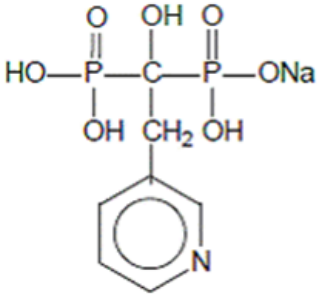
Actonel Once-a-Month

Risedronate sodium

DESCRIPTION

Each Actonel 150 mg tablet contains the equivalent of 150 mg of risedronate sodium. The empirical formula for risedronate sodium is $C_7H_{10}NO_7P_2Na$. The chemical name of risedronate sodium is [1-hydroxy-2-(-3-pyridinyl) ethylidene]bis[phosponic acid] monosodium salt. The chemical structure of risedronate sodium hemi-pentahydrate is the following:

Molecular weight: 305.10



The CAS registry number is 115436-72-1

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

Each Actonel 150 mg tablet contain risedronate sodium,crospovidone, magnesium stearate, microcrystalline cellulose, hydroxypropyl cellulose, hypromellose, macrogol 4000, macrogol 8000, silicon dioxide, indigo carmine and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacology

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 sodium demonstrated potent anti-osteoclast and antiresorptive activity, increasing bone mass and biomechanical strength dose-dependently. The activity of risedronate was confirmed by bone marker measurements during pharmacodynamic and clinical studies. With 5 mg risedronate 5 mg daily, decreases in biochemical markers of bone turnover were observed withhin 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 were similar with risedronate 35 mg Once-a-Week and risedronate 5 mg daily. In a study in men with osteoporosis, decreases in biochemical markers of bone turnover were observed at the earliest time point of 3 months and continued to be observed at 24 months.

Comparison of 5 mg daily dose and 150 mg Once-a-Month

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 precent 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.

Pharmacokinetics

Absorption:

Risedronate is relatively rapidly absorbed (t_{max}≈1hour) 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 (ie., 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%, Actonel 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.

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 not 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 Actonel from the surface of the bone.

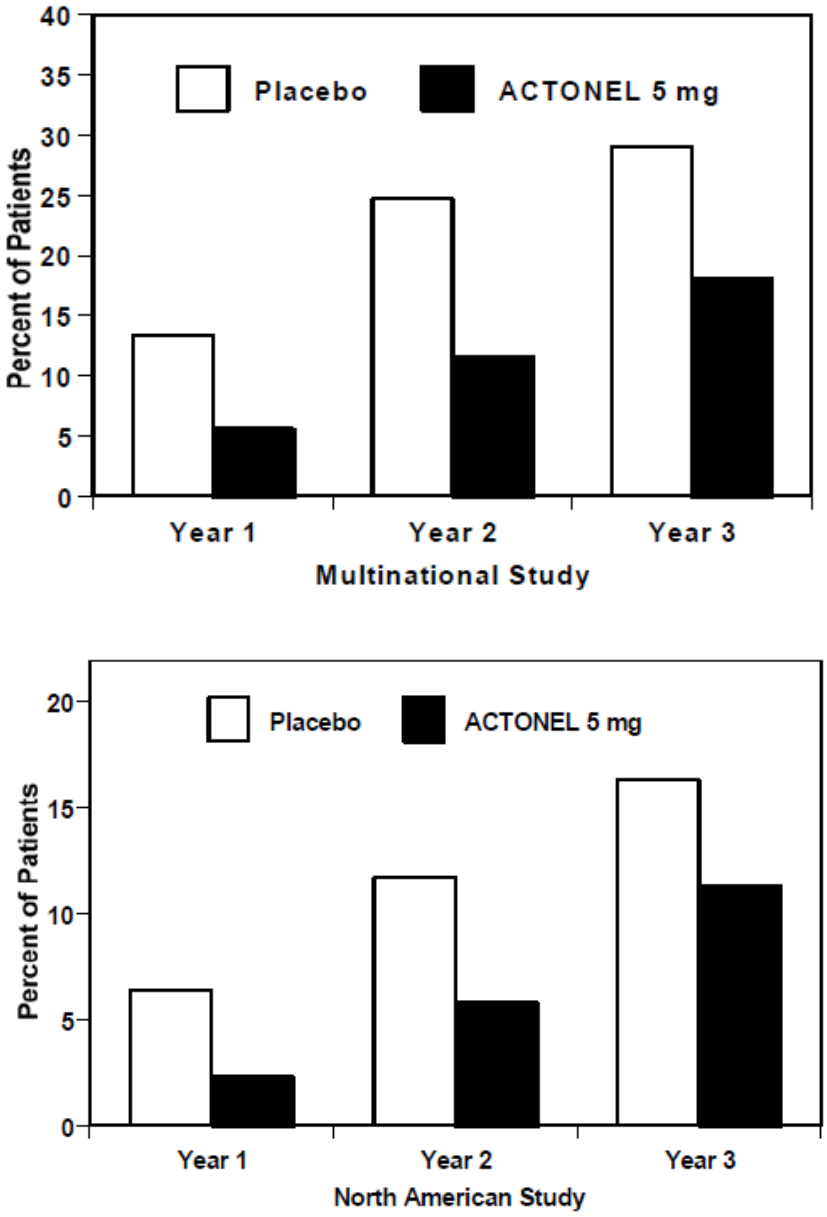
Special Groups:
Paediatric: Safety and efficacy of risedronate have not been established in patients under 18 years of age.
Gender: Bioavailability and pharmacokinetics following oral administration are similar in men and women.
Geriatric: Risedronate pharmacokinetics are similar in older subjects (age 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 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.

CLINICAL TRIALS
Treatment 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 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.

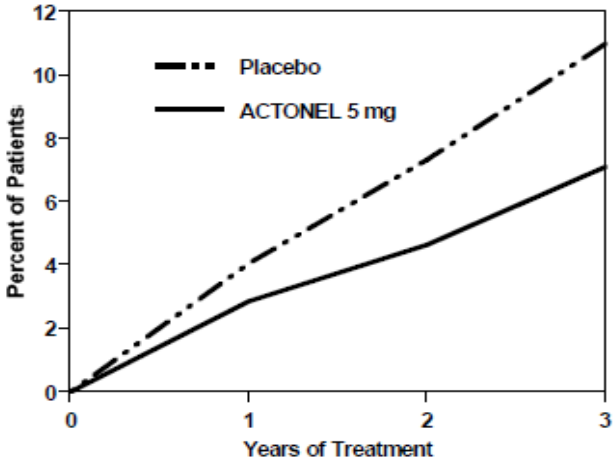
Figure 1: Cumulative Incidence of New Vertebral Fractures



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 1).

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

Table 1: 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.

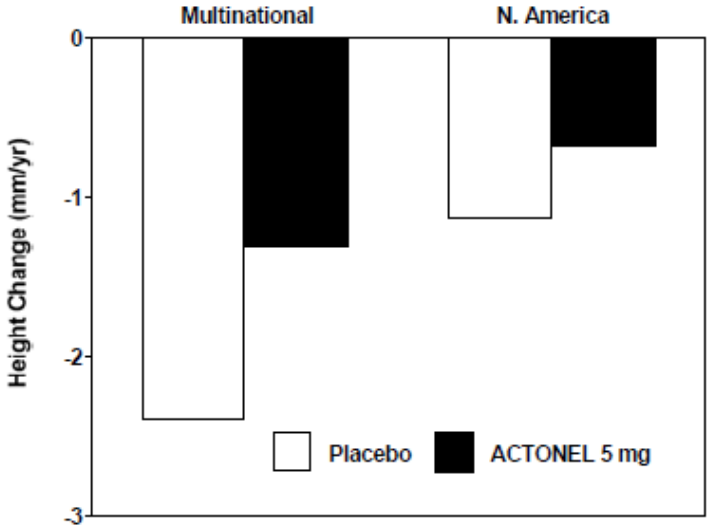
[c] P-value for testing the difference between the placebo and the 5mg risedronate groups using stratified (by study) log-rank test.

-- 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, randomized, 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.

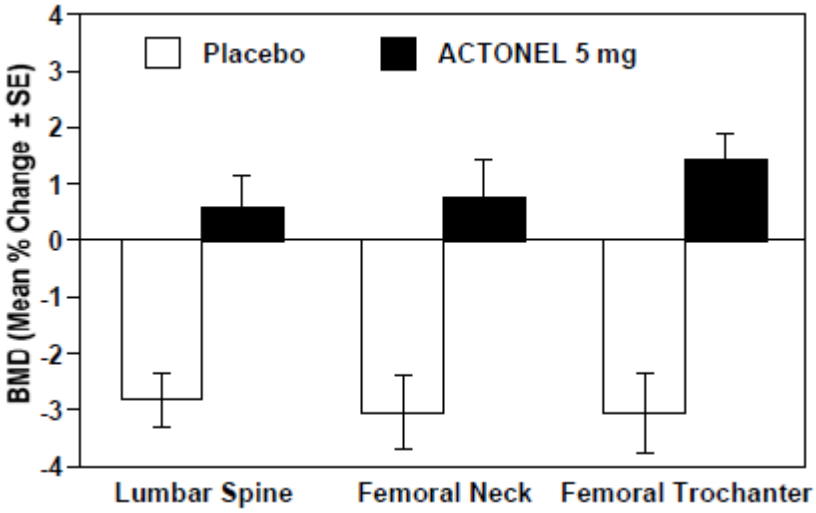
Combined Administration with Hormone Replacement Therapy:
The effects of combining Actonel 5 mg daily with conjugated oestrogen treatment (0.625 mg daily) were compared to the effects of conjugated oestrogen alone in a 1-year, randomized, double-blind study in more than 500 postmenopausal women (mean 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.
150 mg Once-a-Month Dose
In a double-blind, active-controlled, multicenter study of postmenopausal women with osteoporosis, 1 year of treatment with Actonel 150 mg Once-a-Month (n = 650) was shown to be non-inferior to Actonel 5 mg daily (n =642). In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 3.4% (3.0, 3.8; 95% CI) in the 5 mg daily group (n = 561) and 3.5% (3.1, 3.9; 95% CI) in the 150 mg Once-a-Month group (n = 561) with a mean difference between groups being -0.1% (-0.5, 02; 95% CI). The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites. The numbers of patients with new vertebral fractures at Month 12 and Endpoint were similar in the 150 mg Once-a-Month group and the 5 mg daily group (at Endpoint, 150 mg 1.4%; 5 mg daily 1.4%).

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.

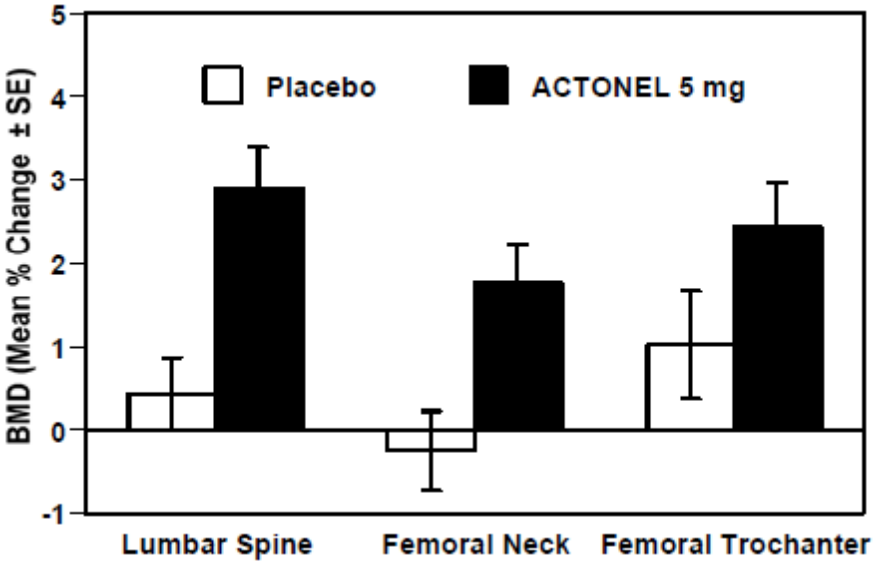
The effect of risedronate discontinuation on bone mineral density was studied in a double blind, placebo controlled study in postmenopausal women with glucocorticoid-dependent rheumatoid arthritis. Women were treated for 2 years with risedronate 2.5 mg daily, cyclic risedronate (averaged 2.5 mg of risedronate 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 analyzed 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 mineralization, 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 mineralization. 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.

INDICATIONS

- Treatment of osteoporosis
- Treatment of glucocorticoid-induced osteoporosis

CONTRAINDICATIONS

Known hypersensitivity to the drug or any of the ingredients.

- Hypocalcaemia (see Precautions)
- Inability to stand or sit upright for at least 30 minutes.

PRECAUTIONS

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

Hypocalcaemia must be corrected before starting Actonel therapy.

Bone and mineral metabolism dysfunction (eg.Vitamin D deficiency and parathyroid abnormalities) should be effectively treated before starting Actonel therapy.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. This is especially important in patients with Paget's disease in whom bone turnover is significantly elevated.

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

Actonel 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 Actonel as per the dosage instructions to patients who have a history of oesophageal disorders.

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

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

INTERACTIONS WITH OTHER MEDICINES

No specific drug interactions studies have been performed. However Actonel 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 (eg. calcium, magnesium, iron, aluminium, antacids) will interfere with the absorption of Actonel and should be taken at a different time of the day.

Actonel 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 Actonel. No clinically relevant interactions were noted. The medications included NSAIDs, aspirin, H2 blockers, proton pump inhibitors, antacids, calcium channel blockers, beta-blockers, thiazides, glucocorticoids, anticoagulants, anticonvulsants and cardiac glycosides. There are no clinical data concerning the concomitant medication with 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 Actonel patients (aspirin/NSAIDs taken ≥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.

Effect on Laboratory Tests
Bisphosphonates are known to interfere with the use of bone-imaging agents. However specific studies with Actonel have not been performed.
Small asymptomatic decreases in serum calcium and phosphorus levels have been observed in some patients.

Use in Pregnancy
Category B3
Actonel has not been studied in pregnant women. Actonel 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 0-24 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.

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.

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).

EFFECT 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 0-24h) 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.

Osteomalacia
The potential for Actonel 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. Actonel 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 Actonel administered at therapeutic doses is unlikely to induce osteomalacia.

ADVERSE REACTIONS
One year of treatment with Actonel 5 mg daily was compared to Actonel 150 mg Once-a-Month in a double-blind, multicentre study in postmenopausal women with osteoporosis. The overall safety and tolerability profiles of the 2 oral dosing regimens were similar. The incidence of serious adverse events was 4.2% in the Actonel 5 mg daily group and 6.2% in the Actonel 150 mg Once-a-Month group. The percentage of patients who withdrew from treatment due to adverse events was 9.5% in the Actonel 5 mg daily group and 8.6% in the Actonel 150 mg Once-a-Month group. Table 3 lists the adverse events in ≥ 2% of patients from this trial. Events are shown without attribution of causality.

Table 2: Adverse Events occurring in ≥ 2% of Patients in either treatment group in the 5 mg Daily vs. 150 mg Once a Month (1-year data)

System Organ Class/Preferred Term	5 mg Daily Actonel % (N=642)	150 mg Once a Month % (N=650)
Gastrointestinal disorders		
Abdominal pain upper	6.1	8.2
Diarrhoea	4.7	8.2
Nausea	6.9	6.2
Constipation	7.3	5.8
Dyspepsia	4.4	5.1
Vomiting	3.6	4.5
Abdominal pain	3.3	3.5
Flatulence	2.6	2.3
Gastritis	1.9	2.3
Abdominal distension	2.0	2.2
Hiatus hernia	2.3	0.8
Dry mouth	2.0	0.3
Infections and infestations		
Influenza	4.2	8.9
Nasopharyngitis	6.2	5.8
Urinary tract infection	3.6	5.7
Bronchitis	4.4	3.1
Gastroenteritis	2.2	2.8
Upper respiratory tract infection	1.2	2.0
Cystitis	2.0	0.9
Musculoskeletal and connective tissue disorders		
Back pain	6.4	5.7
Arthralgia	7.3	5.5
Osteoarthritis	3.0	3.7
Pain in extremity	2.6	2.8
Muscle spasms	1.2	2.6
Musculoskeletal pain	1.1	2.0
Neck pain	2.0	1.7
General disorders and administration site conditions		
Asthenia	2.2	3.1
Chest pain	1.2	2.0
Pyrexia	0.8	2.0
Nervous system disorders		
Headache	4.8	4.5
Dizziness	1.9	2.0
Injury, poisoning and procedural complications		
Fall	3.3	4.6
Vascular disorders		
Hypertension	4.8	4.6
Respiratory, thoracic and mediastinal disorders		
Cough	1.2	2.3
Psychiatric disorders		
Depression	1.2	2.0
Metabolism and nutrition disorders		
Hypercholesterolaemia	0.8	2.2

Acute Phase Reactions: Acute phase reaction-like events, defined as adverse events of fever or influenza-like illness with onset within the first 3 days of treatment and duration of 7 days or less, were reported by 9 (1.4%) patients on Actonel 150 mg Once-a-Month, and 1 (0.2%) patient on Actonel 5 mg daily.
Gastrointestinal Adverse Events: The Actonel 150 mg Once-a-Month regimen resulted in a slightly higher incidence of discontinuation due to diarrhoea (0.8% vs. 0.0%) compared to the Actonel 5 mg once daily regimen. All of these events occurred within a few days of the first dose. The incidence of vomiting that led to discontinuation was the same in both groups (0.3% vs. 0.3%).
Ocular Adverse Events: None of the patients treated with Actonel 150 mg Once-a-Month experience ocular inflammation such as uveitis, scleritis or iritis; of patients treated with 5 mg daily, 2 patients reported iritis.
Laboratory Test Findings: When Actonel 5 mg daily and Actonel 150 mg Once-a-Month were compared in postmenopausal women with osteoporosis, the mean percent changes from baseline at 12 months were 0.1% and 0.3% for serum calcium, -2.3% and -2.3% for phosphate, and 8.3% and 4.8% for PTH, respectively. Compared to the Actonel 5 mg daily regimen, Actonel 150 mg Once-a-Month resulted in a slightly higher incidence of hypocalcemia at the end of the first month of treatment (0.2%, 5 mg daily vs. 2.2%, 150 mg). Thereafter, the incidence of hypocalcemia with these regimens was similar at approximately 2%.

Actonel Post-Marketing Data
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.

DOSAGE AND ADMINISTRATION
Actonel must only be taken with **plain water**.
Plain water is the only drink that should be taken with Actonel 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.
Actonel must be taken 30 minutes before the first food or drink other than water. To facilitate delivery to the stomach, Actonel 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.
Only used for the treatment for 12 months.
Osteoporosis:
Actonel 150 mg tablets should be taken orally once a month. The tablet should be taken on the same date each month.
Patients who miss a dose of Actonel 150 mg Once-a-Month should be instructed to take one Actonel 150 mg tablet the morning after the day it is remembered, unless the time to the next month's scheduled doses are within 7 days.
If the next month's scheduled doses of Actonel 150 mg are within 7 days, patients should wait until their next month's scheduled doses and then continue taking Actonel 150 mg as originally scheduled.
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). Actonel is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/minute) due to limited clinical data.
Paediatrics:
Safety and efficacy of Actonel has not been established in patients under 18 years of age.
Compatibility with other Drugs:
Calcium, antacids, alumunium and some oral medications will interfere with the absorption of risedronate and therefore should be taken at a different time of the day.

OVERDOSAGE
No specific information is available on the treatment of overdose with Actonel. Decreases in serum calcium following substantial overdose may be expected in some patients. Signs and simptoms of hypocalcemia may also occur in some of these patients. Administration of milk or antacids (containing magnesium, calcium or alumunium) to chelate Actonel 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 ionized calcium and to relieve signs and symptoms of hypocalcaemia.

STORAGE
Do not store above 30°C
Presentation
ACTONEL 150 mg tablet
1 blister x 1 tablet
Reg. No:

HARUS DENGAN RESEP DOKTER
ON MEDICAL PRESCRIPTION ONLY

Registered by:
PT Pyridam Farma Tbk., Kabupaten Cianjur, Indonesia

Manufactured by:
Balkanpharma – Dupnitsa AD, 3 Samokovsko Shosse Str., 2600 Dupnitsa, Bulgaria