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January 24, 2000

Eric Colman, M.D.
Division of Metabolism and Endocrine Drug Products
Attention: Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

Dear Dr. Colman:

In labeling comments received from the Biopharm reviewer (July 8, 1999) concern was raised about reducing the volume of water used when ACTONEL is administered due to the effect on esophageal transit time. P&GP responded to the concern (submission dated July 13, 1999) with data from our own studies and the published literature which demonstrate that for patients ingesting ACTONEL in an upright position, use of ——— of water is sufficient to obtain a rapid esophageal transit of the film-coated tablet and volumes of water greater than this are unnecessary to assure transit of the tablet to the stomach. We have recently completed another clinical study (Study 1999010, protocol submitted in IND Serial No. 441, June 9, 1999) which further supports our position that ——— of water is sufficient to obtain rapid esophageal transit.

Study 1999010 was a two-way crossover study in 14 healthy postmenopausal women (mean age ~58; Attachment 1, Table A provides additional baseline characteristic information) which compared the esophageal transit, disintegration, and gastric emptying times of a placebo risedronate tablet when administered with either 50 mL or 240 mL of water. The report for this study is not yet available, however, we have just completed the analyses of the major endpoints. The primary analysis was a test of equivalence between the two volumes of water (50 mL and 240 mL) with regard to the esophageal transit time. The equivalence range for the difference in mean esophageal transit time between the two volumes of water was chosen to be ± 8.0 seconds. This range corresponds to approximately twice the standard deviation of the esophageal transit time of an identical cellulose film-coated placebo risedronate tablet administered to elderly subjects with 240 mL of water. If the 90% CI for the difference in mean esophageal transit time was within ± 8.0 seconds, the mean transit times between the two volumes of water were considered equivalent.

An analysis of variance model, with terms for period effect, sequence effect , and dosing effect, was used to analyze the data. Carry-over effect was not included in the model because there was a washout period of at least 48 hours between each visit to clear the radioactivity from the GI tract and because there was no active drug involved in the study.

Esophageal transit times were observed for all 14 subjects. Table 1 summarizes the esophageal transit time by visit and volume of water. Analysis of variance did not indicate a significant difference in mean esophageal transit time between the two volumes of water (50 mL vs. 240 mL) (p-value=0.4716). The mean difference in esophageal transit time between 50 mL and 240 mL was estimated to be -0.67 seconds with a 90% CI (-2.27, 0.93) (Attachment 1, Table B). This CI was within the equivalence range ± 8.0 seconds. No esophageal stasis was observed during the study (esophageal stasis was defined as a esophageal transit time > 20 seconds). The time to complete disintegration and the gastric emptying time were also similar between the two volumes of water (Attachment 1, Table C). Analysis of variance did not indicate a significant difference in mean disintegration time or gastric emptying time between the two volumes of water.

Table 1: Descriptive Statistics for Esophageal Transit Time (seconds)

Sequence	Visit	N	Mean (SD)	Median	Min	Max
50/240 mL	Visit 1 (50 mL)	8	4.7 (3.10)	3.6	—	—
	Visit 2 (240 mL)	8	5.9 (5.25)	4.0	—	—
240/50 mL	Visit 1 (240 mL)	6	4.5 (2.19)	3.6	—	—
	Visit 2 (50 mL)	6	4.4 (1.94)	4.4	—	—

In conclusion, we do not feel that there is any evidence that reducing the volume of water from that currently approved in the Paget's label (6 to 8 ounces) to [redacted] will have any impact on esophageal transit of the risedronate film-coated tablet. The following points summarize our position:

- The esophageal transit study (92024)[1] showing the film-coated tablet reaches the stomach quickly (mean transit time of 3.3 sec) in elderly men and women (mean age ~66 years) when subjects took this dose form with 50 mL (<2 oz) of water. The gelatin capsule phase II formulation had a mean transit time of over 20 seconds. Retention of the capsule in the esophagus occurred in 28% of subjects but was not observed with the tablet formulation.

- A second esophageal transit study (1997007)[2] comparing elderly men and women with or without GERD (mean age ~66 years) showing the mean esophageal transit time (3.1 sec) for the normal group with 240 mL of water was not greater than in Study 92024 with 50 mL of water. This study also showed that transit in normal control group was similar to transit in patients with GERD (4.1 sec).

- A third esophageal transit study (1999010, referred to above) in healthy postmenopausal women comparing the esophageal transit of the film-coated tablet when administered with either 50 mL or 240 mL of water showing the film-coated

[1] Study 92024 Final Report, Paget's NDA, Vs1.115/p.2.
[2] Study 1997007 Final Report, Vs1.288/p.144 (NDA 20-835/S-001, S-002, S-003, Amendment 5).

tablet reaches the stomach quickly with either volume of water. There was no significant difference in mean esophageal transit time between the two volumes of water. The mean esophageal transit time was 4.6 ± 0.69 sec for 50 mL of water and 5.3 ± 1.1 sec for 240 mL water.

- Hey et al[3] examined esophageal transit of 6 commonly shaped pills in 121 healthy volunteers (726 swallowings in total). Subjects used either 25 ml or 100 ml of water to ingest pills in either an upright or supine position. Transit time for all formulations was unaffected by volume of water when subjects remained upright. Transit times were slowed when subjects used the smaller volume of water and ingested pills while recumbent. The authors concluded that patients should remain standing for at least 90 seconds after taking medication, that tablets should be swallowed with at least 100 ml of water, and that that small oval tablets are preferable.

- Kikendall and Johnson[4] reviewed 756 cases of pill-induced esophageal injury with 75 different medications and recommend that all tablets be ingested with at least 4 oz (120 mL) of water and patients should remain upright after dosing for at least 10 minutes prior to lying down.

Please call me at (513) 622-1114 if you have questions on this submission.

Sincerely,

Linda W Manning

Linda W. Manning, Pharm.D.
Senior Scientist
Regulatory Affairs

Desk Copies: Randy Hedin, R.Ph.
Eric Colman, M.D.
Hae-Young Ahn, Ph.D.

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[3] Hey H, Jørgensen F, Sørensen K, Hasselbalch H, Wamberg T. Oesophageal transit of six commonly used tablets and capsules. Brit Med J 1982;285:1717-9.

[4] Kikendall JW, Johnson LF. Pill-induced esophageal injury. In: Castell DO, editor. The esophagus. 2nd ed. Boston: Little Brown;1995. p. 619-33.

ATTACHMENT 1

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Table A

Demographic and Screening Characteristics (All Randomized Subjects)

Parameter	Sequence 1[b]	Sequence 2[c]	Total
Age (years)			
n	8	6	14
Mean ± SEM	58.3 ± 0.80	58.8 ± 1.54	58.5 ± 0.77
Median	58	59	58
Min, Max	55, 61	55, 65	55, 65
Race[a]			
Caucasian	8 (100%)	6 (100%)	14 (100%)
Black	0 (0%)	0 (0%)	0 (0%)
Asian Indian	0 (0%)	0 (0%)	0 (0%)
Asian Oriental	0 (0%)	0 (0%)	0 (0%)
Multi-racial	0 (0%)	0 (0%)	0 (0%)
Weight (kg)			
n	8	6	14
Mean ± SEM	69.7 ± 2.19	66.3 ± 1.13	68.2 ± 1.38
Median	69.5	65.8	67.3
Min, Max	61.0, 76.5	62.3, 70.5	61.0, 76.5
Height (cm)			
n	8	6	14
Mean ± SEM	164.2 ± 1.62	161.8 ± 2.46	163.1 ± 1.39
Median	164.5	162.5	164.0
Min, Max	157.5, 169.0	152.0, 169.0	152.0, 169.0
Tobacco Usage[a]			
Never	6 (75%)	4 (67%)	10 (71%)
Previously	2 (25%)	2 (33%)	4 (29%)
Currently	0 (0%)	0 (0%)	0 (0%)
Alcohol Consumption[a]			
Never	2 (25%)	1 (17%)	3 (21%)
Previously	0 (0%)	0 (0%)	0 (0%)
Currently	6 (75%)	5 (83%)	11 (79%)

[a] Data shown are the number and percentage of subjects.

[b] Subjects took the radiolabeled placebo risedronate tablet with 50 mL of water at Visit 1 and 240 mL of water at Visit 2.

[c] Subjects took the radiolabeled placebo risedronate tablet with 240 mL of water at Visit 1 and 50 mL of water at Visit 2.

Table B

Summary of Esophageal Transit Time
(All Randomized Subjects)

Parameter	50 mL Water (N = 14)	240 mL Water (N = 14)
Esophageal Transit Time (seconds)		
n	14	14
Mean ± SEM	4.6 ± 0.69	5.3 ± 1.11
Median	4.0	4.0
Min, Max		
Treatment A (50 mL water) - Treatment B (240 mL water)		
Difference	-0.67	
90% CI	-2.27, 0.93	

N = number of randomized subjects who received volume of water; n = number of randomized subjects who received volume of water and had a esophageal transit time measurement; SEM = standard error of the mean.

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Table C

Summary of Disintegration and Gastric Emptying Times (All Randomized Subjects)

Outcome Parameter	50 mL Water (N = 14)	240 mL Water (N = 14)
Onset of Disintegration Time (minutes)		
n	4	8
Mean ± SEM	6.5 ± 0.65	6.9 ± 0.97
Median	6.5	6.0
Min, Max		
Treatment A (50 mL water) - Treatment B (240 mL water)		
Difference	NA	
90% CI[b]	NA	
Time to Complete Disintegration (minutes)		
n	14	14
Mean ± SEM	12.3 ± 2.81	12.9 ± 2.34
Median	8.5	12.5
Min, Max		
Treatment A (50 mL water) - Treatment B (240 mL water)		
Difference	-0.25	
90% CI[b]	-4.98, 4.48	
Gastric Emptying Time: T_{50} (minutes)		
n	14	14
Mean ± SEM	19.5 ± 6.21	17.2 ± 2.87
Median	11.0	13.5
Min, Max		
Treatment A (50 mL water) - Treatment B (240 mL water)		
Difference	4.13	
90% CI[b]	-6.86, 15.11	

If any times were subject to censoring (e.g. time to complete disintegration occurred in < 3 minutes) the cut-off time (e.g., 3 minutes) was used in calculations.

[b] Confidence interval estimates were based on XXX.

N = number of randomized subjects who received volume of water and who didn't take additional water;
SEM = standard error of the mean.

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January 12, 2000

Eric Colman, M.D.
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RE: NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

Dear Dr. Colman:

We have received the email dated January 4, 2000 with your final labeling comments on the draft ACTONEL package insert for the treatment and prevention of postmenopausal and corticosteroid-induced osteoporosis. This submission contains our responses to those comments.

Your review of the proposed package insert resulted in the deletion of the nonvertebral fracture statement from the indication for treatment of postmenopausal osteoporosis. We have addressed this comment in detail in Attachment 1, as we feel the statement should not be deleted from the indication statement in the package insert. In this attachment, we point out the importance of osteoporosis-related fractures at sites other than the spine, hip, or wrist and we compare our data to that of alendronate and raloxifene. Our data are robust and clearly support the efficacy of risedronate in the reduction of nonvertebral fractures.

All of your other comments are addressed in the table contained in Attachment 2. The table includes your proposed modifications, our proposal in response, and the rationale for our proposed modifications. The revised draft package insert which incorporates all the changes is provided in Attachment 3.

Please call me at (513) 622-1114 if you have questions on any of our comments. We look forward to finalizing labeling discussions with the Division.

Sincerely,

Linda W. Manning

Linda W. Manning, Pharm.D.
Senior Scientist
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Desk Copy: Randy Hedin, R.Ph.
Eric Colman, M.D.

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December 29, 1999

Solomon Sobel, MD
Director, Division of Metabolism and
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Center for Drug Evaluation and Research
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Rockville, MD 20857

RE: NDA #20-835/ S-001, S-002, S-003, S-004, ACTONEL (risedronate sodium) Tablets
NDA Amendment 9 - COMPLETE RESPONSE to October 18, 1999 Approvable Letter

Dear Dr. Sobel:

This submission provides our "Complete Response" to the October 18, 1999 approvable letter which we received from the Agency for the corticosteroid-induced osteoporosis (CIO) indications (S-001, S-004) and the postmenopausal osteoporosis (PMO) indications (S-002 S-003) for Actonel® (risedronate sodium). The approvable letter requested that a follow-up study be conducted in, at a minimum, the North American osteoporosis trials, in which all-cause mortality, all-cancer mortality, and lung cancer mortality would be assessed. This study has now been completed and a report is provided in this submission.

In previous submissions, we have provided the following other items requested in the approvable letter:

1. In a submission dated October 29, 1999, we provided an English translation of the product labeling related to the approval of risedronate sodium 5 mg tablets (tradename Optinate) in Sweden for the PMO and CIO indications.

2. In a submission dated December 17, 1999 (Amendment 8), we provided updated safety information. This submission also contained additional stability data to support a 36-month expiration date.

The final report of the follow-up mortality study, included in this submission, provides complete follow-up on more than 98% (7845 patients) of those who were randomized and received at least 1 dose of study drug in the 3 North American osteoporosis clinical studies. These studies represent 51% of the patients in the entire risedronate Phase III clinical database and, importantly, 61% of the patients reported to have lung cancer. All-cause mortality was determined through December 31, 1998, while all-cancer and lung cancer mortality were determined through December 31, 1997. The mean per-patient follow-up time was 3.2 years for the all-cancer and lung cancer mortality data and 4.2 years for the all-cause mortality data.

We have enclosed ZIP disks containing the electronic SAS dataset for the mortality follow-up study. The documentation for this dataset is found in Attachments A and B. Attachment A

contains a PROC contents of the SAS dataset. The derived variables and decodes for the coded variables are included in Attachment B.

Mortality Study Results

The complete follow-up mortality data showed no increased relative risk of mortality for the risedronate groups compared with placebo.

- The "all-time" analyses ("on-study" plus "off-study") of the pooled risedronate treatment groups compared to placebo demonstrated no increased relative risk (RR < 1.0) for all-cause, all-cancer, or lung cancer mortality.

- The relative risks of death from all cancer or lung cancer were lower in the 5-mg risedronate treatment group compared with the 2.5-mg group for each of the analysis times ("all-time," "on-study," and "off-study"), confirming the absence of a dose-response relationship.

- The lung cancer deaths which occurred during the "off-study" period in the 2.5-mg risedronate group compared with placebo (RR = 1.1) did not replicate the imbalance seen in lung cancer incident cases reported during the clinical studies (RR = 3.1), or in "on-study" lung cancer deaths (RR = 1.7). In addition, among those patients not previously reported to have lung cancer during the trials, the RR of the 2.5-mg risedronate group compared with placebo in the "off-study" period was 0.56. The 5-mg risedronate treatment group had a consistently low relative risk, compared with placebo, of 0.44 to 0.60 during all analysis periods.

On the basis of these data, we conclude there is no evidence of a causal association or a promotional effect between risedronate use and lung cancer. We believe that incomplete ascertainment of lung cancer cases in the placebo group and chance are plausible explanations for the imbalance of lung cancer reports during the clinical trials.

Presentation of Results to Expert Safety Panel

The results of this mortality follow-up study were reviewed by an expert Safety Advisory Panel on December 17 and 18. A report summarizing this review and the Panel's conclusion is included in this submission (See Meeting Report: Safety Advisory Panel).

During the review of the mortality data, we presented new analyses of the lung cancer incidence data from all 10 Phase III studies to address the possibility that the original observations could have been due to chance. Lung cancer reports from the clinical trial database were analyzed in the context of the set of all the different cancer types reported. Analyses found no significant differences ($p = 0.527$) between the odds ratios (OR) for the 22 different cancer types (combined risedronate groups vs. placebo). Further, there was no evidence that the odds ratios were different from unity (common estimate of OR = 1.03, $p = 0.693$). It was also found, given the number of cancer outcomes considered, that there was a high likelihood ($p = 0.839$) of getting an OR for 1 of the cancers that is equal to, or greater than, that observed for lung cancer even if there were, in fact, no overall cancer treatment effect. In conclusion, the results support that the "on-study" imbalance in lung cancer reports is consistent with chance. A copy of the slides related to the discussion of chance as well as other discussions are included in Attachment 2 of the Meeting Report: Safety Advisory Panel.

The panel stated that the follow-up mortality study was an appropriate tool to resolve whether there were potential study design biases influencing the number of lung cancer reports. The "off-study" finding of a relative increase (placebo group) in the number of "new reports" of lung cancer, i.e., lung cancer deaths in patients who did not have a diagnosis of lung cancer during the "on-study" period, provides evidence that there was an incomplete ascertainment of lung cancer in the placebo group.

The conclusions of the Panel are provided below:

- There is no statistically significant difference in total mortality, any-cancer mortality, or lung cancer mortality between either risedronate treatment group and the placebo group or between both treatment groups combined and the placebo group. These results are based on an unbiased and complete assessment of mortality among North American trial participants in the Phase III program.

- The reports of lung cancer in the clinical trial database represent an incomplete ascertainment of cases and deaths. Underascertainment of lung cancer in the placebo group and the play of chance are plausible explanations for the observed excess of lung cancer reports among risedronate-treated patients in these data.

- The mortality study data, with a systematic ascertainment of lung cancer deaths, show no excess of lung cancer among all patients receiving risedronate. These data are based on a study with sufficient statistical power to evaluate the initial findings from the clinical trial reports. There is no dose-response relationship and the pattern of mortality differences among treatment groups is consistent with chance.

Please let me know if you have any questions or require further clarification on any aspect of this submission. We look forward to the final resolution of this issue.

Sincerely,

Bruce R. DeMark, PhD
Section Head
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December 22, 1999

Eric Colman, M.D
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RE: NDA #20-835/S-001, S-002, S-003, S-004 ACTONEL (risedronate sodium)

Dear Dr. Colman:

In your e-mail of December 17, you referred to our July 28, 1999 submission where we discussed the rationale for not including the same warnings about GI toxicity as those for alendronate. We referenced two alendronate papers by Liberman et al. (NEJM 1995; 333: 1437-1443) and by Black et. al. (Lancet 1996; 348: 1535-1541) and stated that the alendronate studies excluded patients on the basis of recent or current treatment with agents known to have the potential to irritate the GI. We have rechecked these papers and agree that this specific exclusion criterion is not explicitly stated in these papers.

The Liberman study reported the results of two clinical trials (North American and Multinational) which were the basis for the 1995 approval of alendronate for the treatment of PMO. In the separate publications of these two clinical studies by Tucci et.al. (Am J Med 1996; 101: 488-501) and Devogelaer et al. (Bone 1996: 18: 141-150), this exclusion criterion was clearly stated.

Attachment 1 summarizes the GI exclusion criteria from the published accounts of the Liberman/Tocci/Devogelaer studies and the Black study (FIT study data). We have also attached copies of the Tucci and Devogelaer papers for you.

Your December 17 e-mail also asked us to provide the percentage of patients, by treatment group, in RVN, RVE, RCP, RCT, and RBL who were coded at baseline as both "active GI disease" and taking a medication for the active disease. Table 1 on the next page provides a summary of this information.

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This table shows that overall, approximately 7% of the patients enrolled in the 5 studies had both an active upper GI disorder at entry and were taking one of the classes of GI medications indicated in the table. The percentages in this table were calculated using the total ITT population as the denominator.

Table 1
Percentage of Patients with Active Upper GI Disorders at Entry and Taking GI Medications[a] at Entry

Study	Placebo N=1517 n (%)	2.5 mg Risedronate N=1511 n (%)	5 mg Risedronate N=1523 n (%)
RVN	60 (7.4)	60 (7.4)	76 (9.3)
RVE	17 (4.2)	21 (5.1)	26 (6.4)
RBL	2 (1.6)	3 (2.4)	2 (1.5)
RCT	5 (5.3)	8 (8.7)	4 (4.0)
RCP	7 (9.2)	11 (15.1)	7 (9.3)
Total Patients	91 (6.0)	103 (6.8)	115 (7.6)

[a] GI Medications include the WHO Drug Dictionary ATC categories: Antacids (A02A), Drugs for Treatment of Peptic Ulcer (A02B), and Antiregurgitants (A02E)

For your information, we have also prepared a separate presentation (Table 2) showing that about 63% of the patients with active upper GI disorders at baseline were also taking GI medications at study entry. The percentages in this table were calculated using the number of patients that had upper GI disease at baseline, as the denominator.

Table 2
Percentage of Patients Taking GI Medications[a] at Entry among the Subgroup of Patients with Active Upper GI Disorders at Entry

Study	Placebo N=152 n (%)	2.5 mg Risedronate N=153 n (%)	5 mg Risedronate N=188 n (%)
RVN	60 (57.1)	60 (65.2)	76 (61.3)
RVE	17 (63.0)	21 (67.7)	26 (74.3)
RBL	2 (66.7)	3 (50.0)	2 (22.2)
RCP	7 (70.0)	11 (84.6)	7 (54.0)
RCT	5 (71.4)	8 (72.7)	4 (57.1)
Total Patients	91 (60)	103 (67)	115 (61)

[a] GI Medications include the WHO Drug Dictionary ATC categories: Antacids (A02A), Drugs for Treatment of Peptic Ulcer (A02B), and Antiregurgitants (A02E)

Please let me know if you have any additional questions.

Sincerely,

Bruce R. DeMark, Ph.D.
Section Head
U.S. Regulatory Affairs

Attachment

Desk copy: Eric Colman, MD
Randy Hedin, R. Ph.

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Attachment 1

GI-Specific Exclusion Criteria in Risedronate and Alendronate Clinical Trials

Table 1 summarizes the GI-specific exclusion criteria from the key risedronate and alendronate phase III clinical trials.

Studies RVN008993 & RVE009093 are the pivotal vertebral fracture trials for risedronate. The pivotal alendronate data (1) come from two identical trials (2,3). The alendronate FIT data (4) were used to extend the indication to include anti-fracture effects.

Table 1

GI-Specific Exclusion Criteria

RVN008993 & RVE009093	ALENDRONATE: Liberman	ALENDRONATE: FIT
none	Active peptic ulcer disease	Significant upper GI bleeding within the past 5 years, requiring hospitalization and/or transfusion[4,5]
	Major GI disease within 12 months of study start[5]	Dyspepsia requiring daily medication[4,5]
	Active upper gastrointestinal disease[2]	Esophageal or gastric vances[5]
	Medications (alternative versions): 1. Daily use of medications which have appreciable potential for gastrointestinal irritation[2] 2. Recent or current treatment with the potential to ..... cause irritation of the gastrointestinal mucosa[3] 3. Regular use (> 4 times/week) of medications with the potential for GI irritation, such as NSAIDs[5]	Documented recent or recurrent ulcer disease (1 episode in the preceding 12 months or 2 or more episodes in the preceding 5 years)[5]

In all the risedronate phase III trials there were no GI-specific exclusion criteria in the study protocols.

In the publication of the pivotal alendronate data (1), reference is made to patients being excluded if they have active peptic ulcer disease. It is noteworthy that the publications on the separate halves of this trial (2,3) give details of additional exclusion criteria, as does a review of alendronate tolerability (5). Copies of these three publications are attached. The GI-specific exclusions appear somewhat broader in scope and cover upper gastrointestinal disease in general plus medications with the potential for GI irritation. With regard to medication use, the exact criterion is unclear but references are made to both current and recent use of these medications.

The publication of the clinical fracture arm of the FIT study (4) only makes reference to patients being excluded for recent or current GI disorders. Interestingly, the publication giving the design details of the FIT study (6) gives less information on the GI-specific exclusion criteria than the publication presenting the results. It is therefore unclear whether exclusion criteria covered the use of medications with the potential to irritate the GI tract.

Conclusions

The key alendronate trials contained a widespread set of exclusions covering patients with recent or current GI-disease and those taking medications with the potential to irritate the GI tract. In contrast, the risedronate trials made no equivalent exclusions.

It might therefore be expected that the risedronate phase III population will be more predictive of the post-marketing experience.

References

1. Liberman UA, Weiss SR et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. NEJM 1995; 333: 1437-1443.

2. Tucci JR, Tonino RP et al. Effect of three years of roral alendronate treatment in postmenopausal women with osteoporosis. Am J Med 1996; 101: 488-501.

3. Devogelaer JP, Broll H et al. Oral alendronate induces progressive increases in bone mass of the spine, hip and total body over 3 years in postmenopausal women with osteoporosis. Bone 1996: 18: 141-150.

4. Black DM, Cummings SR et al. Randomised trial of the effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996; 348: 1535-1541.

5. Watts N, Freedholm D et al. The clinical tolerability profile of alendronate. IJCP Supplement April 1999: 51-61.

6. Black DM, Reiss TF et al. Design of the Fracture Intervention Trial. Osteoporosis Int 1993; Suppl 3: S29-39.

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December 17, 1999

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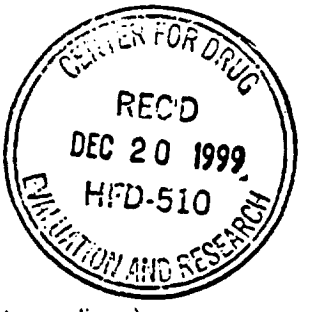

RE: NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

NDA Amendment 8 - Partial Response Letter
Part A: 3-Year Stability Data for the 5 mg Tablet;
Part B: Safety Update

Dear Dr Sobel:

The purpose of this amendment to NDA #20-835/S-001, S-002, S-003, and S-004 is to provide a partial response to the deficiencies addressed in the approvable letter received from the Division on October 18, 1999. Specifically, Part A of this submission contains 3-year stability data for the 5 mg tablet and Part B provides updated safety information for ACTONEL. The archival copy of this submission contains sections in paper and electronic formats. Parts A and B (3 volumes) are provided in paper format. The case report forms, submitted as part of the safety update, are PDF files (approximately — megabytes in size) provided on one CD-ROM. Norton AntiVirus 5.0 was used to assure the electronic portion of the submission is free of viruses.

In the approvable letter received from the Division, a statement was made that the stability data submitted in the sNDA only support a — month expiry date In a telephone discussion (October 18, 1999) between Dr. Harry Welles (P&GP) and Dr. Sheldon Markofsky, Dr. Markofsky agreed that P&GP could submit to the sNDA the 3-year stability data for the 5 mg tablet and, if the data were acceptable, he would extend the expiration date to 3 years at the time of approval. As a follow-up to that discussion, the 3-year stability data for the 5 mg tablet at the ICH long term storage condition are included in this submission to support an extension of the expiry date to 36 months. The data demonstrate that the 5 mg tablet is stable in the commercial package for at least 3 years.

A request was also made in the approvable letter for updated safety information for ACTONEL. A proposal outlining the content of this safety update was submitted to the Division on November 2, 1999 and accepted by the Division on November 8, 1999. Per that proposal, safety information from 3 ACTONEL studies for which unblinded data are now available is

being submitted in this safety update. Review of these data support the conclusions presented in the original Integrated Summary of Safety and the 180-day Safety Update, and thus there are no proposed revisions to the safety sections of the submitted package insert for ACTONEL *(version dated 2-December-1999)* for the indications of postmenopausal osteoporosis or corticosteroid-induced osteoporosis.

Please note that the final report for the mortality follow-up study which was requested in the approvable letter is currently being written and will be provided to the Division in a subsequent amendment later this month.

Please call me if there are any questions and/or clarifications regarding the information provided in this submission.

Sincerely,

Linda W Manning

Linda W. Manning, Pharm.D.
Senior Scientist
Regulatory Affairs
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Desk Copy: Randy Hedin, R.Ph. - Parts A and B
Sheldon Markofsky, Ph.D. - Part A
Eric Colman, M.D. - Part B

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S-003/M

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Noted
/S/
1/3/00

December 10, 1999

Eric Colman, M.D.
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attention: Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
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Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 14 1999
HFD-510

RE: NDA #20-835/S-003; ACTONEL (risedronate sodium)
Treatment of Postmenopausal Osteoporosis

/S/ 12/13/99

Dear Dr. Colman:

RVN008993 is one of the pivotal Phase III trials to assess efficacy and safety of risedronate in the treatment of postmenopausal women with established osteoporosis-related vertebral deformities. At the time the ACTONEL supplemental NDA for the treatment of postmenopausal osteoporosis was submitted, all patients had completed the 3-year double-blind, placebo-controlled portion of the trial and were in the fourth and final year of the study. This fourth year was a drug-free, follow-up year in which former placebo and 5-mg risedronate patients received only calcium. The follow-up year of the study is now complete and an addendum to the RVN final study report has been written. The addendum report text and end-of-text tables are included in this submission, for your information. The full report with appendices has been filed to the risedronate IND. If you would like to review this additional information, I refer you to IND ——— Serial No. 464.

Please call me if there are any questions and/or clarifications regarding this submission.

Sincerely,

Linda W Manning

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December 2, 1999

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attention: Document Control Room 14B-19
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Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

Dear Dr. Sobel:

Included with this submission is the revised draft package insert for ACTONEL® (risedronate sodium) for the indications of treatment and prevention of postmenopausal (PMO) and corticosteroid-induced osteoporosis (CIO). This revised draft is being submitted as a follow-up to the action letter received from the Division (dated October 18, 1999) which granted approvable status to the 4 supplements to NDA #20-835. Information pertaining to the PMO indications has been reinserted into the package insert so that all indications covered in the 4 supplements are now included in the label. We have revised the PMO text from that submitted in the original sNDA (December 18, 1998) in three places. The package insert is provided with the revised text underlined to highlight the changes (Attachment 1). A copy without the revised text highlighted is also provided (Attachment 2).

Please note that all previous labeling comments received from the Biopharm, Medical, and Pharmacology reviewers were addressed during the CIO labeling review (submissions dated July 13, 1999, July 28, 1999, and August 27, 1999, respectively). The revisions were incorporated into the CIO package insert submitted in Amendment 7 (August 27, 1999) and are included in the draft of the PMO/CIO package insert contained in this submission.

Also included in this submission is the revised patient information leaflet for ACTONEL (Attachment 3). Several changes have been made to the patient information which was submitted in the original sNDA (December 18, 1998). A table summarizing the revisions is provided for ease of review.

Please call me if there are any questions and/or clarifications regarding this submission. We look forward to further discussions with the Division on the revised labeling.

Sincerely,

Linda W. Manning

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November 9, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #20-835/ S-001, S-002, S-003, S-004, ACTONEL (risedronate sodium)

Dear Dr. Sobel:

We are in receipt of the approvable letter dated October 18, 1999 for the corticosteroid-induced osteoporosis (CIO) indications (S-001, S-004) and the postmenopausal osteoporosis (PMO) indications (S-002, S-003) for Actonel® (risedronate sodium). The letter requested that P&GP conduct a follow-up study in which all-cause mortality, all-cancer mortality, and lung cancer mortality are assessed prior to the Division's approval decision for these indications. The present correspondence provides additional details on the scope and analysis plans for this mortality follow-up study for your review and approval.

Background

The potential design of the mortality follow-up study was discussed in a meeting with the Division and with Drs. Jenkins and Temple on September 23. During this meeting, we addressed several questions related to the study which were raised by the Division in a September 17 FAX. These included questions about the source for the death certificate information, the proposed date for the end of death ascertainment, expected mortality, and study power. Details of these discussions were included in meeting minutes which were submitted to the Division in an October 8 correspondence to this NDA. Due to the difficulty in obtaining an accurate diagnosis of primary lung cancers which result in uncertainty associated with the lung cancer cases, it was agreed that follow-up data on all-cancer mortality would be an important outcome variable in addition to all-cause and lung cancer mortality. A copy of these meeting minutes is provided in **Attachment 1** for your convenience.

On October 6, we submitted protocol amendments (IND ——, serial #454) for the 3 North American post-menopausal osteoporosis trials, for the purpose of gathering follow-up mortality data from these studies. We have recently received a FAX from the Division (October 19) with comments on these protocol amendments. These comments specified 3 outcome variables: all-cause mortality, all-cancer mortality, and lung cancer mortality, consistent with our September 23 discussions. These comments also specified analyses which should be performed and requested that the duration of the mortality follow-up study be specified. A copy of the protocol amendments and the October 19 FAX is provided in **Attachment 2**.

Proposed Mortality Study

A proposal for the mortality study, including the statistical analysis plans, is provided in **Attachment 3**. Briefly, for the patients who were randomized and received at least 1 dose of study drug, the proposed mortality study would evaluate all-cause mortality through the end of 1998, all-cancer mortality through the end of 1997, and lung-cancer mortality through the end of 1997, from the 3 North American PMO trials totaling more than 7900 patients (RVN008993, RHN009193, and RON009393). For the all-cancer mortality, we will break out the specific types of cancer identified during follow-up. After obtaining patient identifiers, the database file will be submitted for matching against the National Death Index (NDI), or provincial death indices for Canadian sites. The follow-up period for each of the outcome variables was selected based on the timing for NDI database updates.

There were 6 patients in the current clinical trial database with radiographic evidence of cancer in the lung prior to any drug exposure. Since these patients had a pre-existing condition which will lead to an outcome of interest during follow-up (death due to lung cancer), we believe these patients should be excluded from an assessment of the mortality follow-up data, in order to explore causal association with the drug. Therefore, in addition to analyses including all patients, we will present separate analyses excluding these 6 patients for each of the outcome variables.

These North American studies initiated patient enrollment from November 18, 1993 until March 6, 1995 and they represent 51% of the patients in the risedronate Phase III study database. Including all lung cancers, 61% of the cases coded to lung cancer occurred in these studies, with the imbalance in incident lung cancer cases (placebo: 9 cases, 2.5 mg risedronate: 23 cases, 5 mg risedronate: 10 cases) representative of the entire Phase III safety database. Adjusted for person-years exposure during the study, the relative risk of lung cancer in the pooled treatment groups was 2.0.

The feasibility of similarly gathering additional follow-up mortality data from our European PMO studies has been assessed (see **Attachment 4**). This would involve the collection of patient identifiers from the study site, followed by matching with death certificate information. Due to a recent European Union Data Privacy Directive, which is currently being enacted in each member country, our Procter & Gamble European counsel, as well as outside counsel **(Attachment 5)**, believe that there is significant uncertainty in our ability to obtain access to individual patient identifiers without additional consent in many if not all of the countries. The process will also be more difficult as risedronate has been recently approved in Europe (Sweden) without a need for mortality follow-up data. In addition, even if we had some success in obtaining the patient identifiers, obtaining the death certificate information is not straightforward. In nearly all countries, it would be necessary to go back to the municipalities (city town hall or Church Parish) to collect the death certificate information. Based on all of the above, the overall feasibility of this approach is highly questionable, especially since the Data Privacy Directive is new and has not been tested.

An alternative approach in Europe, which would not require the Sponsor to know the patient identifiers, would be to ask our investigators to contact their former patients or their families directly to determine vital status and cause of death on our behalf. In many cases, this would have to be done by first going through the patient's General Practicioner. The success rate for this approach is unknown and may also be subject to the Data Privacy Directive. In any event, we would not anticipate more than a 35% success rate, given that these investigators were only about 35% successful in contacting patients who discontinued early for follow-up visits at

the end of the studies. In addition, the collection of reliable cause-of-death information in this manner would be expected to variable and incomplete.

In conclusion, the collection of meaningful mortality data from our European studies is highly unlikely. We believe that much more reliable information will be obtained from the North American trials, based on completeness of the information and the consistent assessment of the data. In addition, since the North American studies are representative of the entire risedronate clinical trial database with respect to the lung cancer question, these studies should be sufficient to provide confirmatory evidence that risedronate is not causally associated with an increase in lung cancer. A discussion of the expected follow-up mortality data is provided in the following section.

Expected Follow-up Data

The total person-years follow-up in our current database and the expected additional follow-up through 1997 for the determination of all-cancer and lung-cancer mortality is provided in **Table 1**. Complete mortality data through 1997 for the patients enrolled in the 3 studies would increase the total patient-years follow-up from 17,967 to 27,156 person-years, a 51% increase. The person-years reported would be slightly reduced by the amount of observation time after the death of a patient. The available observation time is at least 3 years for 93% of the 7981 patients. For all-cause mortality through 1998, total follow-up time for the 3 treatment groups would be ~35,000 person-years, an increase of approximately 2-fold compared to the "on-study" database.

Table 1

Patient-Years of Follow-up for RON009393, RVN008993, and RHN009193

	Placebo				2.5 mg Risedronate				5 mg Risedronate			
Study	# of pt.[a]	"On-study" pt yrs[b]	"Off-study" pt yrs through 1997[c]	Total pt yrs	# of pt.[a]	"On-study" pt yrs[b]	"Off-study" pt yrs through 1997[c]	Total pt yrs	# of pt.[a]	"On-study" pt yrs[b]	"Off-study" pt yrs through 1997[c]	Total pt yrs
RON009393	217	273	497	770	210	278	466	744	216	276	481	757
RVN008993	815	2420	432	2852	811	1265	1571	2836	813	2401	460	2861
RHN009193	1646	3678	1810	5488	1615	3681	1716	5397	1638	3695	1756	5451
Total	2678	6371	2739	9110	2636	5224	3753	8977	2667	6372	2697	9069

[a] Number of patients randomized and took at least one dose of study medication.
[b] "On-study" patient years (pt yrs) is based on time between start of study drug and last observation time in the clinical trial database.
[c] Additional "off-study" patient years through 1997 is based on the time between the last day "on-study" and December 31, 1997.

Expected Mortality Rates

The expected mortality rates for the patients in the North American trials and the power calculations for follow-up period for each of the 3 outcome variables—1998 all-cause mortality, 1997 all-cancer mortality, and 1997 lung cancer mortality—are provided within **Attachment 3**. As requested by the Agency, we will separately analyze each of the outcome variables in 3 ways as described on the statistical analysis plans:

1. For deaths occurring while the person was "on-study". The "on-study" period is defined as the time between start of study drug and last observation time in the clinical trial database, including available follow-up data. (See "on-study" definition in **Attachment 3, Section 2**.)

2. For deaths occurring while the person was "off-study". These deaths are any which are identified during the follow-up study which are not in our current "on-study" database.

3. For deaths occurring between start of study drug and the completion of the follow-up period, regardless of whether the death occurred while the person was "on-study" or "off-study".

The estimated results of these analyses are discussed in the sections below.

"On-Study" Mortality

The all-cause mortality, all-cancer mortality, and the lung cancer mortality during the "on-study" period covered by the current clinical database for the 3 North American PMO trials is shown in **Table 2**. These data indicate a relative risk for the combined treatment groups of 0.87 for all-cause mortality, 0.64 for all-cancer mortality, and 1.1 for lung cancer mortality.

Table 2

"On-Study" Mortality
Studies RON009393, RVN008993, and RHN009193

	Placebo	2.5 mg Risedronate	5 mg Risedronate	RR*
All-Cause Mortality	83 13.0/1000	64 12.3/1000	67 10.5/1000	0.87
All-Cancer Mortality**	18 2.8/1000	15 2.9/1000	6 0.94/1000	0.64
Lung Cancer Mortality^	6 0.94/1000	9 1.7/1000	3 0.47/1000	1.1

* Relative risk based on pooled treatment groups vs. placebo.
** Excluding patients with nonmelanotic skin cancer.
^ Based on known mortality and COSTART AE code, not on cause listed on death certificate.

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February 3, 2000

Bruce Stadel, M.D., M.P.H.
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attention. Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE. NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-induced Osteoporosis

Dear Dr. Stadel:

This submission is in response to your question concerning the follow-up obtained on the 42 patients diagnosed with lung cancer (nine placebo, twenty-three 2.5 mg risedronate and ten 5 mg risedronate) during the 3 North American Phase III PMO clinical trials. As shown in Table 1 below (same as Table 5 in the mortality report), of these 42 patients, 29 patients' deaths (eight placebo, fifteen 2.5 mg risedronate, six 5 mg risedronate) were identified by the NDI database or the Canadian Provincial database mortality search process, and 25 of the 29 had lung cancer listed on the death certificate (six placebo, fourteen 2.5 mg risedronate, and five 5 mg risedronate). There were 4 patients who had lung cancer according to the clinical database, but lung cancer was not listed on the death certificate.

Table 1
Accountability of the 42 Patients with Lung Cancer Reported in the Clinical Database as of 12/31/97

	Placebo n = 9	2.5 mg Risedronate n = 23	5 mg Risedronate n = 10	Total n = 42
Patients who died with lung cancer listed on death certificate in mortality study	6	14	5	25
Patients who died without lung cancer listed on death certificate in mortality study	2	1	1	4
Patients with lung cancer in clinical studies who were alive as of 12/31/97	1	8	4	13

As stated in Section 4.1.4.3 of the mortality report, the analysis rules for the determination of any-cancer and lung cancer mortality were established such that the cause of death information was based on the external database searches for both "on-study" and "off-study" deaths. This rule maintained a consistent approach across these 2 time periods of the study

and the overall "all-time" analysis study period. Accordingly, the adverse event COSTART codes that were associated with cancer in the clinical database were not used to assign any-cancer and lung cancer cause of death.

Application of this rule resulted in the exclusion of the 4 patients (two placebo, one 2.5 mg risedronate, one 5 mg risedronate) listed in Table 1 above, who died without lung cancer listed on death certificate, from the lung cancer mortality analysis shown below in Table 2 (same as Table 10 of the mortality report). Therefore, for the all-time analysis in Table 2, six of the 14 placebo deaths, 14 of the twenty 2.5 mg risedronate deaths, and 5 of the seven 5 mg risedronate deaths are patients who were in the original group of 42 diagnosed with lung cancer in the clinical trial database.

All patients diagnosed with lung cancer in the clinical database and known to have died on-study were captured in the NDI or Canadian Provincial databases (five placebo, eight 2.5 mg risedronate, and three 5 mg risedronate).

Table 2
Mortality Comparisons Across Treatment Groups
Lung Cancer Listed on the Death Certificate through December 31, 1997
(Intent-to-treat)

Time Period Treatment	N	Patient Years[a]	Number of Deaths	Mortality Rate (per 1000 Patient Years)	Relative Risk	95% CI[b]	P-value*
All Time							
Placebo	2676	8655.1	14	1.62	--	--	--
Risedronate 2.5 mg	2634	8527.8	20	2.35	1.45	(0.73, 2.86)	0.291
Risedronate 5 mg	2665	8640.7	7	0.81	0.50	(0.20, 1.24)	0.133
Risedronate Combined	**5299**	**17168.5**	**27**	**1.57**	**0.97**	**(0.51, 1.85)**	**0.927**
On Study							
Placebo	2676	5947.1	5	0.84	--	--	--
Risedronate 2.5 mg	2634	4973.8	8	1.61	1.69	(0.55, 5.17)	0.361
Risedronate 5 mg	2665	5945.1	3	0.50	0.60	(0.14, 2.51)	0.486
Risedronate Combined	5299	10918.9	11	1.01	1.16	(0.40, 3.34)	0.787
Off Study							
Placebo	2346	2708.0	9	3.32	--	--	--
Risedronate 2.5 mg	2331	3554.0	12	3.38	1.11	(0.46, 2.69)	0.817
Risedronate 5 mg	2334	2695.6	4	1.48	0.44	(0.14, 1.44)	0.177
Risedronate Combined	4665	6249.6	16	2.56	0.79	(0.35, 1.81)	0.584

N = Number of patients whose mortality status could be determined through December 31, 1997

-- = Not applicable or not performed

* P-value for testing the difference between placebo and the risedronate groups using Cox regression stratified by study

[a] "On study" patient years of observation (time from the start of the study to the last observation in the clinical database)
"Off study" patient years of observation (time from the last observation in the clinical database to December 31, 1997 or the date of death, whichever occurred first)

[b] Relative risk and 95% confidence interval based upon Cox regression model between individual risedronate dose and placebo stratified by study

[Source program: /home7/RISEDRONATE/mortality/survival.sas; program run on 17DEC99 at 10:50 by TF6225.]

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Of the 4 patients who died without lung cancer listed on the death certificate, three (1 in each treatment group) had another cancer listed, of which 1 patient had breast cancer and the other 2 patients had cancer of an unspecified site. All 4 patients were included in the all-cause mortality analysis (Table 7 of the mortality report), and the 3 patients with cancer were included in the any-cancer analysis (Table 9 of the mortality report).

Table 3 provides a tabulation of the deaths with lung cancer listed as identified by the mortality process. Twenty-five deaths were found from the cases in the clinical database (Line B). Sixteen new lung cancer deaths (eight placebo, six 2.5 mg risedronate, two 5 mg risedronate) were identified by the NDI or Canadian Provincial databases through 12/31/97 (Line C). Therefore, 41 patients (fourteen placebo, twenty 2.5 mg risedronate, seven 5 mg risedronate) deaths were identified with lung cancer listed on the death certificate through December 31, 1997 (Line D). This corresponds to the 41 all-time deaths in Table 2 above.

Table 3
Accountability of the Deaths with Lung Cancer Listed on Death Certificate as of 12/31/97

Line		Placebo	2.5 mg Risedronate	5 mg Risedronate	Total
A	Lung cancer cases recorded in clinical database	9	23	10	42
B	Clinical database cases identified in NDI or Canadian Provincial Database with lung cancer listed	6	14	5	25
C	New lung cancer deaths in NDI or Canadian Provincial Database	8	6	2	16
D	Total deaths (B+C)	14	20	7	41

Please call me if there are any questions and/or clarifications regarding this submission.

Sincerely,

Linda W. Manning

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APPEARS THIS WAY
ON ORIGINAL

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January 24, 2000

Eric Colman, M.D.
Division of Metabolism and Endocrine Drug Products
Attention: Document Control Room 14B-19
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RE: NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

Dear Dr. Colman:

In labeling comments received from the Biopharm reviewer (July 8, 1999) concern was raised about reducing the volume of water used when ACTONEL is administered due to the effect on esophageal transit time. P&GP responded to the concern (submission dated July 13, 1999) with data from our own studies and the published literature which demonstrate that for patients ingesting ACTONEL in an upright position, use of ——— of water is sufficient to obtain a rapid esophageal transit of the film-coated tablet and volumes of water greater than this are unnecessary to assure transit of the tablet to the stomach. We have recently completed another clinical study (Study 1999010, protocol submitted in IND Serial No. 441, June 9, 1999) which further supports our position that ——— of water is sufficient to obtain rapid esophageal transit.

Study 1999010 was a two-way crossover study in 14 healthy postmenopausal women (mean age ~58; Attachment 1, Table A provides additional baseline characteristic information) which compared the esophageal transit, disintegration, and gastric emptying times of a placebo risedronate tablet when administered with either 50 mL or 240 mL of water. The report for this study is not yet available, however, we have just completed the analyses of the major endpoints. The primary analysis was a test of equivalence between the two volumes of water (50 mL and 240 mL) with regard to the esophageal transit time. The equivalence range for the difference in mean esophageal transit time between the two volumes of water was chosen to be ± 8.0 seconds. This range corresponds to approximately twice the standard deviation of the esophageal transit time of an identical cellulose film-coated placebo risedronate tablet administered to elderly subjects with 240 mL of water. If the 90% CI for the difference in mean esophageal transit time was within ± 8.0 seconds, the mean transit times between the two volumes of water were considered equivalent.

An analysis of variance model, with terms for period effect, sequence effect , and dosing effect, was used to analyze the data. Carry-over effect was not included in the model because there was a washout period of at least 48 hours between each visit to clear the radioactivity from the GI tract and because there was no active drug involved in the study.

Esophageal transit times were observed for all 14 subjects. Table 1 summarizes the esophageal transit time by visit and volume of water. Analysis of variance did not indicate a significant difference in mean esophageal transit time between the two volumes of water (50 mL vs. 240 mL) (p-value=0.4716). The mean difference in esophageal transit time between 50 mL and 240 mL was estimated to be -0.67 seconds with a 90% CI (-2.27, 0.93) (Attachment 1, Table B). This CI was within the equivalence range ± 8.0 seconds. No esophageal stasis was observed during the study (esophageal stasis was defined as a esophageal transit time > 20 seconds). The time to complete disintegration and the gastric emptying time were also similar between the two volumes of water (Attachment 1, Table C). Analysis of variance did not indicate a significant difference in mean disintegration time or gastric emptying time between the two volumes of water.

Table 1: Descriptive Statistics for Esophageal Transit Time (seconds)

Sequence	Visit	N	Mean (SD)	Median	Min	Max
50/240 mL	Visit 1 (50 mL)	8	4.7 (3.10)	3.6	—	—
	Visit 2 (240 mL)	8	5.9 (5.25)	4.0	—	—
240/50 mL	Visit 1 (240 mL)	6	4.5 (2.19)	3.6	—	—
	Visit 2 (50 mL)	6	4.4 (1.94)	4.4	—	—

In conclusion, we do not feel that there is any evidence that reducing the volume of water from that currently approved in the Paget's label (6 to 8 ounces) to [redacted] will have any impact on esophageal transit of the risedronate film-coated tablet. The following points summarize our position:

- The esophageal transit study (92024)[1] showing the film-coated tablet reaches the stomach quickly (mean transit time of 3.3 sec) in elderly men and women (mean age ~66 years) when subjects took this dose form with 50 mL (<2 oz) of water. The gelatin capsule phase II formulation had a mean transit time of over 20 seconds. Retention of the capsule in the esophagus occurred in 28% of subjects but was not observed with the tablet formulation.

- A second esophageal transit study (1997007)[2] comparing elderly men and women with or without GERD (mean age ~66 years) showing the mean esophageal transit time (3.1 sec) for the normal group with 240 mL of water was not greater than in Study 92024 with 50 mL of water. This study also showed that transit in normal control group was similar to transit in patients with GERD (4.1 sec).

- A third esophageal transit study (1999010, referred to above) in healthy postmenopausal women comparing the esophageal transit of the film-coated tablet when administered with either 50 mL or 240 mL of water showing the film-coated

[1] Study 92024 Final Report, Paget's NDA, Vs1.115/p.2.
[2] Study 1997007 Final Report, Vs1.288/p.144 (NDA 20-835/S-001, S-002, S-003, Amendment 5).

tablet reaches the stomach quickly with either volume of water. There was no significant difference in mean esophageal transit time between the two volumes of water. The mean esophageal transit time was 4.6 ± 0.69 sec for 50 mL of water and 5.3 ± 1.1 sec for 240 mL water.

- Hey et al[3] examined esophageal transit of 6 commonly shaped pills in 121 healthy volunteers (726 swallowings in total). Subjects used either 25 ml or 100 ml of water to ingest pills in either an upright or supine position. Transit time for all formulations was unaffected by volume of water when subjects remained upright. Transit times were slowed when subjects used the smaller volume of water and ingested pills while recumbent. The authors concluded that patients should remain standing for at least 90 seconds after taking medication, that tablets should be swallowed with at least 100 ml of water, and that that small oval tablets are preferable.

- Kikendall and Johnson[4] reviewed 756 cases of pill-induced esophageal injury with 75 different medications and recommend that all tablets be ingested with at least 4 oz (120 mL) of water and patients should remain upright after dosing for at least 10 minutes prior to lying down.

Please call me at (513) 622-1114 if you have questions on this submission.

Sincerely,

Linda W Manning

Linda W. Manning, Pharm.D.
Senior Scientist
Regulatory Affairs

Desk Copies: Randy Hedin, R.Ph.
Eric Colman, M.D.
Hae-Young Ahn, Ph.D.

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[3] Hey H, Jørgensen F, Sørensen K, Hasselbalch H, Wamberg T. Oesophageal transit of six commonly used tablets and capsules. Brit Med J 1982;285:1717-9.

[4] Kikendall JW, Johnson LF. Pill-induced esophageal injury. In: Castell DO, editor. The esophagus. 2nd ed. Boston: Little Brown;1995. p. 619-33.

ATTACHMENT 1

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Table A

Demographic and Screening Characteristics
(All Randomized Subjects)

Parameter	Sequence 1[b]	Sequence 2[c]	Total
Age (years)			
n	8	6	14
Mean ± SEM	58.3 ± 0.80	58.8 ± 1.54	58.5 ± 0.77
Median	58	59	58
Min, Max	55, 61	55, 65	55, 65
Race[a]			
Caucasian	8 (100%)	6 (100%)	14 (100%)
Black	0 (0%)	0 (0%)	0 (0%)
Asian Indian	0 (0%)	0 (0%)	0 (0%)
Asian Oriental	0 (0%)	0 (0%)	0 (0%)
Multi-racial	0 (0%)	0 (0%)	0 (0%)
Weight (kg)			
n	8	6	14
Mean ± SEM	69.7 ± 2.19	66.3 ± 1.13	68.2 ± 1.38
Median	69.5	65.8	67.3
Min, Max	61.0, 76.5	62.3, 70.5	61.0, 76.5
Height (cm)			
n	8	6	14
Mean ± SEM	164.2 ± 1.62	161.8 ± 2.46	163.1 ± 1.39
Median	164.5	162.5	164.0
Min, Max	157.5, 169.0	152.0, 169.0	152.0, 169.0
Tobacco Usage[a]			
Never	6 (75%)	4 (67%)	10 (71%)
Previously	2 (25%)	2 (33%)	4 (29%)
Currently	0 (0%)	0 (0%)	0 (0%)
Alcohol Consumption[a]			
Never	2 (25%)	1 (17%)	3 (21%)
Previously	0 (0%)	0 (0%)	0 (0%)
Currently	6 (75%)	5 (83%)	11 (79%)

[a] Data shown are the number and percentage of subjects.

[b] Subjects took the radiolabeled placebo risedronate tablet with 50 mL of water at Visit 1 and 240 mL of water at Visit 2.

[c] Subjects took the radiolabeled placebo risedronate tablet with 240 mL of water at Visit 1 and 50 mL of water at Visit 2.

Table B

Summary of Esophageal Transit Time
(All Randomized Subjects)

Parameter	50 mL Water (N = 14)	240 mL Water (N = 14)
Esophageal Transit Time (seconds)		
n	14	14
Mean ± SEM	4.6 ± 0.69	5.3 ± 1.11
Median	4.0	4.0
Min, Max		
Treatment A (50 mL water) - Treatment B (240 mL water)		
Difference	-0.67	
90% CI	-2.27, 0.93	

N = number of randomized subjects who received volume of water; n = number of randomized subjects who received volume of water and had a esophageal transit time measurement; SEM = standard error of the mean.

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Table C

Summary of Disintegration and Gastric Emptying Times (All Randomized Subjects)

Outcome Parameter	50 mL Water (N = 14)	240 mL Water (N = 14)
Onset of Disintegration Time (minutes)		
n	4	8
Mean ± SEM	6.5 ± 0.65	6.9 ± 0.97
Median	6.5	6.0
Min, Max		
Treatment A (50 mL water) - Treatment B (240 mL water)		
Difference	NA	
90% CI[b]	NA	
Time to Complete Disintegration (minutes)		
n	14	14
Mean ± SEM	12.3 ± 2.81	12.9 ± 2.34
Median	8.5	12.5
Min, Max		
Treatment A (50 mL water) - Treatment B (240 mL water)		
Difference	-0.25	
90% CI[b]	-4.98, 4.48	
Gastric Emptying Time: T_{50} (minutes)		
n	14	14
Mean ± SEM	19.5 ± 6.21	17.2 ± 2.87
Median	11.0	13.5
Min, Max		
Treatment A (50 mL water) - Treatment B (240 mL water)		
Difference	4.13	
90% CI[b]	-6.86, 15.11	

If any times were subject to censoring (e.g. time to complete disintegration occurred in < 3 minutes) the cut-off time (e.g., 3 minutes) was used in calculations.

[b] Confidence interval estimates were based on XXX.

N = number of randomized subjects who received volume of water and who didn't take additional water;
SEM = standard error of the mean.

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January 12, 2000

Eric Colman, M.D.
Division of Metabolism and Endocrine Drug Products
Attention: Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

Dear Dr. Colman:

We have received the email dated January 4, 2000 with your final labeling comments on the draft ACTONEL package insert for the treatment and prevention of postmenopausal and corticosteroid-induced osteoporosis. This submission contains our responses to those comments.

Your review of the proposed package insert resulted in the deletion of the nonvertebral fracture statement from the indication for treatment of postmenopausal osteoporosis. We have addressed this comment in detail in Attachment 1, as we feel the statement should not be deleted from the indication statement in the package insert. In this attachment, we point out the importance of osteoporosis-related fractures at sites other than the spine, hip, or wrist and we compare our data to that of alendronate and raloxifene. Our data are robust and clearly support the efficacy of risedronate in the reduction of nonvertebral fractures.

All of your other comments are addressed in the table contained in Attachment 2. The table includes your proposed modifications, our proposal in response, and the rationale for our proposed modifications. The revised draft package insert which incorporates all the changes is provided in Attachment 3.

Please call me at (513) 622-1114 if you have questions on any of our comments. We look forward to finalizing labeling discussions with the Division.

Sincerely,

Linda W. Manning

Linda W. Manning, Pharm.D.
Senior Scientist
Regulatory Affairs

Desk Copy: Randy Hedin, R.Ph.
Eric Colman, M.D.

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December 29, 1999

Solomon Sobel, MD
Director, Division of Metabolism and
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RE: NDA #20-835/ S-001, S-002, S-003, S-004, ACTONEL (risedronate sodium) Tablets
NDA Amendment 9 - COMPLETE RESPONSE to October 18, 1999 Approvable Letter

Dear Dr. Sobel:

This submission provides our "Complete Response" to the October 18, 1999 approvable letter which we received from the Agency for the corticosteroid-induced osteoporosis (CIO) indications (S-001, S-004) and the postmenopausal osteoporosis (PMO) indications (S-002 S-003) for Actonel® (risedronate sodium). The approvable letter requested that a follow-up study be conducted in, at a minimum, the North American osteoporosis trials, in which all-cause mortality, all-cancer mortality, and lung cancer mortality would be assessed. This study has now been completed and a report is provided in this submission.

In previous submissions, we have provided the following other items requested in the approvable letter:

1. In a submission dated October 29, 1999, we provided an English translation of the product labeling related to the approval of risedronate sodium 5 mg tablets (tradename Optinate) in Sweden for the PMO and CIO indications.

2. In a submission dated December 17, 1999 (Amendment 8), we provided updated safety information. This submission also contained additional stability data to support a 36-month expiration date.

The final report of the follow-up mortality study, included in this submission, provides complete follow-up on more than 98% (7845 patients) of those who were randomized and received at least 1 dose of study drug in the 3 North American osteoporosis clinical studies. These studies represent 51% of the patients in the entire risedronate Phase III clinical database and, importantly, 61% of the patients reported to have lung cancer. All-cause mortality was determined through December 31, 1998, while all-cancer and lung cancer mortality were determined through December 31, 1997. The mean per-patient follow-up time was 3.2 years for the all-cancer and lung cancer mortality data and 4.2 years for the all-cause mortality data.

We have enclosed ZIP disks containing the electronic SAS dataset for the mortality follow-up study. The documentation for this dataset is found in Attachments A and B. Attachment A

contains a PROC contents of the SAS dataset. The derived variables and decodes for the coded variables are included in Attachment B.

Mortality Study Results

The complete follow-up mortality data showed no increased relative risk of mortality for the risedronate groups compared with placebo.

- The "all-time" analyses ("on-study" plus "off-study") of the pooled risedronate treatment groups compared to placebo demonstrated no increased relative risk (RR < 1.0) for all-cause, all-cancer, or lung cancer mortality.

- The relative risks of death from all cancer or lung cancer were lower in the 5-mg risedronate treatment group compared with the 2.5-mg group for each of the analysis times ("all-time," "on-study," and "off-study"), confirming the absence of a dose-response relationship.

- The lung cancer deaths which occurred during the "off-study" period in the 2.5-mg risedronate group compared with placebo (RR = 1.1) did not replicate the imbalance seen in lung cancer incident cases reported during the clinical studies (RR = 3.1), or in "on-study" lung cancer deaths (RR = 1.7). In addition, among those patients not previously reported to have lung cancer during the trials, the RR of the 2.5-mg risedronate group compared with placebo in the "off-study" period was 0.56. The 5-mg risedronate treatment group had a consistently low relative risk, compared with placebo, of 0.44 to 0.60 during all analysis periods.

On the basis of these data, we conclude there is no evidence of a causal association or a promotional effect between risedronate use and lung cancer. We believe that incomplete ascertainment of lung cancer cases in the placebo group and chance are plausible explanations for the imbalance of lung cancer reports during the clinical trials.

Presentation of Results to Expert Safety Panel

The results of this mortality follow-up study were reviewed by an expert Safety Advisory Panel on December 17 and 18. A report summarizing this review and the Panel's conclusion is included in this submission (See Meeting Report: Safety Advisory Panel).

During the review of the mortality data, we presented new analyses of the lung cancer incidence data from all 10 Phase III studies to address the possibility that the original observations could have been due to chance. Lung cancer reports from the clinical trial database were analyzed in the context of the set of all the different cancer types reported. Analyses found no significant differences ($p = 0.527$) between the odds ratios (OR) for the 22 different cancer types (combined risedronate groups vs. placebo). Further, there was no evidence that the odds ratios were different from unity (common estimate of OR = 1.03, $p = 0.693$). It was also found, given the number of cancer outcomes considered, that there was a high likelihood ($p = 0.839$) of getting an OR for 1 of the cancers that is equal to, or greater than, that observed for lung cancer even if there were, in fact, no overall cancer treatment effect. In conclusion, the results support that the "on-study" imbalance in lung cancer reports is consistent with chance. A copy of the slides related to the discussion of chance as well as other discussions are included in Attachment 2 of the Meeting Report: Safety Advisory Panel.

The panel stated that the follow-up mortality study was an appropriate tool to resolve whether there were potential study design biases influencing the number of lung cancer reports. The "off-study" finding of a relative increase (placebo group) in the number of "new reports" of lung cancer, i.e., lung cancer deaths in patients who did not have a diagnosis of lung cancer during the "on-study" period, provides evidence that there was an incomplete ascertainment of lung cancer in the placebo group.

The conclusions of the Panel are provided below:

- There is no statistically significant difference in total mortality, any-cancer mortality, or lung cancer mortality between either risedronate treatment group and the placebo group or between both treatment groups combined and the placebo group. These results are based on an unbiased and complete assessment of mortality among North American trial participants in the Phase III program.

- The reports of lung cancer in the clinical trial database represent an incomplete ascertainment of cases and deaths. Underascertainment of lung cancer in the placebo group and the play of chance are plausible explanations for the observed excess of lung cancer reports among risedronate-treated patients in these data.

- The mortality study data, with a systematic ascertainment of lung cancer deaths, show no excess of lung cancer among all patients receiving risedronate. These data are based on a study with sufficient statistical power to evaluate the initial findings from the clinical trial reports. There is no dose-response relationship and the pattern of mortality differences among treatment groups is consistent with chance.

Please let me know if you have any questions or require further clarification on any aspect of this submission. We look forward to the final resolution of this issue.

Sincerely,

Bruce R. DeMark, PhD
Section Head
US Regulatory Affairs

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Bruce Stadel, MD, MPH
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NDA SUPPLEMENT

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December 22, 1999

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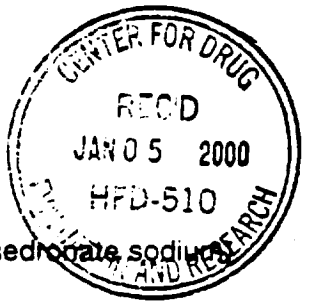

RE: NDA #20-835/S-001, S-002, S-003, S-004 ACTONEL (risedronate sodium)

Dear Dr. Colman:

In your e-mail of December 17, you referred to our July 28, 1999 submission where we discussed the rationale for not including the same warnings about GI toxicity as those for alendronate. We referenced two alendronate papers by Liberman et al. (NEJM 1995; 333: 1437-1443) and by Black et. al. (Lancet 1996; 348: 1535-1541) and stated that the alendronate studies excluded patients on the basis of recent or current treatment with agents known to have the potential to irritate the GI. We have rechecked these papers and agree that this specific exclusion criterion is not explicitly stated in these papers.

The Liberman study reported the results of two clinical trials (North American and Multinational) which were the basis for the 1995 approval of alendronate for the treatment of PMO. In the separate publications of these two clinical studies by Tucci et.al. (Am J Med 1996; 101: 488-501) and Devogelaer et al. (Bone 1996: 18: 141-150), this exclusion criterion was clearly stated.

Attachment 1 summarizes the GI exclusion criteria from the published accounts of the Liberman/Tocci/Devogelaer studies and the Black study (FIT study data). We have also attached copies of the Tucci and Devogelaer papers for you.

Your December 17 e-mail also asked us to provide the percentage of patients, by treatment group, in RVN, RVE, RCP, RCT, and RBL who were coded at baseline as both "active GI disease" and taking a medication for the active disease. Table 1 on the next page provides a summary of this information.

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This table shows that overall, approximately 7% of the patients enrolled in the 5 studies had both an active upper GI disorder at entry and were taking one of the classes of GI medications indicated in the table. The percentages in this table were calculated using the total ITT population as the denominator.

Table 1
Percentage of Patients with Active Upper GI Disorders at Entry and Taking GI Medications[a] at Entry

Study	Placebo N=1517 n (%)	2.5 mg Risedronate N=1511 n (%)	5 mg Risedronate N=1523 n (%)
RVN	60 (7.4)	60 (7.4)	76 (9.3)
RVE	17 (4.2)	21 (5.1)	26 (6.4)
RBL	2 (1.6)	3 (2.4)	2 (1.5)
RCT	5 (5.3)	8 (8.7)	4 (4.0)
RCP	7 (9.2)	11 (15.1)	7 (9.3)
Total Patients	91 (6.0)	103 (6.8)	115 (7.6)

[a] GI Medications include the WHO Drug Dictionary ATC categories: Antacids (A02A), Drugs for Treatment of Peptic Ulcer (A02B), and Antiregurgitants (A02E)

For your information, we have also prepared a separate presentation (Table 2) showing that about 63% of the patients with active upper GI disorders at baseline were also taking GI medications at study entry. The percentages in this table were calculated using the number of patients that had upper GI disease at baseline, as the denominator.

Table 2
Percentage of Patients Taking GI Medications[a] at Entry among the Subgroup of Patients with Active Upper GI Disorders at Entry

Study	Placebo N=152 n (%)	2.5 mg Risedronate N=153 n (%)	5 mg Risedronate N=188 n (%)
RVN	60 (57.1)	60 (65.2)	76 (61.3)
RVE	17 (63.0)	21 (67.7)	26 (74.3)
RBL	2 (66.7)	3 (50.0)	2 (22.2)
RCP	7 (70.0)	11 (84.6)	7 (54.0)
RCT	5 (71.4)	8 (72.7)	4 (57.1)
Total Patients	91 (60)	103 (67)	115 (61)

[a] GI Medications include the WHO Drug Dictionary ATC categories: Antacids (A02A), Drugs for Treatment of Peptic Ulcer (A02B), and Antiregurgitants (A02E)

Please let me know if you have any additional questions.

Sincerely,

Bruce R. DeMark, Ph.D.
Section Head
U.S. Regulatory Affairs

Attachment

Desk copy: Eric Colman, MD
Randy Hedin, R. Ph.

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Attachment 1

GI-Specific Exclusion Criteria in Risedronate and Alendronate Clinical Trials

Table 1 summarizes the GI-specific exclusion criteria from the key risedronate and alendronate phase III clinical trials.

Studies RVN008993 & RVE009093 are the pivotal vertebral fracture trials for risedronate. The pivotal alendronate data (1) come from two identical trials (2,3). The alendronate FIT data (4) were used to extend the indication to include anti-fracture effects.

Table 1

GI-Specific Exclusion Criteria

RVN008993 & RVE009093	ALENDRONATE: Liberman	ALENDRONATE: FIT
none	Active peptic ulcer disease[1]	Significant upper GI bleeding within the past 5 years, requiring hospitalization and/or transfusion[4,5]
	Major GI disease within 12 months of study start[5]	Dyspepsia requiring daily medication[4,5]
	Active upper gastrointestinal disease[4]	Esophageal or gastric varices[5]
	Medications (alternative versions): 1. Daily use of medications which have appreciable potential for gastrointestinal irritation[2] 2. Recent or current treatment with the potential to ..... cause irritation of the gastrointestinal mucosa[3] 3. Regular use (> 4 times/week) of medications with the potential for GI irritation, such as NSAIDs[5]	Documented recent or recurrent ulcer disease (1 episode in the preceding 12 months or 2 or more episodes in the preceding 5 years)[5]

In all the risedronate phase III trials there were no GI-specific exclusion criteria in the study protocols.

In the publication of the pivotal alendronate data (1), reference is made to patients being excluded if they have active peptic ulcer disease. It is noteworthy that the publications on the separate halves of this trial (2,3) give details of additional exclusion criteria, as does a review of alendronate tolerability (5). Copies of these three publications are attached. The GI-specific exclusions appear somewhat broader in scope and cover upper gastrointestinal disease in general plus medications with the potential for GI irritation. With regard to medication use, the exact criterion is unclear but references are made to both current and recent use of these medications.

The publication of the clinical fracture arm of the FIT study (4) only makes reference to patients being excluded for recent or current GI disorders. Interestingly, the publication giving the design details of the FIT study (6) gives less information on the GI-specific exclusion criteria than the publication presenting the results. It is therefore unclear whether exclusion criteria covered the use of medications with the potential to irritate the GI tract.

Conclusions

The key alendronate trials contained a widespread set of exclusions covering patients with recent or current GI-disease and those taking medications with the potential to irritate the GI tract. In contrast, the risedronate trials made no equivalent exclusions.

It might therefore be expected that the risedronate phase III population will be more predictive of the post-marketing experience.

References

1. Liberman UA, Weiss SR et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. NEJM 1995; 333: 1437-1443.

2. Tucci JR, Tonino RP et al. Effect of three years of roral alendronate treatment in postmenopausal women with osteoporosis. Am J Med 1996; 101: 488-501.

3. Devogelaer JP, Broll H et al. Oral alendronate induces progressive increases in bone mass of the spine, hip and total body over 3 years in postmenopausal women with osteoporosis. Bone 1996: 18: 141-150.

4. Black DM, Cummings SR et al. Randomised trial of the effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996; 348: 1535-1541.

5. Watts N, Freedholm D et al. The clinical tolerability profile of alendronate. IJCP Supplement April 1999: 51-61.

6. Black DM, Reiss TF et al. Design of the Fracture Intervention Trial. Osteoporosis Int 1993; Suppl 3: S29-39.

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December 17, 1999

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attention: Document Control Room 14B-19
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1/4/00

RE: NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

NDA Amendment 8 - Partial Response Letter
Part A: 3-Year Stability Data for the 5 mg Tablet;
Part B: Safety Update

Dear Dr Sobel:

The purpose of this amendment to NDA #20-835/S-001, S-002, S-003, and S-004 is to provide a partial response to the deficiencies addressed in the approvable letter received from the Division on October 18, 1999. Specifically, Part A of this submission contains 3-year stability data for the 5 mg tablet and Part B provides updated safety information for ACTONEL. The archival copy of this submission contains sections in paper and electronic formats. Parts A and B (3 volumes) are provided in paper format. The case report forms, submitted as part of the safety update, are PDF files (approximately — megabytes in size) provided on one CD-ROM. Norton AntiVirus 5.0 was used to assure the electronic portion of the submission is free of viruses.

In the approvable letter received from the Division, a statement was made that the stability data submitted in the sNDA only support a — month expiry date. In a telephone discussion (October 18, 1999) between Dr. Harry Welles (P&GP) and Dr. Sheldon Markofsky, Dr. Markofsky agreed that P&GP could submit to the sNDA the 3-year stability data for the 5 mg tablet and, if the data were acceptable, he would extend the expiration date to 3 years at the time of approval. As a follow-up to that discussion, the 3-year stability data for the 5 mg tablet at the ICH long term storage condition are included in this submission to support an extension of the expiry date to 36 months. The data demonstrate that the 5 mg tablet is stable in the commercial package for at least 3 years.

A request was also made in the approvable letter for updated safety information for ACTONEL. A proposal outlining the content of this safety update was submitted to the Division on November 2, 1999 and accepted by the Division on November 8, 1999. Per that proposal, safety information from 3 ACTONEL studies for which unblinded data are now available is

being submitted in this safety update. Review of these data support the conclusions presented in the original Integrated Summary of Safety and the 180-day Safety Update, and thus there are no proposed revisions to the safety sections of the submitted package insert for ACTONEL *(version dated 2-December-1999)* for the indications of postmenopausal osteoporosis or corticosteroid-induced osteoporosis.

Please note that the final report for the mortality follow-up study which was requested in the approvable letter is currently being written and will be provided to the Division in a subsequent amendment later this month.

Please call me if there are any questions and/or clarifications regarding the information provided in this submission.

Sincerely,

Linda W Manning

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Desk Copy: Randy Hedin, R.Ph. - Parts A and B
Sheldon Markofsky, Ph.D. - Part A
Eric Colman, M.D. - Part B

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S-003 SLR

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Noted
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December 10, 1999

Eric Colman, M.D.
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Rockville, Maryland 20857

RE: NDA #20-835/S-003; ACTONEL (risedronate sodium)
Treatment of Postmenopausal Osteoporosis

/S/ 12/13/99

Dear Dr. Colman:

RVN008993 is one of the pivotal Phase III trials to assess efficacy and safety of risedronate in the treatment of postmenopausal women with established osteoporosis-related vertebral deformities. At the time the ACTONEL supplemental NDA for the treatment of postmenopausal osteoporosis was submitted, all patients had completed the 3-year double-blind, placebo-controlled portion of the trial and were in the fourth and final year of the study. This fourth year was a drug-free, follow-up year in which former placebo and 5-mg risedronate patients received only calcium. The follow-up year of the study is now complete and an addendum to the RVN final study report has been written. The addendum report text and end-of-text tables are included in this submission, for your information. The full report with appendices has been filed to the risedronate IND. If you would like to review this additional information, I refer you to IND ——— Serial No. 464.

Please call me if there are any questions and/or clarifications regarding this submission.

Sincerely,

Linda W Manning

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December 2, 1999

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
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Rockville, Maryland 20857

RE: NDA #20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium) Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

Dear Dr. Sobel:

Included with this submission is the revised draft package insert for ACTONEL® (risedronate sodium) for the indications of treatment and prevention of postmenopausal (PMO) and corticosteroid-induced osteoporosis (CIO). This revised draft is being submitted as a follow-up to the action letter received from the Division (dated October 18, 1999) which granted approvable status to the 4 supplements to NDA #20-835. Information pertaining to the PMO indications has been reinserted into the package insert so that all indications covered in the 4 supplements are now included in the label. We have revised the PMO text from that submitted in the original sNDA (December 18, 1998) in three places. The package insert is provided with the revised text underlined to highlight the changes (Attachment 1). A copy without the revised text highlighted is also provided (Attachment 2).

Please note that all previous labeling comments received from the Biopharm, Medical, and Pharmacology reviewers were addressed during the CIO labeling review (submissions dated July 13, 1999, July 28, 1999, and August 27, 1999, respectively). The revisions were incorporated into the CIO package insert submitted in Amendment 7 (August 27, 1999) and are included in the draft of the PMO/CIO package insert contained in this submission.

Also included in this submission is the revised patient information leaflet for ACTONEL (Attachment 3). Several changes have been made to the patient information which was submitted in the original sNDA (December 18, 1998). A table summarizing the revisions is provided for ease of review.

Please call me if there are any questions and/or clarifications regarding this submission. We look forward to further discussions with the Division on the revised labeling.

Sincerely,

Linda W. Manning

Linda W. Manning, Pharm.D.
Senior Scientist
Regulatory Affairs
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Desk Copy: Randy Hedin, R.Ph.
Eric Colman, M.D.

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November 9, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and
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Center for Drug Evaluation and Research
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5600 Fishers Lane
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RE: NDA #20-835/ S-001, S-002, S-003, S-004, ACTONEL (risedronate sodium)

Dear Dr. Sobel:

We are in receipt of the approvable letter dated October 18, 1999 for the corticosteroid-induced osteoporosis (CIO) indications (S-001, S-004) and the postmenopausal osteoporosis (PMO) indications (S-002, S-003) for Actonel® (risedronate sodium). The letter requested that P&GP conduct a follow-up study in which all-cause mortality, all-cancer mortality, and lung cancer mortality are assessed prior to the Division's approval decision for these indications. The present correspondence provides additional details on the scope and analysis plans for this mortality follow-up study for your review and approval.

Background

The potential design of the mortality follow-up study was discussed in a meeting with the Division and with Drs. Jenkins and Temple on September 23. During this meeting, we addressed several questions related to the study which were raised by the Division in a September 17 FAX. These included questions about the source for the death certificate information, the proposed date for the end of death ascertainment, expected mortality, and study power. Details of these discussions were included in meeting minutes which were submitted to the Division in an October 8 correspondence to this NDA. Due to the difficulty in obtaining an accurate diagnosis of primary lung cancers which result in uncertainty associated with the lung cancer cases, it was agreed that follow-up data on all-cancer mortality would be an important outcome variable in addition to all-cause and lung cancer mortality. A copy of these meeting minutes is provided in **Attachment 1** for your convenience.

On October 6, we submitted protocol amendments (IND ——— serial #454) for the 3 North American post-menopausal osteoporosis trials, for the purpose of gathering follow-up mortality data from these studies. We have recently received a FAX from the Division (October 19) with comments on these protocol amendments. These comments specified 3 outcome variables: all-cause mortality, all-cancer mortality, and lung cancer mortality, consistent with our September 23 discussions. These comments also specified analyses which should be performed and requested that the duration of the mortality follow-up study be specified. A copy of the protocol amendments and the October 19 FAX is provided in **Attachment 2**.

Proposed Mortality Study

A proposal for the mortality study, including the statistical analysis plans, is provided in **Attachment 3**. Briefly, for the patients who were randomized and received at least 1 dose of study drug, the proposed mortality study would evaluate all-cause mortality through the end of 1998, all-cancer mortality through the end of 1997, and lung-cancer mortality through the end of 1997, from the 3 North American PMO trials totaling more than 7900 patients (RVN008993, RHN009193, and RON009393). For the all-cancer mortality, we will break out the specific types of cancer identified during follow-up. After obtaining patient identifiers, the database file will be submitted for matching against the National Death Index (NDI), or provincial death indices for Canadian sites. The follow-up period for each of the outcome variables was selected based on the timing for NDI database updates.

There were 6 patients in the current clinical trial database with radiographic evidence of cancer in the lung prior to any drug exposure. Since these patients had a pre-existing condition which will lead to an outcome of interest during follow-up (death due to lung cancer), we believe these patients should be excluded from an assessment of the mortality follow-up data, in order to explore causal association with the drug. Therefore, in addition to analyses including all patients, we will present separate analyses excluding these 6 patients for each of the outcome variables.

These North American studies initiated patient enrollment from November 18, 1993 until March 6, 1995 and they represent 51% of the patients in the risedronate Phase III study database. Including all lung cancers, 61% of the cases coded to lung cancer occurred in these studies, with the imbalance in incident lung cancer cases (placebo: 9 cases, 2.5 mg risedronate: 23 cases, 5 mg risedronate: 10 cases) representative of the entire Phase III safety database. Adjusted for person-years exposure during the study, the relative risk of lung cancer in the pooled treatment groups was 2.0.

The feasibility of similarly gathering additional follow-up mortality data from our European PMO studies has been assessed (see **Attachment 4**). This would involve the collection of patient identifiers from the study site, followed by matching with death certificate information. Due to a recent European Union Data Privacy Directive, which is currently being enacted in each member country, our Procter & Gamble European counsel, as well as outside counsel **(Attachment 5)**, believe that there is significant uncertainty in our ability to obtain access to individual patient identifiers without additional consent in many if not all of the countries. The process will also be more difficult as risedronate has been recently approved in Europe (Sweden) without a need for mortality follow-up data. In addition, even if we had some success in obtaining the patient identifiers, obtaining the death certificate information is not straightforward. In nearly all countries, it would be necessary to go back to the municipalities (city town hall or Church Parish) to collect the death certificate information. Based on all of the above, the overall feasibility of this approach is highly questionable, especially since the Data Privacy Directive is new and has not been tested.

An alternative approach in Europe, which would not require the Sponsor to know the patient identifiers, would be to ask our investigators to contact their former patients or their families directly to determine vital status and cause of death on our behalf. In many cases, this would have to be done by first going through the patient's General Practicioner. The success rate for this approach is unknown and may also be subject to the Data Privacy Directive. In any event, we would not anticipate more than a 35% success rate, given that these investigators were only about 35% successful in contacting patients who discontinued early for follow-up visits at

the end of the studies. In addition, the collection of reliable cause-of-death information in this manner would be expected to variable and incomplete.

In conclusion, the collection of meaningful mortality data from our European studies is highly unlikely. We believe that much more reliable information will be obtained from the North American trials, based on completeness of the information and the consistent assessment of the data. In addition, since the North American studies are representative of the entire risedronate clinical trial database with respect to the lung cancer question, these studies should be sufficient to provide confirmatory evidence that risedronate is not causally associated with an increase in lung cancer. A discussion of the expected follow-up mortality data is provided in the following section.

Expected Follow-up Data

The total person-years follow-up in our current database and the expected additional follow-up through 1997 for the determination of all-cancer and lung-cancer mortality is provided in **Table 1**. Complete mortality data through 1997 for the patients enrolled in the 3 studies would increase the total patient-years follow-up from 17,967 to 27,156 person-years, a 51% increase. The person-years reported would be slightly reduced by the amount of observation time after the death of a patient. The available observation time is at least 3 years for 93% of the 7981 patients. For all-cause mortality through 1998, total follow-up time for the 3 treatment groups would be ~35,000 person-years, an increase of approximately 2-fold compared to the "on-study" database.

Table 1

Patient-Years of Follow-up for RON009393, RVN008993, and RHN009193

	Placebo				2.5 mg Risedronate				5 mg Risedronate			
Study	# of pt.[a]	"On-study" pt yrs[b]	"Off-study" pt yrs through 1997[c]	Total pt yrs	# of pt.[a]	"On-study" pt yrs[b]	"Off-study" pt yrs through 1997[c]	Total pt yrs	# of pt.[a]	"On-study" pt yrs[b]	"Off-study" pt yrs through 1997[c]	Total pt yrs
RON009393	217	273	497	770	210	278	466	744	216	276	481	757
RVN008993	815	2420	432	2852	811	1265	1571	2836	813	2401	460	2861
RHN009193	1646	3678	1810	5488	1615	3681	1716	5397	1638	3695	1756	5451
Total	2678	6371	2739	9110	2636	5224	3753	8977	2667	6372	2697	9069

[a] Number of patients randomized and took at least one dose of study medication.
[b] "On-study" patient years (pt yrs) is based on time between start of study drug and last observation time in the clinical trial database.
[c] Additional "off-study" patient years through 1997 is based on the time between the last day "on-study" and December 31, 1997.

Expected Mortality Rates

The expected mortality rates for the patients in the North American trials and the power calculations for follow-up period for each of the 3 outcome variables—1998 all-cause mortality, 1997 all-cancer mortality, and 1997 lung cancer mortality—are provided within **Attachment 3**. As requested by the Agency, we will separately analyze each of the outcome variables in 3 ways as described on the statistical analysis plans:

1. For deaths occurring while the person was "on-study". The "on-study" period is defined as the time between start of study drug and last observation time in the clinical trial database, including available follow-up data. (See "on-study" definition in **Attachment 3, Section 2**.)

2. For deaths occurring while the person was "off-study". These deaths are any which are identified during the follow-up study which are not in our current "on-study" database.

3. For deaths occurring between start of study drug and the completion of the follow-up period, regardless of whether the death occurred while the person was "on-study" or "off-study".

The estimated results of these analyses are discussed in the sections below.

"On-Study" Mortality

The all-cause mortality, all-cancer mortality, and the lung cancer mortality during the "on-study" period covered by the current clinical database for the 3 North American PMO trials is shown in **Table 2**. These data indicate a relative risk for the combined treatment groups of 0.87 for all-cause mortality, 0.64 for all-cancer mortality, and 1.1 for lung cancer mortality.

Table 2

"On-Study" Mortality
Studies RON009393, RVN008993, and RHN009193

	Placebo	2.5 mg Risedronate	5 mg Risedronate	RR*
All-Cause Mortality	83 13.0/1000	64 12.3/1000	67 10.5/1000	0.87
All-Cancer Mortality**	18 2.8/1000	15 2.9/1000	6 0.94/1000	0.64
Lung Cancer Mortality^	6 0.94/1000	9 1.7/1000	3 0.47/1000	1.1

* Relative risk based on pooled treatment groups vs. placebo.
** Excluding patients with nonmelanotic skin cancer
^ Based on known mortality and COSTART AE code, not on cause listed on death certificate.

"Off-study" and total "on-study" plus "off-study" all-cause and all-cancer mortality

We have assumed the all-cause and all-cancer mortality, as reported by the NDI and Canadian provincial databases, will have a relative risk of approximately 1.0 during the "off-study" follow-up period. If this is the case, the relative risk of death due to all-causes through 1998 and the relative risk of death due to all cancers through 1997 will be approximately 1.0 for the pooled risedronate treatment groups compared to placebo.

"Off-study" and total "on-study" plus "off-study" lung cancer mortality

The lung cancer mortality shows that only 18 of the 42 incident lung cancer cases died during the study. Of the remaining 24 patients who were still alive "on-study", 3 patients were in the placebo group, 14 were in the 2.5-mg risedronate group, and 7 were in the 5-mg risedronate group. If these patients die during the "off-study" follow-up period, the imbalance observed in the incident lung cancer cases during the study will be carried forward into both the analysis of "off-study" lung cancer mortality as well as the overall analysis of lung cancer mortality occurring between time of first dose and the completion of the follow-up period.

As lung cancer has about a 50% survival in 1 year and approximately a 10% survival in 5 years, the effect due to these cases is not expected to be completely overcome during the follow-up period, even if there is no lung cancer mortality imbalance during follow-up among the patients not previously diagnosed with lung cancer. For this reason, the distribution of lung cancer deaths (excluding the incident cases) should be evaluated separately to provide an independent perspective, as this is truly new data. Accordingly, 1 additional analysis for the outcome variable of death due to lung cancer while the person was "off-study" has been added. This analysis would exclude the patients who had a lung cancer COSTART during the "on-study" period in order to allow an independent analysis of those patients who did not have a lung cancer diagnosis during the study.

In the 2 tables that follow (**Tables 3** and **4**), the anticipated lung cancer mortality results under 2 separate scenarios are presented. In each case, it is assumed that the 24 incident lung cancer cases will die during the "off-study" follow-up period, but uses 2 different mortality rates for the patients who did not have a lung cancer COSTART "on-study".

The first scenario assumes that the "off-study" follow up of the patients who did not have a lung cancer COSTART during the study will have a relative risk of dying of lung cancer of 1.0. As shown in **Table 3**, when these patients are combined with the 24 incident lung cancer cases expected to die during follow-up, the estimated overall relative risk during the "off-study" follow-up period and the complete "on-study" plus "off-study" follow-up periods would be 1.7 and 1.6, respectively.

Table 3

Estimated Mortality Due to Lung Cancer
Assumes RR* of 1.0 During "Off-Study" Follow-up of Non-incident Lung Cancer Cases
Studies RON009393, RVN008993, and RHN009193

	Placebo	2.5 mg Risedronate	5 mg Risedronate	RR*
"On-study" deaths	6 0.94/1000	9 1.7/1000	3 0.47/1000	1.1
"Off-study" deaths				
• Assume incident lung cancer patients die during follow-up	3 1.1/1000	14 3.7/1000	7 2.6/1000	3.0
• Additional follow-up deaths expected**	5.8 2.1/1000	7.9 2.1/1000	5.7 2.1/1000	1.0
• Total "off-study" Deaths if all incident cases die in follow-up	8.8 3.2/1000	21.9 5.8/1000	12.7 4.7/1000	1.7
Total "on-study" plus "off-study" deaths through 12/31/97	14.8 1.6/1000	30.9 3.4/1000	15.7 1.7/1000	1.6

* Relative risk based on pooled treatment groups.

** Excludes patients who had a lung cancer COSTART during the "on-study" period. Rates are based on US National mortality rates for white women and the age distribution in the 3 studies.

The estimates presented in **Table 3** included the 6 patients with radiographic evidence of lung cancer prior to taking any study medication. If these patients are excluded, the estimated overall relative risk during both the "off-study" and complete "on-study" plus "off-study" follow-up periods would be 1.4.

In the second scenario (**Table 4**), it is assumed that follow up of the patients who did not have a lung cancer COSTART during the study will have a relative risk of dying of lung cancer of 2.0, which approximates the relative risk for the "on-study" incident lung cancer cases in the risedronate clinical trial database. In this situation, the "off-study" and complete "on-study" plus "off-study" follow-up periods would result in a relative risk of 2.3 and 2.1, respectively.

Based on these estimates, relative risks of lung cancer mortality during follow-up which are less than 2.3 "off-study" and less than 2.1 for the total mortality follow-up period would not suggest a replication of the previously observed lung cancer imbalance. Such an observation, together with a relative risks at or near 1.0 for all-cause and all-cancer mortality, would support a conclusion that risedronate is not causally associated with lung cancer.

Table 4

Estimated Mortality Due to Lung Cancer
Assumes RR* of 2.0 during "Off-Study" Follow-up of Non-incident Lung Cancer Cases
Studies Studies RON009393, RVN008993, and RHN009193

	Placebo	2.5 mg Risedronate	5 mg Risedronate	RR*
"On-study" deaths	6 0.94/1000	9 1.7/1000	3 0.47/1000	1.1
"Off-study" deaths				
• Assume incident lung cancer patients die during follow-up	3 1.1/1000	14 3.7/1000	7 2.6/1000	3.0
• Additional follow-up deaths **	5.8 2.1/1000	15.8 4.2/1000	11.3 4.2/1000	2.0
• Total "off-study" Deaths if all incident cases die in follow-up	8.8 3.2/1000	29.8 7.9/1000	18.3 6.8/1000	2.3
Total "on-study" plus "off-study" deaths through 12/31/97	14.8 1.6/1000	38.8 4.3/1000	21.3 2.4/1000	2.1

* Relative risk based on pooled treatment groups.

** Excludes patients who had a lung cancer COSTART during the "on-study" period. Placebo rate based on US National mortality rates for white women; assumes the relative risk during follow-up is 2.0 for each risedronate treatment group.

The estimates presented in **Table 4** included the 6 patients with radiographic evidence of lung cancer prior to taking any study medication. If these patients are excluded, the estimated relative risk "off-study" would be 2.1 and the total "on-study" plus "off-study" relative risk would be 1.9.

We believe that, because of the issues around the accuracy of reporting specific causes of death on a death certificate, the overall mortality rate and relative risks determined from this study will be most reliable, followed by those for all cancers, and finally by those for lung cancers. Therefore, when the likelihood of chance imbalances in the distributions of specific causes are considered, we believe that it would be inappropriate to conclude that there is a causal link with a specific cancer type if the all-cancer mortality risk is around 1.0 or less.

APPEARS THIS WAY
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If after reviewing the information contained in this submission, you have any questions or comments on our approach, please contact me at (513) 622-5022. We would be very happy to meet with you, Dr. Jenkins, and the Center Level to further discuss the likely outcomes and interpretation of this mortality study.

Thank you for your help on this issue.

Sincerely,

Bruce R. DeMark, Ph.D.
Section Head
U.S. Regulatory Affairs

Desk Copies: Solomon Sobel, M.D.
Robert Temple, M.D.
Murray Lumpkin, M.D.
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November 2, 1999

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attention: Document Control Room 14B-19
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Rockville, Maryland 20857

RE: NDA 20-835/S-001, S-002, S-003, S-004; ACTONEL (risedronate sodium)
Treatment and Prevention of Postmenopausal and Corticosteroid-Induced Osteoporosis

Dear Dr. Sobel:

In the approvable letter received from the Division on October 18, 1999, a request was made for updated safety information regarding ACTONEL (risedronate sodium). The purpose of this submission is to gain the Division's agreement with an alternate proposal for the information to be provided in the next safety update. This alternate proposal addresses the studies we would like to include in the next update and the specific data from each that we would like to present.

There are three ACTONEL studies, for which unblinded data are now available, that have not previously been submitted to the sNDA either in the 180-day safety update submitted June 17, 1999 (Amendment 5) or in response to questions/labeling comments received from Division reviewers. We propose to include data from these three studies in the next safety update. The studies are as follows:

- RVN008993 (Year 4, Drug-Free Follow-up) - A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study to Determine the Efficacy and Safety of Risedronate (NE-58095) in the Treatment of Postmenopausal Women with Established Osteoporosis-Related Vertebral Deformities.

  RVN008993 is one of the pivotal Phase III trials to assess efficacy and safety of risedronate in the treatment of postmenopausal women with established osteoporosis-related vertebral deformities. At the time the sNDA was submitted all patients had completed the 3-year double-blind, placebo-controlled portion of the trial and were in the fourth and final year of the study. This fourth year was a drug-free, follow-up year in which former placebo and 5-mg risedronate patients received only calcium. The follow-up year of the study is now complete.

- 1998012 - A Six-Month, Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel-Group Trial to Evaluate the Safety of Modified Dosing Instructions for 5 mg Oral Risedronate in Postmenopausal Osteopenic and Osteoporotic Women

- 1999033 - Randomized, Double-Blind, Parallel Group Study in Healthy Postmenopausal Women to Assess the Safety and Tolerability of Once Weekly Oral Dosing with Risedronate (35 or 50 mg), Compared to Daily Oral Dosing with 5 mg Risedronate and Placebo

Previously, safety data from our two hip fracture trials (RHN009193 and RHE009293), as well as safety data from a gastrointestinal (GI) endoscopy study with risedronate and aspirin (Study 1998013) and an esophageal transit study with a placebo film-coated risedronate tablet (Study 1997007) were included in the 180-day safety update. Additional safety data from an endoscopy study comparing risedronate with alendronate (Study 1998054) were submitted in response to the medical reviewers' labeling comments (July 28, 1999) and the final report from this study was submitted to the sNDA on September 22, 1999.

As the Division determined that the information most relevant for review in the 180-day safety update were serious adverse events and GI events (upper and lower regardless of causality), we propose that these same safety data be presented in the next safety update for the three new studies listed above. We will include summary tables and listings for the GI events. Summary tables, listings, and patient narratives will be included for the serious adverse events. We will also include case report forms for each patient in these studies who died during the trial or who did not complete the study because of an adverse event. A discussion will be prepared which compares these safety data with information contained in the Integrated Summary of Safety and the 180-day safety update.

It is our belief that a safety update containing the data outlined in this proposal will provide the Division reviewers with the information that is most relevant to their assessment of the safety of ACTONEL and avoids replication of information previously submitted.

Please contact me if there are any questions regarding this submission.

Sincerely,

Linda W. Manning

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Desk Copy: Randy Hedin, R.Ph.
Eric Colman, M.D.

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October 29, 1999

Eric Colman, M.D
Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA #20-835/S-001, S-002, S-003, S-004 ACTONEL (risedronate sodium)

Dear Dr. Colman:

As I mentioned to you in a recent telephone conversation, we have received marketing authorization in Sweden for the use of risedronate sodium 5 mg tablets for post-menopausal and corticosteroid-induced osteoporosis indications. We have also received approval for use of the 30 mg tablet for Paget's disease. The trade name for the product in this country is Optinate. I have attached a copy of the approved marketing authorization certificates and the Summary of Product Characteristics (product labeling) for the osteoporosis indications.

Please let me know if you have any questions.

/S/
11-10-99

/S/ 11/9/99

/S/
11-19-99

Sincerely,

Bruce R. DeMark

Bruce R. DeMark, Ph.D.
Section Head
U.S. Regulatory Affairs

Attachment

Desk copy: Eric Colman, MD
Randy Hedin, R. Ph.

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ MEMO

/S/ 11/22/99

CSO INITIALS DATE