Cross-Discipline Team Leader Review

Date	July 21, 2009
From	Theresa Kehoe, M.D., Clinical Team Leader Division of Reproductive and Urologic Products (DRUP)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 20-835 035
Applicant	Procter & Gamble Pharmaceuticals, Inc
Date of Submission	January 26, 2009
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Proprietary Name / **Established (USAN) names**	Actonel® Risedronate sodium
Dosage forms / Strength	Tablet
Proposed Indication(s)	None sought
Recommended:	**Approval**

1 Introduction

Procter and Gamble Pharmaceuticals, Inc has submitted this supplemental new drug application seeking (1) pediatric exclusivity with the fulfillment of the Written Request for pediatric studies and (2) approval of labeling changes to the Pediatric Use section of the Actonel® (risedronate sodium) label. No pediatric indication is being sought.

A Written Request for pediatric studies was issued April 19, 2002, and amended twice. To obtain needed pediatric information on risedronate sodium, the Agency requested that the Applicant conduct two studies. Study 1 was a single-dose pharmacokinetic study in pediatric patients with osteogenesis imperfecta (OI). This study was to be completed and submitted to the Agency prior to the initiation of Study 2. Study 2 was a randomized, double-blind, placebo-controlled, parallel group study of one-year duration to determine the safety and efficacy of risedronate in the treatment of children with mild, moderate, or severe osteogenesis imperfecta.

The Applicant has conducted the two studies, which are submitted for review. To meet the requirements for Study 1, the Applicant conducted Study 2002020, an open-label, randomized, multicenter, parallel group study to investigate the safety, tolerability and pharmacokinetics of risedronate administered as a single oral dose of 2.5 mg or 5 mg risedronate in children ≤ 30 kg and 5 mg or 10 mg risedronate in children > 30 kg with osteogenesis imperfecta. The study report was initially submitted to IND 31,029 on June 3, 2004 as required by the Written Request.

To meet the requirements for Study 2, the Applicant conducted Study 2003100, a randomized, double-blind, placebo-controlled, parallel group study of one-year duration followed by 2 years of open-label treatment to determine the safety and efficacy of orally administered 2.5 mg or 5.0 mg daily risedronate, in children ≥ 4 to < 16 years old with osteogenesis imperfecta. The mean percent change in lumbar spine bone mineral density (BMD) at Month 12 was the primary endpoint of the study.

2 Background

Actonel, risedronate sodium, is an oral bisphosphonate medication. Actonel 30 mg daily was approved for treatment of Paget's disease of bone in March, 1998. Actonel 5 mg daily was approved in April, 2000, for prevention of postmenopausal osteoporosis, for treatment of postmenopausal osteoporosis, for prevention of corticosteroid-induced osteoporosis, and for treatment of corticosteroid-induced osteoporosis. Actonel 35 mg once weekly was approved for the prevention and treatment of postmenopausal osteoporosis in May, 2002. The 35 mg once weekly dosing regimen was also approved for treatment to increase bone mass in men with osteoporosis in August, 2006. Actonel 75 mg per day for two consecutive days per month was approved for the prevention and treatment of postmenopausal osteoporosis in April, 2007. Actonel 150 mg once monthly was approved for the treatment of postmenopausal osteoporosis in April, 2008.

Bisphosphonates are incorporated into the hydroxyapatite crystals of bone and act by inhibition of osteoclasts. The result of osteoclast inhibition is decreased bone resorption and increased bone mass. Incorporation of the bisphosphonate into bone hydroxyapatite results in a long residency time in bone. In adults, oral bisphosphonates have been associated with a number of safety issues including upper gastrointestinal adverse events, osteonecrosis of the jaw, musculoskeletal adverse events related to pain, inflammatory eye events, and more recently, possible atypical fracture of the femur. Due to the long-term safety concerns with bisphosphonates and their long residency time in bone, the Division's approach to pediatric studies is that the investigation of bisphosphonate safety and efficacy in the pediatric population should occur in patients who have the greatest potential benefit – those at high risk of fracture. Such a population is children with osteogenesis imperfecta (OI).

Actonel is the third bisphosphonate to have conducted a trial in the pediatric OI population. The two previously conducted and reviewed trials (for alendronate and zoledronic acid) in the pediatric OI population revealed that while BMD significantly increased, there was no clear benefit for reduction in fracture risk. In addition, safety concerns were raised, including an increased risk of hypocalcemia, the potential negative effect of bisphosphonates on fracture healing, the potential negative effect of bisphosphonates on linear growth, and the potential negative effect of bisphosphonates on bone mineralization. These concerns regarding the potential negative impact of Actonel treatment in the pediatric OI population have been evaluated in depth by the clinical reviewer, Dr. Stephen Voss, in his primary Clinical Review.

3 CMC/Device

No new Chemistry, Manufacturing and Control (CMC) data was submitted in this supplemental application. The Applicant submitted a request for categorical exclusion from filing an

environmental assessment for risedronate sodium because of the approval of this labeling supplement is not likely to increase the use of risedronate. This request was acceptable. Please refer to Dr. David Lewis's and Dr. Jean Salemme's reviews for complete details.

4 Nonclinical Pharmacology/Toxicology

No new pharmacology or toxicology data were submitted with this supplemental NDA. A complete pharmacology/toxicology program including pharmacology, ADME, subchronic and chronic repeat-dose toxicity, carcinogenicity, reproductive and developmental toxicity, and genotoxicity studies was conducted and has previously been reviewed.

Dr. Reid recommended changes to sections 8.1 Pregnancy and 13 Nonclinical Toxicology sections of the Actonel label. I agree with her recommendations as the changes clarify language and provide for consistency among the bisphosphonate labels. These changes have been accepted by the Applicant and Dr. Reid has reviewed and concurred with the relevant sections of the final-to-be–approved label.

5 Clinical Pharmacology/Biopharmaceutics

A complete clinical pharmacology program was conducted in adults for all of the Actonel dose regimens and has been reviewed previously. Because of the very low bioavailability of risedronate, serum concentrations are generally very low or below the limit of detection using currently available analytical methodology. Therefore, simultaneous pharmacokinetic modeling of serum and urinary data instead of traditional non-compartmental analyses for pharmacokinetic characterization are used for risedronate sodium. Risedronate is rapidly, though poorly, absorbed in the upper gastrointestinal tract with a Tmax of approximately 1 hour. The mean absolute oral bioavailability (BA) of risedronate tablets as determined previously is 0.63% (90% CI: 0.54% to 0.75%). The bioavailability is significantly impaired when taken with food. In young healthy adult subjects, approximately half of the absorbed dose of risedronate was excreted in urine within 24 hours. Risedronate is primarily excreted through the kidney. Based on simultaneous modeling of serum and urine data, mean renal clearance was 105 mL/min and mean total clearance was 122 mL/min, with the difference primarily reflecting non-renal clearance or clearance due to adsorption to bone.

To evaluate the pharmacokinetics of risedronate in children and to fulfill the Study 1 requirements outlined in the Written Request, the Applicant conducted an open label, single-dose, randomized, parallel-group pharmacokinetic study in 28 children with OI. Patients were stratified based on body weight (10-30 kg or > 30 kg). Within each body weight group, subjects were randomized to one of two doses: 2.5 mg or 5 mg risedronate in the 10-30 kg cohort and 5 mg or 10 mg risedronate in the > 30 kg BW cohort. Each dose group enrolled approximately eight patients. The pharmacokinetic parameters of risedronate were obtained by simultaneous pharmacokinetic analysis of serum concentration-time and urinary excretion rate-time data from the patients. Similar to that seen in adults, Tmax occurred within an hour after dose administration. As outlined in Table 1 (reproduced from Dr. Sandhya Apparaju's review), peak risedronate concentrations (Cmax) increased in relation to dose within each of the body weight cohorts. There was no trend for increasing AUC with increasing risedronate dose within each weight group. Baseline covariates of interest including gender, age, and body weight were not found to significantly influence the exposure of risedronate in pediatric patients.

Table 1. Study 2002020: Pharmacokinetic Parameters, Mean ± SD (% CV)

	10-30 Kg BW Cohort		30 Kg BW Cohort	
Parameter	**2.5 mg (n = 5 - 7)**	**5 mg (n = 5 - 7)**	**5 mg (n = 2 – 3)**	**10 mg (n = 2 – 3)**
Cmax (ng/ml)	0.85 ± 0.42 (48 %)	1.42 ± 0.38 (26 %)	1.47 ± 0.05 (13 %)	2.10 ± 0.56 (27 %)
Tmax (h); median (range)	0.35 (0.23 -0.59)	0.26 (0.13-0.88)	0.45 (0.42-0.49)	0.66 (0.18-1.99)
AUC 0-∞; (ng.h/ml)	6.19 ± 2.45 (40 %)	5.82 ± 1.28 (22 %)	13.6 ± 1.51 (11 %)	14.67 ± 2.86 (19 %)
T1/2, (h)	322 ± 269 (83 %)	397 ± 332 (84 %)	264 ± 232 (88 %)	490 ± 224 (45 %)
Ae'; (%)	0.37 ± 0.19 (50 %)	0.24 ± 0.16 (66 %)	0.21 ± 0.11 (50 %)	0.37 ± 0.26 (46 %)
Ae': Cumulative urinary excretion rate normalized by dose and expressed as %				

Source: Dr. Sandhya Apparaju's review, Table 1

The risedronate analyses in serum and urine samples were conducted using validated enzyme linked immunosorbent assays. The accuracy and precision values for the standards and quality controls (QCs) during sample analyses runs were within the acceptable range. However, it should be noted that the analytical bioanalysis of serum and urinary concentrations in Study 2002020 was conducted by (b) (4). Per the Agency's position on bioanalyses conducted at this facility during the 2000-2004 timeframe, the validity of this data was questioned. At the request of the agency, the sponsor had previously submitted a report from an independent audit conducted by (b) (4) to support the validity of the (b) (4) results to support bioanalytical findings for adult Actonel studies. As part of the assessment for these adult studies, the FDA's Division of Scientific Investigation (DSI) also conducted as audit of (b) (4). Based on the DSI audit of the adult PK studies, questions were raised regarding the reliability of the independent audits conducted by (b) (4) as they pertained to both the adult studies and the pediatric study submitted in the Application. While the assays for risedronate in human serum and urine were done in adherence to the assay protocols and SOPs in place at the time, there were issues identified with the acceptance criteria for standards specified in the analytical protocol. Specifically, DSI noted that the assay protocol allowed partial masking of one of the duplicate calibration points when mean of duplicates exceeds 20 % of nominal. A % CV-based criterion was also not required for accepting calibration standards.

Because of the findings from the audit of the adult PK studies, the validity of the PK results from pediatric PK study 2002020 was questioned. During the current review cycle, the Applicant provided a response regarding the issues raised that specially pertained to pediatric Study 2002020. As part of their response, the Applicant reprocessed analytical data from the four (one serum and three urine) affected runs from study 2002020. As detailed in Dr. Apparaju's review, data from the one affected serum run (run 7A) were not included in the final PK parameters analyses due to greater than 20 % deviations between the first analysis and the reprocessed analysis.

Overall, after review of the analytical study data, the independent audit, and the Applicant's response to the request for more information, Dr. Apparaju found that the analytical methodologies employed for risedronate analysis in serum and urine samples are sufficiently validated and the pharmacokinetic study results for study 2002020 are valid. However, because of the small number of subjects for whom acceptable analytical data were obtained and high variability of the pediatric data, as well as the simultaneous modeling rather than noncompartmental analyses used for PK determination, Dr. Apparaju recommends that pediatric PK information should not be placed in the Actonel label. These recommendations are acceptable from a clinical perspective, in part, because revised labeling will state that Actonel is not indicated for use in children based primarily on the findings from Phase 3 Study 2003100 and safety and efficacy data from children reviewed by the Division for other bisphosphonates.

Dr. Apparaju has reviewed the relevant sections of the to-be-approved labeling and finds them acceptable.

6 Clinical Microbiology

There are no clinical microbiology issues to be addressed related to the supplemental NDA as there are no CMC changes.

7 Clinical/Statistical- Efficacy

The original intent of the Applicant's pediatric clinical development program was to support pediatric exclusivity and to seek an indication for Actonel in the treatment of osteogenesis imperfecta. As previously noted, Actonel is the third bisphosphonate to have been evaluated in the pediatric OI population. Treatment of OI would require chronic therapy. The two previously reviewed Phase 3 clinical trials with bisphosphonates in children with OI (for alendronate and zoledronic acid) did not demonstrate a clear benefit for reduction in fracture risk despite significant increases in BMD. Specific safety concerns raised include an increased risk of hypocalcemia, and the potential negative effects of bisphosphonates on fracture healing, linear growth, and disordered bone mineralization. In adults, oral bisphosphonates have been associated with a number of safety issues including upper gastrointestinal adverse events, osteonecrosis of the jaw, musculoskeletal adverse events related to pain, inflammatory eye events, and more recently, possible atypical fracture of the femur. These safety issues raise great concern regarding the long-term risk/benefit profile of bisphosphonate use in children, even those at high risk of fracture. The Division's concerns were discussed with the Applicant at the pre-NDA meeting, and it was agreed that a pediatric indication would not be sought in the Supplement. The pediatric efficacy study conducted is reviewed for adequacy to support label changes in the pediatric section of the product label.

The basis for the proposed clinical language in the pediatric section of the product label is Study 2003100 (2003100-HMR4003I/3001): "A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel Group Study of One-year Duration Followed by 2 Years of Open-label Treatment to Determine the Safety and Efficacy of Orally Administered 2.5 mg or 5.0 mg Daily Risedronate, in Children ≥ 4 to < 16 Years Old with Osteogenesis Imperfecta."

In support of this Supplemental NDA, the Applicant submitted a Final Study Report for Year 1 of the clinical trial. The Applicant plans to submit efficacy and safety data from the 2-year open extension (limited safety data from the extension were provided in the Safety Update) at a later date after completion of the extension.

7.1 Study Design

Study population: Subjects enrolled in the study were age 4 to 15 years, diagnosed with osteogenesis imperfecta type I, III, or IV, considered to be at high risk of fracture. As outlined in Dr. Voss's review, the study population was expanded to include patients with the milder form of OI (type I) because of difficulties recruiting treatment naïve patients with more severe forms of OI and the ethical considerations of placebo treatment in the more severe populations. Patients were considered at high risk of fracture if they had a history of one radiographically confirmed low or no trauma fracture with a BMD Z-score of -1.0 (1.0 standard deviations below age matched controls) or a low bone mineral density with or without a fracture history, defined as a Z-score of -2.0.

Study treatments: Eligible subjects were stratified within each country into 2 groups based on age (4-9 years and 10-15 years) and then randomized 2:1 to receive risedronate or placebo. The dose of study medication given was based on body weight with patients weighing 10-30 kg receiving risedronate 2.5 mg tablet or placebo daily and patients weighing more than 30 kg receiving risedronate 5 mg tablet or placebo daily. Patients were to take the study drug with 120 mL of water 30 minutes before breakfast. Patients would could not swallow the study drug tablet were allowed to dissolve the tablet in 10 mL of water using a specific spoon device (an (b) (4) Spoon).

All subjects were encouraged to remain on calcium and vitamin D supplementation (500-1000 mg calcium and 200-600 IU vitamin D daily). However, calcium and vitamin D were not considered study drugs and were not subject to study drug accountability procedures.

Efficacy measures: The primary endpoint of this trial was percent change in lumbar spine bone mineral density (BMD) at Month 12 compared to placebo. Secondary endpoints included lumbar spine BMD at month 6, and changes from baseline in total body BMD, total body and lumbar spine bone mineral content (BMC), total body and lumbar spine Z-scores (BMD standard deviations from the mean for age-matched controls), and lumbar spine and total body bone area. Other secondary endpoints included morphometric and clinical vertebral fractures, nonvertebral fractures, bone turnover markers, pain (assessed by the Wong-Baker FACES pain rating scale); and quality of life assessed by a patient reported outcome (PRO) instrument.

As outlined in Dr. Kate Dwyer's statistical review, the Applicant's statistical analysis plan included testing for secondary endpoints in a hierarchical order with the incidence of new vertebral fractures, last in the order. Therefore, if the preceding secondary endpoints were not statistically significant, the incidence of new vertebral fractures endpoint would not be tested. While this closed testing procedure was an appropriate method for controlling type I error rate, the incidence of new vertebral fracture is an important endpoint to evaluate. The Applicant performed analysis of this endpoint using Fisher's Exact Test instead of the pre-specified Cochran-Mantel-Haenszel (CMH) test which would control for two strata: age group (4 through

9 and 10 through 15) and pooled country. To address the issue, the statistical review team performed an analysis on fracture data using the CMH test.

The primary efficacy measurement was change from baseline at Month 12 (or last observation carried forward [LOCF] if a month 12 measurement was not available) for lumbar spine (L1 to L4) BMD. It is to be expected that BMD values will increase as a natural process of growth, especially in children at puberty. Therefore, BMD Z-score (standard deviations from the mean for age matched healthy controls), rather than percent change from baseline in BMD, might be a better parameter to assess changes in BMD in this growing population. Change in BMD Z-score was evaluated as a secondary endpoint in the trial, so this data is available to complement the primary endpoint.

7.2 Results

Disposition: A total of 147 subjects were enrolled into the study. As outlined in the following table, 93% of the enrolled population completed Month 12 of the study (Table 2). Of those subjects that did not complete the study, four (three in the risedronate group and one in the placebo group) received no study medication and seven (all in the risedronate group) discontinued from the study before Month 12. The most common reason for withdrawal was the withdrawal of consent by 4 (4%) subjects. Withdrawal due to an adverse event occurred in one subject (1%).

Table 2. Study 2003100: Patient Disposition

	Number (%)	
	Risedronate	**Placebo**
N, enrolled	97	50
Did not receive study drug	3 (3)	1 (2)
Discontinued	7 (7)	0 (0)
Adverse Event	1 (1)	0 (0)
Lost to follow-up	1 (1)	0 (0)
Protocol Violation	1 (1)	0 (0)
Withdrew consent	4 (4)	0 (0)
N, completed	87 (90)	49 (98)
N, ITT	94 (97)	49 (98)
N, ITT for primary endpoint	86 (89)	47 (94)
N, safety	94 (97)	49 (98)

Source: 2003100 study report, table 4

Demographics: As outlined in Table 3 below, baseline subject demographics were generally balanced across the treatment groups. The average age of enrollees was approximately 9 years. Fifty percent (50%) of subjects were male and 83% were Caucasian. Eighty-five percent (85%) of the population had Type I OI and 94% of subjects had a history of at least one fracture. The mean baseline lumber spine BMD Z-score was -2.08.

Table 3. Study 2003100: Patient Demographics, ITT

	Risedronate	Placebo
N	**94**	**49**
Age (yrs, mean ± SD)	8.9 ± 3.4	8.6 ± 3.1
Age Range	4 - 15	4 - 14
Age Group, n (%)		
4 – 9 years	53 (56)	28 (57)
10 – 15 years	41 (44)	21 (43)
Sex, n (%)		
Female	49 (52)	22 (45)
Male	45 (48)	27 (55)
Race, n (%)		
White	77 (82)	41 (84)
Hispanic	9 (10)	4 (8)
Oriental	2 (2)	2 (4)
Other	6 (6)	2 (4)
Height (cm, mean)	129 ± 22	127 ± 20
Weight (kg, mean)	32 ± 15	31 ± 14
Weight Group, n (%)		
≤ 30 kg	52 (55)	28 (57)
> 30 kg	42 (45)	21 (43)
OI Phenotype		
I	81 (86)	40 (82)
III	2 (2)	3 (6)
IV	11 (12)	6 (12)
History of Fx		
Yes	88 (94)	46 (94)
Prevalent Vertebral Fx at baseline	57 (61)	31 (67)
LS BMD Z score	-2.07	-2.09

Source: Dr. Stephen Voss's review, table 2

Change in Lumbar Spine BMD: The percent change in lumbar spine BMD at Month 12 was the primary endpoint of the trial. As outlined in Table 4, the mean percent change in lumbar spine BMD at Month 12 (with LOCF), evaluated using an ANCOVA model adjusted for baseline values, age group, treatment, and pooled center, was 16.3% in the risedronate group and 8.6% in the placebo group. The mean percent difference (risedronate – placebo) was 8.7% with 95% confidence interval of 5.69 – 11.70. It should be noted that the enrolled population exhibited an impressive percent increase in BMD at one year. In children and adolescents, bones grow in both width and length, resulting in a dramatic increase in bone mass and bone mineral density. In this population, BMD values are affected by age, gender, pubertal stage and skeletal maturation. Because of these changing parameters, comparison to age and sex matched controls may be more appropriate and informative. The BMD Z-score is the standard deviations from the mean for age-

matched controls. When the change in lumbar spine BMD Z-score was evaluated, the mean percent change in BMD Z-score was 25% in the risedronate group and -5% in the placebo group.

Table 4. Study 2003100: Lumbar Spine BMD, ITT (LOCF)

	Risedronate	Placebo
N, ITT	94	49
N, ITT with post baseline DXA	86	47
Month 12, LS Mean percent change from Baseline	16.29 %	7.59 %
Mean difference between groups (95% CI)	8.70 % (5.688 , 11.703)	
p-value	<0.0001	
Month 12, Z-score, LS Mean change from Baseline	0.428	-0.002
Mean difference (95% CI)	0.431 (0.256 , 0.605)	
p-value	<0.0001	
Month 12, Z-score, LS Mean Percent change from Baseline	24.87 %	-4.60 %
Mean difference between groups (95% CI)	29.467 % (18.449 , 40.486)	
p-value	<0.0001	

Source: compiled from Dr. Stephen Voss's review, table 4

Secondary Efficacy Endpoints: As outlined in Dr. Dwyer's review, the Applicant utilized a closed testing procedure to control the Type-I error rate at the 0.05 level for the 18 secondary efficacy endpoints. Because the test result for the second endpoint (change from baseline in quality of life as determined by the PedsQL questionnaire) in the ordered list of secondary endpoints was not statistically significant, the type-I error rate was protected only for the primary efficacy analysis (percent change from baseline in lumbar spine BMD at Month 12) and the first analysis in the closed testing procedure (percent change from baseline in total body BMC at Month 12). Because of the lack of statistical significance, which would not support including them for labeling, the majority of the secondary endpoints are not discussed in this memo with the exception of the lumbar spine BMD Z-score findings, as discussed above, and the fracture findings which have clinical importance.

Fractures: Bone fracture and deformity are major sequelae of osteogenesis imperfecta. Fracture outcomes evaluated in Study 2003100 included morphometric vertebral fractures and clinical vertebral and nonvertebral fractures. Lateral spine x-rays for evaluation of new morphometric vertebral fractures were done at screening and Month 12. Clinical vertebral and nonvertebral fractures were reported as adverse events. All clinical fractures required radiographic confirmation. At the preNDA meeting, the Applicant was also asked to provide an analysis of long bone fractures in patients with and without hardware (i.e., orthopedic support for long bones).

New morphometric vertebral fracture: A total of 139 subjects (91 in the risedronate group and 48 in the placebo group) had screening and Month 12 spinal x-rays for evaluation of morphometric vertebral fractures. A total of 29 (32%) subjects in the risedronate group and 8 (17%) subjects in the placebo group sustained a new morphometric vertebral fracture during the 12 month study period. As reported by the Applicant using an exact T-test, the p-value was

0.0693 without any prespecified adjustments. However, as outlined in Dr. Dwyer's review, when evaluated by logistic regression analysis including age group, gender, race and pooled country as covariates, age group was statistically significant. Therefore, Dr. Dwyer used the Cochran-Mantel-Haenszel test stratified by age group to test for the treatment difference. Using the CMH test, the treatment difference was statistically significant (p-value = 0.0448) for all subjects. When evaluated by age group, in subjects 4 – 9 years of age, 19 (38%) risedronate-treated subjects and 7 (25%) placebo treated subjects sustained a new morphometric vertebral fracture (p=0.2457). In subjects 10 – 15 years of age, 10 (24%) risedronate-treated subjects and one (5%) placebo treated subject sustained a new morphometric vertebral fracture (p=0.0667).

Clinical vertebral and nonvertebral fracture: Clinical fractures were reported as adverse events. No clinical (symptomatic) vertebral fractures were reported during the 12 months of this study. Clinical nonvertebral fractures were reported by 29 (31%) subjects in the risedronate group and 24 (49%) subjects in the placebo group. Of these nonvertebral fractures, long bone fractures occurred in 18 (19%) subjects in the risedronate group and 17 (35%) subjects in the placebo group.

Because of potential differences in fracture rates in patients with and without long bone orthopedic hardware, the Applicant was asked to provide an analysis of long bone fractures with and without previously implanted orthopedic hardware. The presence of orthopedic hardware was not systematically assessed at baseline in this study. The Applicant reviewed information concerning the presence of hardware as determined from the whole body DXA scans obtained during the trial. This information was checked against the medical and surgical histories and general comments to validate both the positive and negative findings. Overall, 13 (14%) subjects in the risedronate group and 6 (12%) subjects in the placebo group had pre-existing long bone orthopedic hardware at baseline. In subjects without preexisting hardware, nonvertebral fractures occurred in 11/81 (14%) subjects in the risedronate group and 13/43 (30%) subjects in the placebo group. In patients with preexisting hardware, nonvertebral fractures occurred in 7/13 (54%) subjects in the risedronate group and 4/6 (67%) subjects in the placebo group. In OI population, fracture at the site of orthopedic hardware is common. The potential benefit of risedronate therapy in decreasing nonvertebral fractures appears to be driven predominantly by subjects without previously implanted orthopedic hardware.

7.3 Summary of Efficacy

Similar to other bisphosphonates, treatment with Actonel increases bone mineral density in patients with osteogenesis imperfecta. However, a clear benefit in prevention of new fractures is not evident in this study. There did appear to be a trend in the prevention of new nonvertebral fractures with risedronate use. However, this trend is most evident in subjects without orthopedic hardware. In subjects with preexisting orthopedic hardware, the improvement in fracture incidence is not as robust. In addition, there was a statistically significant worsening in the incidence of new morphometric vertebral fractures with risedronate use.

8 Safety

8.1 Safety Findings

Safety Events and exposure: As noted in Table 5, in Study 2003100 there were, in general, comparable adverse event rates between the risedronate and placebo treatment groups. The percentage of subjects, however, who discontinued prematurely from the Study was higher in the risedronate group (7%) compared to that in the placebo group (0%). The mean days of exposure was 348 ± 75 days in the placebo group and 367 ± 10 days in the placebo group. In the first year of the trial, 94% of risedronate-treated subjects and 100% of the placebo treated subjects took study drug for at least 270 days.

Table 5. Study 2003100: Safety Events

	Number (%)	
	Risedronate	**Placebo**
N, enrolled	97	50
N, safety	94	49
Discontinued	7 (7)	0 (0)
N, completed	87 (93)	49 (100)
Death	0 (0)	0 (0)
Serious Adverse Event	11 (12)	8 (16)
Withdrawal due to AE	1 (1)	0 (0)
Adverse Event	86 (92)	47 (96)

Source: compiled from 2003100 study report table 35

Deaths: No deaths occurred during either Study 2002020 (PK Study) or Study 2003100.

Serious adverse events: In study 2002020, one serious adverse event was reported in a 15 year old male who developed gastrointestinal adverse event symptoms approximately 31/2 weeks after receiving a single dose of 10 mg risedronate. He was ultimately diagnosed with Crohn's disease.

In study 2003100, serious adverse events (SAEs) were reported by 11 (12%) subjects in the risedronate group and 8 (16%) subjects in the placebo group. Fractures were the most common serious adverse event in both groups (8 [9%] of risedronate subjects and 8 [16%] placebo subjects). Other SAEs were reported by 4 subjects in the risedronate group. An 8-year-old girl in the 2.5 mg risedronate group with a history of abdominal pain and irritable bowel syndrome (IBS) had a recurrence of abdominal pain and IBS symptoms after starting risedronate. A 9-year-old boy who had a history of Crohn's disease developed a relapse of symptoms 2 weeks after starting risedronate 2.5 mg. Study drug was ultimately stopped and the patient was withdrawn from the study. A 5-year-old boy receiving 2.5 mg risedronate developed cellulitis following a mosquito bite and required hospitalization approximately 5 months after initiation of therapy. He was treated with intravenous antibiotics and was discharged 2 days later. A 6-year-old girl with a history of dentogenesis imperfecta, was treated with 2.5 mg risedronate and developed mastoiditis approximately 4 ½ months after initiation of therapy. She underwent mastoidectomy

and at the time of surgery a large defect in the eardrum was noted. The patient recovered post surgery and was discharged.

It is unusual that two subjects in these small trials developed serious adverse events related to Crohn's disease. I agree, however, with Dr. Voss that these findings are likely coincidence.

Adverse events leading to withdrawal from study: One subject from study 2003100, assigned to the risedronate group discontinued from the trial due to a serious adverse event related to Crohn's disease exacerbation, as discussed above.

Adverse events: In study 2003100, a total of 133 subjects (86 [92%] in the risedronate group and 47 [96%] in the placebo group) reported at least one adverse event. The adverse events that occurred more frequently in the risedronate group compared than in the placebo group included pain in extremity (21% vs. 16%); headache (20% vs. 8%); back pain (17% vs. 10%); vomiting (15% vs. 6%); pain (15% vs. 10%); upper abdominal pain (11% vs. 8%); and bone pain (10% vs. 4%). When compared to the risedronate safety database in adults, the adverse events that are seen more commonly in the pediatric population include headache and vomiting.

Adverse events of special interest

Fractures: See the efficacy section of the Memorandum for a discussion of fractures that occurred during this trial. Fracture healing time was not routinely reported. One 6 year-old girl from the 2.5 mg risedronate group sustained a left femur fracture. After 6 weeks of conservative therapy, the fracture was not thought to be healing, and she underwent surgical intervention.

Gastrointestinal disorders: Oral, nitrogen-containing bisphosphonates are well known to cause gastroesophageal irritation. As outlined in Dr. Voss's review, upper gastrointestinal adverse events were reported by 21 (22%) subjects in the risedronate group and 13 (26%) subjects in the placebo group. There was one report of esophagitis in a risedronate treated subject who was using the dosing spoon.

An increase in nausea and vomiting with alendronate use compared to placebo was noted in a trial evaluating alendronate therapy in OI patients. In study 2003100, nausea was reported by 4 (4%) of risedronate-treated subjects and 6 (12%) of placebo-treated subjects. Vomiting was reported by 14 (15%) of risedronate-treated subjects and 3 (6%) of placebo-treated subjects. There was no difference in the occurrence of nausea and vomiting between subjects that swallowed the tablet and those that used the dosing spoon to dissolve the tablet prior to swallowing.

Hypocalcemia: Bisphosphonate use has been associated with hypocalcemia. In Study 2003100, enrollees were encouraged to maintain adequate calcium and vitamin D supplementation, but supplements were not provided and usage was not routinely tracked. There were no adverse event reports of hypocalcemia. The lowest calcium levels seen in the routine clinical laboratory analyses were 2.18 mmol/L (8.7 mg/dL) which is within the normal range.

Musculoskeletal Pain: An increased incidence of muscular and bone pain has been reported with bisphosphonate use. Bone pain is also a common complaint for patients with OI. There was an

increased incidence of bone pain reported as an adverse event (10% in risedronate-treated patients, compared to 4% in placebo treated patients). However, as outlined in Dr. Voss's review, there was not a clear increase in bone pain, as assessed with the Wong-Baker FACES.

Osteonecrosis of the Jaw: Both intravenous and oral bisphosphonates have been associated with osteonecrosis of the jaw. There were no cases of ONJ reported in this short one-year trial. It is not known if the underlying collagen disorder of osteogenesis imperfecta will predispose to ONJ with long-term treatment.

Inflammatory Eye Disease: An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. While osteogenesis imperfecta is associated with thinning of the sclera such that uveal tissue appears evident (blue sclera), there does not appear to be an association of OI with inflammatory eye disease. In study 2003100, one 6 year-old girl in the 2.5 mg risedronate group developed ocular discomfort during the trial. There were no reports, however, of uveitis or episcleritis.

Height and Linear Growth: Childhood and adolescence are the time period of maximal linear growth and bone accrual. The effect of bisphosphonates on linear growth in children remains an important unknown safety issue. Growth patterns in OI are perturbed due to the nature of the disease. At Month 12, least squares mean height increased 5.5% in the risedronate group and 4.5% in the placebo with a least squares mean difference of +0.99% (95% CI -0.54 , 2.51) in favor of risedronate. Annualized growth velocity was +1.002 in the risedronate group and +0.895 in the placebo group with a least squares mean difference of 0.107 (95% CI -0.114 , 0.328).

Bone histomorphometry: In prior studies of bisphosphonate use in children with osteogenesis imperfecta, concerns were raised regarding an imbalance in the number of subjects treated with bisphosphonate who had prolonged (> 30 days) mineralization lag times compared to placebo (15 in the drug group and none in placebo in these prior studies). These findings suggest that there may be a potential for a mineralization defect with long term bisphosphonate therapy in patients with osteogenesis imperfecta. In study 2003100, paired (baseline and Month 12) bone biopsy specimens were obtained in 8 patients in the risedronate group and 4 patients in the placebo group. There were no qualitative abnormalities such as woven bone, osteomalacia, or bone marrow fibrosis present in any specimen.

All specimens except for one Month 12 sample from a placebo subject had adequate double demeclocycline label present. In that sample, only a single label was present. Despite the presence of labeling, not all specimens were adequate for determination of all histomorphometry parameters. Dr. Voss has nicely outlined the histomorphometry findings. One would expect that treatment with bisphosphonates would decrease bone remodeling, as evidenced by decreased erosion surface per bone surface (ErodeS/BS) and contribute to increasing cortical width and trabecular thickness. While treatment with risedronate did result in decreased ErodeS/BS, there was an unexpected mean decrease in both cortical width and trabecular thickness compared to baseline, although all values remained within the normal range. As discussed by Dr. Voss, decreased trabecular thickness and decreased cortical width are characteristics seen in the osteogenesis population. Given the small number of biopsy specimens and the underlying

pathology of OI, the clinical implications of the cortical width and trabecular thickness findings are not clear.

Increases in mineralization lag time (MLT) can be the first signs of a mineralization defect. A mineralization lag time greater than 30 days with an osteoid thickness of greater than 10 micrometers can be used to define a mineralization defect. As outlined in Table 31 in Dr. Voss's review, five subjects (three from the risedronate group and two from the placebo group) had a MLT greater than 30 days in one of their biopsies. Two of these subjects, both of whom received risedronate, had mineralization lag times that increased to greater than 40 days at Month 12. However, no subjects had an osteoid thickness that met the criteria for a mineralization defect.

8.2 Safety Update

Dr. Voss has conducted a complete review of the 120 day safety update. Gastrointestinal and musculoskeletal adverse events continue to be reported, predominantly in patients switched from placebo to risedronate therapy. No new safety signals were noted.

8.3 Summary of Safety

The clinical trial data provided in the supplemental NDA demonstrated a risedronate safety profile similar to that seen in adults with osteoporosis, with the exception of higher incidence rates of headache and vomiting. Other adverse events reported in ≥10% of pediatric patients treated with risedronate and with a higher frequency than placebo were: pain in the extremity (21% with risedronate versus 16% with placebo), headache (20% versus 8%), back pain (17% versus 10%), pain (15% versus 10%), upper abdominal pain (11% versus 8%), and bone pain (10% versus 4%). In this small study, there did not appear to be any adverse effects on bone mineralization or growth velocity.

However, given the evolving long-term safety concerns with bisphosphonate use, this study does not provide adequate data to assess the long term risk/benefit profile for risedronate for use in children with osteogenesis imperfecta. Among these long term risks are the development of osteonecrosis of the jaw (ONJ), clinically significant esophageal disease, and the potential negative effect on fracture healing and linear growth.

9 Advisory Committee Meeting

An advisory committee meeting was not held for this supplemental NDA because there were no issues that warranted advisory committee discussion or guidance.

10 Pediatrics

This review focuses on the two pediatric studies submitted in response to the Written Request for pediatric studies. Please see the clinical pharmacology, efficacy and safety sections for an overview of the two studies submitted. The Applicant's submission addressing the requirements outlined in the Written Request for pediatric studies was presented to the Pediatric Exclusivity Board on April 7, 2009. This presentation detailed the potential data integrity issues surrounding

the analysis of risedronate serum and urine samples by (b) (4). After this meeting, further information was requested from the Applicant, as detailed in Section 5 of this review. Based on the data received from the Applicant, these data integrity issues were represented and discussed at a subsequent Pediatric Exclusivity Board meeting on April 23, 2009. After complete review, the Board concurred with the Review Divisions that the Applicant had adequately conducted the two studies described in the Written Request and pediatric exclusivity was granted on April 24, 2009.

11 Other Relevant Regulatory Issues

Financial disclosures: Dr. Voss reviewed the financial disclosure information provided for Study 2003100. No investigator declared any personal financial interest.

DSI audits: No DSI audits were conducted for this sNDA as none were thought to be needed. The analytical site for the risedronate measurement (b) (4)) had previously been inspected for another study as described earlier in the Memorandum.

DDMAC consult: A DDMAC consult was obtained for this sNDA. Dr. Maniwang recommended two changes to the proposed label language.

1) to delete the language "(b) (4)" from the discussion of study 2003100 BMD results. This has been done
2) to better define the term "young" in the discussion of pharmacokinetic elimination in young healthy subjects. This language has been in place since the origination of the Actonel label and was left as written.

12 Labeling

The Applicant proposed the following language for the pediatric section of the Actonel Package Insert:

8.4 Pediatric Use

ACTONEL is not indicated for use in pediatric patients.

The safety and effectiveness of risedronate was assessed in a one-year, randomized, double-blind, placebo controlled study of 143 pediatric patients (94 received risedronate) with osteogenesis imperfecta. The enrolled population included patients with mild, moderate, or severe osteogenesis imperfecta ((b) (4) Type-I, (b) (4)), aged 4 to <16 years, (b) (4) 50% (b) (4) male and 82% Caucasian, with a mean lumbar spine BMD Z-score of -2.08 (2.08 standard deviations below the mean for age-matched controls). Patients received either a 2.5 mg (≤30 kg body weight) or 5 mg (>30 kg body weight) daily oral dose. After one year, (b) (4) increase in lumbar spine BMD in the risedronate group (b) (4) placebo group was observed. However, treatment with risedronate did not result in an overall benefit in the risk of fracture in pediatric patients with osteogenesis imperfecta. (b) (4)

(b) (4)

12.3 Pharmacokinetics
Special Populations
Pediatric: ACTONEL is not indicated for use in pediatric patients (see *Pediatric Use [8.4]*).

The Review Team felt that the presentation of efficacy and safety needed revisions. In addition, as outlined in the clinical pharmacology discussion, language regarding the results of Study 2002020 was also removed for the reasons previously outlined. After negotiations with the Applicant, the following wording for labeling was agreed upon:

8.4 Pediatric Use
ACTONEL is not indicated for use in pediatric patients.

The safety and effectiveness of risedronate was assessed in a one-year, randomized, double-blind, placebo controlled study of 143 pediatric patients (94 received risedronate) with osteogenesis imperfecta. The enrolled population was predominantly patients with mild osteogenesis imperfecta (85% Type-I), aged 4 to <16 years, 50% male and 82% Caucasian, with a mean lumbar spine BMD Z-score of -2.08 (2.08 standard deviations below the mean for age-matched controls). Patients received either a 2.5 mg (≤30 kg body weight) or 5 mg (>30 kg body weight) daily oral dose. After one year, an increase in lumbar spine BMD in the risedronate group compared to the placebo group was observed. However, treatment with risedronate did not result in a reduction in the risk of fracture in pediatric patients with osteogenesis imperfecta. In ACTONEL-treated subjects, no mineralization defects were noted in paired bone biopsy specimens obtained at baseline and month 12.

The overall safety profile of risedronate in OI patients treated for up to 12 months was generally similar to that of adults with osteoporosis. However, there was an increased incidence of vomiting compared to placebo. In this study, vomiting was observed in 15% of children treated with risedronate and 6% of patients treated with placebo. Other adverse events reported in ≥10% of patients treated with risedronate and with a higher frequency than placebo were: pain in the extremity (21% with risedronate versus 16% with placebo), headache (20% versus 8%), back pain (17% versus 10%), pain (15% versus 10%), upper abdominal pain (11% versus 8%), and bone pain (10% versus 4%).

12.3 Pharmacokinetics
Special Populations
Pediatric: ACTONEL is not indicated for use in pediatric patients (see *Pediatric Use [8.4]*).

Other changes to the prior approved Package Insert included:

- Updated language in Warnings and Precautions, subsection 5.3, Osteonecrosis of the Jaw
- Correction of language in Section 6.1, Adverse Reactions, Clinical Trials Experience, subsection Treatment and Prevention of Glucocorticoid Induced Osteoporosis
- Updated language in Section 8, Use in Special Populations, subsection 8.1, Pregnancy
- Updated language Section 8, Use in Special Populations, subsection 8.6, Renal Impairment
- Updated language Section 8, Use in Special Populations, subsection 8.7, Hepatic Impairment
- Updated language Section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility, subsections Carcinogenesis and Impairment of Fertility
- Updated language Section 13.2, Animal Toxicology and/or Pharmacology

Final acceptable labeling was submitted by the Applicant on July 17, 2009.

13 Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

This reviewer recommends Approval of this supplemental NDA with revision of the Package Insert based upon the language agreed-to by the Applicant. The most significant change to labeling will be the inclusion of the findings from Study 2003100 in Subsection 8.4 (Pediatric Use). The Applicant did not seek a pediatric indication for Actonel and to-be-approved labeling will include the following statement: "ACTONEL is not indicated for use in pediatric patients" in Subsections 8.4 and 12.3 (Pharmacokinetics).

13.2 Risk Benefit Assessment

With this supplemental NDA and complete response to the Written Request for pediatric studies, the Applicant was seeking to add clinical trial information to the Package Insert, regarding the findings from pediatric Study 2003100, but was not seeking a new pediatric indication. Treatment with risedronate clearly increases BMD in pediatric patients afflicted with predominantly mild osteogenesis imperfecta. These findings are consistent with those previously reported with other bisphosphonates. The efficacy of risedronate in reducing fractures, however, this population of children with osteogenesis imperfecta is not clear. While there did appear to be a trend toward benefit of risedronate treatment for nonvertebral fractures (nonvertebral fractures were reported for 29 [31%] subjects in the risedronate group and 24 [49%)] subjects in the placebo group), that trend was not evident in the evaluation of morphometric vertebral fractures. A total of 29 (32%) subjects in the risedronate group and 8 (17%) subjects in the placebo group sustained a new morphometric vertebral fracture during the 12 month study period.

Risedronate over one year of use in pediatric patients with mild to severe osteogenesis imperfecta was generally well tolerated and the safety profile did not raise any significant concerns. The safety profile appeared to be similar to that seen in adults with osteoporosis, with the exception of higher incidence rates of headache and vomiting, which should be included in labeling. In this small study, there did not appear to be any adverse effects on bone mineralization or growth velocity. However, given the evolving long-term safety concerns with bisphosphonate use, this study does not provide adequate data to assess the long term risk/benefit profile for risedronate for use in children with osteogenesis imperfecta. Among these long term risks are the development of osteonecrosis of the jaw (ONJ), clinically significant esophageal disease, and the potential negative effect on fracture healing and linear growth. Because of these unanswered safety concerns and the lack of strong evidence that treatment with risedronate reduces the risk of clinical fractures, it remains appropriate to include the language "Actonel is not indicated for use in children" in product labeling.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Postmarketing risk evaluation and management strategies are not necessary for this supplemental NDA because the safety data contained in the Application did not raise any new concerns and no new indications are to-be-approved.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

No postmarketing requirements or commitments, other than on-going pharmacovigilance related to the previously approved indications for risedronate, are necessary for this supplemental NDA.

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/s/

Theresa Kehoe
7/21/2009 01:49:54 PM
MEDICAL OFFICER

Scott Monroe
7/21/2009 02:57:10 PM
MEDICAL OFFICER
I concur with Dr. Kehoe's conclusions and recommendations.