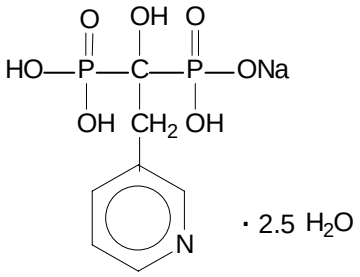
ACTONEL®
(risedronate sodium tablets)

DESCRIPTION

ACTONEL (risedronate sodium tablets) is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Each ACTONEL tablet for oral administration contains the equivalent of 5, 30, or 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.

Inactive Ingredients:

Crospovidone, ferric oxide red (35-mg tablets only), ferric oxide yellow (5 and 35-mg tablets only), hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

CLINICAL PHARMACOLOGY

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 (e.g., lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that ACTONEL treatment reduces bone turnover (activation frequency, i.e., 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} ~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.

Special Populations:

Pediatric:

Risedronate pharmacokinetics have not been studied in patients <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 (>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 <30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance ≥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 (<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.

Pharmacodynamics:
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 (<1%) and serum phosphate (<3%) and compensatory increases in serum PTH levels (<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%).

Glucocorticoid-Induced Osteoporosis:

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs in both males and females of all ages. The relative risk of a hip fracture in patients on >7.5 mg/day prednisone is more than doubled (RR = 2.27); the relative risk of vertebral fracture is increased 5-fold (RR = 5.18). Bone loss occurs most rapidly during the first 6 months of therapy with persistent but slowing bone loss for as long as glucocorticoid therapy continues. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. ACTONEL decreases bone resorption without directly inhibiting bone formation.

In two 1-year clinical trials in the treatment and prevention of glucocorticoid-induced osteoporosis, ACTONEL 5 mg decreased urinary collagen cross-linked N-telopeptide (a marker of bone resorption), and serum bone specific alkaline phosphatase (a marker of bone formation) by 50% to 55% and 25% to 30%, respectively, within 3 to 6 months after initiation of therapy.

Paget's Disease:

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disordered bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, 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, the most frequently used biochemical marker of disease activity, provides an objective measure of disease severity and response to therapy.

In pagetic patients treated with ACTONEL 30 mg/day for 2 months, bone turnover returned to normal in a majority of patients as evidenced by significant reductions in serum alkaline phosphatase (a marker of bone formation), and in urinary hydroxyproline/creatinine and deoxypyridinoline/creatinine (markers of bone resorption). Radiographic structural changes of bone lesions, especially improvement of a majority of lesions with an osteolytic front in weight-

bearing bones, were also observed after ACTONEL treatment. In addition, histomorphometric data provide further support that ACTONEL can lead to a more normal bone structure in these patients.

Radiographs taken at baseline and after 6 months from patients treated with ACTONEL 30 mg daily demonstrate that ACTONEL decreases the extent of osteolysis in both the appendicular and axial skeleton. Osteolytic lesions in the lower extremities improved or were unchanged in 15/16 (94%) of assessed patients; 9/16 (56%) patients showed clear improvement in osteolytic lesions. No evidence of new fractures was observed.

CLINICAL STUDIES

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.

The safety and efficacy of once weekly ACTONEL 35 mg in women without osteoporosis are currently being studied, but data are not yet available.

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 (i.e., 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

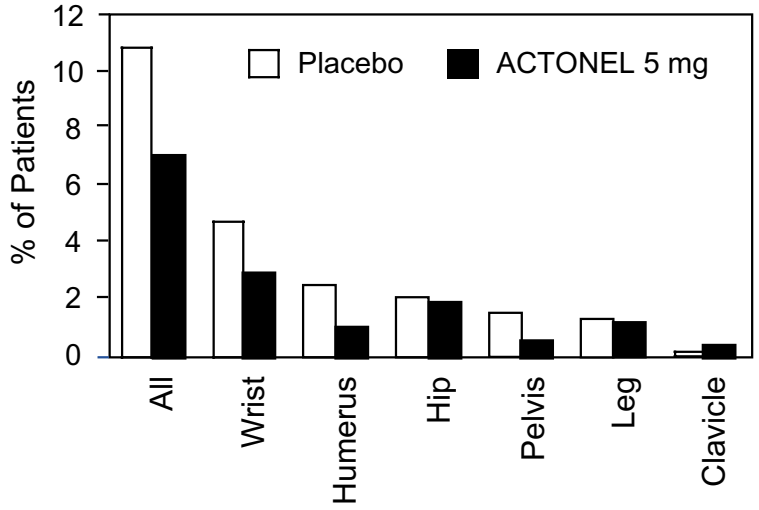
	Proportion of Patients with Fracture (%)[a]			
VERT NA	Placebo n = 678	ACTONEL 5 mg n = 696	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 - 1 Year	7.2	3.9	3.3	49
0 - 2 Years	12.8	8.0	4.8	42
0 - 3 Years	18.5	13.9	4.6	33
New				
0 - 1 Year	6.4	2.4	4.0	65
0 - 2 Years	11.7	5.8	5.9	55
0 - 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 - 1 Year	15.3	8.2	7.1	50
0 - 2 Years	28.3	13.9	14.4	56
0 - 3 Years	34.0	21.8	12.2	46
New				
0 - 1 Year	13.3	5.6	7.7	61
0 - 2 Years	24.7	11.6	13.1	59
0 - 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% vs. 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. Thus, overall ACTONEL reverses the loss of BMD, a central factor in the progression of osteoporosis. 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

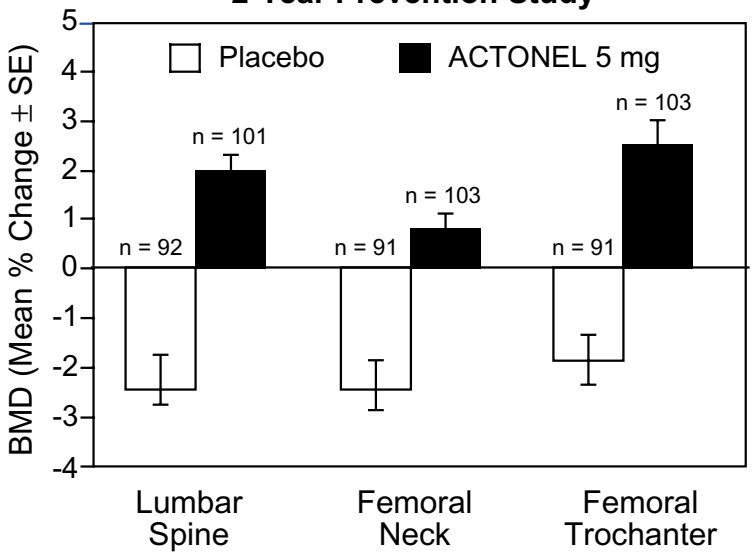
Histology/Histomorphometry:

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:

ACTONEL 5 mg daily prevented bone loss in a majority of postmenopausal women (age range 42 to 63 years) within 3 years of menopause in a 2-year, double-blind, placebo-controlled study in 383 patients (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



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.

Glucocorticoid-Induced Osteoporosis:

Bone Mineral Density:

Two 1-year, double-blind, placebo-controlled trials in patients who were taking ≥7.5 mg/day of prednisone or equivalent demonstrated that ACTONEL 5 mg once daily was effective in the prevention and treatment of glucocorticoid-induced osteoporosis in men and women who were either initiating or continuing glucocorticoid therapy.

The prevention study enrolled 228 patients (ACTONEL 5 mg, n = 76) (18 to 85 years of age), each of whom had initiated glucocorticoid therapy (mean daily dose of prednisone 21 mg) within the previous 3 months (mean duration of use prior to study 1.8 months) for rheumatic, skin, and pulmonary diseases. The mean lumbar spine BMD was normal at baseline (average T score 0.684). All patients in this study received supplemental calcium 500 mg/day. By the third month of treatment, and continuing through the year-long treatment, the placebo group experienced losses in BMD at the lumbar spine, femoral neck, and trochanter, while BMD was maintained or increased in the ACTONEL 5-mg group. At each skeletal site there were statistically significant differences between the ACTONEL 5-mg group and the placebo group at all timepoints (Months 3, 6, 9, and 12). The treatment differences increased with continued treatment. Although BMD increased at the distal radius in the ACTONEL 5-mg group compared to the placebo group, the difference was not statistically significant. The differences between placebo and ACTONEL 5 mg after 1 year were 3.8% at the lumbar spine, 4.1% at the femoral neck, and 4.6% at the trochanter, as shown in Figure 3. The results at these skeletal sites were similar to the overall results when the subgroups of men and postmenopausal women, but not premenopausal women, were analyzed separately. ACTONEL was effective at the lumbar spine, femoral neck, and trochanter regardless of age (<65 vs. ≥65), gender, prior and concomitant glucocorticoid dose, or baseline BMD. Positive treatment effects were also observed in patients taking glucocorticoids for a broad range of rheumatologic disorders, the most common of which were rheumatoid arthritis, temporal arteritis, and polymyalgia rheumatica.

The treatment study of similar design enrolled 290 patients (ACTONEL 5 mg, n = 100) (19 to 85 years of age) with continuing, long-term (≥6 months) use of glucocorticoids (mean duration of use prior to study 60 months; mean daily dose of prednisone 15 mg) for rheumatic, skin, and pulmonary diseases. The baseline mean lumbar spine BMD was low (1.63 SD below the young healthy population mean), with 28% of the patients more than 2.5 SD below the mean. All patients in this study received supplemental calcium 1000 mg/day and vitamin D 400 IU/day.

After 1 year of treatment, the BMD of the placebo group was within ±1% of baseline levels at the lumbar spine, femoral neck, and trochanter. ACTONEL 5 mg increased BMD at the lumbar spine (2.9%), femoral neck (1.8%), and trochanter (2.4%). The differences between ACTONEL and placebo were 2.7% at the lumbar spine, 1.9% at the femoral neck, and 1.6% at the trochanter as shown in Figure 4. The differences were statistically significant for the lumbar spine and femoral neck, but not at the femoral trochanter. ACTONEL was similarly effective on lumbar spine BMD regardless of age (<65 vs. ≥65), gender, or pre-study glucocorticoid dose. Positive treatment effects were also observed in patients taking glucocorticoids for a broad range of rheumatologic disorders, the most common of which were rheumatoid arthritis, temporal arteritis, and polymyalgia rheumatica.

Figure 3
Change in BMD from Baseline
Patients Recently Initiating
Glucocorticoid Therapy

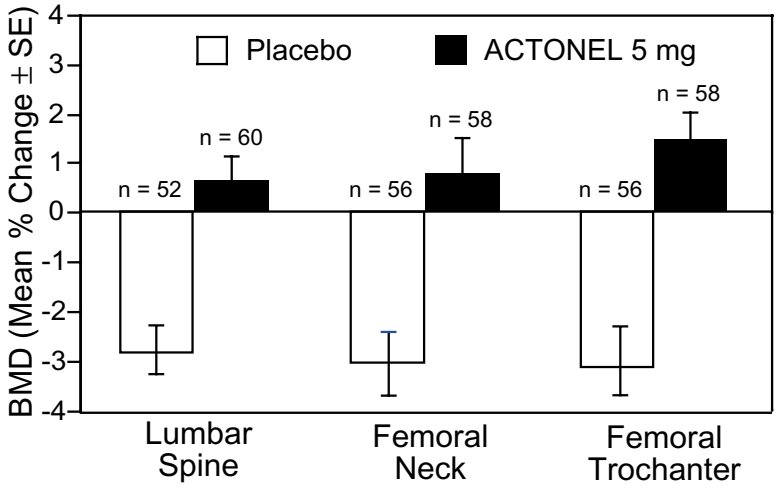
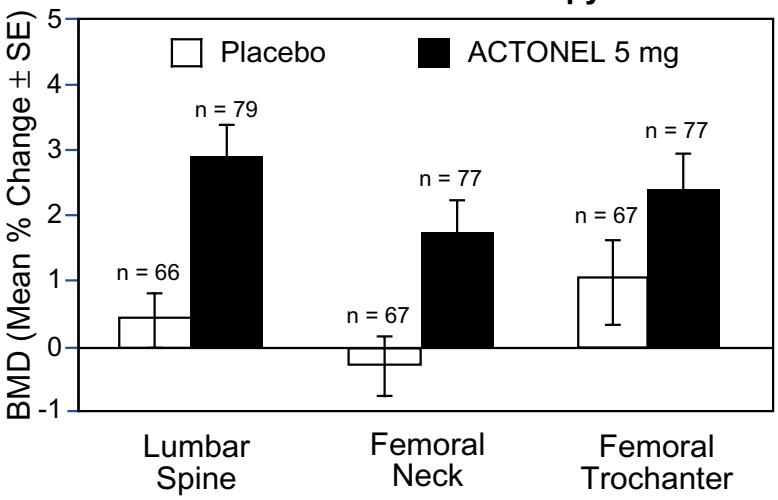


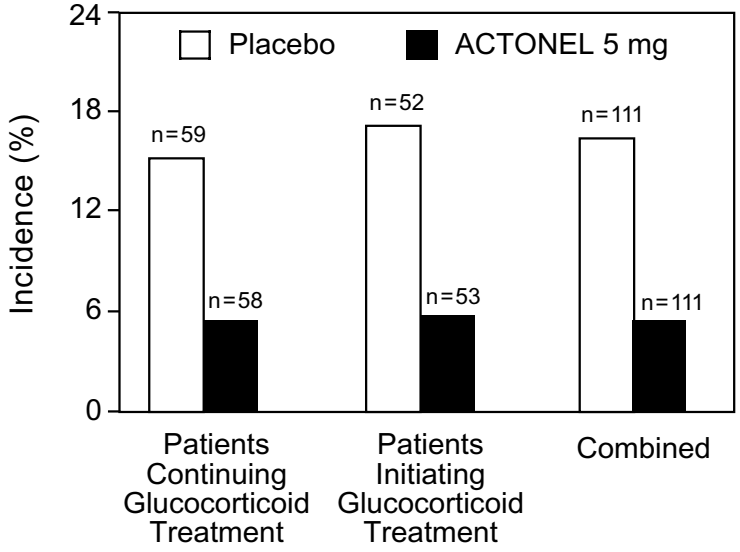
Figure 4
Change in BMD from Baseline
Patients on Long-Term
Glucocorticoid Therapy



Vertebral Fractures:

In the prevention study of patients initiating glucocorticoids, the incidence of vertebral fractures at 1 year was reduced from 17% in the placebo group to 6% in the ACTONEL group. In the treatment study of patients continuing glucocorticoids, the incidence of vertebral fractures was reduced from 15% in the placebo group to 5% in the ACTONEL group (Figure 5). The statistically significant reduction in vertebral fracture incidence in the analysis of the combined studies corresponded to an absolute risk reduction of 11% and a relative risk reduction of 70%. All vertebral fractures were diagnosed radiographically; some of these fractures also were associated with symptoms (i.e., clinical fractures).

Figure 5
Incidence of Vertebral Fractures in Patients Initiating or Continuing Glucocorticoid Therapy



Histology/Histomorphometry:
Bone biopsies from 40 patients on glucocorticoid therapy were obtained at endpoint. Patients had received daily ACTONEL (2.5 mg or 5 mg) or placebo for 1 year. Histologic evaluation (n = 33) showed that bone formed during treatment with ACTONEL was of normal lamellar structure and normal mineralization, with no bone or marrow abnormalities observed. The histomorphometric parameter mineralizing surface, a measure of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 10 patients treated with ACTONEL 5 mg. Mineralizing surface decreased 24% (median percent change) in these patients. Only a small number of placebo-treated patients had both baseline and post-treatment biopsy samples, precluding a meaningful quantitative assessment.

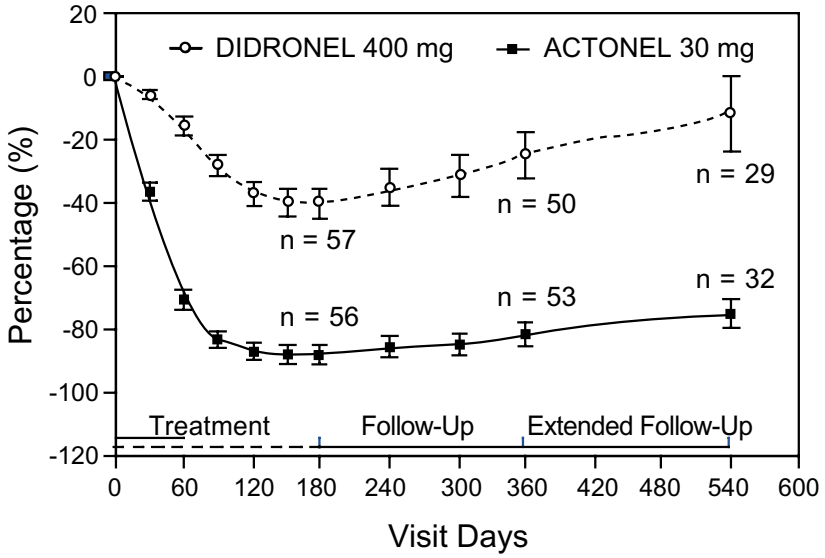
Treatment of Paget's Disease:

The efficacy of ACTONEL was demonstrated in 2 clinical studies involving 120 men and 65 women. In a double-blind, active-controlled study of patients with moderate-to-severe Paget's disease (serum alkaline phosphatase levels of at least 2 times the upper limit of normal), patients were treated with ACTONEL 30 mg daily for 2 months or Didronel® (etidronate disodium) 400 mg/day for 6 months. At Day 180, 77% (43/56) of ACTONEL-treated patients achieved normalization of serum alkaline phosphatase levels, compared to 10.5% (6/57) of patients treated with Didronel ($p<0.001$). At Day 540, 16 months after discontinuation of therapy, 53% (17/32) of ACTONEL-treated patients and 14% (4/29) of Didronel-treated patients with available data remained in biochemical remission.

During the first 180 days of the active-controlled study, 85% (51/60) of ACTONEL-treated patients demonstrated a ≥75% reduction from baseline in serum alkaline phosphatase excess (difference between measured level and midpoint of the normal range) with 2 months of treatment compared to 20% (12/60) in the Didronel-treated group with 6 months of treatment

($p<0.001$). Changes in serum alkaline phosphatase excess over time (shown in Figure 6) were significant following only 30 days of treatment, with a 36% reduction in serum alkaline phosphatase excess at that time compared to only a 6% reduction seen with Didronel treatment at the same time point ($p<0.01$).

Figure 6
Mean Percent Change from Baseline in Serum Alkaline Phosphatase Excess by Visit



Response to ACTONEL therapy was similar in patients with mild to very severe Paget's disease. Table 4 shows the mean percent reduction from baseline at Day 180 in excess serum alkaline phosphatase in patients with mild, moderate, or severe disease.

Table 4
Mean Percent Reduction from Baseline at Day 180 in Total Serum Alkaline Phosphatase Excess by Disease Severity

Subgroup: Baseline Disease Severity (AP)	ACTONEL 30 mg n	ACTONEL 30 mg Baseline Serum AP (U/L)*	ACTONEL 30 mg Mean % Reduction	DIDRONEL 400 mg n	DIDRONEL 400 mg Baseline Serum AP (U/L)*	DIDRONEL 400 mg Mean % Reduction
>2, <3x ULN	32	271.6 ± 5.3	-88.1	22	277.9 ± 7.45	-44.6
≥3, <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.

Response to ACTONEL therapy was similar between patients who had previously received anti-pagetic therapy and those who had not. In the active-controlled study, 4 patients previously non-responsive to 1 or more courses of anti-pagetic therapy (calcitonin, Didronel) responded to treatment with ACTONEL 30 mg daily (defined by at least a 30% change from baseline). Each of these patients achieved at least 90% reduction from baseline in serum alkaline phosphatase excess, with 3 patients achieving normalization of serum alkaline phosphatase levels.

Histomorphometry of the bone was studied in 14 patients with bone biopsies: 9 patients had biopsies from pagetic bone lesions and 5 patients from non-pagetic bone. Bone biopsy results in non-pagetic bone did not reveal osteomalacia, impairment of bone remodeling, or induction of a significant decline in bone turnover in patients treated with ACTONEL.

ANIMAL PHARMACOLOGY AND/OR TOXICOLOGY

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 5 mg 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 5-mg 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 5-mg 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 5-mg 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 5-mg dose based on surface area (mg/m^2). This indicates that ACTONEL administered at the therapeutic dose is unlikely to induce osteomalacia.

INDICATIONS AND USAGE

Postmenopausal Osteoporosis:

ACTONEL is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

Treatment of Osteoporosis:

In postmenopausal women with osteoporosis, ACTONEL increases BMD and reduces the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures (see **CLINICAL STUDIES**). Osteoporosis may be confirmed by the presence or history of osteoporotic fracture, or by the finding of low bone mass (for example, at least 2 SD below the premenopausal mean).

Prevention of Osteoporosis:

ACTONEL may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

Factors such as family history of osteoporosis, previous fracture, smoking, BMD (at least 1 SD below the premenopausal mean), high bone turnover, thin body frame, Caucasian or Asian race, and early menopause are associated with an increased risk of developing osteoporosis and fractures. The presence of these risk factors may be important when considering the use of ACTONEL for prevention of osteoporosis.

Glucocorticoid-Induced Osteoporosis:

ACTONEL is indicated for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoid treatment (daily dosage equivalent to 7.5 mg or greater of prednisone) for chronic diseases. Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

Paget's Disease:

ACTONEL is indicated for treatment of Paget's disease of bone (osteitis deformans). Treatment is indicated in patients with Paget's disease of bone (1) who have a level of serum alkaline phosphatase at least 2 times the upper limit of normal, or (2) who are symptomatic, or (3) who are at risk for future complications from their disease, to induce remission (normalization of serum alkaline phosphatase).

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General:

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, especially 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).

Bisphosphonates have been associated with gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience, but has not been found in most pre-approval clinical trials, including those conducted with ACTONEL. Patients should be advised that taking the medication according to the instructions is important to minimize the risk of these events. They should take ACTONEL with sufficient plain water (6 to 8 oz) to facilitate delivery to the stomach, and should not lie down for 30 minutes after taking the drug.

Glucocorticoid-Induced Osteoporosis:

The risk versus benefit of ACTONEL for the prevention and treatment of glucocorticoid-induced osteoporosis at daily doses of glucocorticoids <7.5 mg of prednisone or equivalent has not been established. Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

The efficacy of ACTONEL for this indication has been established in studies of 1-year duration. The efficacy of ACTONEL beyond 1 year has not been studied.

Information for Patients:

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 oz). 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 5 mg or 35 mg and to re-read it each time the prescription is renewed.

Drug Interactions:

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.

Drug/Laboratory Test Interactions:
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 up to 24 mg/kg/day (approximately 7.7 times the maximum recommended human daily dose of 30 mg 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 6.4 times the 30-mg/day 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. Risedronate was positive in a chromosomal aberration assay in CHO cells at highly cytotoxic concentrations (>675 mcg/mL, survival of 6% to 7%). When the assay was repeated at doses exhibiting appropriate cell survival (29%), there was no evidence of chromosomal damage.

Impairment of Fertility:
In female rats, ovulation was inhibited at an oral dose of 16 mg/kg/day (approximately 5.2 times the 30-mg/day human dose based on surface area, mg/m^2). Decreased implantation was noted in female rats treated with doses ≥7 mg/kg/day (approximately 2.3 times the 30-mg/day 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 (approximately 13 times the 30-mg/day 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 5.2 times the 30-mg/day 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 8 times the 30-mg/day human dose based on surface area, mg/m^2). These findings tended to increase in severity with increased dose and exposure time.

Pregnancy:
Pregnancy Category C: Survival of neonates was decreased in rats treated during gestation with oral doses ≥16 mg/kg/day (approximately 5.2 times the 30-mg/day human dose based on surface area, mg/m^2). Body weight was decreased in neonates from dams treated with 80 mg/kg (approximately 26 times the 30-mg/day 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 2.3 times the 30-mg/day human dose based on surface area, mg/m^2). Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses ≥16 mg/kg/day (approximately 5.2 times the 30-mg/day 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 ≥3.2 mg/kg/day (approximately 1 time the 30-mg/day 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 (approximately 6.7 times the 30-mg/day 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 1 time the 30-mg/day 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:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

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. The corresponding proportions were 26% and 11% in glucocorticoid-induced osteoporosis trials, and 40% and 26% in Paget's disease trials. 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.

Use in Men:

Safety and effectiveness have been demonstrated in clinical studies in men receiving ACTONEL both for Paget's disease and for treatment and prevention of glucocorticoid-induced osteoporosis. However, the safety and effectiveness in men for osteoporosis due to other causes have not been established.

ADVERSE REACTIONS

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 5 lists adverse events from the Phase 3 osteoporosis trials reported in ≥2% of patients and in more ACTONEL-treated patients than placebo-treated patients. Adverse events are shown without attribution of causality.

Table 5
Adverse Events Occurring at a Frequency ≥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
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

Table 5 Adverse Events Occurring at a Frequency ≥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)
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 (<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 6 lists the adverse events in ≥2% of patients from this trial. Events are shown without attribution of causality.

Table 6
Adverse Events Occurring in ≥ 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
Metabolic and Nutritional Disorders		

Table 6
Adverse Events Occurring in ≥ 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)
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

Paget's Disease:

ACTONEL has been studied in 392 patients with Paget's disease of bone. As in trials of ACTONEL for other indications, the adverse experiences reported in the Paget's disease trials have generally been mild or moderate, have not required discontinuation of treatment, and have not appeared to be related to patient age, gender, or race.

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

Table 7
Adverse Events Reported in ≥2% of ACTONEL-Treated Patients* in Phase 3 Paget's Disease Trials

Body System	30 mg/day x 2 months ACTONEL % (n = 61)	400 mg/day x 6 months DIDRONEL % (n = 61)
Body as a Whole		
Flu Syndrome	9.8	1.6
Chest Pain	6.6	3.3
Asthenia	4.9	0.0
Neoplasm	3.3	1.6
Gastrointestinal		
Diarrhea	19.7	14.8
Abdominal Pain	11.5	8.2
Nausea	9.8	9.8
Constipation	6.6	8.2
Belching	3.3	1.6
Colitis	3.3	3.3
Metabolic and Nutritional Disorders		
Peripheral Edema	8.2	6.6
Musculoskeletal		
Arthralgia	32.8	29.5
Bone Pain	4.9	4.9
Leg Cramps	3.3	3.3
Myasthenia	3.3	0.0
Nervous		
Headache	18.0	16.4
Dizziness	6.6	4.9
Respiratory		
Bronchitis	3.3	4.9
Sinusitis	4.9	1.6
Skin and Appendages		
Rash	11.5	8.2
Special Senses		
Amblyopia	3.3	3.3
Tinnitus	3.3	3.3
Dry Eye	3.3	0.0

*Considered to be possibly or probably causally related in at least one patient.

Three patients who received ACTONEL 30 mg/day experienced acute iritis in 1 supportive study. All 3 patients recovered from their events; however, in 1 of these patients, the event recurred during ACTONEL treatment and again during treatment with pamidronate. All patients were effectively treated with topical steroids.

Post-marketing Experience:
Very rare hypersensitivity and skin reactions, including angioedema, generalized rash and bullous skin reactions, some severe.

OVERDOSAGE

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 320 to 620 times the 30-mg human dose based on surface area (mg/m^2).

DOSAGE AND ADMINISTRATION

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, ACTONEL should be swallowed while the patient is in an upright position and with a full glass of plain water (6 to 8 oz). Patients should not lie down for 30 minutes after taking the medication (see **PRECAUTIONS, General**).

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see **PRECAUTIONS, General**). Calcium supplements and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of ACTONEL and should be taken at a different time of the day. ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min). No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min or in the elderly.

Treatment of Postmenopausal Osteoporosis (see INDICATIONS AND USAGE):

The recommended regimen is:

- one 5-mg tablet orally, taken daily
  or
- one 35-mg tablet orally, taken once a week

Prevention of Postmenopausal Osteoporosis (see INDICATIONS AND USAGE):

- The recommended regimen is one 5-mg tablet orally, taken daily
- Alternatively, one 35-mg tablet orally, taken once a week may be considered

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis (see INDICATIONS AND USAGE):

The recommended regimen is:

- one 5-mg tablet orally, taken daily

Paget's Disease (see INDICATIONS AND USAGE):

The recommended treatment regimen is 30 mg orally once daily for 2 months. Retreatment may be considered (following post-treatment observation of at least 2 months) if relapse occurs, or if treatment fails to normalize 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 1 course of retreatment.

HOW SUPPLIED

ACTONEL is available as follows:
5-mg film-coated, oval, yellow tablets with RSN on 1 face and 5 mg on the other.
NDC 0149-0471-01 bottle of 30

5-mg film-coated, oval, yellow tablets with RSN on 1 face and 5 mg on the other.
NDC 0149-0471-03 bottle of 2000

30-mg film-coated, oval, white tablets with RSN on 1 face and 30 mg on the other.
NDC 0149-0470-01 bottle of 30

35-mg film-coated, oval, orange tablets with RSN on 1 face and 35 mg on the other.
NDC 0149-0472-01 dose pack of 4

Store at controlled room temperature 20°-25°C (68°-77°F) [See USP].

Sold under U.S. patent No. 5,583,122; 6,096,342 and 6,165,513

Mfg. by: Procter & Gamble Pharmaceuticals, Inc.
Cincinnati, OH 45202, or
OSG Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

Dist. by: Procter & Gamble Pharmaceuticals, Inc., TM Owner
Cincinnati, OH 45202

Marketed with:
Aventis Pharmaceuticals Inc.
Kansas City, MO 64137

JULY 2004

Patient Information
ACTONEL® (AK-toh-nel) Tablets

ACTONEL (risedronate sodium tablets) 5 mg and ACTONEL (risedronate sodium tablets) 35 mg for Osteoporosis

Read this information carefully before you start to use your medicine. Read the information you get every time you get more medicine. There may be new information. This information does not take the place of talking with your health care provider about your medical condition or your treatment. If you have any questions or are not sure about something, ask your healthcare provider or pharmacist.

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

ACTONEL may cause problems in your stomach and esophagus (the tube that connects the mouth and the stomach), such as trouble swallowing (dysphagia), heartburn (esophagitis), and ulcers (See "What are the Possible Side Effects of ACTONEL?").

You must follow the instructions exactly for ACTONEL to work and to lower the chance of serious side effects. (See "How should I take ACTONEL?").

What is ACTONEL?

ACTONEL is a prescription medicine used:

- to prevent and treat osteoporosis in postmenopausal women (See "What is Osteoporosis?").
- to prevent and treat osteoporosis in men and women that is caused by treatment with steroid medicines such as prednisone.
- to treat Paget's disease of bone (osteitis deformans). The treatment for Paget's disease is very different than for osteoporosis and uses a different type of ACTONEL. This leaflet does not cover using ACTONEL for Paget's disease. If you have Paget's disease, ask your healthcare provider how to use ACTONEL.

ACTONEL may reverse bone loss by stopping more loss of bone and increasing bone mass in most people who take it, even though they won't be able to see or feel a difference. ACTONEL helps lower the risk of breaking bones (fractures). Your health care provider may measure the thickness (density) of your bones or do other tests to check your progress.

See the end of this leaflet for information about osteoporosis.

Who should not take ACTONEL?

Do not take ACTONEL if you:

- have low blood calcium (hypocalcemia)
- cannot sit or stand up for 30 minutes

- have kidneys that work poorly
- have an allergy to ACTONEL**.** The active ingredient in ACTONEL is risedronate sodium. (See the end of this leaflet for a list of all the ingredients in ACTONEL.)

Tell your doctor before using ACTONEL if:

- you are pregnant or may become pregnant. We do not know if ACTONEL can harm your unborn child.
- you are breast-feeding or plan to breast-feed. We do not know if ACTONEL can pass through your milk and if it can harm your baby.
- you have kidney problems. ACTONEL may not be right for you.

How should I take ACTONEL?

The following instructions are for both ACTONEL 5-mg (daily) and ACTONEL 35-mg (Once-a-Week):

- Take ACTONEL first thing in the morning before you eat or drink anything except plain water.
- Take ACTONEL while you are sitting or standing up.
- Take ACTONEL with 6 to 8 ounces (about 1 cup) of plain water. Do **not** take it with any other drink besides plain water. Do not take it with coffee, tea, juice, milk, or other dairy drinks.
- Swallow ACTONEL whole. Do not chew the tablet or keep it in your mouth to melt or dissolve.
- After taking ACTONEL you must wait at least 30 minutes **BEFORE**:
    - lying down. You may sit, stand, or do normal activities like read the newspaper or take a walk.
    - eating or drinking anything except plain water.
    - you take vitamins, calcium, or antacids. Take vitamins, calcium, and antacids at a different time of the day from when you take ACTONEL.
- Keep taking ACTONEL for as long as your health care provider tells you.
- For ACTONEL to treat your osteoporosis or keep you from getting osteoporosis, you have to take it as often and in the way it is prescribed.
- Your healthcare provider may tell you to take calcium and vitamin D supplements and to exercise.

What is my ACTONEL schedule?

<u>If your doctor has prescribed **ACTONEL 5-mg daily (a yellow tablet):**</u>

- Take 1 ACTONEL 5-mg tablet every day in the morning.

- If you forget to take your ACTONEL 5-mg in the morning, do **not** take it later in the day. Take only 1 ACTONEL 5-mg tablet the next morning and continue your usual schedule of 1 tablet a day. Do **not** take 2 tablets on the same day.

If your doctor has prescribed **ACTONEL 35-mg Once-a-Week (an orange tablet)**:

- Choose 1 day of the week that you will remember and that best fits your schedule to take your ACTONEL 35-mg. Every week, take 1 ACTONEL 35-mg tablet in the morning on your chosen day.
- If you forget to take your ACTONEL 35-mg in the morning, do **not** take it later in the day. Take only 1 ACTONEL 35-mg tablet the next morning and continue your usual schedule of 1 tablet on your chosen day of the week. Do **not** take 2 tablets on the same day.

What should I avoid while taking ACTONEL?

- Do not eat or drink anything except water before you take ACTONEL and for at least 30 minutes after you take it.
- Do not lie down for at least 30 minutes after you take ACTONEL.
- Foods and some vitamin supplements and medicines can stop your body from absorbing (using) ACTONEL. Therefore, do not take the following products at or near the time you take ACTONEL: food, milk, calcium supplements, or calcium-, aluminum-, or magnesium-containing medicines, such as antacids. (See "How should I take ACTONEL?").

What are the possible side effects of ACTONEL?

Stop taking ACTONEL and tell your health care provider right away if:

- **swallowing is difficult or painful**
- **you have chest pain**
- **you have very bad heartburn or it doesn't get better**

ACTONEL may cause:

- pain or trouble swallowing (dysphagia)
- heartburn (esophagitis)
- ulcers in your stomach and esophagus (the tube that connects the mouth and the stomach)

For patients with osteoporosis, the overall occurrence of side effects with ACTONEL was similar to placebo (sugar pill) and most were either mild or moderate. The most common side effects with ACTONEL include back pain, joint pain, upset stomach, abdominal (stomach area) pain, constipation, diarrhea, gas, and headache. Tell your health care provider if you have pain or discomfort in your stomach or esophagus. Rarely, severe skin reactions may occur.

Patients may get allergic reactions such as rash, hives, or in rare cases, swelling that can be of the face, lips, tongue, or throat, which may cause trouble breathing or swallowing.

These are not all the possible side effects of ACTONEL. You can ask your health care provider or pharmacist about other side effects. Any time you have a medical problem you think may be from ACTONEL, talk to your doctor.

What is osteoporosis?

Osteoporosis is a disease that causes bones to become thinner. Thin bones can break easily. Most people think of their bones as being solid like a rock. Actually, bone is living tissue, just like other parts of the body—your heart, brain, or skin, for example. Bone just happens to be a harder type of tissue. Bone is always changing. Your body keeps your bones strong and healthy by replacing old bone with new bone.

Osteoporosis causes the body to remove more bone than it replaces. This means that bones get weaker. Weak bones are more likely to break. Osteoporosis is a bone disease that is quite common, especially in older women. However, young people and men can develop osteoporosis, too. Osteoporosis can be prevented, and with proper therapy it can be treated.

How can osteoporosis affect me?

- You may not have any pain or other symptoms when osteoporosis begins.
- You are more likely to break (fracture) a bone especially if you fall because osteoporosis makes your bones weaker. You are most likely to break a bone in your back (spine), wrist, or hip.
- You may “shrink” (get shorter).
- You may get a “hump” (curve) in your back.
- You may have bad back pain that makes you stop some activities.

Who is at risk for osteoporosis?

Many things put people at risk for osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who

- are going through or who are past menopause ("the change")
- are white (Caucasian) or Asian

People who

- are thin
- have family member with osteoporosis
- do not get enough calcium or vitamin D
- do not exercise
- smoke

- drink alcohol often
- take bone thinning medicines (like prednisone or other corticosteroids) for a long time

General information about ACTONEL:

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ACTONEL for a condition for which it was not prescribed. Do not give ACTONEL to other people, even if they have the same symptoms you have. It may harm them.

What if I have other questions about ACTONEL?

This leaflet summarizes the most important information about ACTONEL for osteoporosis. If you have more questions about ACTONEL, ask your health care provider or pharmacist. They can give you information written for health care professionals. For more information, call 1-877-**ACTONEL** (toll-free) or visit our web site at www.actonel.com.

What are the ingredients of ACTONEL?

ACTONEL (active ingredient): risedronate sodium.
ACTONEL (inactive ingredients): crospovidone, ferric oxide red (35-mg tablets only), ferric oxide yellow, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, and titanium dioxide.

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