bone formed during treatment with Actonel was of normal lamellar structure and normal mineralisation, with no bone or marrow abnormalities observed. Histomorphometric evaluation indicated that Actonel 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 Actonel treated patients; cortical porosity increased, however, in the placebo group. These findings indicate that bone formed during Actonel treatment is of normal quality.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The mean absolute oral bioavailability of the 30 mg risedronate immediate-release tablet is 0.63% (90% confidence interval [CI]: 0.54% to 0.75%) and is similar to an oral solution. The peak concentration (Tmax) for the immediate-release tablet is achieved at ~1 hour. The enteric-coated Actonel 35 mg tablet achieves Tmax at ~3 hours when administered 4 hours prior to a meal. Using urinary excretion data, the fraction of the dose absorbed from enteric-coated Actonel 35 mg once-a-week is independent of risedronate dose over the range studied (single dose, from 20 mg to 100 mg).

Food Effect

A crossover pharmacokinetic study that evaluated the food effect in relation to the bioavailability of Actonel 35mg enteric-coated (EC) and Actonel 35mg immediate-release (IR) tablet was performed. An assessment of mean risedronate urinary excretion is summarised by treatment regimen in Table 5.

Table 5: Mean Risedronate Urinary Excretion over 72 Hours by Treatment

Parameter		**35mg IR 30-min before food**	**35mg IR Fasted (4 hours before food)**	**35mg EC Fed (5 minutes after food)**	**35mg EC Fasted (4 hours before food)**
A_e (µg)		57.7366	124.6796	126.3972	179.9608
A'_e (%)		0.1649	0.3562	0.3611	0.5142
A_e cumulative amount of drug excreted in urine A'_e cumulative amount of drug excreted in urine over the stated time interval, normalised for dose and expressed as a percentage.					

The bioavailability of the Actonel EC tablets decreased by ~30% when administered immediately after a high-fat breakfast compared to administration 4 hours before a meal. The bioavailability of the Actonel EC tablets administered after a high-fat breakfast was similar to Actonel IR tablets dosed 4 hours before a meal and was approximately 2-fold greater than the Actonel IR tablet administered 30 minutes prior to a high-fat breakfast. The bioavailability of the Actonel EC tablets administered 4 hours before a meal was approximately 3-fold greater than Actonel IR tablets administered 30 minutes prior to a high-fat breakfast.

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 [14C] 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 for the immediate-release tablets. 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. 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 Actonel 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.

Use in the elderly: Of the patients receiving Actonel EC in postmenopausal osteoporosis studies, 59% were 65 and over, while 13% were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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 Actonel 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 Actonel in patients with hepatic impairment. Risedronate is not metabolised in rat, dog, and human liver preparations. Insignificant amounts (< 0.1% of intravenous dose) of risedronate are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Risedronate did not cause gene mutations in bacterial or mammalian cells in vitro, nor did it cause DNA damage in rat hepatocytes in vitro. In clastogenicity assays, risedronate was positive in an in vitro assay using Chinese hamster ovary cells at cytotoxic concentrations (7-18% 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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Actonel EC tablets have a pH-sensitive enteric-coating and contain a chelating agent disodium edetate (EDTA). Each Actonel EC tablet also contains, microcrystalline cellulose, colloidal anhydrous silica, sodium starch glycollate type A, stearic acid, magnesium stearate, methacrylic acid – ethyl acrylate copolymer (1:1), triethyl citrate, – purified talc, iron oxide yellow, simethicone and polysorbate 80.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Actonel EC- Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Actonel EC Once-a-Week tablets are packaged in a clear PVC/aluminium foil blister strip contained in a carton. Pack sizes are 1, 2, 4, 10, 12 or 16 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

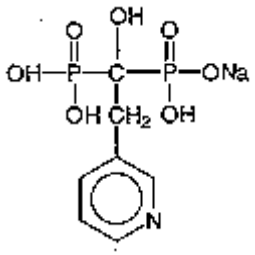
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical Structure

The chemical structure of risedronate sodium is the following:



Chemical Name

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

Molecular Formula

$C_7H_{10}NO_7P_2Na$

Molecular Weight

Anhydrous: 305.10
Hemi-pentahydrate: 350.13

CAS number

115436-72-1 (risedronate sodium)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4- Prescription Only Medicine

8 SPONSOR

Theramex Australia Pty Ltd
Level 22, 60 Margaret Street,
Sydney, NSW 2000
1800 THERAMEX or 1800 843 726

9 DATE OF FIRST APPROVAL

10 March 2011

10 DATE OF REVISION

31 March 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Addition of orbital inflammation to Actonel Post-Marketing Data