CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-823

Trade Name:	Actonel with Calcium Tablets
Generic Name:	Risedronate sodium 35 mg and calcium carbonate 1250 mg.
Sponsor:	Proctor and Gamble
Approval Date:	August 12, 2005
Indications:	Prevention and Treatment of Osteoporosis in Postmenopausal Women

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APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-823

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-823

Procter & Gamble Pharmaceuticals, Inc.
Attention: Linda Manning, Pharm.D.
U.S. Regulatory Affairs
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Manning:

Please refer to your new drug application (NDA) dated August 30, 2004, received August 31, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel With Calcium (risedronate sodium 35 mg and calcium carbonate 1250 mg) Tablets.

We acknowledge receipt of your submissions dated September 29, and December 6, 2004, and January 13, March 14, May 17, and 20, June 17, 21, 24, July 1, 18, 25, 26, and 29, and August 10, 2005.

This new drug application provides for the use of Actonel With Calcium for the prevention and treatment of osteoporosis in postmenopausal women.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The stability data reviewed supports a 36-month expiry for Actonel, and 48-months for calcium carbonate. The expiration date for each co-package of Actonel With Calcium will be the earliest expiration date of either of the component products used in the co-package.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert and patient package insert submitted July 29, 2005, and immediate carton labels submitted August 10, 2005). Marketing this product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. In addition, submit the content of labeling in electronic format as described in 21 CFR 314.50(l)(5) and in the format described at the following website: http://www.fda.gov/oc/datacouncil/spl.html. For administrative purposes, designate this submission "**FPL for approved NDA 21-823.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
And Communications, HFD-42
Food and Drug Administration
5600 Fishers Land
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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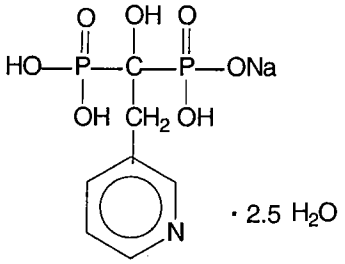
LABELING

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 (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.

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 <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.

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 – 27 years) and elderly (63 – 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 <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 (<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%).

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 (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

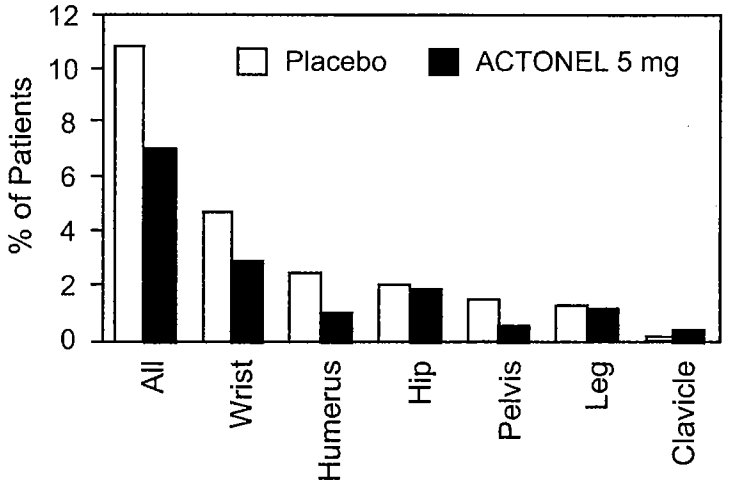
	Proportion of Patients with Fracture (%)[a]			
VERT NA	Placebo n = 678	ACTONEL 5 mg n = 696	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 - 1 Year	7.2	3.9	3.3	49
0 - 2 Years	12.8	8.0	4.8	42
0 - 3 Years	18.5	13.9	4.6	33
New				
0 - 1 Year	6.4	2.4	4.0	65
0 - 2 Years	11.7	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

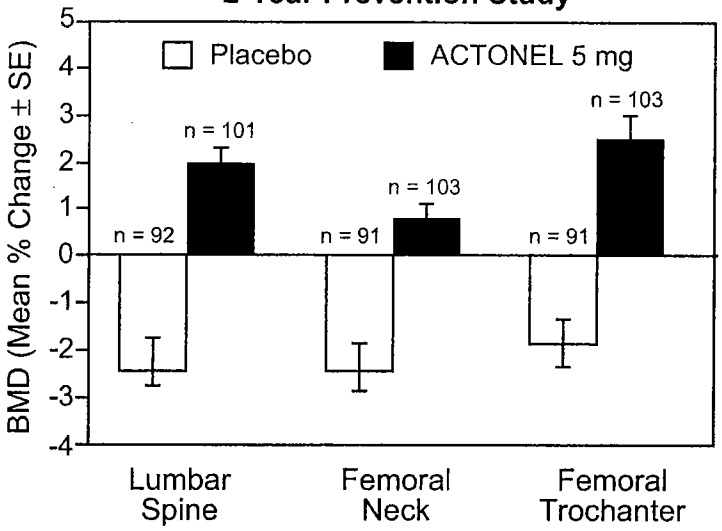
Histology/Histomorphometry:

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.

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.

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.

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 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 <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.

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures such as tooth extraction, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Most

reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.

For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment, prior to the procedure, reduces the risk of osteonecrosis of the jaw. Clinical judgement should guide the management plan of each patient 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.

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 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 35 mg and to re-read it each time the prescription is renewed.

Patients should be reminded to give all of their health care providers an accurate medication history. Instruct patients to tell all of their health care 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 $\geq$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 ≥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 ≥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 ≥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 ≥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 ≥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

Table 4
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)
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
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

Table 4 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)
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 5 lists the adverse events in ≥2% of patients from this trial. Events are shown without attribution of causality.

Table 5
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		
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

Table 5
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)
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

Post-marketing Experience:
Very rare hypersensitivity and skin reactions have been reported, including angioedema, generalized rash and bullous skin reactions, some severe.
Musculoskeletal: bone, joint, or muscle pain, rarely described as severe or incapacitating (see **PRECAUTIONS**, Musculoskeletal Pain).

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 >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):

<u>One 35 mg Actonel tablet orally</u>, 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 oz). 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 <30 mL/min). No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min or in the elderly.

<u>One 1250 mg calcium carbonate tablet (500 mg elemental calcium) orally</u>, 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 <30 mL/min). No dosage adjustment is necessary in patients with a creatinine clearance ≥ 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 0149-0475-01

Store at 20°-25°C (68°-77°F); excursions permitted between 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

Actonel sold under U.S. patent No. 5,583,122; 5,935,602; 5,994,329; 6,015,801; 6,047,829; 6,096,342; 6,165,513; 6,225,294; 6,410,520; 6,432,932; 6,465,443; and 6,562,974.

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

Calcium mfg. by: OSG Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814

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

Marketed with: Aventis Pharmaceuticals, Inc.
Bridgewater, NJ 08807

JULY 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-823

MEDICAL REVIEW

MEDICAL TEAM LEADER MEMORANDUM

DATE: July 15, 2005

NDA: 21-823

DRUG: 35-mg once weekly risedronate tablets with 1250 mg calcium carbonate tablets

INDICATION: Prevention and treatment of postmenopausal osteoporosis

COMPANY: Procter and Gamble

PRIMARY REVIEWER: Patricia Beaston, MD, PhD

I. Background

The 5-mg once-daily dose of risedronate was approved for the prevention and treatment of postmenopausal osteoporosis in 1999, under NDA 20-835. The prevention indication was based on 2-year BMD data in early postmenopausal osteopenic women and the treatment indication was based on 3-year vertebral fracture data in postmenopausal osteoporotic women. All women in these trials were instructed to take 500 mg BID of supplemental elemental calcium. Women in the treatment trial who were considered vitamin D insufficient at baseline were instructed to take up to 500 IU of supplemental vitamin D per day. The currently approved labeling for risedronate includes a recommendation that patients "should receive supplemental calcium and vitamin D if dietary intake is inadequate."

In the spring of 2002, the Division approved a 35-mg once weekly dose of risedronate for the treatment (and prevention) of postmenopausal osteoporosis. This approval was based on a one-year BMD non-inferiority study comparing 5 mg once-daily to 35-mg once-weekly risedronate in a population of postmenopausal women with osteoporosis. All subjects in this trial were instructed to take 500 mg BID of elemental caclium.

Although this trial did not include women who would normally be studied in a prevention of PMO trial, given the experience with the 5-mg once daily doses of risedronate in the treatment and prevention of PMO populations and Procter and Gamble's agreement to conduct a phase 4 study to examine the efficacy and safety of 35-mg once-weekly risedronate vs. placebo in early postmenopausal women with osteopenia, we allowed the dosing and administration section of the risedronate labeling to include a statement that the 35-mg once-weekly dose of the drug could be considered an alternative dosing option for the prevention of PMO. As of this writing, the phase 4 prevention of PMO study is under review by the Division. Prima facie, the data support the efficacy and safety of the

35-mg once-weekly dose for the prevention of PMO. Women in this trial were also instructed to take 500 mg BID of elemental calcium.

II. The Sponsor's Proposal to Copackage Risedronate with Calcium Carbonate

On August 30, 2004, Procter and Gamble submitted a NDA for 35-mg once-weekly risedronate copackaged with 1250 mg calcium carbonate tablets. The company is seeking approval of this copackage for the prevention and treatment of postmenopausal osteoporosis. The sponsor did not conduct new clinical studies for this NDA; rather, they rely on published data to support the efficacy and safety of calcium when used by patients treated with risedronate for the prevention or treatment of postmenopausal osteoporosis.

III. Calcium and Bone

The adult skeleton contains almost all of the calcium found in the body[1]. Calcium provides mechanical stability to bone and serves as a reservoir to maintain the extracellular fluid calcium concentration within a narrow physiological range. In healthy young adults, approximately 250 mg – 500 mg of calcium fluxes into and out of bone per day. This process is mediated by the coupling of osteoclastic bone resorption with osteoblastic bone formation. About 0.5 – 1.0% of calcium found in bone is in chemical equilibrium with the calcium in the extracellular fluid.

Parathyroid hormone (PTH) and 1,25 dihydroxy-vitamin D (active vitamin D) are the two hormones that help maintain extracellular calcium within a normal range. A drop in serum calcium concentration triggers release of PTH, which increases bone resorption and release of calcium and increases reabsorption of calcium in the kidney; it also stimulates synthesis of 1,25 dihydroxy-vitamin D. The active form of vitamin D increases intestinal absorption of dietary calcium. The end result of these physiological actions is an increase in the serum calcium level.

Insufficient intake of calcium (or vitamin D) will lead to secondary hyperparathyroidism. Increased levels of PTH help maintain serum calcium levels, but if sustained, will also increase bone resorption and bone turnover, with resultant loss of bone mass and increased skeletal fragility, the hallmarks of osteoporosis.

Absorption of calcium depends on a number of factors including gastric pH, calcium dose, presence of food, and age.

Reduced gastric acidity, such as that seen in patients with achlorhydria or in those taking proton pump inhibitors, is associated with a reduction in calcium absorption. The amount of calcium that is absorbed in the small intestine is inversely related to the dose. There is little value in taking more than 500 -700 mg of supplemental calcium at one time due to the reduced fractional absorption of calcium at doses above this range. Taking supplemental calcium with food increases calcium absorption; this is particularly true

[1] Harrison's Principles of Internal Medicine – 16th edition. 2005.

with calcium carbonate. Calcium absorption decreases about 0.2% per year in women after the age of 40 years.[2] Older individuals therefore have greater daily requirements for calcium than do younger individuals.

The recommended daily intake of calcium for adults 50 years and older is 1200 mg.[3] The median daily intake of calcium among U.S. women $\geq$ 50 years is estimated to be 500-700 mg.[4,5]

There is an extensive body of literature on the effects of supplemental calcium on bone mineral density and fracture risk. As recently summarized by the authors of a meta-analysis, "calcium supplementation alone has a small positive effect on bone density" and the "data show a trend toward reduction in vertebral fractures, but do not meaningfully address the possible effect of calcium on reducing the incidence of nonvertebral fractures."[6]

The doses of supplemental calcium used in the studies included in this meta-analysis ranged from 500 mg to 2000 mg per day, with many using 1000 mg daily (in divided doses). The forms of calcium used in these studies included calcium carbonate, calcium citrate, and calcium gluconate. There was no compelling evidence that one form of calcium was more effective than any other.

The adverse events associated with supplemental calcium are dose related and include constipation, flatulence, hypercalcemia, and nephrolithiasis. No more than 2000 mg of supplemental calcium should be taken per day.

Since a large percentage of the women prescribed risedronate for the prevention or treatment of PMO have inadequate intake of dietary calcium and they would benefit from taking more than the 500 mg of elemental calcium provided in the risedronate with calcium copackage, I believe Procter and Gamble should pursue marketing of a copackage that provides two 500 mg elemental calcium tablets per day.

---

[2] O' Connell MB, et al. Effects of proton pump inhibitors on calcium carbonate absorption in women: A randomized crossover trial. The American Journal of Medicine. 118:7:778-781.
[3] Institute of Medicine. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. January 1, 1997.
[4] Ervin RB, et al. Dietary intake of selected minerals for the U.S. population:1999-2000.
[5] Park, YK, et al. Calcium intake levels in the United States: issues and considerations. Accessed at http://www.fao.org/docrep/W7336T/w7336t06.htm#TopOfPage, July 15, 2005.
[6] Shea B, et al. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocrine Reviews 2002;4:552-559.

IV. Proposed Labeling

Dr. Beaston has reviewed the sponsor's proposed labeling for the risedronate with calcium copackage. I have added my comments to the proposed labeling, which can be found in the Appendix to this review.

V. Comment and Recommendation

Dr. Beaston has done a thorough review of the risedronate with calcium carbonate copackage NDA. She recommends that the application be approved. Copackaging calcium carbonate tablets with risedronate is a rationale proposal, which in my opinion will provide benefit to the women who are prescribed this bisphosphonate for the prevention or treatment of PMO.

I agree with Dr. Beaston's recommendation that the NDA be approved.

31 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

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/s/

Eric Colman
8/3/05 01:18:02 PM
MEDICAL OFFICER

David Orloff
8/5/05 04:57:04 PM
MEDICAL OFFICER
Concur with Dr. Colman. Application may be approved. Dr. Colman's memo will serve as the division level memo for this application.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-823
Submission Code	4
Letter Date	August 30, 2004
Stamp Date	August 31, 2004
PDUFA Goal Date	June 30, 2005
Reviewer Name	Patricia Beaston, M.D., Ph.D.
Review Completion Date	July 15, 2005
Established Name	Risedronate and Calcium carbonate, USP
(Proposed) Trade Name	Actonel [redacted] Calcium
Therapeutic Class	Bone/Calcium-phosphorus
Applicant	Procter & Gamble
Priority Designation	Standard
Formulation	Tablet/Tablet
Dosing Regimen	Risedronate, oral, once weekly Calcium carbonate, oral, daily 6 days per week
Indication	Osteoporosis
Intended Population	Postmenopausal women

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Risedronate sodium and calcium carbonate are considered to be a rationale combination for the indication 'treatment of postmenopausal osteoporosis' and co-packaging should be approved with the labeling changes as outlined.

This review discusses NDA 21-823 and the co-packaging of risedronate sodium and calcium carbonate.

There are no new data (pre-clinical, clinical, or manufacturing) for risedronate.

Calcium carbonate (or acetate) is currently marketed as a dietary supplement and is recommended to patients who do not have adequate dietary intake. With the exception of dissolution studies for the calcium carbonate tablets, no data were submitted.

1.2 Recommendation on Postmarketing Actions

None indicated

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Procter and Gamble Pharmaceuticals, Inc. has submitted this new drug application for risedronate sodium 35 mg and calcium carbonate 1250 mg (500 mg elemental calcium) co-package, proposed trade name Actonel [redacted] Calcium. Risedronate is a member of the bisphosphonate class of medications. Risedronate is already indicated for the prevention and treatment of osteoporosis in postmenopausal (PMO) women. In addition to risedronate therapy, it is recommended that patients receive additional calcium and vitamin D, if dietary intake is inadequate. Actonel [redacted] Calcium has been developed as a convenience package to provide the approved 35 mg risedronate tablet (to be taken one day per week), and six 1250 mg calcium carbonate tablets (1 to be taken the remaining 6 days of the weekly cycle) in blister packages. The indications sought in this application include the treatment of postmenopausal osteoporosis, the prevention of postmenopausal osteoporosis; and to help ensure adequate calcium supplementation.

1.3.2 Efficacy

Risedronate: The efficacy of risedronate for the prevention and treatment of postmenopausal osteoporosis has been established and has been approved under NDA 20-835.

Calcium: Calcium has served as baseline therapy in all trials examining the efficacy of risedronate for the treatment of postmenopausal osteoporosis. Small studies using calcium with or without vitamin D have shown that calcium treatment increases BMD and decreases fractures in some populations[1]. Furthermore, the use of calcium in the

treatment of postmenopausal osteoporosis with other therapies (bisphosphonates, estrogen, parathyroid hormone) is considered the standard of care.

COMMENT: [redacted] the **inclusion of 1250 mg calcium carbonate (500 mg elemental calcium) with risedronate in a co-package for the treatment of postmenopausal osteoporosis provides a convenient product for patients who take both risedronate and calcium.**

1.3.3 Safety

Risedronate: The safety of risedronate for the prevention and treatment of postmenopausal osteoporosis has been established and has been approved under NDA 20-835.

Calcium: There are no clinical studies examining the use of this co-package. Calcium is generally safe when used in the recommended quantities (< 2000 mg per day). When taken in higher quantities, absorption is decreased. The most common side effects of calcium intake are mainly gastrointestinal and include constipation, flatulence, nausea, abdominal pain, and bloating. Increased calcium intake can cause nephrocalcinosis and renal calculi in susceptible patients.

Calcium preparations should not be used for patients with hyperparathyroidism, hypercalcemia of malignancy, or sarcoidosis. Calcium preparations should be used with caution for patients with renal disease.

COMMENT: Current recommendations[2] are that women over the age of 50 years have a total daily intake of elemental calcium of at least 1200 mg (> 8400 mg per week). The National Osteoporosis Foundation (NOF) reports that postmenopausal American women typically consume about 600 mg per day (4200 mg per week) of elemental calcium in their diet, less than or equal to one-half of the recommended intake. Total calcium intake can be increased by improving the diet to include calcium rich or fortified foods or, more easily the use of calcium tablets. The total weekly calcium provided in the co-package is 3000 mg of elemental calcium (6 tablets containing 500 mg of elemental calcium). Therefore, the calcium provided in the co-package is unlikely to provide the recommended amount. Healthcare providers and their patients may make the false assumption that the Actonel [redacted] Calcium co-package provides sufficient calcium and patients may be under-treated for their daily calcium needs.

While this issue does not present a safety concern that would prevent approval of the currently proposed co-package, the label should clearly outline the possible needs of additional calcium and P&G should be encouraged to produce a co-package that would contain 1000 mg of elemental calcium (two 500 mg tablets) per day. Some studies for the registration of bisphosphonates, including risedronate 5

mg daily, used 1000 mg of elemental calcium. There was no obvious increase in adverse events related to this intake of calcium.

1.3.4 Dosing Regimen and Administration

1.3.5 Drug-Drug Interactions

Risedronate sodium is poorly absorbed and must be taken first thing in the morning on an empty stomach, ingesting only water for one-hour after taking the tablet to allow for maximal absorption. Calcium should not, and is not, intended to be taken at the same time as risedronate because it will significantly decrease the absorption of the risedronate and the calcium.

Calcium may also interfere with the absorption of other drugs (other bisphosphonates, thyroid hormone, tetracycline, and iron) and should not be taken with these drugs. Calcium absorption is increased with vitamin D analogues (calcitriol, doxercalciferol, and paricalcitol) and is reduced by co-administration with corticosteroids. Thiazide diuretics reduce the renal excretion of calcium.

1.3.6 Special Populations

Risedronate is currently approved for use for the treatment and prevention of postmenopausal and glucocorticoid-induced osteoporosis and for the treatment of Paget's disease of bone, and patients with glucocorticoid osteoporosis. [redacted]

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Risedronate sodium (Actonel) was approved under NDA 20-835 and is given either as a 5 mg oral dose daily or as a single 35 mg oral dose once weekly for the treatment and prevention of postmenopausal osteoporosis. Risedronate is also indicated for the treatment and prevention of glucocorticoid-induced osteoporosis (5 mg daily) and Paget's disease (30 mg daily for 2 months).

Calcium is a essential mineral in the diet and must be ingested in adequate amounts to maintain bone mineralization. A 1250 mg calcium carbonate tablet (USP) contains 500 mg of elemental calcium. The recommended total daily intake of calcium in postmenopausal women is 1200 mg of elemental calcium.

2.2 Currently Available Treatment for Indications

Current medications approved for the treatment and prevention of postmenopausal osteoporosis include 1) salmon calcitonin (Miacalcin nasal spray, for treatment only; 2) bisphosphonates: alendronate sodium (Fosamax; daily and weekly), risedronate sodium (Actonel; daily and weekly), and ibandronate sodium (Boniva; daily and monthly); the selective estrogen receptor modulator raloxifene (Evista); and teriparatide (Forteo).

Supplemental calcium and vitamin D are considered the 'standard of care' for the treatment and prevention of postmenopausal osteoporosis and are included as such in the Surgeon General's report on bone health and osteoporosis[3].

2.3 Availability of Proposed Active Ingredient in the United States

Risedronate sodium is currently available in 5 mg daily and 35 mg weekly tablets.

Calcium is a component of many foods, especially dairy based foods. Calcium is also widely available in tablet form as calcium carbonate and calcium citrate.

2.4 Important Issues With Pharmacologically Related Products

Bisphosphonates are used for the treatment of Paget's disease, hypercalcemia of malignancy, boney metastasis, and the prevention and treatment of postmenopausal osteoporosis, osteoporosis in men, glucocorticoid-induced osteoporosis. Safety concerns with oral bisphosphonates include esophageal and gastric irritation and ulceration. Newer concerns have emerged in the post-marketing period including bone pain, osteonecrosis of the jaw, and eye inflammation. Class labeling for bisphosphonates regarding the use of these drugs in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug has been implemented.

The principal safety concern with calcium preparations is excessive intake with resultant hypercalcemia, particularly in patients with predisposing conditions such as hyperparathyroidism, hypercalcemia of malignancy, or sarcoidosis.

2.5 Presubmission Regulatory Activity

Presubmission discussions focused on the regulatory status of co-packaging risedronate with calcium and noted that the determinations regarding calcium's status in the combination would be as a dietary supplement or a drug. It was noted that the determination would be made after consulting both CFSAN [redacted]

The remainder of the discussions was related to 1) changes in the label (clarification of dosing instructions, [redacted] and 2) package design to help patients take the different tablets (risedronate or calcium) according to instructions.

2.6 Other Relevant Background Information

Calcium homeostasis and bone[4]: Entire textbooks are written on the regulation of calcium, and a complete discussion of this topic is beyond the scope of this review. However, it is important for the reader to understand the basics of calcium homeostasis and why adequate dietary calcium intake is essential for mineralization of bone, maintenance or improvement in BMD, and the prevention of fracture.

Calcium is a critical component in nervous system conduction and muscle contraction. Maintenance of serum calcium levels within a normal range is essential for life and is therefore tightly regulated by the actions of parathyroid hormone and vitamin D. Calcium is also the major component of bone (50 – 70%), where it provides mechanical rigidity and load-bearing strength.

Bone also serves as a reservoir for serum calcium. Bone is not static but is always undergoing remodeling through a balance in the activity of osteoblasts and osteoclasts. In an optimal physiological state, the balance between the destruction of bone and production of bone is maintained. Furthermore, the balance of calcium released from the bone and incorporated into the bone matrix is also maintained. Changes in any of the multiple factors affecting the balance of bone turnover and calcium balance results in either a decrease or increase in bone mineral density.

Estrogen is critical for bone growth in children and for maintenance of the balance of osteoclast and osteoblast function. Decreases in circulating estrogen changes the balance causing more bone to be destroyed then laid down leading to reduce bone mass and skeletal fragility and contributing to the development of postmenopausal osteoporosis (PMO). As a result of this increase in bone turnover, these patients are in negative calcium balance. This imbalance is aggravated by the decrease in functional calcium intake in many older patients, due to lactose intolerance, and decreased calcium absorption from the small intestine.

Vitamin D deficiency or insufficiency also occurs in older patients, again because of poor diet, reduced intestinal absorption, avoidance of the sun, or as a result of decreased renal 1-alpha hydroxylation of 25OHD. Because vitamin D (specifically 1,25 dihydroxy

vitamin D) promotes calcium absorption from the gastrointestinal tract and reabsorption from the kidney, vitamin D deficiency or insufficiency further increases the negative calcium balance.

Parathyroid hormone (PTH) levels increase in response to the negative calcium balance in order to maintain adequate levels of serum calcium. PTH stimulates conversion of the fat stores of vitamin D (25 hydroxy vitamin D) to the active 1,25 dihydroxyvitamin D to increase the absorption of calcium. PTH increases calcium reabsorption in the kidney and calcium release from the bone.

Increasing calcium intake, either from increasing the intake of food rich in calcium or more easily with calcium tablets, has been shown to improve calcium balance as evidenced by increases in serum calcium, decreases in markers of bone turnover and serum PTH and increases in BMD.

The roles of calcium and vitamin D in bone mineral accumulation are well established and ensuring adequate levels in considered the standard of care. The importance of these agents is emphasized by the fact that trials for any new drug for the treatment or prevention of postmenopausal osteoporosis be performed on the background of adequate dietary calcium and vitamin D. Therefore, although the trials are labeled as 'placebo-controlled' they are actually add-on therapy trials because it would be considered unethical to not ensure adequate calcium and vitamin D to all participants. The trials for risedronate were done on the background of additional calcium (1000 mg) in all patients and 500 IU vitamin D for all patients found to have vitamin D insufficiency (< 40 nmol/L)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No CMC issues were reported. Please see Dr. Yvonne Yang's Chemistry Review for details. Specific labeling comments have been incorporated into this review.

3.2 Animal Pharmacology/Toxicology

No new preclinical studies were performed for this NDA. P&G provided references for studies examining the effects of calcium (deficiency in diet and excess in diet) in animal studies. Please refer to Dr. Karen Davis-Bruno's review for complete details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

The submission is limited to referenced literature for calcium supplementation to support this combination of risedronate and calcium carbonate for the treatment and prevention of postmenopausal osteoporosis.

4.1 Review Strategy

This review focuses on the literature examining the effects of calcium administration on bone density and fracture.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

P&G provided the results of *in vitro* dissolution studies for USP calcium carbonate. There are no new studies related to risedronate. Please see Dr. Johnny Lau's review for complete details.

5.2 Pharmacodynamics

P&G provided references in support of the use of calcium in the treatment and prevention of postmenopausal osteoporosis. Please refer to section 2.6 in this review for a discussion of the actions of calcium on bone. Please also refer to Dr. Lau's review.

5.3 Exposure-Response Relationships

Risedronate 5 mg per day or 35 mg per week has been shown to be safe and efficacious for the treatment of postmenopausal osteoporosis. In the trials to support registry of risedronate all patients ('placebo' and risedronate treated) received calcium and vitamin D treatment.

The exposure-response relationship to calcium is highly variable and is dependent on many factors including, but not limited to, the patient's dietary calcium intake, vitamin D status, presence/absence of malabsorption, and renal function.

In general, healthy postmenopausal patients (especially those who are not receiving estrogen treatment) have increased bone turnover and are in negative calcium balance. Increasing calcium intake, most easily accomplished with calcium tablets, results in decreased markers of bone turnover, and slight decreases in PTH and increases in urine calcium.

6 INTEGRATED REVIEW OF EFFICACY

The submission is limited to referenced literature for calcium supplementation to support this combination for the treatment and prevention of postmenopausal osteoporosis.

Calcium: Calcium has served as baseline therapy in all trials examining the efficacy of risedronate for the treatment of postmenopausal osteoporosis. Small studies using calcium with or without vitamin D have shown that calcium treatment increases BMD and decreases fractures in some populations[5]. Furthermore, the use of calcium in the treatment of postmenopausal osteoporosis with other therapies (bisphosphonates, estrogen, parathyroid hormone) is considered the standard of care.

COMMENT: [redacted] **The inclusion of 1250 mg calcium carbonate (500 mg elemental calcium) with risedronate in a co-package for the treatment of postmenopausal osteoporosis is for convenience.**

7 INTEGRATED REVIEW OF SAFETY

The submission is limited to referenced literature for calcium supplementation to support this combination for the treatment and prevention of postmenopausal osteoporosis.

Calcium carbonate may cause gastrointestinal adverse effects such as constipation, flatulence, nausea, abdominal pain, and bloating. Calcium carbonate also causes nephrocalcinosis and renal calculi in susceptible patients.

Calcium preparations should not be used for patients with hyperparathyroidism, hypercalcemia of malignancy, or sarcoidosis. Calcium preparations should be used with caution for patients with renal disease.

COMMENT: Current recommendations[6] are that women over the age of 50 years have a total daily intake of elemental calcium of at least 1200 mg (> 8400 mg per week). The National Osteoporosis Foundation (NOF) reports that the postmenopausal American women typically consume about 600 mg per day (4200 mg per week) of elemental calcium in their diet, less than or equal to one-half of the recommended intake. Total calcium intake can be increased by improving the diet to include calcium rich or fortified foods or, more easily the use of calcium tablets. The total weekly calcium provided in the co-package is 3000 mg of elemental calcium (6 tablets containing 500 mg of elemental calcium). Therefore, the calcium provided in the co-package is unlikely to provide the recommended amount. Healthcare providers and their patients may make the false assumption that the Actonel [redacted] Calcium co-package provides sufficient calcium and patients may be under treated for their daily calcium needs.

While this issue does not present a safety concern that would prevent approval of the currently proposed co-package, the label should clearly outline the possible needs of additional calcium and the P&G should be encouraged to produce a co-package that would contain 1000 mg of elemental calcium (two 500 mg tablets) per day. Some studies for the registration of bisphosphonates, including risedronate 5 mg daily, used 1000 mg of elemental calcium. There was no increase in adverse events related to this higher intake of calcium.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

P&G proposes to co-package risedronate 35 mg with calcium carbonate 1250 mg (500 mg elemental calcium) tablets to be taken as follows: 1 risedronate tablet on the first day of a 7-day dosing cycle and 1 calcium carbonate tablet on the 2nd through 7th day of the cycle.

Risedronate, as with other bisphosphonates, is to be taken first thing in the morning on an empty stomach with a large glass of water. The patient is to remain upright and abstain from eating or drinking for at least one-half hour after taking risedronate. These

instructions are necessary because the bisphosphonates are poorly absorbed and have been associated with esophageal erosions. The 35 mg dose to be taken once weekly is a currently approved dose.

Calcium carbonate, on the other hand, is to be taken with meals. This is because calcium carbonate is better absorbed at a lower pH and is poorly absorbed in patients with achlorhydria.

The two issues that arise from the co-packaging are:

1) The concern that patients will confuse the dosing instructions for the different tablets – i.e. take risedronate with meals and calcium on an empty stomach.

> DMETS has expressed concerns regarding the co-packaging of these two drugs which require very different dosing instructions. (Please refer to the DMETS consult for complete details.

and,

2) That the 500 mg of elemental calcium (1250 mg calcium carbonate tablet) is insufficient to meet prescribing guidelines and that patients may:

> a) Be under treated for their calcium requirements. The current NOF guidelines recommend that physicians 'Advise all patients to consume adequate amounts of calcium (at least 1200 mg per day, including supplements if necessary) and vitamin D (400 to 800 IU per day for individuals at risk of deficiency)'.
>
> b) May take additional calcium incorrectly – i.e. take more than 500 mg of elemental calcium at one time, which would be poorly absorbed, or take the additional calcium with the risedronate which would decrease the absorption of risedronate.

Successful use of this co-package requires careful evaluation and instruction from the health care provider and clear labeling on the package itself and in the patient instructions.

8.2 Drug-Drug Interactions

Risedronate sodium is poorly absorbed must be taken first in the morning on an empty stomach ingesting only water for one-hour to allow for maximal absorption. Calcium should not, and is not, intended to be taken at the same time as risedronate because it will significantly decrease the absorption of risedronate and the calcium.

Calcium may also interfere with the absorption of other drugs (bisphosphonates, thyroid hormone, tetracycline, and iron) and should not be taken with these drugs. Calcium

absorption is increased with vitamin D analogues (calcitriol, doxercalciferol, and paricalcitol) and is reduced by co-administration with corticosteroids. Thiazide diuretics reduce renal excretion of calcium.

8.3 Special Populations

8.4 Pediatrics

The safety and effectiveness of risedronate has not been established in children. The safety and efficacy of risedronate for the treatment of osteogenesis imperfecta in children is currently under study in response to a Written Request.

Calcium intake is important in children to allow for normal bone formation and mineralization. However, risedronate plus calcium is only indicated for the treatment and prevention of postmenopausal women and therefore is inappropriate for use in children.

8.5 Advisory Committee Meeting

None.

8.6 Literature Review

All literature provided by P&G was reviewed. Additional literature was referenced when appropriate and is cited at the end of this review.

8.7 Postmarketing Risk Management Plan

None indicated.

9 OVERALL ASSESSMENT

9.1 Conclusions

Risedronate is approved for the treatment and prevention of postmenopausal osteoporosis (PMO). All studies for the registration of risedronate for PMO were performed on a background of calcium (1000 mg of elemental calcium per day). The labeling for risedronate (and other drugs indicated for PMO) recommend that all patients have a total daily intake of 1200 mg of elemental calcium. Therefore, the co-packaging of risedronate with calcium carbonate is considered to be a rationale combination.

9.2 Recommendation on Regulatory Action

Approval.

9.3 Recommendation on Postmarketing Actions

None indicated.

9.4 Labeling Review

The proposed label is an edited version of the existing label. Because the combination will only be indicated for the treatment and prevention of postmenopausal osteoporosis,

31 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

REFERENCES

[1] Holbrook, T.L, et al. (1988) Dietary calcium and risk of hip fracture: 14-year prospective population study. Lancet, Nov. 5:1046-1049.

Dawson-Hughes B., et al. (1997) Effect of calcium and vitamin D supplementation on bone density in en and women 65 years of age or older.NEJM, 337:670-676.

Chapuy, M.C.; et al. (1994) Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ, 308:1081-1082

Recker, R.R.; et al. (1996) Correcting calcium nutritional deficiency prevents spine fractures in elderly women.JBMR, 11:1961-1966.

Reid, I.R.; et al. (1995) Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: A randomized controlled trial.Amer. J. Med., 98:331-335

Chevalley, T.; el al. (1994) Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients..Osteoporosis Int., 4:245-252.

[2] Recommendation of the National Academy of Sciences, The National Osteoporosis Foundation, ASBMR

[3] U.S. Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General.* Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General, 2004.

[4] Primer on the Metabolic Bone Diseases and Disorders on Mineral Metabolism, Fifth Edition. (2003) M.J. Flavus, Editor. Published by the American Society for Bone and Mineral Research.

[5] Refer to reference 1.

[6] Recommendation of the National Academy of Sciences, The National Osteoporosis Foundation, ASBMR

[7] M.A. Rodriguez-Martinez at al. Role of Ca2+ and vitamin D in the prevention and treatment of osteoporosis. Pharmacol Therap **93**:37-49 (2002).

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/s/

Patricia Beaston
7/15/05 02:03:22 PM
MEDICAL OFFICER

Eric Colman
7/15/05 02:09:08 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-823

CHEMISTRY REVIEW(S)

NDA 21-823

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

Procter & Gamble Pharmaceuticals, Inc.

Yvonne Yang, Ph.D.

Division of Metabolic and Endocrine Drug Products
HFD-510

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Chemistry Review Data Sheet

1. NDA 21-823

2. REVIEW #: #1

3. REVIEW DATE: Jun-24-2005

4. REVIEWER: Yvonne Yang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 20-835 Meeting minutes for May-19-2004 teleconference	Jun-16-2004 in DFS
NDA 20-835 Meeting minutes for Aug-12-2004 teleconference	Sept-01-2004 in DFS

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	Aug-30-2004
Amendment	Dec-06-2004
Amendment	Mar-14-2005
Amendment	May-17-2005
Amendment	Jun-17-2005

Amendment dated Dec-06-2004 provides for the revised (1) establishment information, (2) post-approval stability commitment, and (3) package artwork. Amendment dated Mar-14-2005 provides information for the Procter & Gamble Pharmaceuticals, Germany GmbH facility for Actonel®. Amendment dated May-17-2005 provides for (1) COA for FDC Blue Aluminum Lake, and (2) executed batch record for the calcium carbonate tablets. Amendment dated Jun-17-2005 provides information regarding reprocessing of the calcium carbonate tablets.

7. NAME & ADDRESS OF APPLICANT:

Name:	Procter & Gamble Pharmaceuticals, Inc.
U. S. Representative:	Procter & Gamble Pharmaceuticals, Inc. Lenore Faulhaber, Ph.D., M.B.A. Associate Director, Regulatory Affairs
Address of U. S. Representative:	Health Care Research Center 8700 Mason-Montgomery Road Mason, OH 45040
Telephone:	(513) 622-4356

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ACTONEL® [redacted] CALCIUM
b) Non-Proprietary Name (USAN): Risedronate sodium tablets and calcium carbonate tablets, USP
c) Code Name/# (ONDC only): NE-58095
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

This NDA is submitted for the Actonel® [redacted] Calcium co-package. Actonel® (risedronate sodium tablets) is currently approved under NDA 20-835 for the prevention and treatment of postmenopausal osteoporosis. Calcium (calcium carbonate tablets, USP), in this co-package, is regarded as a new drug product, not as a dietary supplement, to promote bone health.

10. PHARMACOL. CATEGORY: Bone/calcium-phosphorous metabolism

11. DOSAGE FORM: Tablet/Tablet

12. STRENGTH/POTENCY: Actonel® (35mg risedronate sodium tablets) / Calcium (1250 mg calcium carbonate tablets, USP; equivalent to 500 mg of elemental calcium)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _____X____ Rx _____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

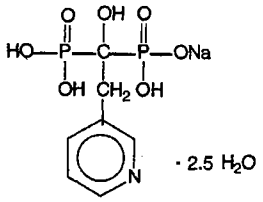
_____ SPOTS product – Form Completed

_____X_____ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Risedronate sodium:
[1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt
$C_7H_{10}NO_7P_2Na \bullet 2.5\ H_2O$

MW = 305.10 (anhydrous), MW = 350.13 (hemi-pentahydrate)



Calcium carbonate:
Carbonic acid, calcium salt (1:1)
$CaCO_3$ MW = 100.1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF No.	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	1	Adequate	Jun-24-2005	Reviewed by Yvonne Yang
	III			3	Adequate	May-02-2002	Reviewed by Elsbeth Chikhale
	III			1	Adequate	May-25-2005	Reviewed by Yvonne Yang
	III			3	Adequate	May-02-2002	Reviewed by Elsbeth Chikhale

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,394	Actonel®
NDA	20-835	Actonel®

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Acceptable cGMP	Overall OC recommendation May-26-2005	Yvonne Yang
EA	Categorical exclusion granted	CMC review #1 dated Jun-24-2005	Yvonne Yang
Pharm/Tox	Approval	Apr-18-2005	Karen Davis-Bruno
Biopharm	Acceptable pending labeling	Jun-14-2005	Johnny S. W. Lau
ODS/DMETS	DMETS does not recommend (1) the use of the proprietary name, (2) co-packaging of the two products**. DDMAC finds the proprietary name acceptable from a promotional perspective.	Jun-02-2005	Nora Roselle
Biometrics	N/A		
LNC	N/A		
Methods Validation	N/A		
Microbiology	N/A		

** Acceptability of the proposed proprietary name, Actonel® [redacted] Calcium, is pending the final decision from the Division of Metabolic and Endocrine Products (HFD-510).

The Chemistry Review for NDA 21-823

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-823 is recommended for **Approval** from the standpoint of chemistry, manufacturing and controls (CMC). The manufacture of Actonel® (risedronate sodium tablets) is currently approved under NDA 20-835. The CMC information provided for calcium carbonate tablets, USP supports its approval as a drug in this application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

This NDA is submitted for the **Actonel®** [redacted] **Calcium** co-package. **Actonel®** (risedronate sodium tablets) is currently approved under NDA 20-835 for the prevention and treatment of postmenopausal osteoporosis. **Calcium** (calcium carbonate tablets, USP), in this co-package, is proposed as a new drug product, not as a dietary supplement, to promote bone health.

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

Actonel® [redacted] **Calcium**

Actonel® [redacted] Calcium is a co-package of risedronate sodium tablets (35 mg) and calcium carbonate tablets (1250 mg calcium carbonate tablets, USP; equivalent to 500 mg of elemental calcium). Each package of Actonel® [redacted] Calcium is supplied with 4 (four) Actonel® 35 mg tablets and 24 (twenty-four) calcium carbonate tablets. Each package contains two [redacted] foil blister cards holding 2 (two) Actonel® tablets and 12 (twelve) calcium carbonate tablets. Each package of Actonel® [redacted] Calcium is intended to deliver a 28-day regimen. Actonel® [redacted] Calcium will be marketed by both Procter & Gamble Pharmaceuticals, Inc. [redacted]

Name used in Patient Labeling	No. of Tablets	Color of Tablet	Strength (mg)	To-Be-Administered	Inactive Ingredients
Actonel® (risedronate sodium tablets)	4	orange	35	One tablet, once a week	crospovidone, ferric oxide red, ferric oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, silicon dioxide, and titanium dioxide
Calcium (calcium carbonate tablets, USP)	24	blue	1250	One tablet on each of the remaining six days of the week	pregelatinized starch, sodium starch glycolate, FD&C Blue #2, magnesium stearate, polyethylene glycol 3350, hypromellose 2910, Opaspray Blue, and polysorbate 80

Actonel® 35 mg

Actonel® (risedronate sodium tablets) is currently approved under NDA 20-835 for the prevention and treatment of postmenopausal osteoporosis. Actonel® is available in 5, 30, or 35 mg strengths intended for oral administration. Only Actonel® 35 mg (once-a-week tablet) is supplied in the Actonel® [redacted] Calcium co-package. Actonel® 35 mg tablets contain 35 mg of the active pharmaceutical ingredient risedronate sodium. Actonel® 35 mg is a film-coated, oval, orange tablet with RSN on one face and 35 mg on the other (NDC 0149-0472-01).

Calcium 1250 mg

Calcium (calcium carbonate tablets, USP), in the Actonel® [redacted] Calcium co-package, is proposed as a new drug product, not as a dietary supplement. Calcium carbonate tablets 1250 mg are intended to deliver 500 mg of elemental calcium per tablet. **The proposed expiry for calcium carbonate tablets is 48 months when stored at controlled room temperature 20-25 °C (68-77 °F). The expiry for calcium carbonate tablets is adequately supported by the available stability data.**

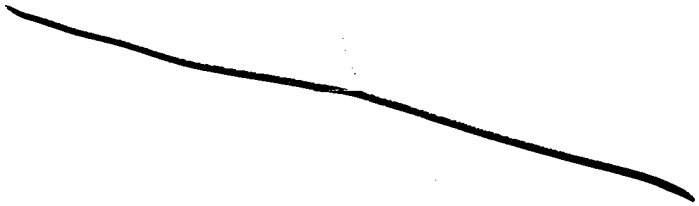
Drug Substance:

Risedronate Sodium for Actonel®

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. Risedronate sodium is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism.

Calcium Carbonate for Calcium Carbonate Tablets

Calcium carbonate is supplied as a calcium carbonate/starch [redacted] discussed in DMF [redacted] and found adequate. Calcium carbonate occurs in



B. Description of How the Drug Product is Intended to be Used

Actonel® [redacted] Calcium is a co-package of risedronate sodium tablets (35 mg) and calcium carbonate tablets, USP (1250 mg). Each package of Actonel® [redacted] Calcium is intended to deliver a 28-day regimen [redacted]. One tablet of Actonel® is to be administered once a week; one calcium carbonate tablet is to be administered daily on each of the remaining six days of the week.

Patients are instructed to swallow the whole Actonel® tablet (do not chew the tablet or keep it in the mouth to melt or dissolve), on the same day of the week, first thing in the morning with 6-8 oz. of water while sitting or standing. Patients are also instructed to start their daily activities, but not to lie down, eat, drink, or take any other medications for 30 minutes. Patients are advised to take supplemental vitamin D if dietary intake is inadequate. Calcium supplements and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of Actonel®. Therefore, if additional supplemental calcium were to be taken, calcium should be taken at a different time of the day and with food.

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.

The current expiry for Actonel® is 36 months when stored at controlled room temperature 20-25 °C (68-77 °F). The proposed expiry for calcium carbonate tablets is 48 months when stored at controlled room temperature 20-25 °C (68-77 °F). The proposed expiry for calcium carbonate tablets is adequately supported by the available stability data. The expiration date of each batch of the Actonel® [redacted] Calcium co-package will be the earliest expiration date of either of the component products used in the specific batch of the combination pack.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-823 is recommended for **Approval** from the standpoint of chemistry, manufacturing and controls (CMC) pending minor revisions to the labeling.

Approval is based on the following criteria:

- Actonel® is a currently approved drug product (NDA 20-835) with no outstanding CMC issues.
- Adequate CMC information was provided for the calcium carbonate/starch [redacted] (drug substance).
- Adequate CMC information was provided for the calcium carbonate tablets, USP (drug product).
- Adequate stability data was provided to support the proposed expiration dating period for the calcium carbonate tablets, USP (48 months).
- Overall cGMP status, for all manufacturing and testing facilities, for both Actonel® tablets (35 mg) and calcium carbonate tablets, USP (1250 mg), was found acceptable.

III. Administrative

A. Reviewer's Signature in DFS

B. Endorsement Block in DFS

C. CC Block in DFS

30 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yvonne Yang
6/29/05 01:20:27 PM
CHEMIST

Sheldon Markofsky
6/29/05 01:54:34 PM
CHEMIST
Signed by S. Markofsky, Acting Team Leader, for Mamta Gautam-Basak

NDA FILEABILITY CHECKLIST

NDA Number: 21-823
Applicant: Procter & Gamble Pharmaceuticals, Inc.
Letter Date: Aug-30-2004
Drug Name: Actonel® [redacted] Calcium
(a combination package Actonel® tablets, 35 mg and calcium carbonate tablets, 1250 mg, USP)

1. Is the CMC Section of the Application Fileable? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?		X	Vol. 1.3, p. 21 Vol. 1.3, pp. 44, 118
5	Is a statement provided that all facilities are ready for GMP inspection?	X		Cover letter: Vol. 1.1, p. 5
6	Has an environmental assessment report or categorical exclusion been provided?	X		Vol. 1.1, p. 51 Claims categorical exclusion: 21 CFR 25.31(b) and 25.31(c)
7	Does the section contain controls for the drug substance?	X		Residronate: referenced to NDA 20-835 Calcium carbonate/starch [redacted] in application Vol. 1.3, pp. 13-15
8	Does the section contain controls for the drug product?	X		Actonel® tablet: referenced to NDA 20-835 Calcium carbonate tablet: USP monograph cited in application (Vol. 1.3, p. 55)
9	Has stability data and analysis been provided to support the requested expiration date?	X		DS: Vol. 1.3, pp. 17-24 DP: Vol. 1.3, pp. 80-120
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	N/A
11	Have draft container labels been provided?	X		Vol. 1.1, pp. 175-178
12	Has the draft package insert been provided?	X		Vol. 1.1, pp. 73-130
13	Has an investigational formulations section been provided?	X		Vol. 1.3, section 4.E.1, pp. 28-31
14	Is there a Methods Validation package?		X	Actonel® tablets: currently approved Calcium carbonate tablets: USP methods
15	Is a separate microbiological section included?		X	N/A

Review Chemist: Yvonne Yang, Ph.D. Date: Oct-07-2004
Team Leader: Mamta Gautam-Basak, Ph.D.

cc: Original NDA 21-823
HFD-510/Division File
HFD-510/R Hedin/Y Yang/M Gautam-Basak

NDA Number: 21-823
Applicant: Procter & Gamble Pharmaceuticals, Inc.
Drug Name: Actonel® [redacted] Calcium

2. Stability Data Required For Fileability:

	Stability Data Required	Yes	No
1	Does the NDA include 12 or more months of stability data?	X	
2	Does the stability data cover the expiry date?	X	
3	Does the stability data include only the largest & smallest container sizes?	Only one size	
4	Does the stability data include all package sizes?	X	
5	Are there tabular data for each size and batch?	X	
6	Are there graphical data for each size and batch?		X Not needed
7	Is a statistical consult required?		X
8	Is a stability protocol included?	X	
9	Are the stability indicating assays described?	X (USP methods)	
10	Is there the three point stability commitment?		X

3. Have all DMF References been Identified? **Yes**

DMF No.	DMF Holder	Description	LOA Included	Status
[redacted]			Dated Apr-22-2004 (Vol. 1.3, p. 8)	Need to be reviewed
			Dated May-10-2004 (Vol. 1.3, p. 64)	Need to be reviewed
			Dated Apr-13-2004 (Vol. 1.3, p. 39)	Need to be reviewed
			Dated May-06-2004 (Vol. 1.3, p. 63)	Adequate

Draft Information Request to be Included in the 74-Day Filing Review Letter:

1. Please provide information regarding all of the facilities (including contract facilities and test laboratories) identified with full street addresses, CFN numbers, and its respective functions.

2. Please provide the appropriate stability commitment.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yvonne Yang
10/12/04 03:45:13 PM
CHEMIST

Mamta Gautam-Basak
10/12/04 04:01:52 PM
CHEMIST
Concur, Can be Filed

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-823

PHARMACOLOGY REVIEW

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA #: 21-823

Product Name : Actonel [redacted] calcium
(risedronate sodium & calcium carbonate)

Sponsor: Procter & Gamble

Indication: treatment & prevention of osteoporosis

Division: DMEDP

Reviewer: Karen Davis-Bruno

Date: 4/18/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-823**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**9/1/04**
PRODUCT:	**Actonel [redacted] calcium (risedronate + $CaCO_3$)**
INTENDED CLINICAL POPULATION:	**treatment & prevention of osteoporosis**
SPONSOR:	**Procter & Gamble**
DOCUMENTS REVIEWED:	**Vol. 1-3**
REVIEW DIVISION:	**Division of Metabolic & Endocrine Drug Products**
(HFD-510)	
PHARM/TOX SUPERVISOR:	**Karen Davis-Bruno**
DIVISION DIRECTOR:	**David Orloff**
PROJECT MANAGER:	**Randy Hedin**

Date of review submission to Division File System (DFS): 4/18/05

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: approval (AP)

B. Recommendation for nonclinical studies: N/A

C. Recommendations on labeling- for track changes see pg. 13

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 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/m2), 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
In a 104-week carcinogenicity study, rats were administered daily oral doses up to 24 mg/kg/day (approximately 50 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m2). 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/m2). There were no significant drug-induced tumor findings in male or female mice.

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 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/m2). 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/m2). 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/m2). 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/m2).

Pregnancy:

Pregnancy Category C: Survival of neonates was decreased in rats treated during gestation with oral doses ≥ 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/m2). 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/m2). Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses ≥ 16 mg/kg/day (approximately 30 ~~5.2~~ 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 ≥ 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/m2). 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/m2) has resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The [redacted] of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the [redacted] dose and duration of bisphosphonate use. [redacted]

[redacted] 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 [redacted]

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:

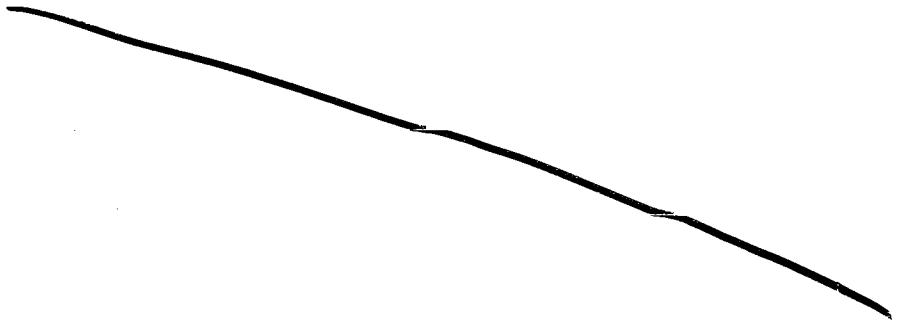
Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period postdosing, indicating a small degree of lacteal transfer. It is not known whether risedronate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse 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.

OVERDOSAGE

ACTONEL

Decreases in serum calcium and phosphorus following substantial overdose may be expected insome 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 >1000 times the 35 mg/week human dose based on surface area (mg/m2).

CALCIUM



II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: A complete nonclinical development program including pharmacology, pharmacokinetics, single and repeat dose toxicity, genotoxicity, carcinogenicity, and reprotoxicity were performed for Actonel (risedronate) in NDA 20-835 which includes marketing of a 35 mg/week dose for postmenopausal osteoporosis. Referenced published literature for calcium carbonate has been provided. Publications have recommended increased intake of calcium, particularly for the elderly. Intake up to 1500 mg/day or twice the current RDA=800 mg/kg/day has been advised. Adverse effects of combined dietary and supplemental calcium >2g/day have been associated with adverse effects such as renal failure, soft tissue calcification, irritability, headache and clinical signs. Toxic levels of calcium in animals have been reported to cause osteochondrosis, renal failure and death. The proposed supplementation with Actonel [redacted] Calcium is 1250 mg/day calcium carbonate (500 mg elemental calcium).

B. Pharmacologic activity

Actonel has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent and inhibits osteoclasts. Histomorphometry in animals has shown reduced bone turnover (the rate of bone remodeling initiation). Calcium has been associated with bone health. Inadequate calcium may result in fractures and reduced bone mass. Calcium is needed for mineralization and has an antiresorptive effect on bone, suppresses PTH and decreases bone turnover.

C. Nonclinical safety issues relevant to clinical use: N/A

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

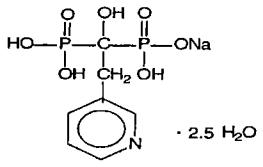
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-823
Review number: 1
Sequence number/date/type of submission: 000, 9/1/04
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Proctor & Gamble
Manufacturer for drug substance: Risedronate P&G or [redacted]

Reviewer name: Davis-Bruno
Division name: DMEDP
HFD #: 510
Review completion date: 4/18/05

Drug:

Trade name: Actonel +calcium
Generic name: risedronate sodium + $CaCO_3$
Code name: NE-5095 (risedronate)
Chemical name: 1-hydroxy-2-(3-pyridinyl)[ethylidene] bis[phosphonic acid] monosodium salt and calcium carbonate CAS registry #471-34-1
Structure/Molecular formula/molecular weight: $CaCO_3$ =100.09; risedronate



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.

Inactive ingredients for $CaCO_3$: pregelatinized starch, sodium starch glycolate, FD&C Blue #2, magnesium stearate, polyethylene glycol 3350, hypromellose, Opaspray Light Blue, polysorbate 80

Relevant INDs/NDAs/DMFs: IND 31,029, NDA 20-835

Drug class: bisphosphonate + carbonic acid, calcium salt

Intended clinical population: treatment and prevention of osteoporosis

Route of administration: oral tablets co-packaged

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-823 are owned by Proctor & Gamble or are data for which they have obtained a written right of reference. Any information or data necessary for approval of NDA 21-823 that Proctor & Gamble does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Proctor & Gamble does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-823.
Studies reviewed within this submission: N/A
Studies not reviewed within this submission: **N/A**

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary see NDA 20-835

2.6.2.2 Primary pharmacodynamics

Mechanism of action:
Actonel has an affinity for hydroxyapatite crystals in bone and acts as an anti-resorptive agent. Actonel inhibits osteoclast activity. Histomorphometry data in rats, dogs and minipigs demonstrate reduction of bone turnover (activation frequency; the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites with Actonel administration.
Calcium is a major substrate for mineralization and has antiresorptive effects 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 where increased bone turnover is a risk factor for fractures.

Drug activity related to proposed indication: references provided
1. J. Bone & Mineral Research 12(97):820-831
Female Wistar rats (4.5 months old) were treated as 1) control, 2) sham operation, 3) sham + low Ca diet, 4) ovariectomized (ovx), 5) ovx + low Ca diet, 6) ovx +estrogen and 7) ovx + low Ca diet + estrogen and observed for 3, 6, 9 months post-surgery. Low dietary calcium reduced bone mineral, geometry, and strength, exerted a great potential for weakening cortical bone and synergistically accelerated ovx-induced osteopenia.

2. Jap J Pharmacol. 71(3):239-246, 1996
Calcium restricted diets decreased lumbar BMD by 19% at month 2 and 30% by month 17 compared to baseline in dogs, but ovx had a minimal effect on bone mass in dogs with restricted calcium uptake. The magnitude of the BMD reduction of the forelimb was less remarkable than the lumbar spine. Urinary hydroxyproline excretion and plasma osteocalcin levels were increased by calcium restriction suggesting a high bone turnover.

3. J Bone & Mineral Research 10(1):81-95; 1995
Weanling rats were given various calcium diets (0.25%-deficient, 0.5%-normal , 1 % - excess calcium) for 8 weeks. An additional 3 groups given 0.25% for 8 weeks and were further randomized into three diet groups and fed until 37 weeks old. Increasing calcium intake after adolescence (12 week old) in females consuming a low calcium diet will not substantially alter the adult bone volume in the metaphyseal region of the proximal tibia. Low calcium intakes through adolescence retard and prolong longitudinal bone growth. However rats fed a diet providing 0.5% calcium or twice the required level (1%) through adolescence had greater tibial bone volume as an adult fed diets containing 1% calcium after this time period. The mechanism appears to involve a protection from resorption and increased bone formation/mineralization. Low calcium intakes through adolescence have an irreversible, deleterious effect on bone mass, whereas higher intakes promote greater peak bone mass and provide potential protection from age-related bone loss.

4. Bone 16(5):575-582; 1995
Female Wistar rats (1.5 months old) were fed diets containing twice the concentration of vitamin D and calcium (1.2%/kg diet) as in the usual diet (calcium 0.6%/kg diet). At 24 months old significantly higher bone mineral density (62%, 48%) and vertebral calcium content (73%, 84%) were found in these respective groups than in controls. Vertebral alkaline phosphatase was significantly lower (-47%, -45%) in the enriched diet groups than controls. Likewise the ratio of alkaline phosphatase/acid phosphatase activity was markedly reduced (-57%, -59% respectively) suggesting a diminished rate of bone turnover. The trabecular bone volume decreased in all groups during aging although the calcium enriched diet fed rats was elevated compared to controls. Vitamin D and calcium increased the axial bone mineral content and reduce bone turnover. The effect on trabecular bone was not investigated.

5. Bone 16(1):149-156; 1995
Authors use a rat model of postmenopausal osteoporosis to examine histomorphometry, bone markers and bone mineral changes induced by 1 month of estrogen and/or dietary calcium deficiency in the mature rat. Seven treatment groups were examined: 1) control 2) sham, fed 0.1% calcium (deficient) diet 3) sham, fed regular 1% calcium diet 4) ovx on calcium deficient diet 5) ovx on a regular calcium diet 6) ovx on calcium deficient diet with estrogen and 7) ovx on a regular calcium diet with estrogen. Ovariectomy or low calcium elevated bone turnover markers (osteocalcin, pyridinolone). Reductions in cancellous bone mass and trabecular connectivity were observed. Ovariectomy plus low calcium resulted in a greater increase in osteocalcin and pyridinolone and greater decrease in cancellous bone mass and trabecular connectivity. Estrogen treatment was

effective in preventing bone loss from estrogen and calcium deficiencies. Using BMD measurements, the authors observed that dietary calcium deficiency induced bone loss in both cancellous-rich and cortical-abundant sites whereas estrogen deficiency affected cancellous-rich bone sites only.

2.6.2.3 Secondary pharmacodynamics See NDA 20-835
2.6.2.4 Safety pharmacology See NDA 20-835
2.6.2.5 Pharmacodynamic drug interactions
See NDA 20-835

2.6.3 PHARMACOLOGY TABULATED SUMMARY
See NDA 20-835

2.6.4 PHARMACOKINETICS/TOXICOKINETICS
See NDA 20-835

2.6.5 PHARMACOKINETICS TABULATED SUMMARY
See NDA 20-835

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary
See NDA 20-835

2.6.6.2 Single-dose toxicity See NDA 20-835

2.6.6.3 Repeat-dose toxicity See NDA 20-835

2.6.6.4 Genetic toxicology See NDA 20-835

2.6.6.5 Carcinogenicity See NDA 20-835

2.6.6.6 Reproductive and developmental toxicology See NDA 20-835 and published reference below regarding fertility effects of calcium

Fertility and early embryonic development

Fd Chem Toxic 31(12):953-961; 1993
This study evaluated the developmental effects of moderate increases in dietary calcium in rats. Female rats were given 0.5 (control), 0.75, 1, 1.25% dietary calcium carbonate for 6 weeks before mating, through gestation day 20. Caesarean sections were performed on gestation day 20 with unremarkable findings.

2.6.6.7 Local tolerance See NDA 20-835

2.6.6.8 Special toxicology studies See NDA 20-835

2.6.6.9 Discussion and Conclusions See NDA 20-835

2.6.6.10 Tables and Figures See NDA 20-835

2.6.7 TOXICOLOGY TABULATED SUMMARY See NDA 20-835

OVERALL CONCLUSIONS AND RECOMMENDATIONS

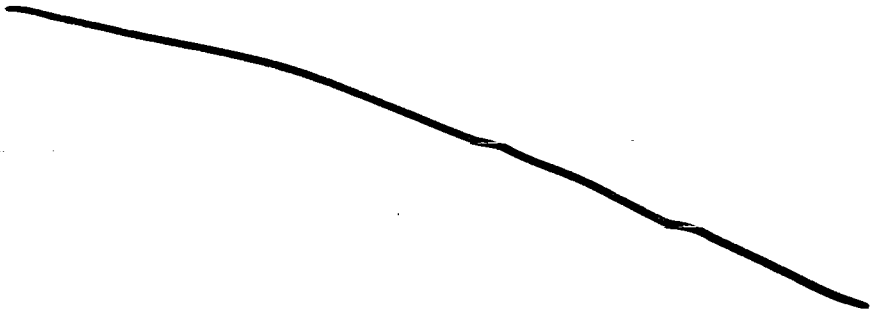
Conclusions: This application proposes a co-package of risedronate (35 mg/week) and calcium (500 mg/day for 6 days elemental calcium, 1250 mg/day $CaCO_3$) for prevention and treatment of osteoporosis. Risedronate (Actonel) was approved for marketing as NDA 20-835 which includes a 25 mg/week dose for treatment of postmenopausal osteoporosis. The intention of co-packaging with calcium is convenience and increased patient compliance with a daily osteoporosis treatment program. Calcium supplementation at 1200 mg/day in addition to vitamin D (400-800 IU/day) is considered part of the standard of care for treatment of osteoporosis. The 1,25 dihydroxy-vitamin D is needed to increase calcium transport in the small intestine and colon. The calcium is not provided on the same day as the Actonel administration in this co-packaged product. Daily intake of calcium <400 mg from all sources including diet, is associated with increased bone resorption and fracture risk. Intake of calcium >2 g/day is associated with adverse effects due to hypercalcemia including renal stones. The clinical sequelae of calcium homeostasis is well established in humans and animals.

Unresolved toxicology issues: none

Recommendations: Approval (AP)

Suggested labeling: Labeling changes reflect calculation of the exposure multiples based on the proposed 35 mg/week human dose (3 mg/m^2).

ANIMAL PHARMACOLOGY AND/OR TOXICOLOGY
ACTONEL



4 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Pharm/Tox-*1

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/s/

Karen Davis-Bruno
4/14/05 03:42:46 PM
PHARMACOLOGIST
AP pending labeling changes

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA #21-823
Original Submission
Actonel® [redacted] Calcium
Procter and Gamble Pharmaceuticals, Inc.
Date received: September 1, 2004

NDA #:	21-823
Submission date:	August 30, 2004
Drug:	Risedronate [redacted] calcium carbonate (copackaged)
Dosage form:	Tablets: 35 mg Actonel (take once a week), plus 1250 mg calcium carbonate (500 mg Ca) taken daily on each of remaining six days of 7-day treatment cycle
Indications:	Treatment and prevention of osteoporosis in postmenopausal women
IND#:	31,029

This new NDA is for a co-package of risedronate (35 mg/week) and calcium (500 mg/day, for 6 days). Proposed indications are prevention and treatment of postmenopausal osteoporosis, [redacted]. The calcium is not taken on the day of dosing with the antiresorptive. Originally, the recommended oral human dose for osteoporosis was a daily dose of 5mg. Subsequently, treatment with a weekly dose of 35 mg/day was studied and approved for postmenopausal osteoporosis.

The application was submitted as a new NDA because the calcium is considered a new drug product, not a dietary supplement. The NDA was submitted in paper and electronic format, and consists of new labeling (PI and PIL, electronic) with supporting clinical and nonclinical references for the effects of calcium, an application summary, and a CMC section. No new nonclinical or clinical studies were performed by the applicant.

A complete Pharm/Tox development program, including pharmacology, pharmacokinetics, single and repeat dose toxicity, carcinogenicity, reprotoxicity, genotoxicity, and special toxicity studies has been carried out with risedronate (NDA 20-835). Cross reference is made to Item 5 of NDA 20-835 for all nonclinical studies.

The new label describes the effects of ACTONEL and CALCIUM separately in the various labeling sections and is annotated with references to published literature for the effects of calcium. For Pharmacology/ Toxicology, the following labeling sections need to be reviewed for adequacy: Clinical Pharmacology, Animal Pharmacology/Toxicology, Precautions (Mutagenesis, Fertility), Overdosage.

From the point of view of Pharmacology/Toxicology this NDA can be filed.

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be	X		

completed?			
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission, communications/discussions, completed and submitted in this NDA?	X		
Have electronic files of the carcinogenicity studies been submitted for statistical review?	N/A		
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	N/A		

6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	N/A		
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	N/A		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file: N/A			

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-823

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-823
Submission Date	August 31, 2004, Original; January 13, 2005, N-000-BB
Brand Name	ACTONEL© [redacted]
Generic Names	Risedronate sodium and calcium carbonate
Reviewer	S.W. Johnny Lau
Team Leader	Hae-Young Ahn
OCPB Division	DPE II (HFD-870)
ORM Division	Metabolic and Endocrine (HFD-510)
Sponsor	Procter & Gamble Pharmaceuticals, Inc.
Relevant IND	31,029
Submission Type; Code	Original; S
Formulation; Strength(s)	Copackaged oral 35 mg risedronate tablet + 1250 mg $CaCO_3$ tablet
Indication	To treat and prevent osteoporosis [redacted]

Table of Contents **Page**

1 Executive Summary

The sponsor submitted NDA 21-823 to seek approval for the copackaged oral weekly 35 mg risedronate tablet and oral daily (for the remaining 6 days of the weekly treatment cycle) 1250 mg calcium carbonate tablet for the following proposed indications:

- to treat osteoporosis in postmenopausal women
- to prevent osteoporosis in postmenopausal women
- [redacted]

The sponsor markets the oral weekly 35 mg risedronate tablet for the same proposed indications above [redacted] The approved risedronate labeling recommends "Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. 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." Risedronate is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption as well as turnover.

The sponsor did not conduct any clinical efficacy/safety study and neither did any clinical pharmacology and biopharmaceutics study to support NDA 21-823. The sponsor referenced risedronate original NDA's (20-835) Human Pharmacokinetics and Bioavailability section for NDA 21823. Per prior agreement with the Division of Metabolic and Endocrine drug Products, the sponsor did not provide the Human Pharmacokinetics and Bioavailability section for calcium but provided annotated labeling for calcium with copies of supporting references.

The sponsor will not change the components, composition, manufacturing sites, manufacturing process, or specification for the approved 35 mg risedronate tablet.

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) reviewed NDA 21-823's clinical pharmacology and biopharmaceutics information and finds it acceptable, if the sponsor agrees to the labeling comments from pages 5 - 13 of this review.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The calcium carbonate tablets that were used in the pivotal clinical studies for risedronate's original NDA approval were identical to the to-be-marketed calcium carbonate tablets for NDA 21-823. The in vitro dissolution of the calcium carbonate tablets that were used in the pivotal clinical studies for risedronate's original NDA approval met the USP acceptance criterion. The to-be-marketed calcium carbonate tablets will meet USP monograph's in vitro dissolution method and acceptance criterion.

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-823 was conducted on May 31, 2005; participants included H. Malinowski, J. Hunt, Ahn, and J. Lau.

FT signed by Hae-Young Ahn, Ph.D., Team Leader 5/ /05

2 Question-Based Review

2.1 General Attributes

2.1.1 What are the formulation for the to-be-marketed 35 mg risedronate and 1250 mg calcium carbonate tablets?

The sponsor will not change the components, composition, manufacturing sites, manufacturing process, or specification for the approved 35 mg risedronate tablet, which is the to-be-marketed 35 mg risedronate tablets. Table 1 below details the to-be-marketed 1250 mg calcium carbonate tablet's composition as:

Ingredient	Function	Unit Quantity (mg/tablet)
[redacted]		
Calcium carbonate, USP	Active	1250.0[a,b]
Pregelatinized starch, NF	[redacted]	
Sodium starch glycolate, NF		
Magnesium stearate, NF		
FD&C Blue #2 Aluminum Lake		
Subtotal		
[redacted]		
Polyethylene glyco[redacted]		
Hypromellos[redacted]		
Opaspray Blu[redacted]		
[redacted]		
Polysorbate 80, NF		
Purified water, USP[d]		
Subtotal		

Target Total Film-Coated Tablet Weight = 1392.4 mg

a Equivalent to 500 mg elemental calcium.

[redacted]

a

2.1.2 What is NDA 21-823's proposed indication and dosage regimen?

To treat and prevent osteoporosis in postmenopausal women [redacted]
Patients should orally take a 35 mg risedronate tablet once a week and then orally take a 1250 mg calcium carbonate tablet daily for the remaining 6 days of the 7-day treatment cycle.

2.2 General Clinical Pharmacology

Risedronate's clinical pharmacology information is available in:

- Dunn and Goa. Risedronate: a review of its pharmacological properties and clinical use in resorptive bone disease. *Drugs* **61**:685-712 (2001)
- J.H. Lin. Bisphosphonates: a review of their pharmacokinetic properties. *Bone* **18**:75-85 (1996)

Calcium's clinical pharmacology information is available in:

- Rodriguez-Martinez et al. Role of Ca^{2+} and vitamin D in the prevention and treatment of osteoporosis. *Pharmacol Ther* **93**:37-49 (2002)

2.2.1 How are the risedronate and calcium doses selected for the copackaged product?
The proposed oral 35 mg risedronate weekly dosing via the copackaged product is the same as the approved oral 35 mg risedronate alone tablet weekly dosing. The NIH Consensus Conference report (*JAMA* **272**:1942-8 (1994)) recommends oral daily 1000 – 1500 mg elemental calcium intake for postmenopausal women. The proposed oral 500 mg elemental calcium daily dosing contributes to part of the recommended daily elemental calcium intake for postmenopausal women.

2.3 General Biopharmaceutics
2.3.1 Does difference exist between the to-be-marketed formulation and the clinically-tested formulation?
No. The to-be-marketed risedronate tablet in the copackaged product is the same as the approved 35 mg risedronate tablet. The to-be-marketed calcium carbonate tablet is the same as the calcium carbonate tablet that was used in the pivotal clinical Phase III studies that supported risedronate's NDA 20-835/S001.

2.3.2 What is evidence that supports the in vivo bioavailability of the to-be-marketed 1250 mg calcium carbonate tablet?
The key clinical pharmacology and biopharmaceutics issue for this copackaged 35 mg risedronate tablet and 1250 mg calcium carbonate tablet product is to establish the evidence of in vivo bioavailability for its calcium component, which can be shown via (see Attachment):

- CFR 320.24(b)(4) Well-controlled clinical trials in humans that establish the safety and effectiveness of the drug product, for purposes of establishing bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. Reasons:
  - The sponsor used identical formulation as the to-be-marketed calcium carbonate tablet in the Phase III pivotal studies for NDA 20-835/S-001 of 5 mg risedronate daily in the treatment and prevention of postmenopausal osteoporosis. The manufacturing and testing specifications of these calcium carbonate tablets met USP acceptance criteria.

2.3.3 What is the proposed in vitro dissolution test and acceptance criterion for the calcium carbonate tablet?
The sponsor proposed the USP test monograph for calcium carbonate tablets and its in vitro dissolution method and acceptance criterion follow (Table 2):

	Calcium Carbonate
Apparatus	USP Type 2 (paddle)
In vitro dissolution medium	0.1 N hydrochloric acid
Volume of dissolution medium	900 mL
Medium temperature	37 ± 0.5°C
Stirring speed	75 rpm
Sampling Time	30 minute
Acceptance criterion	Not less than [redacted] (Q) of the labeled amount of $CaCO_3$ is dissolved in 30 minutes

2.4 Analytical
Are the bioanalytical methods used to support NDA 21-823 acceptable?
Not applicable since no clinical study was conducted.

9 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	21-823	Brand Name	ACTONEL® [redacted]
OCPB Division	2	Generic Name	Risedronate Na + $CaCO_3$
Medical Division	DMEDP, HFD-510	Drug Class	Bisphosphonate + Ca
OCPB Reviewer	S.W. Johnny Lau	Indication(s)	Treat/prevent osteoporosis + [redacted]
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Copackaged tablets
Date of Submission	30-AUG-2004	Dosing Regimen	1 ACTONEL® tab/week & 1 $CaCO_3$ tab/day
Estimated Due Date of OCPB Review	5-MAY-2005	Route of Administration	Oral
Division Due Date	26-MAY-2005	Sponsor	P&G Pharmaceuticals, Inc.
PDUFA Due Date	30-JUN-2005	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	x			Published literature: 11 articles for Clinical Pharmacology section; 7 articles for Drug Interactions section
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		Published book chapter
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		Published literature
multiple dose:				
Patients-				
single dose:	X	3		Published literature
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	4		Published literature
In-vivo effects of primary drug:	X	3		Published literature
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1		Published literature
pediatrics:				
geriatrics:	X	1		Published literature
renal impairment:				
hepatic impairment:				
Achlorhydria	[redacted]	[redacted]		Published literature
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
Bioequivalence studies -				
traditional design; multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	18		Published literature

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	X	• Did the in vitro dissolution of the calcium carbonate tablets that were used in the pivotal clinical studies for risedronate's original NDA approval meet the USP acceptance criteria? • Were the calcium carbonate tablets that were used in the pivotal clinical studies for risedronate's original NDA approval identical to the to-be-marketed calcium carbonate tablets for NDA 21-823?
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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/s/

S.W. Johnny Lau
11/9/04 07:19:55 PM
BIOPHARMACEUTICS

Hae-Young Ahn
11/29/04 10:54:49 AM
BIOPHARMACEUTICS

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA:	21-823
Compound:	Risedronate sodium plus calcium carbonate (ACTONEL® [redacted]
Sponsor:	P & G Pharmaceuticals. Inc.
Submission Date:	August 30, 2004
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor submitted NDA 21-823 to seek approval for the copackaged weekly oral 35 mg risedronate + daily oral 1250 mg calcium carbonate (except the day taking risedronate) tablets to:

- treat osteoporosis in postmenopausal women
- prevent osteoporosis in postmenopausal women
- [redacted]

The sponsor markets the weekly oral 35 mg risedronate tablet (ACTONEL®), which has the following indications:

- treatment of osteoporosis in postmenopausal women
- prevention of osteoporosis in postmenopausal women
- prevention and treatment of glucocorticoid induced osteoporosis
- treatment of Paget's disease

[redacted] that the calcium component of ACTONEL® [redacted] is a new drug product.

Findings

The sponsor:

- did not conduct any study to support NDA 21-823
- referenced NDA 21-823's Human Pharmacokinetics and Bioavailability section to that of NDA 20-835's. ACTONEL®'s approval is under NDA 20-835.
- proposed labeling with annotation for calcium
- provided 11 and 7 published articles to support the Clinical Pharmacology and Drug Interactions sections, respectively, for the calcium labeling changes from the ACTONEL® label.
- stated that "The drug product will meet USP criteria for calcium carbonate tablets." The USP does have a monograph for calcium carbonate tablet, which has the in vitro dissolution method and acceptance criteria (tolerance).

The filing meeting was on October 7, 2004.

[redacted]

3 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

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/s/

S.W. Johnny Lau
5/31/05 05:18:47 PM
BIOPHARMACEUTICS

Hae-Young Ahn
6/14/05 11:23:33 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-823

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Vol 1/p 20

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-823

NAME OF APPLICANT / NDA HOLDER
Procter & Gamble Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Actonel Calcium

ACTIVE INGREDIENT(S)	STRENGTH(S)
risedronate sodium and calcium carbonate	35 mg and 1250 mg (500 mg elemental), respectively

DOSAGE FORM
Oral

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,583,122	12/10/1996	12/10/2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
The Procter & Gamble Company	1 Procter & Gamble Plaza	
	City/State: Cincinnati, OH	
	ZIP Code: 45202	FAX Number *(if available)*
	Telephone Number: 513-622-5502	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 20, 21 and 23	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Actonel (risedronate sodium tablets) is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
MP McMahon	08/26/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

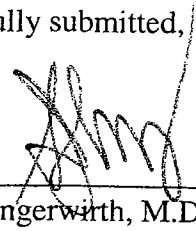
☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Mary Pat McMahon	
Address 8700 Mason Montgomery Road	City/State Mason, OH
ZIP Code 45040	Telephone Number 513-622-5502
FAX Number *(if available)* 513-622-3300	E-Mail Address *(if available)* mcmahon.mp@pg.com

Certification Pursuant to the Generic Drug Enforcement Act of 1992

No clinical studies are included as part of NDA #21-823. In compliance with 21 CFR 314 Procter & Gamble Pharmaceuticals hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA #21-823.

Respectfully submitted,



Steven Jungerwirth, M.D.
Director
Global Clinical Development and Clinical Operations
Procter & Gamble Pharmaceuticals

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 4, 2005

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510

VIA: Randy Hedin, Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products, HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of the Patient Labeling (PPI) for
Actonel with Calcium (risedronate sodium tablets) and (calcium carbonate tablets), NDA 21-823

Background and Summary

The patient labeling which follows is our recommend revised Patient Labeling for Actonel with Calcium (risedronate sodium tablets) and (calcium carbonate tablets), NDA 21-823. Actonel already has an approved PPI and the sponsor proposed revisions to reflect the addition of calcium. We have simplified the wording, made it consistent with the PI, and removed other unnecessary information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor on July 18, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI

Comment

The sponsor states in the **PI, PRECAUTIONS section, Information for patients subsection,** "Physicians should instruct their patients to read the Patient Information before starting therapy with Actonel and to re-read it each time a prescription is renewed." Since distribution of the PPI would be voluntary, the sponsor should state how a patient is to obtain the PPI for Actonel with Calcium. The sponsor could package the PPI with the product as the product is packaged in unit-of use packaging. If the sponsor does not plan on packaging the PPI with the product then the above

statement in the PI should be revised to reflect the mechanism(s) available for a patient to obtain the PPI.

We can provide a marked and clean copy of our revisions in Word. Please call us if you have any questions.

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: November 4, 2004	**DESIRED COMPLETION DATE:** January 4, 2004 **PDUFA:** June 30, 2005	**ODS CONSULT #:** 04-0281

TO: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Randy Hedin
Project Manager
HFD-510

PRODUCT NAME: **Actonel [redacted] Calcium** (Risedronate Sodium) Tablets 35 mg and (Calcium Carbonate) Tablets 1250 mg **NDA#: 21-823**	**NDA SPONSOR:** Proctor & Gamble Pharmaceuticals, Inc.

SAFETY EVALUATOR: Nora Roselle, PharmD

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Actonel [redacted] Calcium. In addition, DMETS does not recommend co-packaging the two products, Actonel and Calcium, as proposed. We recommend implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

2. DDMAC finds the proprietary name, Actonel [redacted] Calcium, acceptable from a promotional perspective.

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Carol Holquist
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 28, 2004

NDA#: 21-823

NAME OF DRUG: **Actonel [redacted] Calcium**
(Risedronate Sodium) Tablets 35 mg
and (Calcium Carbonate) Tablets 1250 mg

NDA HOLDER: Proctor & Gamble Pharmaceuticals, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the proprietary name "Actonel [redacted] Calcium", regarding potential name confusion with other proprietary or established drug names. Draft blister labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Actonel [redacted] Calcium is a dose pack containing both Actonel tablets and Calcium tablets. Actonel Calcium is indicated for the treatment and prevention of osteoporosis in postmenopausal women [redacted] Actonel [redacted] Calcium will be supplied in a 28 day dose pack containing four Actonel tablets (35 mg) and twenty-four calcium carbonate tablets (1250 mg calcium carbonate equivalent to 500 mg elemental calcium). The recommended regimen for the treatment and prevention of postmenopausal osteoporosis is one 35 mg Actonel tablet taken once a week and one 1250 mg calcium carbonate tablet taken daily on each of the remaining six days of the 7-day treatment cycle. According to the proposed package insert, Actonel should be taken at least 30 minutes before the first food or drink of the day other than water. Actonel should be swallowed while the patient is in an upright position and with a full glass of plain water. Patients should not lie down for 30 minutes after taking the medication. In addition, calcium should be taken at a different time of the day and with food.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Actonel [redacted] Calcium to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Actonel [redacted] Calcium. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Actonel [redacted] Calcium, acceptable from a promotional perspective.

2. Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Actonel [redacted] Calcium. These products are listed in table 1 (see page 4), along with the dosage forms available and usual dosage. Additionally, the Expert Panel noted that the modifier [redacted] Calcium" might be disregarded, omitted, or abbreviated ("+ Calcium" or "+ Ca") on a prescription order.

[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, 2005, Facts and Comparisons, St. Louis, MO.
[3] The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, Drugs@FDA, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by [redacted]

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other
Actonel [redacted] Calcium	**Risedronate Sodium Tablets: 35 mg and Calcium Carbonate Tablets: 1250 mg**	**Actonel: Take one Actonel tablet by mouth once weekly. Actonel should be taken at least 30 minutes before the first food or drink of the day other than water. Calcium: Take one calcium tablet once daily with food on each of the remaining six days of the 7-day treatment cycle.**	
Actonel	Risedronate Sodium Tablets: 5 mg and 30 mg Once-a-week tablet dose pack: 35 mg (4 tablets per pack)	Postmenopausal Osteoporosis treatment and prevention: 5 mg by mouth once daily or 35 mg once a week Glucocorticoid-Induced Osteoporosis: 5 mg once daily Paget's Disease: 30 mg once daily for 2 months	Look-alike, Sound-alike
Actos	Pioglitazone HCl Tablets: 15 mg, 30 mg, and 45 mg	Monotherapy: Initial: 15 mg-30 mg once daily, maximum dose is 45 mg once daily. Combination therapy: Initial: 15 mg – 30mg	Look-alike
Actoplus Met*** (NDA 21-842) DMETS found name acceptable	Pioglitazone HCl and Metformin HCl Tablets, 15 mg/500 mg and 15 mg/850 mg	Dose should be individualized based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of the individual component (Actos 45 mg/day and Metformin 2550 mg/day)	Look-alike, Sound-alike
[redacted]			

*Frequently used, not all-inclusive.
NOTE: This review contains proprietary and confidential information that should not be released to the public.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA did not identify any additional names considered to have significant phonetic or orthographic similarities to Actonel [redacted] Calcium.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Actonel [redacted] Calcium with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Inpatient orders and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Actonel [redacted] Calcium (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Actonel [redacted] Calcium UD 1 month Supply	Actonel [redacted] Calcium Use as directed. Give one month supply.
Inpatient RX: ~~Actonel plus Calcium UD 1 mos supply~~	

2. Results:

One of the respondents from the written inpatient study misinterpreted the name to be Actonel, a currently marketed drug in the United States. In addition, misinterpretations of the modifier [redacted] Calcium" were also noted [redacted] See appendix A for the complete listing of interpretations from the verbal and written studies.

D. AERS SEARCH

A search of the FDA Adverse Event Reporting System (AERS) database was conducted in order to determine any post-marketing safety reports of medication errors associated with Actonel. The MedDRA Preferred Terms (PTs), "Medication Error", and the drug names "Actonel%" and "Risedronate%" were used to perform the search. These searches identified twenty cases of confusion with Actonel. The error reports received by the Agency are dated from 2001 to 2004.

The errors can be categorized as follows:

1. Wrong Dosing Interval (n=10)

Ten of the twenty cases involved the incorrect dosing regimen of Actonel 30 mg. Of the ten cases, eight described errors where Actonel 30 mg once weekly was prescribed, but Actonel 30 mg once daily was dispensed and administered to the patient. The remaining two cases involved mistakes where Actonel 30 mg once daily was prescribed instead of Actonel 30 mg once weekly. The cases involved a combination of prescribing, transcription, dispensing, and administration errors. Reported adverse events included headaches, nausea, upset stomach, leg pain, stomach pain, reflux, fatigue, joint pain, diarrhea, and back pain. Many of the error reports listed the indication of use as osteoporosis (6) or osteopenia (2). This prompted us to search the literature as Actonel 30 mg (once daily) is approved for the treatment of Paget's disease, while Actonel 5 mg (once daily) and Actonel 35 mg (once weekly) are approved for the treatment of osteoporosis. Various literature studies[6,7] from 2002 and 2003 show that Actonel 30 mg is being used once weekly for the treatment of osteoporosis and osteopenia. Thus, this helps us understand why there is confusion in practice as the drug is also being used off label once weekly for the treatment of osteoporosis and osteopenia in addition to once daily for the treatment of Paget's disease. However, this dual dosing schedule is not noticed in the package insert and pharmacists may not be aware of the alternate unapproved dosing regimens.

[6] Gordon MS, Gordon MB. Response of bone mineral density to once-weekly administration of risedronate. Endocr Pract. 2002 May-Jun;8(3):202-7.

[7] Delaney MF, Hurwitz S, Shaw J, LeBoff MS. Bone density changes with once weekly risedronate in postmenopausal women. J Clin Densitom. 2003 Spring;6(1):45-50.

2. Wrong Strength (n=3)

Three of the twenty cases involved confusion between Actonel 30 mg and Actonel 5 mg. In all three cases Actonel 30 mg was dispensed, but Actonel 5 mg was prescribed. One error was a dispensing error by a nurse and the remaining two were pharmacy dispensing errors. In all three cases, the patient was administered the incorrect dose. Reported adverse events included upset stomach, mouth blisters, swollen tongue, and "side effects".

3. Name Confusion (n=7)

The remaining seven cases described errors involving confusion between Actos and Actonel. The cases describe errors where Actos 30 mg was prescribed; however, Actonel 30 mg was dispensed (5) or vice versa (2). Poor handwriting, lack of knowledge, pharmacy distractions, and incorrect computer product selection were all mentioned in the report narratives as possible causes of the errors. It was noted by one reporter that the pharmacist selected the drug ACTOnel instead of ACTOs in the pharmacy computer system possibly by typing in the 1st four letters of the word and selecting the 1st drug name to come up. The patient was administered the incorrect drug in six of the seven cases. Adverse events such as kidney stones, elevated blood sugar levels, anaphylactoid reaction, and hospitalization were noted in the cases.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Actonel [redacted] Calcium, the primary concerns related to look-alike and sound-alike confusion with Actonel, Actoplus Met***, [redacted]*** Additionally, the use of the modifier [redacted] Calcium" was of concern and is discussed below. DMETS is also concerned with the proposed packaging of this drug product.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Actonel [redacted] Calcium could be confused with Actonel. One respondent from the written inpatient study interpreted the name as Actonel and omitted the modifier. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

1. Error Prone Packaging

DMETS believes that the two products, Actonel and Calcium, should not be co-packaged as currently proposed. Each of the drug products has a different dosing regimen. Actonel is to be taken once weekly and Calcium is to be taken once daily on each of the remaining six days of the 7-day treatment cycle. In addition, the sponsor indicates that the Actonel should be taken at least 30 minutes before the first food or drink of the day while Calcium should be taken with food. Actonel is taken on an empty stomach because the absorption of the drug is considerably reduced when taken with food. Calcium, on the other hand, is better absorbed by the body when taken with food.

*** **NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

We already have post-marketing errors with Actonel given daily vs. once weekly as noted in the AERS section (II-D) of the Risk Assessment. From the literature, it appears that Actonel 30 mg is being used off-label once weekly for the treatment of osteoporosis and osteopenia. Currently, Actonel 30 mg (once daily) is approved for the treatment of Paget's disease, while Actonel 5 mg (once daily) and Actonel 35 mg (once weekly) are approved for the treatment of osteoporosis. Co-packaging Actonel 35 mg (once weekly) with a product that is given once daily (calcium) may increase the risk of inadvertent daily administration of Actonel. If the Division proceeds with the approval of this proposed packaging, we recommend revising the labels and labeling as outlined in section III-C of this review.

2. Modifier Concerns

3. Look and Sound-Alike Name Confusion

a. Actonel has a look- and sound-alike similarity to Actonel [redacted] Calcium if the [redacted] Calcium" modifier is inadvertently omitted from the name since each name contains the root stem 'Actonel'. Actonel is used in the treatment and prevention of osteoporosis in postmenopausal women and in the treatment of Paget's Disease of the bone. Actonel is available in 5 mg, 30 mg, and 35 mg oral tablets.

Actonel and Actonel [redacted] Calcium share an overlapping dosage form (tablet), route of administration (oral), dosing regimen (once daily), indication for use (osteoporosis), and overlapping strength (35 mg). In addition, both products will be used by the same prescriber and patient populations and will have similar packaging. Actonel and Actonel [redacted] Calcium will both be available in a dose pack configuration which will contain a one month supply of medication. The two drug products are likely to reside in close proximity to one another on the pharmacy shelf further increasing the risk of selection and dispensing errors. A selection error may also occur when the first few letters of the name ("Acto") are typed in the computer and the single ingredient product, Actonel, is inadvertently selected instead of the combination product. There has been post-marketing reports of confusion between Actonel 30 mg and Actonel 5 mg and between Actonel 30 mg daily and Actonel 30 mg weekly, as mentioned above. DMETS is concerned that the introduction of a new product will increase confusion and error within the Actonel product line.

DMETS envisions situations where an order for Actonel [redacted] Calcium might also be interpreted as Actonel if the modifier is omitted. It should be noted that one respondent from the written inpatient study misinterpreted the name to be "Actonel" omitting the modifier [redacted] *Calcium* when identifying the proposed name. This theoretical concern is supported by research conducted by Timothy S. Lesar, Pharm.D., at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms. Analysis of 402 medication errors that occurred over a 16-month period (Sept. 1999 – Dec. 2000) demonstrates that the most common

error was due to the failure to specify a controlled-release dosage formulation through the use of a modifier (280 cases or 69.7%).[8]

We believe this may also apply to other types of name modifiers, such as [redacted] Calcium", as the omission of the modifier is possible regardless of the modifier choice. Due to the numerous overlapping similarities, DMETS believes there is increased risk for confusion and error between Actonel and Actonel [redacted] Calcium.

Actonel Actonel [redacted] Calcium

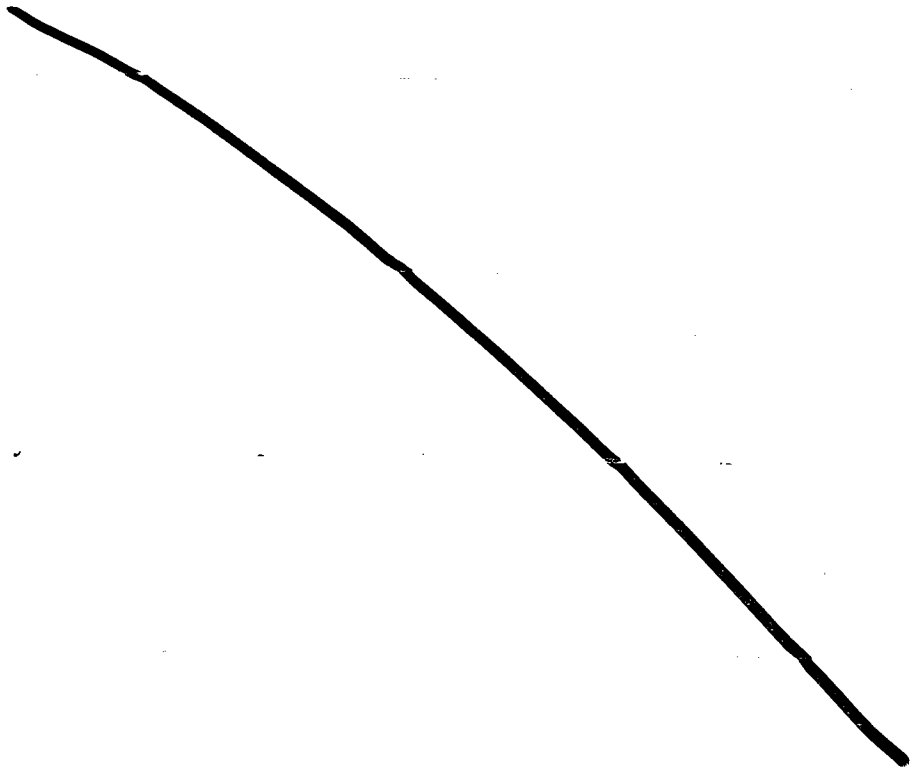
b. Actoplus Met*** may look and sound similar to Actonel [redacted] Calcium, especially when comparing "Actonel [redacted] " with "Actoplus". Actoplus Met is currently under review at the Agency. DMETS found the proprietary name acceptable in ODS consult #04-0023. Actoplus Met is an oral antihypoglycemic agent indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus. It is for use in patients who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone. Actoplus Met will be available as a combination tablet containing the active ingredients pioglitazone and metformin in strengths of 15 mg/500 mg and 15 mg/850 mg. The dosage of Actoplus Met should be individualized based on effectiveness and tolerability while not exceeding the maximum daily dose of the individual component (Actos 45 mg/day and metformin 2550 mg/day). Actonel [redacted] Calcium and Actoplus Met may look and sound-alike because they both begin with the letters "Acto" and contain the letters [redacted] in the middle of the name. Currently, we have post-marketing confusion between Actos and Actonel. It was noted by one reporter that the pharmacist selected the drug ACTOnel instead of ACTOs in the pharmacy computer system possibly by typing in the 1st four letters of the word and selecting the 1st drug name to come up, which may also be of possible risk for confusion and error with the two proposed proprietary names. Furthermore, Actonel [redacted] Calcium and Actoplus Met share an overlapping dosage form (tablet), route of administration (oral), dosing regimen (both may be given as one tablet once daily for the Actoplus Met and the calcium), prescriber population, and may be located in close proximity to one another on pharmacy shelves. The two products have different indications for use (diabetes vs. osteoporosis) and strengths (15 mg/500 mg and 15 mg/850 mg vs. 35 mg/1250 mg). Some members of DMETS expressed concerns about the increased potential for confusion and error with Actonel [redacted] Calcium and Actoplus Met as they may be launched into the marketplace near or at the same time as each other. While the two names have differences in strength and indication, DMETS believes that the overlapping product characteristics, verbal and written similarities, potential to be launched into the marketplace in conjunction with each other, and existing confusion between Actonel and Actos, increase the risk of confusion between Actoplus Met and Actonel [redacted] Calcium.

Actoplus Met Actonel [redacted] Calcium

[8] Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.

*** **NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

c. /



d. The AERS search identified name confusion between Actos and Actonel. DMETS believes that the addition of a product to the Actonel line ("Actonel [redacted] Calcium") may lead to additional confusion with Actos, as there has been post-marketing confusion between Actonel and Actos. Prescribers may believe that the drug is Actos [redacted] Calcium, instead of Actonel [redacted] Calcium. While there is no documented interaction between Actos and Calcium, the patient could potentially receive the incorrect medication. Actos is used in the treatment of type 2 diabetes mellitus and is available as 15 mg, 30 mg, and 45 mg tablets. Actos and Actonel share orthographic qualities because each name contains the beginning letters, "Acto". Both drugs share an overlapping dosage form (tablet), route of administration (oral), dosing interval (once daily), and strength (30 mg). The Actonel and Actos drug products are likely to reside in close proximity to one another on the pharmacy shelf further increasing the risk of selection and dispensing errors. A search of the FDA Adverse Event Reporting System (AERS) found seven cases where Actos 30 mg was prescribed; however, Actonel 30 mg was dispensed (5) or vice versa (2). Poor handwriting, lack of knowledge, pharmacy distractions, and incorrect computer product selection were all mentioned as possible causes of the errors. It was noted by one of the reporters that the pharmacist selected the drug ACTOnel instead of ACTOs in the pharmacy computer system possibly by typing in the 1st four letters of the word and selecting the 1st drug name to come up. It is possible that if approved, confusion may occur between Actos and Actonel [redacted] Calcium if the [redacted] Calcium" modifier is inadvertently omitted from the name, based on post-marketing confusion between

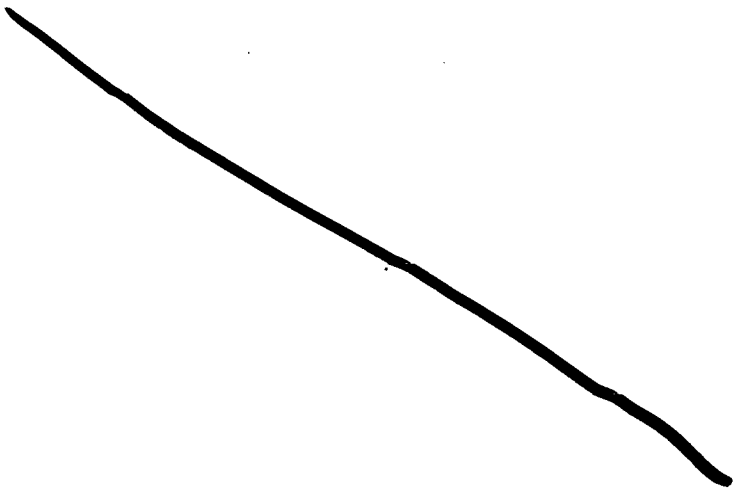
Actonel and Actos (see below). We believe that the addition of Actonel [redacted] Calcium to the marketplace will only cause more confusion and error especially since there is already post-marketing confusion between Actos and Actonel.

Actos Actonel [redacted] Calcium

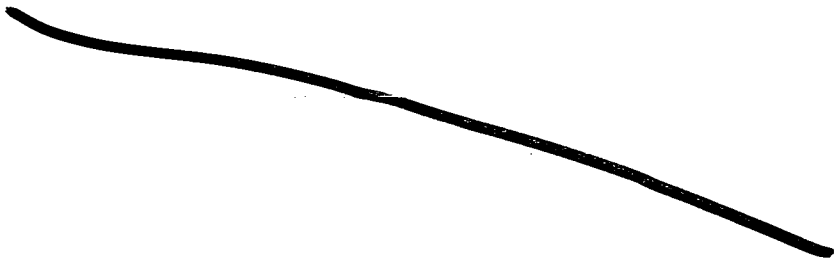
III. COMMENTS TO THE SPONSOR

In reviewing the proprietary name Actonel [redacted] Calcium, the primary concern related to look-alike and sound-alike confusion with Actonel and Actos. Additionally, the use of the modifier [redacted] Calcium" was of concern and is discussed below. DMETS is also concerned with the proposed packaging of this drug product.

A. Error Prone Packaging



B. Modifier Concerns



C. Look and Sound-Alike Name Confusion

a. Actonel has a look- and sound-alike similarity to Actonel [redacted] Calcium if the Calcium" modifier is inadvertently omitted from the name since each name contains the root stem 'Actonel'. Actonel is used in the treatment and prevention of osteoporosis in postmenopausal women and in the treatment of Paget's Disease of the bone. Actonel is available in 5 mg, 30 mg, and 35 mg oral tablets.

Actonel and Actonel [redacted] Calcium share an overlapping dosage form (tablet), route of administration (oral), dosing regimen (once daily), indication for use (osteoporosis), and overlapping strength (35 mg). In addition, both products will be used by the same prescriber and patient populations and will have similar packaging. Actonel and Actonel [redacted] Calcium will both be available in a dose pack configuration which will contain a one month supply of medication. The two drug products are likely to reside in close proximity to one another on the pharmacy shelf further increasing the risk of selection and dispensing errors. A selection error may also occur when the first few letters of the name ("Acto") are typed in the computer and the single ingredient product, Actonel, is inadvertently selected instead of the combination product. There has been post-marketing reports of confusion between Actonel 30 mg and Actonel 5 mg and between Actonel 30 mg daily and Actonel 30 mg weekly, as mentioned above. DMETS is concerned that the introduction of a new product will increase confusion and error within the Actonel product line.

DMETS envisions situations where an order for Actonel [redacted] Calcium might also be interpreted as Actonel if the modifier is omitted. It should be noted that one respondent from the written inpatient study misinterpreted the name to be "Actonel" omitting the modifier [redacted]*Calcium* when identifying the proposed name. This theoretical concern is supported by research conducted by Timothy S. Lesar, Pharm.D, at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms. Analysis of 402 medication errors that occurred over a 16-month period (Sept. 1999 – Dec. 2000) demonstrates that the most common error was due to the failure to specify a controlled-release dosage formulation through the use of a modifier (280 cases or 69.7%).[8]

We believe this may also apply to other types of name modifiers, such as [redacted] Calcium", as the omission of the modifier is possible regardless of the modifier choice. Due to the numerous overlapping similarities, DMETS believes there is increased risk for confusion and error between Actonel and Actonel [redacted] Calcium.

Actonel Actonel [redacted] Calcium

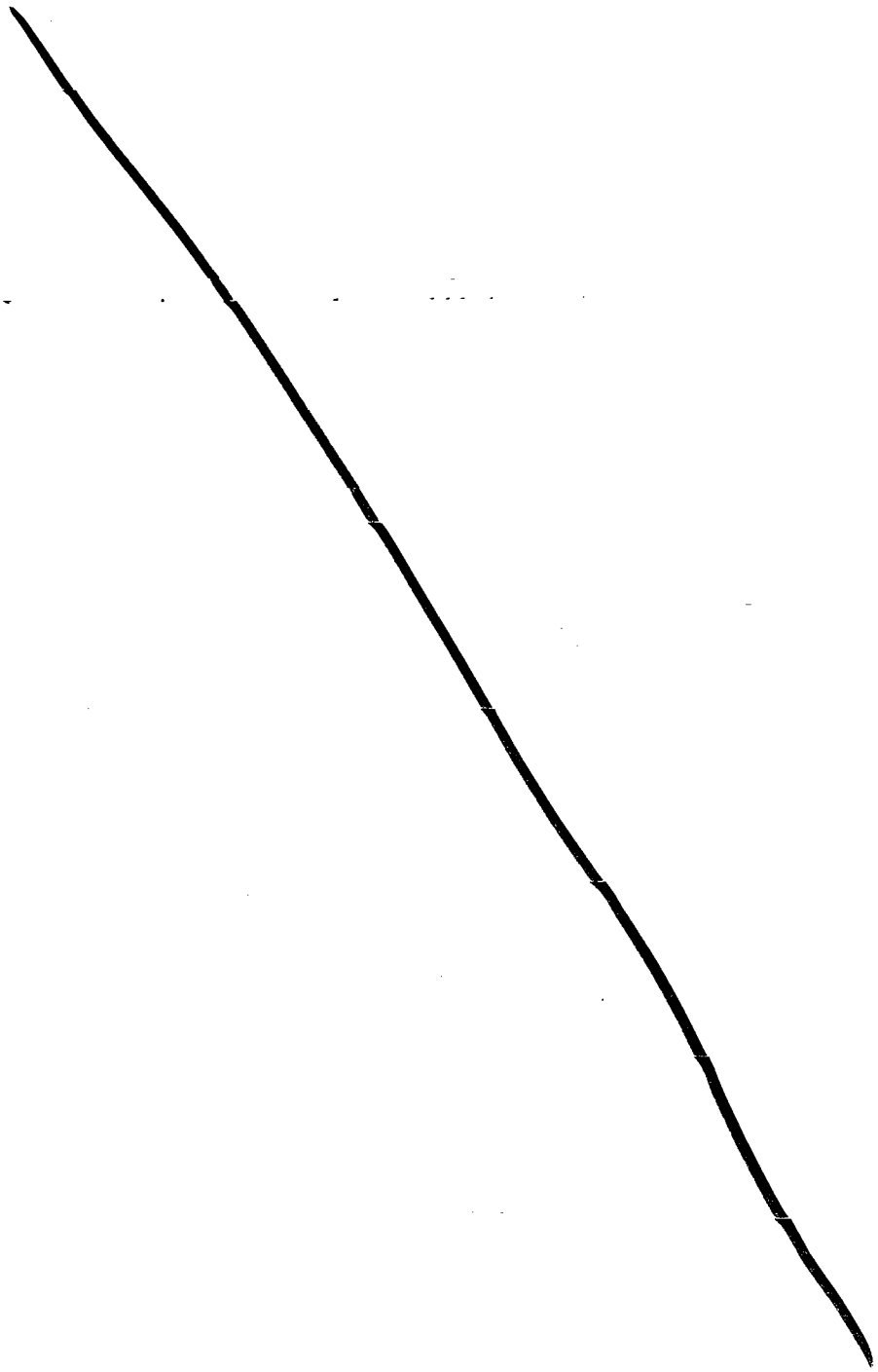
b. DMETS believes that the addition of a product to the Actonel line ("Actonel [redacted] Calcium") may lead to additional confusion with Actos, as there has been post-marketing confusion between Actonel and Actos. Prescribers may believe that the drug is Actos [redacted] Calcium, instead of Actonel [redacted] Calcium. While there is no documented interaction between Actos and Calcium, the patient could potentially receive the incorrect medication. Actos is used in the treatment of type 2 diabetes mellitus and is available as 15 mg, 30 mg, and 45 mg tablets. Actos and Actonel share orthographic qualities because each name contains the beginning letters, "Acto". Both drugs share an overlapping dosage form (tablet), route of administration (oral), dosing interval (once daily), and strength (30 mg). The Actonel and Actos drug products are likely to reside in close proximity to one another on the pharmacy shelf further increasing the risk of selection and dispensing errors. Post-marketing experience has shown errors where Actos 30 mg was prescribed; however, Actonel 30 mg was dispensed or vice versa. Poor handwriting, lack of knowledge, pharmacy distractions, and incorrect computer product selection were all mentioned as possible causes of the errors. It was noted by one of the reporters that the pharmacist selected the drug ACTOnel instead of ACTOs in the pharmacy computer system possibly by typing in the 1st four letters of the word and selecting the 1st drug name to come up. It is possible that if approved, confusion may occur between Actos and Actonel [redacted] Calcium if the [redacted] Calcium" modifier is

[8] Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.

inadvertently omitted from the name, based on post-marketing confusion between Actonel and Actos (see below). We believe that the addition of Actonel — Calcium to the marketplace will only cause more confusion and error especially since there is already post-marketing confusion between Actos and Actonel.

Actos Actonel + Calcium

D. Labeling, Packaging and Safety Related Issues



1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name, Actonel [redacted] Calcium. In addition, DMETS does not recommend co-packaging the two products, Actonel and Calcium, as proposed. We recommend implementation of the label revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

B. DDMAC finds the proprietary name, Actonel [redacted] Calcium, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh, MS
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

3 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

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/s/

Nora L. Roselle
6/2/05 09:06:02 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/2/05 02:58:41 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/2/05 04:13:58 PM
DRUG SAFETY OFFICE REVIEWER
A;sp signing for Carol Holquist, Director, DMETS in her absence

From: Hedin, Durand M
Sent: Monday, December 27, 2004 2:04 PM
To: 'faulhaber.lm@pg.com'
Subject: Actonel [redacted] Calcium Tablets, NDA 21-823

Dear Ms. Faulhaber:

We have the following requests for information concerning the biopharm review of Actonel [redacted] Calcium Tablets, NDA 21-823:

- Did the in vitro dissolution of the calcium carbonate tablets that were used in the pivotal clinical studies for risedronate's original NDA approval meet the USP acceptance criteria?

- Were the calcium carbonate tablets that were used in the pivotal clinical studies for risedronate's original NDA approval identical to the to-be-marketed calcium carbonate tablets for NDA 21-823?

If you have any questions contact me at, 301-827-6392.

Sincerely,

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn 14B-45, HFD-510
5600 Fishers Lane
Rockville MD 20857

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/s/

Randy Hedin
12/27/04 02:47:31 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-823

FILING COMMUNICATION

Procter & Gamble Pharmaceuticals, Inc.
Attention: Lenore Faulhaber, Ph.D.
Associate Director, Regulatory Affairs
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Faulhaber:

Please refer to your August 30, 2004 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel [redacted] Calcium (risedronate sodium) and (calcium carbonate) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on October 30, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues and request that you submit the following information:

1. Submit information regarding all of the facilities (including contract facilities and test laboratories) identified with full street addresses, CFN numbers, and the facilities respective function.

2. Submit an appropriate stability commitment.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
11/3/04 01:38:12 PM
Signing for Kati Johnson

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-823

Proctor & Gamble Pharmaceuticals, Inc.
Attn: Lenore Faulhaber, Ph.D., M.B.A.
Associate Director, Regulatory Affairs
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Faulhaber:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Actonel® [redacted] Calcium (risedronate sodium and calcium carbonate) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	August 30, 2004
Date of Receipt:	August 31, 2004
Our Reference Number:	NDA 21-823

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 30, 2004 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be June 30, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
9/8/04 12:33:34 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

Vol 1/p 50

See Instructions on Reverse Side Before Completing This Form

..ompleted form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

. APPLICANT'S NAME AND ADDRESS
'rocter & Gamble Pharmaceuticals, Inc.
;700 Mason-Montgomery Road
Mason, OH 45040

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-823

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NDA #20-835
(APPLICATION NO. CONTAINING THE DATA).

TELEPHONE NUMBER *(Include Area Code)*
513) 622-5278

PRODUCT NAME
ctonel Calcium

6. USER FEE I.D. NUMBER
4811

IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

IAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

)lic reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing ructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. id comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

)artment of Health and Human Services
d and Drug Administration
ER, HFM-99
1 Rockville Pike
kville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

TURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Wendy M. Sauber	Director, U.S. Regulatory Affairs	8/17/2004

M FDA 3397 (12/03)

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-823	Efficacy Supplement Type SE-	Supplement Number	
Drug: Actonel [redacted] Calcium (risedronate sodium & calcium carbonate) Tablets		Applicant: Procter & Gamble Pharmaceuticals, Inc.	
RPM: Randy Hedin		HFD-510	Phone # 301-827-6392

Application Type: ( ) 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (X) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	4
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	June 30, 2005
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4811
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	X
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	November 3, 2004 June 21, 2005

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	July 29, 2005
• Original applicant-proposed labeling	August 30, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC July 25, 2005 DMETS June 2, 2005 DSRCS August 4, 2005
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	August 30, 2004 August 10, 2005
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	None
• Other	None
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Team Leader Memo August 5, 2005
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	July 15, 2005
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	None
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	No Clinical Data
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	None
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	None
❖ Demographic Worksheet *(NME approvals only)*	None
❖ Statistical review(s) *(indicate date for each review)*	None
❖ Biopharmaceutical review(s) *(indicate date for each review)*	November 29, 2004 June 14, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	None
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	None
• Bioequivalence studies	None
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	June 29, 2005
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	June 29, 2005
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: May 26, 2005 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	April 24, 2005
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	None
❖ CAC/ECAC report	None

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Randy Hedin
8/12/05 02:23:09 PM