

Data Sheet

Actonel[®]

NAME OF THE MEDICINE

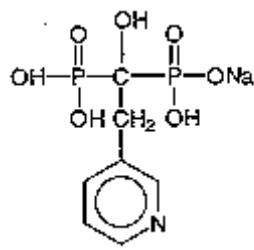
Non-proprietary Name

Actonel is risedronate sodium. Each Actonel tablet contains the equivalent of 5, 30 or 35mg 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(phosphonic acid) monosodium salt.

Chemical Structure

The chemical structure of risedronate sodium is the following:

Molecular Weight: 305.10



The CAS registry number is 115436-72-1.

DESCRIPTION

Risedronate sodium is a fine, white to off-white, odourless, crystalline powder. It is soluble in water and aqueous solutions and essentially insoluble in common organic solvents. Each Actonel tablet contains risedronate sodium (5, 30 or 35mg), lactose, crospovidone, magnesium stearate, microcrystalline cellulose, hydroxypropyl cellulose, hypromellose, macrogol 400, macrogol 8000, silicon dioxide, iron oxide yellow CI77492 (5mg and 35mg tablets only) iron oxide red CI77491(35mg tablets only) and titanium dioxide.

PHARMACOLOGY

Actonel

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

In preclinical studies Actonel demonstrated potent anti-osteoclast and anti-resorptive activity, increasing bone mass and biomechanical strength dose-dependently. The activity of Actonel was confirmed by bone marker measurements during pharmacodynamic and clinical studies.

With Actonel 5mg 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 Actonel causes a moderate reduction in bone resorption and bone turnover. The new steady state approximates the rate of bone turnover seen in pre-menopausal women. Decreases in biochemical markers of bone turnover were similar with Actonel 35mg Once-a-Week and Actonel 5mg 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 5mg daily dose and 35mg Once-a-Week dose

Based on a lumbar spine BMD (bone mineral density), Actonel 35mg Once-a-Week (n=485) was shown to be therapeutically equivalent to Actonel 5mg daily (n=480) in a one-year, double blind multicentre study of postmenopausal women with osteoporosis. The two treatment groups were

also similar at one year with regard to BMD increases at the total proximal femur, femoral neck and trochanter.

Pharmacokinetics

Actonel

Absorption:

Actonel is relatively rapidly absorbed ($t_{\max} \approx 1$ hour) throughout the upper gastrointestinal (GI) tract. Absorption is independent of dose over the range studied (2.5 to 30mg; multiple dose studies, 2.5 to 5mg daily and up to 50mg dosed weekly). In a 13-week pharmacokinetic study with 5mg daily and 35mg weekly and 50mg weekly dosing (N~19/group), a comparison of the average serum concentration (C_{avg}) for 35mg/week and 5mg/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 35mg dose compared to the 5mg 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 Actonel is administered with food. Bioavailability was similar in men and women. Although administration of Actonel 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 [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. This is likely to be considerably lower in humans who excrete 65% of an intravenously administered dose in the urine in 24 hours. 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 Actonel.

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 35mg versus 5mg 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 Actonel 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: Actonel 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: Actonel 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 \geq 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 OF POSTMENOPAUSAL OSTEOPOROSIS

The clinical program involved a wide range of early and late postmenopausal women with and without fracture, including those with a history of GI disease and those using aspirin, NSAIDs, proton pump inhibitors and H₂-blockers.

Treatment of Osteoporosis

The fracture efficacy of Actonel 5mg 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 1000mg/day. Patients with low vitamin D levels also received supplemental vitamin D 500 IU/day. The number of evaluable patients treated were :

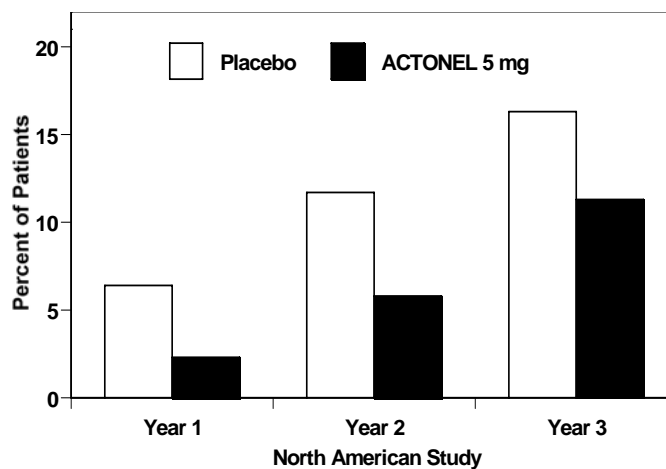
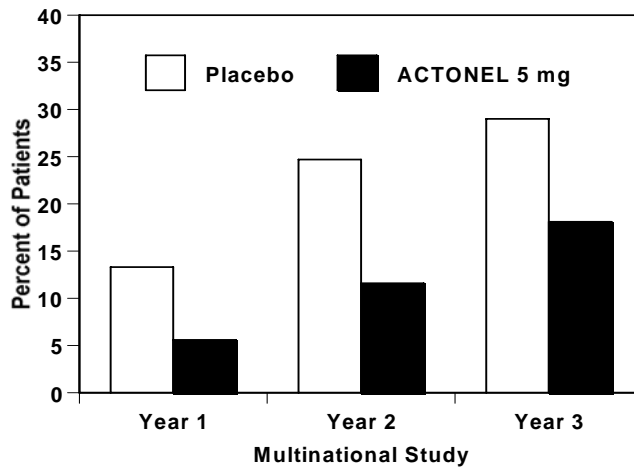
RVN – 5mg risedronate n = 696; placebo n = 678

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

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

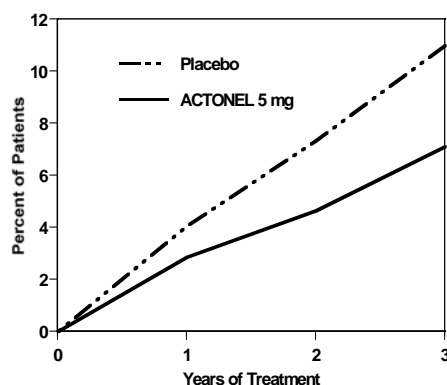
Effect on Vertebral Fracture: The pivotal studies of Actonel in the treatment of postmenopausal osteoporosis clearly demonstrate that Actonel 5mg daily reduces vertebral fracture incidence in patients with low bone mass and vertebral fractures, regardless of age, years since menopause, or disease severity at baseline. Actonel 5mg daily significantly reduced the risk of new vertebral fractures in each of the two large treatment studies. In the multinational study, treatment with Actonel 5mg 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 5mg 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 5mg 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 5mg 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 5mg 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.

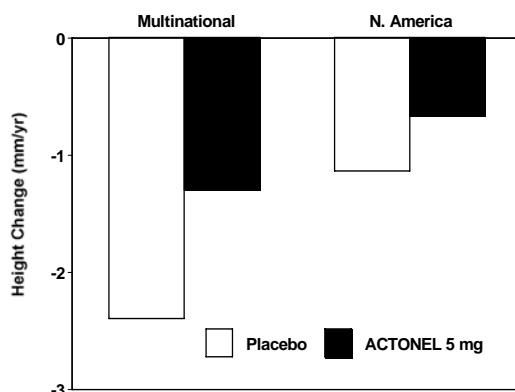
^b Relative risk and 95% confidence interval based upon Cox regression model comprising terms for treatment group and study.

^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 5mg 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 5mg 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 5mg 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 5mg

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 5mg 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 5mg 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 5mg daily with conjugated oestrogen treatment (0.625mg 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 5mg 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 5mg for more than 6 months.

35mg Once-a-Week Dose

Actonel 35mg Once-a-Week (n=485) was shown to be therapeutically equivalent to Actonel 5mg daily (n=480) in a 1-year double-blind multicentre study of postmenopausal women with osteoporosis. In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 4.0%(3.7,4.3; 95% CI) in the 5mg group (n=391) and 3.9%

(3.6,4.3; 95% CI) in the 35mg group (n=387) and the mean difference between 5mg daily and 35mg Once-a-Week was 0.1% (-0.42, 0.55; 95% CI) (see Table 2). While once a week doses of Actonel resulted in slightly smaller increases in lumbar spine BMD compared to daily doses of 5mg after 6 months, the two regimens are equivalent after 12 months. The clinical relevance of these 6-month BMD differences is unknown. The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites. This study is of 2 years' duration, the results of which will be included as soon as they are available.

Analysis Visit	5mg Daily Risedronate		35mg Once-a-Week Risedronate		Mean Difference (95% CI)
	N	Mean	N	Mean	5mg Daily vs.35mg Once-a-Week
Lumbar spine					
Month 6	402	3.12 ^a	389	2.68 ^a	0.44 ^b (0.01; 0.87) p=0.045
Month 12	391	4.00 ^a	387	3.94 ^a	0.06 (-0.42; 0.55) p=0.799

^aIndicates statistically significant difference from baseline
^bIndicates statistically significant difference between treatment groups

Very few patients in any treatment group had new fractured vertebrae at Month 12 (5mg daily:1.5%; 35mg Once-a-Week: 1.3%). No patient had more than one new fractured vertebra. There were no statistically significant differences in the percentage of patients with new vertebral fractures among the 2 treatment groups.

Treatment of Osteoporosis in Men

Actonel 35mg Once-a-Week demonstrated efficacy in men with osteoporosis (age range 36 to 84 years) in a 2-year, double-blind, placebo-controlled study in 284 patients (risedronate sodium 35mg n = 191). All patients received supplemental calcium and vitamin D. The primary efficacy endpoint was assessed by the percentage change from baseline in lumbar spine BMD at endpoint (Month 24 or last post-baseline observation). Secondary efficacy measures included lumbar spine and proximal femur BMD at 6, 12 and 24 months; BMD responders (defined as patients who had a positive lumbar spine BMD change at Month 24); bone turnover markers at 6, 12 and 24 months; body height; incidence of new vertebral fractures and incidence of clinical fractures. Increases in BMD were observed as early as 6 months following initiation of risedronate sodium treatment. The primary analysis showed a statistically significant difference between risedronate and placebo in least squares mean percent change from baseline to endpoint (p<0.0001). The estimated difference at endpoint between risedronate and placebo in the ITT population was 4.53% (95% CI: 3.46%, 5.60%). Actonel 35mg Once-a-Week produced mean increases in BMD at the lumbar spine, femoral neck, trochanter and total hip compared to placebo after 2 years of treatment. The bone effect (BMD increase and BTM decrease) of risedronate sodium is similar in males and females.

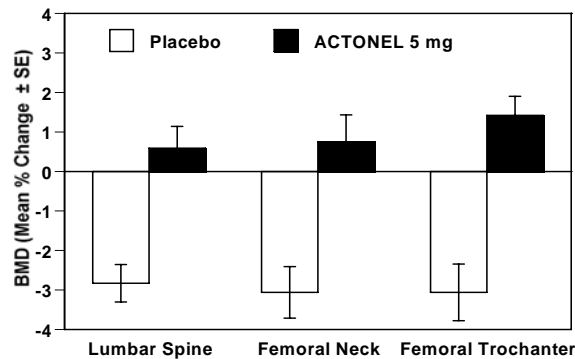
CORTICOSTEROID-INDUCED OSTEOPOROSIS

Bone Mineral Density: Two 1-year, double-blind, placebo-controlled trials demonstrated that Actonel 5mg 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 (\geq 7.5mg/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 500mg/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 5mg 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.

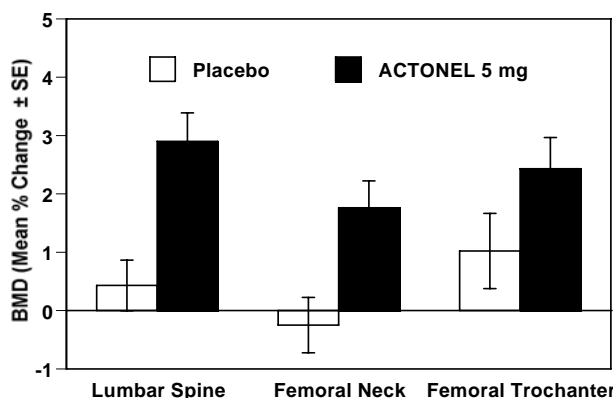
The effect of risedronate discontinuation on bone mineral density was studied in a double blind, placebo controlled study in postmenopausal women with glucocorticoid-dependent rheumatoid arthritis. Women were treated for 2 years with risedronate 2.5mg daily, cyclic risedronate (averaged 2.5mg of risedronate 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 1000mg/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 5mg 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 5mg 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 5mg 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.

PAGET'S DISEASE

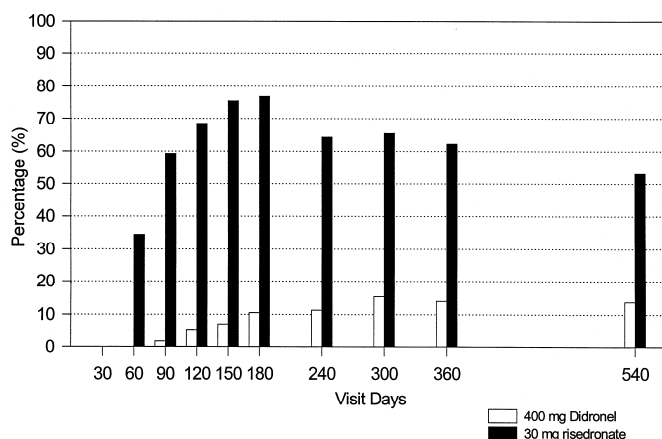
Paget's disease is a chronic, focal skeletal disorder characterised by increased and disordered bone remodelling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation. This leads to the replacement of normal bone architecture by disorganised, enlarged and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe bone pain, bone deformity, pathological fractures and neurological disorders.

Serum alkaline phosphatase (SAP), the most frequently used biochemical marker of disease activity provides an objective measure of disease severity and response to therapy.

The efficacy of Actonel was demonstrated in two clinical studies involving 120 male and 65 female patients. In a double-blind, active-controlled study of patients with moderate-to-severe Paget's disease (SAP levels of at least two times the upper limit of normal), patients were treated with Actonel 30mg daily for 2 months or etidronate 400mg daily for 6 months. Figure 6 shows that at Day 180, 77% (43/56) of Actonel treated patients achieved normalisation of SAP levels compared to 10.5% of patients treated with etidronate ($p < 0.001$). At day 540, 16 months after discontinuation of therapy, 53% (17/32) of Actonel treated patients and 14% (4/29) of etidronate treated patients with available data remained in biochemical remission.

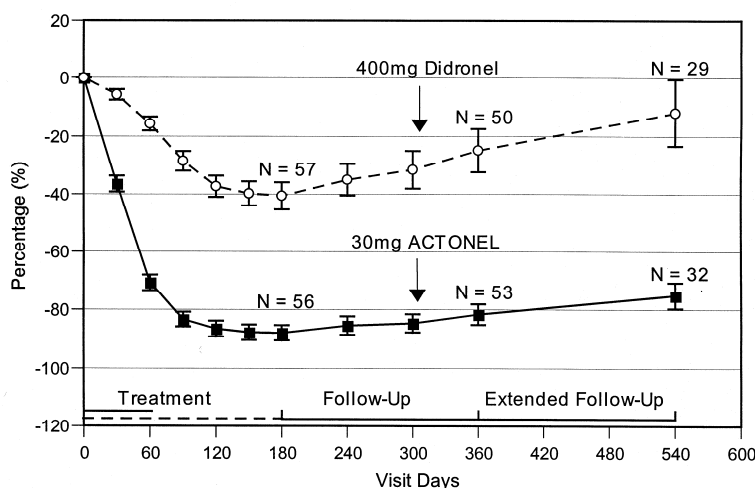
Figure 6: Patients with normal serum alkaline phosphatase values by visit



During the first 180 days of the active-controlled study, 85% (51/60) of Actonel treated patients demonstrated a $\geq 75\%$ reduction from baseline in excessive SAP levels (difference between measured level and midpoint of the normal range). This was achieved with 2 months of treatment compared to 20% (12/60) in the etidronate treated group with 6 months of treatment ($p < 0.001$).

Changes in excessive SAP levels over time (shown in the figure below) are significant following only 30 days of treatment, with a 36% reduction in SAP levels at that time compared to only 6% seen with etidronate treatment at the same time point ($p < 0.01$).

Figure 7: Mean % change from baseline in serum alkaline phosphatase excess by visit



Response to Actonel therapy was similar in patients with Paget's disease, irrespective of disease severity. Table 3 shows the mean percent reduction from baseline at Day 180 in excess SAP levels in patients with mild, moderate, or severe disease.

Subgroup: Baseline Disease Severity (SAP)	30mg Actonel			400mg Etidronate		
	N	Baseline Serum SAP (U/L)*	Mean % Reduction	N	Baseline Serum SAP (U/L)*	Mean % Reduction
>2 and <3 x ULN	32	271.6 ± 5.3	-88.1	22	277.9 ± 7.45	-44.6
≥3 and <7x ULN	14	475.3 ± 28.8	-87.5	25	480.5 ± 26.44	-35.0
≥7x ULN	8	1336.5 ± 134.19	-81.8	6	1331.5 ± 167.58	-47.2

* Values shown are mean ± SEM; ULN = upper limit of normal; U/L = upper limit

Response to Actonel was similar between patients who had previously received anti-pagetec therapy and those who had not. In the active-controlled study, four patients previously non-responsive to one or more courses of anti-pagetec therapy (calcitonin, etidronate) responded to treatment with Actonel 30mg daily (defined by at least a 30% change from baseline). Each of these patients achieved at least 90% reduction from baseline in excess serum alkaline phosphatase levels with three patients achieving normalisation of serum alkaline phosphatase levels.

Histomorphometry of the bone was studied in 14 patients with paired bone biopsies. Nine patients had paired biopsies from pagetic bone lesions and five patients from non-pagetec bone. Bone biopsy results in non-pagetec bone did not reveal osteomalacia, impairment of bone remodelling or induction of a significant decline in bone turnover in patients treated with Actonel.

INDICATIONS

- Treatment of Osteoporosis.
- Prevention of Glucocorticoid-induced Osteoporosis.
- Treatment of Paget's disease of the bone.
- Treatment of Postmenopausal 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 Actonel 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 medications 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 osteoporosis trials with 5mg 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.

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 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

Actonel 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 Actonel 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, fetuses from Actonel treated dams showed ossification changes in sternbrae and/or skull at doses as low as 3.2mg/kg/day. This is equivalent to the human 30mg dose and 6 times the human 5mg dose based on surface area, mg/m². Treatment with Actonel during mating and gestation with doses of 3.2mg/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 24mg/kg/day) or mice (treated for 80 weeks with up to 32mg/kg/day). Systemic exposure (serum AUC_{0-24h}) at the high dose in rats was 160 times greater than that in humans dosed at 30mg/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, Actonel 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).

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_{0-24h}) about 30 times higher than that in humans dosed at 30mg/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 (5mg/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

Osteoporosis – Actonel 5mg daily dosing

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 4 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 4: 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 5mg % (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].

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 5mg 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 35mg Once-a-Week dosing

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

Table 5: Adverse Events Occurring in ≥ 5% of Patients of Either Treatment Group in the Daily vs Once-a-Week Osteoporosis Treatment Study in Postmenopausal Women		
Body System	5mg Daily Actonel % (N = 480)	35mg Once-a-Week Actonel % (N = 485)
Body as a Whole		
Infection	19.0	20.6
Accidental Injury	10.6	10.7
Pain	7.7	9.9
Back Pain	9.2	8.7
Flu Syndrome	7.1	8.5
Abdominal Pain	7.3	7.6
Headache	7.3	7.2
Overdose	6.9	6.8
Asthenia	3.5	5.4
Cardiovascular System		
Hypertension	5.8	4.9
Digestive System		
Constipation	12.5	12.2

Dyspepsia	6.9	7.6
Nausea	8.5	6.2
Diarrhoea	6.3	4.9
Musculoskeletal System		
Arthralgia	11.5	14.2
Traumatic Bone Fracture	5.0	6.4
Myalgia	4.6	6.2
Nervous System		
Dizziness	5.8	4.9

In a 2-year study in men with osteoporosis, the overall safety and tolerability were similar between the treatment and the placebo groups. Adverse experiences were consistent with those previously observed in women

Paget's Disease

Actonel was studied in 392 patients with Paget's disease. The adverse events reported were usually mild or moderate and did not generally require discontinuation of treatment. There was no correlation between adverse events and the age or gender of the patient.

In a double-blind, active-controlled study, the adverse event profile was similar for Actonel and etidronate. 6.6% (4/61) of patients treated with Actonel 30mg/day for 2 months discontinued treatment due to adverse events, compared with 8.2% (5/61) of patients treated with etidronate 400mg/day for 6 months.

Adverse events reported in $\geq 5\%$ of Actonel treated patients in the Phase 3 study are shown in Table 6 below:

BODY SYSTEM	30mg/day x 2 months Actonel % (N=61)	400mg/day x 6 months Etidronate % (N=61)
Body as a Whole		
Flu Syndrome	9.8	1.6
Chest Pain	6.6	3.3
Gastrointestinal		
Diarrhoea	19.7	14.8
Abdominal Pain	11.5	8.2
Nausea	9.8	9.8
Constipation	6.6	8.2
Metabolic & Nutritional		
Peripheral Oedema	8.2	6.6
Musculoskeletal		
Arthralgia	32.8	29.5
Nervous		
Headache	18.0	16.4
Dizziness	6.6	4.9
Skin		
Rash	11.5	8.2

^TConsidered to be possibly or probably causally related in at least one patient

Three patients that received Actonel 30mg/day experienced acute iritis in one supportive study. All three patients recovered from their events; however, in one of these patients, the event recurred during Actonel treatment and again during treatment with pamidronate. All patients were

effectively treated with topical steroids.

In the Phase 3 comparative study vs etidronate, patients with a history of upper GI disease or abnormalities and patients on NSAIDs or aspirin were also included. The proportion of Actonel treated patients [12 (19.7%)] with mild or moderate upper GI adverse events was similar to that in the etidronate treated group [12 (19.7%)]. No severe upper GI adverse events were observed in either group.

As expected the incidence of GI adverse events in patients who took concomitant NSAIDs or aspirin was higher than in non-users. However in these patients the incidence of GI adverse events was similar in the etidronate [10 (16.4%)] and Actonel [11 (18%)] treated patients.

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 5mg, 30mg & 35mg Tablets:

Actonel must only be taken with **plain water**.

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.

Osteoporosis: The recommended dose is 5mg daily, or 35mg once a week taken on the same day each week.

Paget's disease: The recommended treatment regimen is 30mg once daily for 2 months.

Actonel is indicated in patients whose symptoms are attributed to Paget's disease and in patients who are at risk for future complications from their disease, to induce remission (normalisation of serum alkaline phosphatase).

Retreatment may be considered (following post-treatment observation of at least 2 months) if relapse occurs, or if treatment fails to normalise serum alkaline phosphatase. For retreatment the dose and duration of therapy are the same as for initial treatment. No data are available on more than one course of retreatment.

N.B. Suppression of Paget's disease may last up to 12 months or longer and re-treatment should be withheld until there are further manifestations of the disease.

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.

Children: Safety and efficacy of Actonel has not been established in patients under 18 years of age.

Men: The dosage is 35mg/week.

Compatibility with other Drugs

Calcium, antacids, aluminium and some oral medications will interfere with the absorption of Actonel 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 symptoms of hypocalcaemia may also occur in some of these patients

Administration of milk or antacids (containing magnesium, calcium or aluminium) 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 ionised calcium and to relieve signs and symptoms of hypocalcaemia.

PRESENTATION AND STORAGE CONDITIONS

Actonel 5mg and 30mg tablets are packaged in an opaque PVC/aluminium foil blister strip contained in a carton. The 5mg tablets are supplied in pack sizes of 7 and 28 tablets and the 30mg tablets are supplied in pack sizes of 14 and 28 tablets.

Actonel 35mg Once-a-Week tablets are packaged in a clear PVC/aluminium foil blister strip contained in a carton. Pack sizes are 1 or 4 tablets.

Actonel 5mg tablets: oval yellow film-coated tablets with RSN embossed on one side and 5mg on the other.

Actonel 30mg tablets: oval, white film-coated tablets with RSN embossed on one side and 30mg on the other.

Actonel 35mg Once-a-Week tablets: oval light orange film-coated tablets with RSN embossed on one side and 35mg on the other.

Actonel tablets should be stored below 25°C.

MEDICINE CLASSIFICATION

Prescription only Medicine

NAME AND ADDRESS OF SPONSOR

sanofi-aventis new zealand limited

Level 8, James & Wells Tower

56 Cawley Street

Ellerslie

Auckland

Telephone: (09) 580 1810

Date of Preparation

25th June 2007