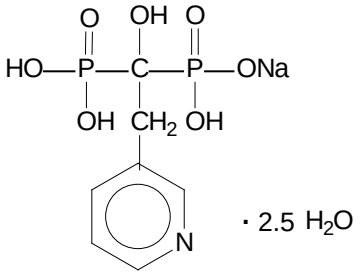
ACTONEL® with CALCIUM
(risedronate sodium tablets with calcium carbonate tablets, USP)

DESCRIPTION
ACTONEL® with CALCIUM is a co-package product containing ACTONEL® (risedronate sodium tablets, 35 mg) for once weekly dosing and calcium carbonate tablets, USP (1250 mg, equivalent to 500 mg elemental calcium) for daily dosing for the remaining 6 days of the week. Each package contains a 28-day course of therapy.

ACTONEL
ACTONEL (risedronate sodium tablets) is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Each ACTONEL tablet in the ACTONEL with CALCIUM co-package contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. The empirical formula for risedronate sodium hemi-pentahydrate is $C_7H_{10}NO_7P_2Na \cdot 2.5\ H_2O$. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt. The chemical structure of risedronate sodium hemi-pentahydrate is the following:



Molecular Weight:	
Anhydrous:	305.10
Hemi-pentahydrate:	350.13

Risedronate 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.

Calcium
The empirical formula for calcium carbonate is $CaCO_3$ and the molecular weight is 100.09.

Calcium carbonate is supplied as a calcium carbonate tablet, USP containing 1250 mg calcium carbonate (equivalent to 500 mg elemental calcium). Calcium carbonate is a fine, white, odorless, tasteless powder. It is stable and non-hygroscopic.

Calcium carbonate is formulated per USP standards to meet disintegration or dissolution, weight, purity, and potency requirements.

Inactive Ingredients:
ACTONEL
Crospovidone, ferric oxide red, ferric oxide yellow, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

Calcium
Pregelatinized starch, sodium starch glycolate, FD&C Blue #2, magnesium stearate, polyethylene glycol 3350, hypromellose, Opaspray Light Blue, polysorbate 80.

CLINICAL PHARMACOLOGY
ACTONEL
Mechanism of Action:
ACTONEL has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, ACTONEL inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (for example, lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that ACTONEL treatment reduces bone turnover (activation frequency, that is, the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

Pharmacokinetics:
Absorption:
Absorption after an oral dose is relatively rapid (t_{max} approximately 1 hour) and occurs throughout the upper gastrointestinal tract. The fraction of the dose absorbed is independent of dose over the range studied (single dose, 2.5 to 30 mg; multiple dose, 2.5 to 5 mg). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean absolute oral bioavailability of the 30 mg tablet is 0.63% (90% CI: 0.54% to 0.75%) and is comparable to a solution. The extent of absorption of a 30 mg dose (three 10 mg tablets) when administered 0.5 hours before breakfast is reduced by 55% compared to dosing in the fasting state (no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces the extent of absorption by 30% compared to dosing in the fasting state. Dosing either 0.5 hours prior to breakfast or 2 hours after dinner (evening meal) results in a similar extent of absorption. ACTONEL is effective when administered at least 30 minutes before breakfast.

Distribution:
The mean steady-state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was in the range of 0.001% to 0.01%.

Metabolism:
There is no evidence of systemic metabolism of risedronate.

Elimination:
Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine over 28 days. Mean renal clearance is 105 mL/min (CV = 34%) and mean total clearance is 122 mL/min (CV = 19%), with the difference primarily reflecting nonrenal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. Once risedronate is absorbed, 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. This terminal half-life is hypothesized to represent the dissociation of risedronate from the surface of bone.

Calcium
Calcium is a major substrate for mineralization and has an antiresorptive effect on bone. Calcium suppresses PTH secretion and decreases bone turnover. Increased levels of PTH are known to contribute to age-related bone loss, especially at cortical sites, while increased bone turnover is an independent risk factor of fractures.

Pharmacokinetics:
Absorption:
Calcium is released from calcium complexes during digestion in a soluble, ionized form, for absorption from the small intestine. Absorption can be by both passive and active mechanisms. Active absorption of calcium is highly dependent on vitamin D, and vitamin D deficiency decreases the absorption of calcium. As calcium intake increases, the active transfer mechanism becomes saturated and an increasing proportion of calcium is absorbed via passive diffusion. Absorption of calcium carbonate is dose-dependent, with fractional absorption being highest when at doses up to 500 mg. Absorption of calcium is also dependent on pH with reduced absorption in alkaline conditions. The absorption of calcium from calcium carbonate is increased when taken with food.

Distribution:
Approximately 50% of calcium in the serum is in the physiologically active ionized form; about 10% is complexed to phosphate, citrate or other anions. The remaining 40% is bound to proteins, primarily albumin.

Elimination:
Unabsorbed calcium from the small intestine is excreted in the feces. Renal excretion depends largely on glomerular filtration and calcium tubular reabsorption with more than 98% of calcium reabsorbed from the glomerular filtrate. This process is regulated by active vitamin D and PTH.

Special Populations:
ACTONEL
Pediatric:
Risedronate pharmacokinetics have not been studied in patients less than 18 years of age.

Gender:
Bioavailability and pharmacokinetics following oral administration are similar in men and women.

Geriatric:
Bioavailability and disposition are similar in elderly (greater than 60 years of age) and younger subjects. No dosage adjustment is necessary.

Race:
Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency:
Risedronate is excreted unchanged primarily via the kidney. As compared to persons with normal renal function, the renal clearance of risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 mL/min. ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 30 mL/min.

Hepatic Insufficiency:
No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in rat, dog, and human liver preparations. Insignificant amounts (less than 0.1% of intravenous dose) of drug are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.

Calcium
Absorption of calcium from calcium carbonate is poor in patients with achlorhydria unless taken with food.

Gender:
Absorption of calcium from calcium carbonate has not been adequately studied with respect to gender.

Geriatric:
There are no clinically significant differences in bioavailability following administration of 1 g elemental calcium as calcium carbonate between young (20 to 27 years) and elderly (63 to 71 years) females.

Race:
The effect of race on calcium absorption from oral calcium carbonate has not been studied.

Renal Insufficiency:
Renal disease affects calcium homeostasis through its effects on vitamin D metabolism, phosphorus excretion, and PTH. Calcium should be administered cautiously to patients with renal disease (creatinine clearance less than 30 mL/min) to avoid elevations of the calcium-phosphorus ion product (Ca x Phos) and the development of calcinosis.

Pharmacodynamics:
ACTONEL

Treatment and Prevention of Osteoporosis in Postmenopausal Women:
Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist.

The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. Osteoporosis occurs in both men and women but is more common among women following menopause. In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly-formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of bone fracture. After menopause, the risk of fractures of the spine and hip increases; approximately 40% of 50 year-old women will experience an osteoporosis-related fracture during their remaining lifetimes. After experiencing 1 osteoporosis-related fracture, the risk of future fracture increases 5-fold compared to the risk among a non-fractured population.

ACTONEL treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of ACTONEL to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxypyridinoline/creatinine and urinary collagen cross-linked N-telopeptide (markers of bone resorption) and serum bone specific alkaline phosphatase (a marker of bone formation). At the 5 mg dose, decreases in deoxypyridinoline/creatinine were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and bone formation; decreases in bone specific alkaline phosphatase of about 20% were evident within 3 months of treatment. Bone turnover markers reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years. Bone turnover is decreased as early as 14 days and maximally within about 6 months of treatment, with achievement of a new steady-state that more nearly approximates the rate of bone turnover seen in premenopausal women. In a 1-year study comparing daily versus weekly oral dosing regimens of ACTONEL for the treatment of osteoporosis in postmenopausal women, ACTONEL 5 mg daily and ACTONEL 35 mg once-a-week decreased urinary collagen cross-linked N-telopeptide by 60% and 61%, respectively. In addition, serum bone-specific alkaline phosphatase was also reduced by 42% and 41% in the ACTONEL 5 mg daily and ACTONEL 35 mg once-a-week groups, respectively. ACTONEL is not an estrogen and does not have the benefits and risks of estrogen therapy.

As a result of the inhibition of bone resorption, asymptomatic and usually transient decreases from baseline in serum calcium (less than 1%) and serum phosphate (less than 3%) and compensatory increases in serum PTH levels (less than 30%) were observed within 6 months in patients in osteoporosis clinical trials. There were no significant differences in serum calcium, phosphate, or PTH levels between the ACTONEL and placebo groups at 3 years. In a 1-year study comparing daily versus weekly oral dosing regimens of ACTONEL in postmenopausal women, the mean changes from baseline at 12 months were similar between the ACTONEL 5

mg daily and ACTONEL 35 mg once-a-week groups, respectively, for serum calcium (0.4% and 0.7%), phosphate (-3.8% and -2.6%) and PTH (6.4% and 4.2%).

Calcium

Calcium administration decreases the elevated rate of bone turnover typically seen in postmenopausal women with osteoporosis. In randomized, placebo controlled studies in postmenopausal women, calcium administration (500 mg to 1600 mg) decreased biochemical markers of bone turnover, including urine N-telopeptide, urine free pyridinoline (markers of bone resorption), alkaline phosphatase and osteocalcin (markers of bone formation) relative to placebo treated women.

Calcium administration may transiently increase levels of serum calcium with compensatory reductions in serum PTH and an increase in urinary calcium. However, urinary and serum calcium levels usually remain within the normal reference range.

CLINICAL STUDIES

ACTONEL

Treatment of Osteoporosis in Postmenopausal Women:

The fracture efficacy of ACTONEL 5 mg daily in the treatment of postmenopausal osteoporosis was demonstrated in 2 large, randomized, placebo-controlled, double-blind studies that enrolled a total of almost 4000 postmenopausal women under similar protocols. The Multinational study (VERT MN) (ACTONEL 5 mg, n = 408) was conducted primarily in Europe and Australia; a second study was conducted in North America (VERT NA) (ACTONEL 5 mg, n = 821). Patients were selected on the basis of radiographic evidence of previous vertebral fracture, and therefore, had established disease. The average number of prevalent vertebral fractures per patient at study entry was 4 in VERT MN, and 2.5 in VERT NA, with a broad range of baseline bone mineral density (BMD) levels. All patients in these studies received supplemental calcium 1000 mg/day. Patients with low vitamin D levels (approximately 40 nmol/L or less) also received supplemental vitamin D 500 IU/day.

Positive effects of ACTONEL treatment on BMD were also demonstrated in each of 2 large, randomized, placebo-controlled trials (BMD MN and BMD NA) in which almost 1200 postmenopausal women (ACTONEL 5 mg, n = 394) were recruited on the basis of low lumbar spine bone mass (more than 2 SD below the premenopausal mean) rather than a history of vertebral fracture.

ACTONEL 35 mg once-a-week (n = 485) was shown to be therapeutically equivalent to ACTONEL 5 mg daily (n = 480) in a 1-year, double-blind, multicenter 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% confidence interval [CI]) in the 5 mg daily group (n = 391) and 3.9% (3.6, 4.3; 95% CI) in the 35 mg once-a-week group (n = 387) and the mean difference between 5 mg daily and 35 mg weekly was 0.1% (-0.42, 0.55; 95% CI). 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.

Effect on Vertebral Fractures:

Fractures of previously undeformed vertebrae (new fractures) and worsening of pre-existing vertebral fractures were diagnosed radiographically; some of these fractures were also associated with symptoms (that is, clinical fractures). Spinal radiographs were scheduled annually and prospectively planned analyses were based on the time to a patient's first diagnosed fracture. The primary endpoint for these studies was the incidence of new and worsening vertebral fractures across the period of 0 to 3 years. ACTONEL 5 mg daily significantly reduced the incidence of new and worsening vertebral fractures and of new vertebral fractures in both VERT NA and VERT MN at all time points (Table 1). 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.

Table 1
The Effect of ACTONEL on the Risk of Vertebral Fractures

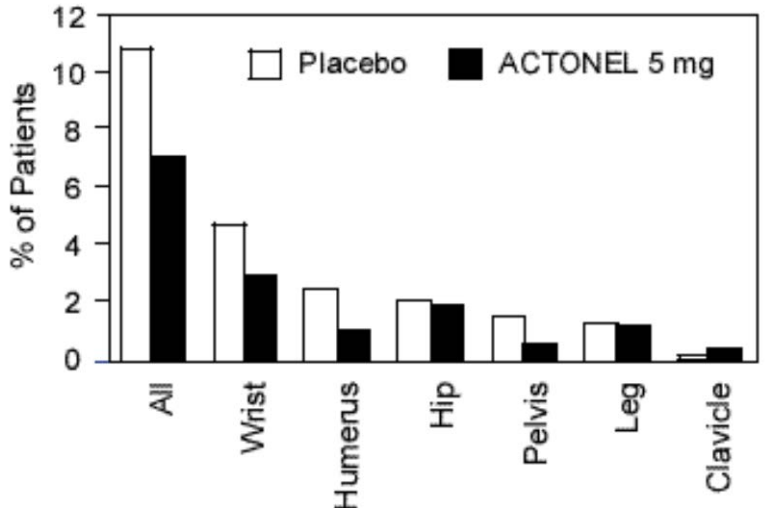
	Proportion of Patients with Fracture (%)[a]			
VERT NA	Placebo n = 678	ACTONEL 5 mg n = 696	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 to 1 Year	7.2	3.9	3.3	49
0 to 2 Years	12.8	8.0	4.8	42
0 to 3 Years	18.5	13.9	4.6	33
New				
0 to 1 Year	6.4	2.4	4.0	65
0 to 2 Years	11.7	5.8	5.9	55
0 to 3 Years	16.3	11.3	5.0	41
VERT MN	Placebo n = 346	ACTONEL 5 mg n = 344	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 to 1 Year	15.3	8.2	7.1	50
0 to 2 Years	28.3	13.9	14.4	56
0 to 3 Years	34.0	21.8	12.2	46
New				
0 to 1 Year	13.3	5.6	7.7	61
0 to 2 Years	24.7	11.6	13.1	59
0 to 3 Years	29.0	18.1	10.9	49

[a]Calculated by Kaplan-Meier methodology.

Effect on Osteoporosis-Related Nonvertebral Fractures:

In VERT MN and VERT NA, a prospectively planned efficacy endpoint was defined consisting of all radiographically confirmed fractures of skeletal sites accepted as associated with osteoporosis. Fractures at these sites were collectively referred to as osteoporosis-related nonvertebral fractures. ACTONEL 5 mg daily significantly reduced the incidence of nonvertebral osteoporosis-related fractures over 3 years in VERT NA (8% versus 5%; relative risk reduction 39%) and reduced the fracture incidence in VERT MN from 16% to 11%. There was a significant reduction from 11% to 7% when the studies were combined, with a corresponding 36% reduction in relative risk. Figure 1 shows the overall results as well as the results at the individual skeletal sites for the combined studies.

Figure 1
Nonvertebral Osteoporosis-Related Fractures
Cumulative Incidence Over 3 Years
Combined VERT MN and VERT NA



Effect on Height:
In the two 3-year osteoporosis treatment studies, standing height was measured yearly by stadiometer. Both ACTONEL and placebo-treated groups lost height during the studies. Patients who received ACTONEL had a statistically significantly smaller loss of height than those who received placebo. In VERT MN, the median annual height change was -1.3 mm/yr in the ACTONEL 5 mg daily group compared to -2.4 mm/yr in the placebo group. In VERT NA, the median annual height change was -0.7 mm/yr in the ACTONEL 5 mg daily group compared to -1.1 mm/yr in the placebo group.

Effect on Bone Mineral Density:
The results of 4 randomized, placebo-controlled trials in women with postmenopausal osteoporosis (VERT MN, VERT NA, BMD MN, BMD NA) demonstrate that ACTONEL 5 mg daily increases BMD at the spine, hip, and wrist compared to the effects seen with placebo. Table 2 displays the significant increases in BMD seen at the lumbar spine, femoral neck, femoral trochanter, and midshaft radius in these trials compared to placebo. In both VERT studies (VERT MN and VERT NA), ACTONEL 5 mg daily produced increases in lumbar spine BMD that were progressive over the 3 years of treatment, and were statistically significant relative to baseline and to placebo at 6 months and at all later time points.

Table 2
Mean Percent Increase in BMD from Baseline in Patients Taking ACTONEL 5 mg or Placebo at Endpoint[a]

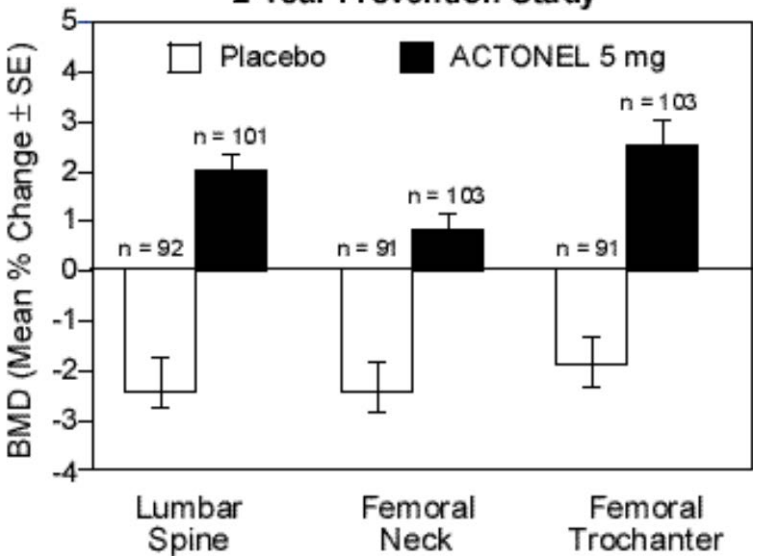
	VERT MN[b]		VERT NA[b]		BMD MN[c]		BMD NA[c]	
	Placebo n = 323	5 mg n = 323	Placebo n = 599	5 mg n = 606	Placebo n = 161	5 mg n = 148	Placebo n = 191	5 mg n = 193
Lumbar Spine	1.0	6.6	0.8	5.0	0.0	4.0	0.2	4.8
Femoral Neck	-1.4	1.6	-1.0	1.4	-1.1	1.3	0.1	2.4
Femoral Trochanter	-1.9	3.9	-0.5	3.0	-0.6	2.5	1.3	4.0
Midshaft Radius	-1.5*	0.2*	-1.2*	0.1*	ND		ND	

[a]The endpoint value is the value at the study's last time point for all patients who had BMD measured at that time; otherwise the last postbaseline BMD value prior to the study's last time point is used.
[b]The duration of the studies was 3 years.
[c]The duration of the studies was 1.5 to 2 years.
*BMD of the midshaft radius was measured in a subset of centers in VERT MN (placebo, n = 222; 5 mg, n = 214) and VERT NA (placebo, n = 310; 5 mg, n = 306)
ND = analysis not done

Histology/Histomorphometry:
Bone biopsies from 110 postmenopausal women were obtained at endpoint. Patients had received daily ACTONEL (2.5 mg or 5 mg) or placebo for 2 to 3 years. Histologic evaluation (n = 103) showed no osteomalacia, impaired bone mineralization, or other adverse effects on bone in ACTONEL-treated women. These findings demonstrate that bone formed during ACTONEL administration is of normal quality. The histomorphometric parameter mineralizing surface, an index of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 23 patients treated with ACTONEL 5 mg and 21 treated with placebo. Mineralizing surface decreased moderately in ACTONEL-treated patients (median percent change: ACTONEL 5 mg, -74%; placebo, -21%), consistent with the known effects of treatment on bone turnover.

Prevention of Osteoporosis in Postmenopausal Women:
The safety and effectiveness of ACTONEL 5 mg daily for the prevention of postmenopausal osteoporosis were demonstrated in a 2-year, double-blind, placebo-controlled study of 383 postmenopausal women (age range 42 to 63 years) within three years of menopause (ACTONEL 5 mg, N = 129). All patients in this study received supplemental calcium 1000 mg/day. Increases in BMD were observed as early as 3 months following initiation of ACTONEL treatment. ACTONEL 5 mg produced significant mean increases in BMD at the lumbar spine, femoral neck, and trochanter compared to placebo at the end of the study (Figure 2). ACTONEL 5 mg daily was also effective in patients with lower baseline lumbar spine BMD (more than 1 SD below the premenopausal mean) and in those with normal baseline lumbar spine BMD. Bone mineral density at the distal radius decreased in both ACTONEL and placebo-treated women following 1 year of treatment.

Figure 2
Change in BMD from Baseline
2-Year Prevention Study



The safety and effectiveness of ACTONEL 35 mg once-a-week for the prevention of postmenopausal osteoporosis were demonstrated in a 1-year, double-blind, placebo-controlled study of 278 patients (ACTONEL 35 mg, N = 136). All patients were supplemented with 1000 mg elemental calcium and 400 IU vitamin D per day. The primary efficacy measure was the percent change in lumbar spine BMD from baseline after 1 year of treatment using LOCF (last observation carried forward). ACTONEL 35 mg once-a-week resulted in a statistically significant mean difference from placebo in lumbar spine BMD of +2.9% (least square mean for risedronate +1.83%; placebo -1.05%). ACTONEL 35 mg once-a-week also showed a statistically significant mean difference from placebo in BMD at the total proximal femur of +1.5% (risedronate +1.01%; placebo -0.53%), femoral neck of +1.2% (risedronate +0.22%; placebo -1.00%), and trochanter of +1.8% (risedronate +1.07%; placebo -0.74%).

Combined Administration with Hormone Replacement Therapy:
The effects of combining ACTONEL 5 mg daily with conjugated estrogen 0.625 mg daily (n = 263) were compared to the effects of conjugated estrogen alone (n = 261) in a 1-year, randomized, double-blind study of women ages 37 to 82 years, who were on average 14 years postmenopausal. The BMD results for this study are presented in Table 3.

Table 3 Percent Change from Baseline in BMD After 1 Year of Treatment		
	Estrogen 0.625 mg n = 261	ACTONEL 5 mg + Estrogen 0.625 mg n = 263
Lumbar Spine	4.6 ± 0.20	5.2 ± 0.23
Femoral Neck	1.8 ± 0.25	2.7 ± 0.25
Femoral Trochanter	3.2 ± 0.28	3.7 ± 0.25
Midshaft Radius	0.4 ± 0.14	0.7 ± 0.17
Distal Radius	1.7 ± 0.24	1.6 ± 0.28
Values shown are mean (± SEM) percent change from baseline.		

Histology/Histomorphometry:
Bone biopsies from 53 postmenopausal women were obtained at endpoint. Patients had received ACTONEL 5 mg plus estrogen or estrogen alone once daily for 1 year. Histologic evaluation (n = 47) demonstrated that the bone of patients treated with ACTONEL plus estrogen was of normal lamellar structure and normal mineralization. The histomorphometric parameter mineralizing surface, a measure of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 12 patients treated with ACTONEL plus estrogen and 12 treated with estrogen alone. Mineralizing surface decreased in both treatment groups (median percent change: ACTONEL plus estrogen, -79%; estrogen alone, -50%), consistent with the known effects of these agents on bone turnover.

ANIMAL PHARMACOLOGY AND/OR TOXICOLOGY

ACTONEL

Risedronate demonstrated potent anti-osteoclast, antiresorptive activity in ovariectomized rats and minipigs. Bone mass and biomechanical strength were increased dose-dependently at oral doses up to 4 and 25 times the human recommended oral dose of 35 mg/week based on surface area, (mg/m^2) for rats and minipigs, respectively. Risedronate treatment maintained the positive correlation between BMD and bone strength and did not have a negative effect on bone structure or mineralization. In intact dogs, risedronate induced positive bone balance at the level of the bone remodeling unit at oral doses ranging from 0.35 to 1.4 times the human 35 mg/week dose based on surface area (mg/m^2).

In dogs treated with an oral dose of 1 mg/kg/day (approximately 5 times the human 35 mg/week dose based on surface area, mg/m^2), risedronate caused a delay in fracture healing of the radius. The observed delay in fracture healing is similar to other bisphosphonates. This effect did not occur at a dose of 0.1 mg/kg/day (approximately 0.5 times the human 35 mg/week dose based on surface area, mg/m^2).

The Schenk rat assay, based on histologic examination of the epiphyses of growing rats after drug treatment, demonstrated that risedronate did not interfere with bone mineralization even at the highest dose tested (5 mg/kg/day, subcutaneously), which was approximately 3500 times the lowest antiresorptive dose (1.5 mcg/kg/day in this model) and approximately 8 times the human

35 mg/week dose based on surface area (mg/m^2). This indicates that ACTONEL administered at the therapeutic dose is unlikely to induce osteomalacia.

Calcium
Published studies have demonstrated that changes in the dietary intake of calcium affect bone growth and skeletal development in animals, as well as bone loss in animal models of estrogen-depletion/ovariectomy and aging.

INDICATIONS AND USAGE
Postmenopausal Osteoporosis:
ACTONEL with CALCIUM is indicated for the treatment and prevention of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, ACTONEL reduces the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures (see **CLINICAL STUDIES**).

Limitations of Use:
The optimal duration of use has not been determined. The safety and effectiveness of ACTONEL with CALCIUM for the treatment of osteoporosis are based on clinical data of three years duration. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low-risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

CONTRAINDICATIONS
ACTONEL
- Hypocalcemia (see **PRECAUTIONS, General**)
- Known hypersensitivity to any component of this product
- Inability to stand or sit upright for at least 30 minutes

Calcium
- Hypercalcemia from any cause including, but not limited to, hyperparathyroidism, hypercalcemia of malignancy, or sarcoidosis.
- Known hypersensitivity to any component of the product.

WARNINGS
ACTONEL
Bisphosphonates may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see **PRECAUTIONS**).

Calcium
See **PRECAUTIONS**

PRECAUTIONS
General:
ACTONEL
Hypocalcemia and Mineral Metabolism:

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ACTONEL therapy. Adequate intake of calcium and vitamin D is important in all patients. ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min).

Upper Gastointestinal Adverse Reactions:

ACTONEL, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when ACTONEL is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers) [see **Adverse Reactions**].

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. In some cases, these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue ACTONEL and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates and/or who fail to swallow it with the recommended full glass (6 to 8 ounces) of water, and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient [see **Dosage and Administration**]. In patients who cannot comply with dosing instructions due to mental disability, therapy with ACTONEL should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

Osteonecrosis of the Jaw:

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including ACTONEL. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (for example, tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (for example, chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders (for example, periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). The risk of ONJ may increase with duration of exposure to bisphosphonates.

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgement of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment.

Musculoskeletal Pain:
In postmarketing experience, there have been infrequent reports of severe and occasionally incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates (see **ADVERSE REACTIONS**). The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping medication. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures:
Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are traverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (for example, prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Calcium

ACTONEL with CALCIUM should not be used to treat hypocalcemia. Total daily intake of calcium above 1500 mg has not demonstrated additional bone benefits while daily intake above 2000 mg has been associated with increased risk of adverse effects, including hypercalcemia and kidney stones.

Administration of calcium has been associated with a slight increase in the risk of kidney stones.

In patients with a history of kidney stones or hypercalciuria, metabolic assessment to seek treatable causes of these conditions is warranted. If administration of calcium tablets should be needed in these patients, urinary calcium excretion and other appropriate testing should be monitored periodically.

Patients with achlorhydria may have decreased absorption of calcium. Taking calcium with food enhances absorption.

Concomitant use of calcium-containing antacids should be monitored to avoid excessive intake of calcium.

Information for Patients:

ACTONEL

The patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to instructions. Specifically, ACTONEL should be taken at least 30 minutes before the first food or drink of the day other than water.

To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, patients should take ACTONEL while in an upright position (sitting or standing) with a full glass of plain water (6 to 8 ounces). Patients should not lie down for 30 minutes after taking the medication (see **PRECAUTIONS, General**). Patients should not chew or suck on the tablet because of a potential for oropharyngeal irritation.

Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or severe persistent or worsening heartburn) they should consult their physician before continuing ACTONEL.

Patients should be instructed that if they miss a dose of ACTONEL 35 mg once-a-week, they should take 1 tablet on the morning after they remember and return to taking 1 tablet once-a-week, as originally scheduled on their chosen day. Patients should not take 2 tablets on the same day.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see **PRECAUTIONS, General**). Calcium supplements or calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of ACTONEL and should be taken at a different time of the day, as with food.

Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as excessive cigarette smoking, and/or alcohol consumption, if these factors exist.

Physicians should instruct their patients to read the Patient Information before starting therapy with ACTONEL 35 mg and to re-read it each time the prescription is renewed.

Patients should be reminded to give all of their healthcare providers an accurate medication history. Instruct patients to tell all of their healthcare providers that they are taking ACTONEL. Patients should be instructed that any time they have a medical problem they think may be from ACTONEL, they should talk to their doctor.

Calcium

Calcium should be used as an adjunct to osteoporosis therapies.

The patient should be informed to take the calcium tablets with food to facilitate calcium absorption.

Drug Interactions:

ACTONEL

No specific drug-drug interaction studies were performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (Cytochrome P450).

Calcium Supplements/Antacids:

Co-administration of ACTONEL and calcium, antacids, or oral medications containing divalent cations will interfere with the absorption of ACTONEL.

Hormone Replacement Therapy:

One study of about 500 early postmenopausal women has been conducted to date in which treatment with ACTONEL (5 mg/day) plus estrogen replacement therapy was compared to estrogen replacement therapy alone. Exposure to study drugs was approximately 12 to 18 months and the primary endpoint was change in BMD. If considered appropriate, ACTONEL may be used concomitantly with hormone replacement therapy.

Aspirin/Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):

Of over 5700 patients enrolled in the ACTONEL Phase 3 osteoporosis studies, aspirin use was reported by 31% of patients, 24% of whom were regular users (3 or more days per week). Forty-eight percent of patients reported NSAID use, 21% of whom were regular users. Among regular aspirin or NSAID users, the incidence of upper gastrointestinal adverse experiences in ACTONEL-treated patients (24.5%) was similar to that in placebo-treated patients (24.8%).

H_2 Blockers and Proton Pump Inhibitors (PPIs):

Of over 5700 patients enrolled in the ACTONEL Phase 3 osteoporosis studies, 21% used H_2 blockers and/or PPIs. Among these patients, the incidence of upper gastrointestinal adverse experiences in the ACTONEL-treated patients was similar to that in placebo-treated patients.

Calcium

Bisphosphonates:

Oral bisphosphonates (such as risedronate, alendronate, etidronate, ibandronate): Decreased absorption of the bisphosphonate may occur when the bisphosphonate and calcium are taken together.

Thyroid hormones:

Levothyroxine: Concomitant intake of levothyroxine and calcium carbonate was found to reduce levothyroxine absorption and increase serum thyrotropin levels.

Fluoroquinolones:
Fluoroquinolones (such as ciprofloxacin, moxifloxacin, and ofloxacin): Concomitant administration of a fluoroquinolone and calcium carbonate may decrease the absorption of the fluoroquinolone.

Systemic glucocorticoids:
Calcium absorption is reduced when calcium carbonate is taken concomitantly with systemic glucocorticoids.

Tetracyclines:
Tetracyclines (such as doxycycline, minocycline, tetracycline): Concomitant administration of a tetracycline and calcium carbonate may decrease the absorption of the tetracycline.

Thiazide diuretics:
Reduced urinary excretion of calcium has been reported during concomitant use of calcium carbonate and thiazide diuretics.

Vitamin D:
Vitamin D and vitamin D analogues (such as calcitriol, doxercalciferol, and paricalcitol): Absorption of calcium may be increased when calcium carbonate is given concomitantly with vitamin D analogues.

Iron:
Calcium may interfere with the absorption of iron. Patients being treated for iron deficiency should take iron and calcium at different times of the day.

Drug/Laboratory Test Interactions:
ACTONEL
Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ACTONEL have not been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis:
In a 104-week carcinogenicity study, rats were administered daily oral doses of risedronate up to 24 mg/kg/day (approximately 50 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). There were no significant drug-induced tumor findings in male or female rats. The high dose male group of 24 mg/kg/day was terminated early in the study (Week 93) due to excessive toxicity, and data from this group were not included in the statistical evaluation of the study results. In an 80-week carcinogenicity study, mice were administered daily oral doses up to 32 mg/kg/day (approximately 30 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). There were no significant drug-induced tumor findings in male or female mice.

Mutagenesis:
Risedronate did not exhibit genetic toxicity in the following assays: *In vitro* bacterial mutagenesis in *Salmonella* and *E. coli* (Ames assay), mammalian cell mutagenesis in

CHO/HGPRT assay, unscheduled DNA synthesis in rat hepatocytes and an assessment of chromosomal aberrations *in vivo* in rat bone marrow.

Impairment of Fertility:
In female rats, ovulation was inhibited at an oral dose of risedronate of 16 mg/kg/day (approximately 30 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). Decreased implantation was noted in female rats treated with doses ≥7 mg/kg/day (14 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). In male rats, testicular and epididymal atrophy and inflammation were noted at 40 mg/kg/day (80 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). Testicular atrophy was also noted in male rats after 13 weeks of treatment at oral doses of 16 mg/kg/day (approximately 30 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). There was moderate-to-severe spermatid maturation block after 13 weeks in male dogs at an oral dose of 8 mg/kg/day (approximately 50 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2).

Pregnancy:
Pregnancy Category C: Survival of neonates was decreased in rats treated during gestation with oral doses of risedronate greater than or equal to 16 mg/kg/day (approximately 30 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). Body weight was decreased in neonates from dams treated with 80 mg/kg (approximately 160 times the 35 mg/week human dose based on surface area, mg/m^2). In rats treated during gestation, the number of fetuses exhibiting incomplete ossification of sternebrae or skull was statistically significantly increased at 7.1 mg/kg/day (approximately 14 times the 35 mg/week human dose based on surface area, mg/m^2). Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses greater than or equal to 16 mg/kg/day (approximately 30 times the 35 mg/week human dose based on surface area, mg/m^2). A low incidence of cleft palate was observed in fetuses from female rats treated with oral doses greater than or equal to 3.2 mg/kg/day (approximately 20 times the 35 mg/week human dose based on surface area, mg/m^2). The relevance of this finding to human use of ACTONEL is unclear. No significant fetal ossification effects were seen in rabbits treated with oral doses up to 10 mg/kg/day during gestation (40 times the 35 mg/week human dose based on surface area, mg/m^2). However, in rabbits treated with 10 mg/kg/day, 1 of 14 litters were aborted and 1 of 14 litters were delivered prematurely.

Similar to other bisphosphonates, treatment during mating and gestation with doses as low as 3.2 mg/kg/day (approximately 20 times the 35 mg/week human dose based on surface area, mg/m^2) has resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over periods of weeks to years. The amount of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as

time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been studied.

There are no adequate and well-controlled studies of ACTONEL in pregnant women. ACTONEL should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Women:
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. Because many drugs are excreted in human milk and because of 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.

Pediatric Use:
ACTONEL
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:
ACTONEL
Of the patients receiving ACTONEL in postmenopausal osteoporosis studies (see **CLINICAL STUDIES**), 47% were between 65 and 75 years of age, and 17% were over 75. No overall differences in efficacy or safety were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

Calcium
There are no published data that specifically compare the efficacy and safety between postmenopausal women above and below the age of 65 years.

Use in Men:
ACTONEL
The safety and effectiveness in men for the treatment of primary osteoporosis have not been established.

ADVERSE REACTIONS
ACTONEL
Osteoporosis:
ACTONEL has been studied in over 5700 patients enrolled in the Phase 3 glucocorticoid-induced osteoporosis clinical trials and in postmenopausal osteoporosis trials of up to 3-years duration. The overall adverse event profile of ACTONEL 5 mg in these studies was similar to that of placebo. Most adverse events were either mild or moderate 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 5 mg 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 5 mg groups, respectively. Table 4 lists adverse events from the Phase 3 osteoporosis trials reported in

greater than or equal to 2% of patients and in more ACTONEL-treated patients than placebo-treated patients. Adverse events are shown without attribution of causality.

Table 4
Adverse Events Occurring at a Frequency greater than or equal to 2% and in More ACTONEL-Treated Patients than Placebo-Treated Patients
Combined Phase 3 Osteoporosis Trials

Body System	Placebo % (N = 1914)	ACTONEL 5 mg % (N = 1916)
Body as a Whole		
Infection	29.7	29.9
Back Pain	23.6	26.1
Pain	13.1	13.6
Abdominal Pain	9.4	11.6
Neck Pain	4.5	5.3
Asthenia	4.3	5.1
Chest Pain	4.9	5.0
Neoplasm	3.0	3.3
Hernia	2.5	2.9
Cardiovascular		
Hypertension	9.0	10.0
Cardiovascular Disorder	1.7	2.5
Angina Pectoris	2.4	2.5
Digestive		
Nausea	10.7	10.9
Diarrhea	9.6	10.6
Flatulence	4.2	4.6
Gastritis	2.3	2.5
Gastrointestinal Disorder	2.1	2.3
Rectal Disorder	1.9	2.2
Tooth Disorder	2.0	2.1
Hemic and Lymphatic		
Ecchymosis	4.0	4.3
Anemia	1.9	2.4
Musculoskeletal		
Arthralgia	21.1	23.7
Joint Disorder	5.4	6.8
Myalgia	6.3	6.6
Bone Pain	4.3	4.6
Bone Disorder	3.2	4.0
Leg Cramps	2.6	3.5
Bursitis	2.9	3.0
Tendon Disorder	2.5	3.0
Nervous		
Depression	6.2	6.8
Dizziness	5.4	6.4
Insomnia	4.5	4.7
Anxiety	3.0	4.3
Neuralgia	3.5	3.8
Vertigo	3.2	3.3
Hypertonia	2.1	2.2

Table 4 Adverse Events Occurring at a Frequency greater than or equal to 2% and in More ACTONEL-Treated Patients than Placebo-Treated Patients Combined Phase 3 Osteoporosis Trials		
Body System	Placebo % (N = 1914)	ACTONEL 5 mg % (N = 1916)
Paresthesia	1.8	2.1
Respiratory		
Pharyngitis	5.0	5.8
Rhinitis	5.0	5.7
Dyspnea	3.2	3.8
Pneumonia	2.6	3.1
Skin and Appendages		
Rash	7.2	7.7
Pruritus	2.2	3.0
Skin Carcinoma	1.8	2.0
Special Senses		
Cataract	5.4	5.9
Conjunctivitis	2.8	3.1
Otitis Media	2.4	2.5
Urogenital		
Urinary Tract Infection	9.7	10.9
Cystitis	3.5	4.1

Duodenitis and glossitis have been reported uncommonly (0.1% to 1%). There have been rare reports (less than 0.1%) of abnormal liver function tests.

Laboratory Test Findings:

Asymptomatic and small decreases were observed in serum calcium and phosphorus levels. Overall, mean decreases of 0.8% in serum calcium and of 2.7% in phosphorus were observed at 6 months in patients receiving ACTONEL. Throughout the Phase 3 studies, serum calcium levels below 8 mg/dL were observed in 18 patients, 9 (0.5%) in each treatment arm (ACTONEL and placebo). Serum phosphorus levels below 2 mg/dL were observed in 14 patients, 11 (0.6%) treated with ACTONEL and 3 (0.2%) treated with placebo.

Endoscopic Findings:

ACTONEL clinical studies enrolled over 5700 patients, many 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 (14.5%) placebo; 75 (11.9%) ACTONEL]. Across treatment groups, the percentage of patients with normal esophageal, gastric, and duodenal mucosa on endoscopy was similar (20% placebo; 21% ACTONEL). The number of patients who withdrew from the studies due to the event prompting endoscopy was similar across treatment groups. Positive findings on endoscopy were also generally comparable across treatment groups. There was a higher number of reports of mild duodenitis in the ACTONEL group, however there were more duodenal ulcers in the placebo group. Clinically important findings (perforations, ulcers, or bleeding) among this symptomatic population were similar between groups (51% placebo; 39% ACTONEL).

Once-a-week Dosing:

In a 1-year, double-blind, multicenter study comparing ACTONEL 5 mg daily and ACTONEL 35 mg once-a-week in postmenopausal women, the overall safety and tolerability profiles of the 2 oral dosing regimens were similar. Table 5 lists the adverse events in greater than or equal to 2% of patients from this trial. Events are shown without attribution of causality.

Table 5
Adverse Events Occurring in greater than or equal to 2% of Patients of Either Treatment Group in the Daily vs. Weekly Osteoporosis Treatment Study in Postmenopausal Women

Body System	5 mg Daily ACTONEL % (N = 480)	35 mg Weekly 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
Chest Pain	2.3	2.7
Allergic Reaction	1.9	2.5
Neoplasm	0.8	2.1
Neck Pain	2.7	1.2
Cardiovascular System		
Hypertension	5.8	4.9
Syncope	0.6	2.1
Vasodilatation	2.3	1.4
Digestive System		
Constipation	12.5	12.2
Dyspepsia	6.9	7.6
Nausea	8.5	6.2
Diarrhea	6.3	4.9
Gastroenteritis	3.8	3.5
Flatulence	3.3	3.1
Colitis	0.8	2.5
Gastrointestinal Disorder	1.9	2.5
Vomiting	1.9	2.5
Dry Mouth	2.5	1.4

Table 5
Adverse Events Occurring in greater than or equal to 2% of Patients of Either Treatment Group in the Daily vs. Weekly Osteoporosis Treatment Study in Postmenopausal Women

Body System	5 mg Daily ACTONEL % (N = 480)	35 mg Weekly ACTONEL % (N = 485)
Metabolic and Nutritional Disorders		
Peripheral Edema	4.2	1.6
Musculoskeletal System		
Arthralgia	11.5	14.2
Traumatic Bone Fracture	5.0	6.4
Myalgia	4.6	6.2
Arthritis	4.8	4.1
Bursitis	1.3	2.5
Bone Pain	2.9	1.4
Nervous System		
Dizziness	5.8	4.9
Anxiety	0.6	2.7
Depression	2.3	2.3
Vertigo	2.1	1.6
Respiratory System		
Bronchitis	2.3	4.9
Sinusitis	4.6	4.5
Pharyngitis	4.6	2.9
Cough Increased	3.1	2.5
Pneumonia	0.8	2.5
Rhinitis	2.3	2.1
Skin and Appendages		
Rash	3.1	4.1
Pruritus	1.9	2.3
Special Senses		
Cataract	2.9	1.9
Urogenital System		
Urinary Tract Infection	2.9	5.2

Osteoporosis Prevention:

There were no deaths in a 1-year, double-blind, placebo-controlled study of ACTONEL 35 mg once-a-week for prevention of bone loss in 278 postmenopausal women without osteoporosis. More treated subjects on risedronate experienced arthralgia (risedronate 13.9%; placebo 7.8%), myalgia (risedronate 5.1%; placebo 2.1%), and nausea (risedronate 7.3%; placebo 4.3%) than subjects on placebo.

Post-marketing Experience:

Hypersensitivity Reactions: Hypersensitivity and skin reactions have been reported, including angioedema, generalized rash, bullous skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal: bone, joint, or muscle pain, occasionally described as severe or incapacitating (see **PRECAUTIONS**, Musculoskeletal Pain).

Pulmonary: Asthma exacerbations

Reactions of eye inflammation including iritis and uveitis have been reported.
Osteonecrosis of the jaw has been reported (see **PRECAUTIONS**, General).

Calcium

Calcium carbonate may cause gastrointestinal adverse effects such as constipation, flatulence, nausea, abdominal pain, and bloating. Administration of calcium may increase the risk of kidney stones, particularly in patients with a history of this condition (see **PRECAUTIONS**).

OVERDOSAGE

ACTONEL

Decreases in serum calcium and phosphorus following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients. Milk or antacids containing calcium should be given to bind ACTONEL and reduce absorption of the drug.

In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug. Standard procedures that are effective for treating hypocalcemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.

Lethality after single oral doses was seen in female rats at 903 mg/kg and male rats at 1703 mg/kg. The minimum lethal dose in mice and rabbits was 4000 mg/kg and 1000 mg/kg. These values represent greater than 1000 times the 35 mg/week human dose based on surface area (mg/m^2).

Calcium

Because of its limited intestinal absorption, overdosage with calcium carbonate is unlikely. However, prolonged use of very high doses can lead to hypercalcemia. Clinical manifestations of hypercalcemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias.

Treatment: Calcium should be discontinued. Other therapies that may be contributing to the condition, such as thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides should also be discontinued. Gastric emptying of any residual calcium should be considered. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics,

bisphosphonates, calcitonin and corticosteroids should also be considered. Serum electrolytes, renal function and vital signs must be monitored.

DOSAGE AND ADMINISTRATION

Treatment and Prevention of Postmenopausal Osteoporosis (see INDICATIONS AND USAGE):

One 35 mg ACTONEL tablet orally, taken once-a-week (Day 1 of the 7-day treatment cycle):

ACTONEL should be taken at least 30 minutes before the first food or drink of the day other than water. ACTONEL should not be taken at the same time as other medications, including calcium.

To facilitate delivery to the stomach, ACTONEL should be swallowed while the patient is in an upright position and with a full glass of plain water (6 to 8 ounces). Patients should not lie down for 30 minutes after taking the medication (see **PRECAUTIONS, General**). ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min). No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 30 mL/min or in the elderly.

One 1250 mg calcium carbonate tablet (500 mg elemental calcium) orally, taken with food daily on each of the remaining six days (Days 2 through 7 of the 7-day treatment cycle):

The recommended total (diet and otherwise) daily calcium intake in postmenopausal women is 1200 mg of elemental calcium. If patients need calcium in excess of that provided by ACTONEL with CALCIUM, this should be taken with food at a separate time of day.

Patients should receive additional vitamin D if dietary intake is inadequate (see **PRECAUTIONS, General**). Co-administration of calcium tablets and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of ACTONEL (see **Drug Interactions**).

ACTONEL with CALCIUM is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min). No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 30 mL/min or in the elderly.

HOW SUPPLIED

ACTONEL ® with CALCIUM is supplied in blister packages containing a 28-day course of therapy.

Four ACTONEL Tablets:
35 mg film-coated, oval, orange tablets with RSN on 1 face and 35 mg on the other

Twenty-four Calcium Carbonate Tablets, USP:

1250 mg calcium carbonate (equivalent to 500 mg elemental calcium) film-coated, oval, light blue tablets with NE 2 engraved on both faces

NDC 0430-0475-14
Store at 20° to 25° C (68° to 77° F); excursions permitted between 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature].

ACTONEL manufactured by:
Warner Chilcott Company, LLC
Manati, Puerto Rico 00674
or
Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Calcium manufactured by:
Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Marketed by:
Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-8813

Medication Guide

ACTONEL ® (AK-toh-nel) with CALCIUM
(*risedronate sodium and calcium carbonate*)
Tablets

Read the Medication Guide that comes with ACTONEL ® with CALCIUM before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about ACTONEL with CALCIUM, there may be new information about it.

What is the most important information I should know about ACTONEL with CALCIUM?

ACTONEL with CALCIUM can cause serious side effects including:

1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Severe jaw bone problems (osteonecrosis)
4. Bone, joint, or muscle pain
5. Unusual thigh bone fractures

1. Esophagus problems.
Some people who take ACTONEL with CALCIUM may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

- **It is important that you take ACTONEL with CALCIUM exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take ACTONEL with CALCIUM?")**
- **Stop taking ACTONEL with CALCIUM and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.**

2. Low calcium levels in your blood (hypocalcemia).

ACTONEL with CALCIUM may lower the calcium levels in your blood. If you have low blood calcium before you start taking ACTONEL with CALCIUM, it may get worse during treatment. Your low blood calcium must be treated before you take ACTONEL with CALCIUM. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take ACTONEL with CALCIUM. Take calcium and vitamin D as your doctor tells you to.

3. Severe jaw bone problems (osteonecrosis).

Severe jaw bone problems may happen when you take ACTONEL with CALCIUM. Your doctor should examine your mouth before you start ACTONEL with CALCIUM. Your doctor may tell you to see your dentist before you start ACTONEL with CALCIUM. It is important for you to practice good mouth care during treatment with ACTONEL with CALCIUM.

4. Bone, joint, or muscle pain.

Some people who take ACTONEL with CALCIUM develop severe bone, joint, or muscle pain.

5. Unusual thigh bone fractures.

Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is ACTONEL with CALCIUM?

ACTONEL with CALCIUM is a prescription medicine used to:

- Treat or prevent osteoporosis in women after menopause. ACTONEL with CALCIUM helps increase bone mass and helps reduce the chance of having a spinal or non-spinal fracture (break).

It is not known how long ACTONEL with CALCIUM works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if ACTONEL with CALCIUM is still right for you.

ACTONEL with CALCIUM is not for use in children.

Who should not take ACTONEL with CALCIUM?

Do not take ACTONEL with CALCIUM if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Have low levels of calcium in your blood
- Are allergic to ACTONEL or any of its ingredients. A list of ingredients is at the end of this leaflet.
- Cannot stand or sit upright for at least 30 minutes

Do not take Calcium if you:

- have high levels of calcium in your blood
- are allergic to ACTONEL with CALCIUM or any of its ingredients. A list of ingredients is at the end of this leaflet

What should I tell my doctor before taking ACTONEL with CALCIUM?

Before you start ACTONEL with CALCIUM, be sure to talk to your doctor if you:

- Have problems with swallowing
- Have stomach or digestive problems
- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant, or plan to become pregnant. It is not known if ACTONEL can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if ACTONEL passes into your milk and may harm your baby. You and your doctor should decide if you will take ACTONEL with CALCIUM or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Certain medicines may affect how ACTONEL with CALCIUM works.

Especially tell your doctor if you take:

- antacids
- aspirin
- Nonsteroidal Anti-Inflammatory (NSAID) medicines
- thyroid medicines
- antibiotics

- iron
- glucocorticoid medicines (steroid hormones)
- a diuretic (water pill)

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take ACTONEL with CALCIUM?

- Take ACTONEL with CALCIUM exactly as your doctor tells you.
- **ACTONEL with CALCIUM works only if taken on an empty stomach.**
- Take 1 ACTONEL with CALCIUM tablet 1 time each week, **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take ACTONEL with CALCIUM while you are sitting or standing.
- **Do not chew or suck on a tablet of ACTONEL with CALCIUM**.
- Swallow ACTONEL with CALCIUM tablet with a full glass (6 to 8 ounces) of plain water only.
- Do **not** take ACTONEL with CALCIUM with mineral water, coffee, tea, soda, or juice.

After swallowing ACTONEL with CALCIUM tablet, wait at least 30 minutes:

- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take your first food or drink except for plain water.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take ACTONEL with CALCIUM and after you eat your first food of the day.

Calcium:

- Take 1 calcium tablet daily with food for the following 6 days of the week.

If you miss a dose of ACTONEL with CALCIUM, **do not** take it later in the day. Take your missed dose the next morning and then return to your normal schedule. Do not take 2 doses at the same time.

If you miss more than 2 doses of ACTONEL with CALCIUM in a month, call your doctor for instructions.

If you take too much ACTONEL with CALCIUM, call your doctor. Do not try to vomit. Do not lie down.

What are the possible side effects of ACTONEL with CALCIUM?

ACTONEL with CALCIUM may cause serious side effects**:**

- See **"What is the most important information I should know about ACTONEL with CALCIUM?"**

The most common side effects of ACTONEL with CALCIUM are:

- pain, including back and joint pain
- stomach area (abdominal) pain
- heartburn

You may get allergic reactions, such as hives, swelling of your face, lips, tongue, or throat.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ACTONEL with CALCIUM. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ACTONEL with CALCIUM?

- Store ACTONEL with CALCIUM at room temperature, 68° F to 77° F (20° C to 25° C).

Keep ACTONEL with CALCIUM and all medicines out of the reach of children.

General information about the safe and effective use of ACTONEL with CALCIUM

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ACTONEL with CALCIUM for a condition for which it was

not prescribed. Do not give ACTONEL with CALCIUM to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ACTONEL with CALCIUM. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ACTONEL with CALCIUM that is written for health professionals.

For more information, go to www.wcrx.com or call 1-800-521-8813.

What are the ingredients in ACTONEL with CALCIUM?

ACTONEL:
Active ingredient: risedronate sodium

Inactive ingredients: crospovidone, ferric oxide red, ferric oxide yellow, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

Calcium:
Active Ingredient: calcium carbonate

Inactive ingredients: pregelatinized starch, sodium starch glycolate, FD&C Blue #2, magnesium stearate, polyethylene glycol 3350, hypromellose, Opaspray Light Blue, polysorbate 80.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ACTONEL manufactured by:
Warner Chilcott Company, LLC
Manati, Puerto Rico 00674
or
Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Calcium manufactured by:
Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Marketed by:
Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-8813

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To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-521-8813 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.