CERTIFICATE OF APPROVAL

MEDICAL PRODUCTS AGENCY

Date	*ASP-no*
1999-10-07	98-0850

Hoechst Marion Roussel AB
Bryggvägen16-18
117 68 Stockholm

In accordance with Section 7 of the Medical Products Act (1992:859) approval has been granted for the following drug

Name **OPTINATE**, tablets 5 mg
Registration number 15296
Marketing authorisation holder Hoechst Marion Roussel AB, Stockholm, Sweden
Manufacturer Procter & Gamble Pharmaceuticals Germany GmbH, Weiterstadt, Germany
Agent -
The product should be a prescription drug [X] Yes [ ] No

The approval is valid for five years and ends 2004-10-07

On behalf of the Medical Products Agency

Thomas Lönngren
(signature)

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

BEVIS OM GODKÄNNANDE AV LÄKEMEDEL

Datum	Ärendebeteckning
1999-10-07	98-0850

Hoechst Marion Roussel AB
Bryggvägen 16-18
117 68 STOCKHOLM

Med stöd av 7§ läkemedelslagen (1992:859) har godkännande beviljats för följande läkemedel

Namn, beredningsform och styrka OPTINATE, tabletter 5 mg
Godkännandenummer 15296
Innehavare av godkännande för försäljning Hoechst Marion Roussel AB, Stockholm, Sverige
Tillverkare Procter & Gamble Pharmaceuticals Germany GmbH, Weiterstadt, Tyskland
Ombud -
Läkemedlet skall vara receptbelagt [X] Ja [ ] Nej

Godkännandet gäller i fem år och löper ut 2004-10-07.

På Läkemedelsverkets vägnar

Thomas Lönngren

LV 20:1

CERTIFICATE OF APPROVAL

MEDICAL PRODUCTS AGENCY

Date	*ASP-no*
1999-10-07	98-0851

Hoechst Marion Roussel AB
Bryggvägen16-18
117 68 Stockholm

In accordance with Section 7 of the Medical Products Act (1992:859) approval has been granted for the following drug

Name **OPTINATE**, tablets 30 mg
Registration number 15297
Marketing authorisation holder Hoechst Marion Roussel AB, Stockholm, Sweden
Manufacturer Procter & Gamble Pharmaceuticals Germany GmbH, Welterstadt, Germany
Agent -
The product should be a prescription drug [X] Yes [ ] No

The approval is valid for five years and ends 2004-10-07

On behalf of the Medical Products Agency

Thomas Lönngren
(signature)

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

BEVIS OM GODKÄNNANDE AV LÄKEMEDEL

Datum	Ärendebeteckning
1999-10-07	98-0851

Hoechst Marion Roussel AB
Bryggvägen 16-18
117 68 STOCKHOLM

Med stöd av 7§ läkemedelslagen (1992:859) har godkännande beviljats för följande läkemedel

Namn, beredningsform och styrka **OPTINATE**, tabletter 30 mg
Godkännandenummer 15297
Innehavare av godkännande för försäljning Hoechst Marion Roussel AB, Stockholm, Sverige
Tillverkare Procter & Gamble Pharmaceuticals Germany GmbH, Weiterstadt, Tyskland
Ombud -
Läkemedlet skall vara receptbelagt [X] Ja [ ] Nej

Godkännandet gäller i fem år och löper ut 2004-10-07.

På Läkemedelsverkets vägnar

Thomas Lönngren

Summary of Product Characteristics

1. Name of the Medicinal Product
Optinate 5 mg film-coated tablets.

2. Qualitative and Quantitative Composition
One film-coated tablet contains 5 mg risedronate sodium which is equivalent to 4.64 mg risedronic acid.

3. Pharmaceutical Form
Film-coated tablets.
Oval yellow with RSN on one side and 5 mg on the other.

4. Clinical Particulars

4.1 Therapeutic indications
Treatment of postmenopausal osteoporosis: to reduce the risk of vertebral fractures.
Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis.

To maintain or increase bone mass in postmenopausal women undergoing long-term, systemic corticosteroid treatment.

4.2 Posology and method of administration
The recommended daily dose in adults is one 5 mg tablet orally. The absorption of Optinate is affected by food, thus to ensure adequate absorption patients should take Optinate either:

- at least 30 minutes before the first food or drink (other than water) of the day,

OR

- at least 2 hours from any food or drink at any other time of the day, and at least 30 minutes before going to bed.

The tablets must be swallowed whole. To aid delivery of the tablet to the stomach Optinate is to be taken while in an upright position with a glass of water (≥120 ml). Patients should not lie down for 30 minutes after taking the tablet (see 4.4, special warnings and special precautions for use).

Supplemental calcium and vitamin D should be considered if the dietary intake is inadequate.

Elderly: No dosage adjustment is necessary since bioavailability, distribution and elimination were similar in elderly (>60 years of age) compared to younger subjects.

Renal impairment: No dosage adjustment is necessary in patients with creatinine clearance ≥30 ml/min. There is limited clinical experience in patients with severe renal impairment (creatinine clearance <30 ml/min), and no dosage recommendation can be made for this population.

Children: Safety and efficacy of Optinate have not been established in children and young adults under 18.

4.3 Contra-indications
Known hypersensitivity to any ingredient of this medicinal product.
Hypocalcaemia (see 4.4, special warnings and special precautions for use).

4.4 Special warnings and special precautions for use
Foods, drinks (other than water) and drugs containing polyvalent cations (such as calcium, magnesium, iron and aluminium) may interfere with the absorption of Optinate and should not be taken at the same time. Therefore Optinate should be taken either, at least 30 minutes before the first food or drink of the day or, at least two hours away from food or drink at any other time of the day.

Some bisphosphonates have been associated with oesophagitis and oesophageal ulcerations. Therefore patients should pay attention to the dosing instructions (see 4.2, posology and method of administration). Prescribers should emphasise the importance of the dosing instructions to patients who have a history of oesophageal disorders e.g. stricture or achalasia.

Hypocalcaemia should be treated before starting Optinate therapy. Other disturbances of bone and mineral metabolism (e.g. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Optinate therapy.

4. 5 Interaction with other medicaments and other forms of interaction
No formal interaction studies have been performed, however no clinically relevant interactions with other medicines were found during clinical trials. Among the women enrolled in the Optinate Phase III postmenopausal osteoporosis treatment studies, acetylic salicylic acid or NSAID use was reported in 29% and 37% of patients respectively. Among regular users (3 or more days per week) the incidence of upper gastrointestinal adverse events in Optinate treated patients was similar to that in control patients.

If considered appropriate Optinate may be used concomitantly with oestrogen supplementation.

Concomitant ingestion of medications containing polyvalent cations (e.g. calcium, magnesium, iron and aluminium) will interfere with the absorption of Optinate (see 4.4, special warnings and special precautions for use).

Optinate is not systemically metabolised, does not induce cytochrome P450 enzymes, and has low protein binding.

4.6 Pregnancy and lactation
Data from treatment of pregnant women is lacking for risedronate. Animal studies have shown reproduction toxicological effects (see 5.3, preclinical safety data). The significance of these to humans is unknown. Optinate should be used during pregnancy only when treatment is absolutely necessary. Optinate should not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines
None known.

4.8 Undesirable effects

The majority of undesirable effects observed in clinical trials were mild to moderate in severity and usually did not require cessation of therapy.

Common (>1/100)	*GI*: Abdominal pain (2%) *Musculoskeletal*: Musculoskeletal pain (3%)
Uncommon (1/100 - 1/1000)	*GI*: Duodenitis, Glossitis *Opthamological*: Iritis

Laboratory findings: Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels have been observed in some patients. Rarely abnormal liver function tests have been reported.

4.9 Overdose

No specific information is available on the treatment of acute overdose with Optinaterisedronate.

Decreases in serum calcium following substantial overdose may be expected. Signs and symptoms of hypocalcaemia may also occur in some of these patients.

Milk or antacids containing magnesium, calcium or aluminium should be given to bind risedronate and reduce absorption of the drug. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Medicinal product for the treatment of bone diseases (M05 BA Bisphosphonates).

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. The bone turnover is reduced while the osteoblast activity and bone mineralisation is preserved. In preclinical studies risedronate demonstrated potent anti-osteoclast and antiresorptive activity, and dose dependently increased bone mass and biomechanical skeletal strength. The activity of risedronate sodium was confirmed by measuring biochemical markers for bone turnover during pharmacodynamic and clinical studies. Decreases in biochemical markers of bone turnover were observed within 1 month and reached a maximum in 3-6 months.

Treatment and Prevention of Postmenopausal Osteoporosis: The clinical programme contained early and late postmenopausal women with and without fracture. Results of these studies demonstrate that:

- Optinate 5 mg daily given for 3 years reduced the risk of new vertebral fractures in postmenopausal women with osteoporosis relative to the control group which was treated with calcium and vitamin D. An effect of treatment was seen as early as the end of the first year of treatment. Benefits were also demonstrated in women with multiple fractures at baseline. Optinate 5 mg daily also reduced the yearly height loss compared to the control group.

- Optinate 5 mg daily reduced the overall incidence of non-vertebral osteoporosis-related fractures (hip, wrist, humerus, clavicle, pelvis, and leg). Specific effect on the risk of new hip fractures has not been documented.
- Optinate 5 mg daily given for 3 years increased BMD relative to control at the lumbar spine, femoral neck, trochanter and wrist and prevented bone loss at the mid-shaft radius.
- Optinate 5 mg daily in postmenopausal women taking oestrogen, increased BMD at sites rich in cortical bone, such as the femoral neck and mid-shaft radius, compared to oestrogen alone.
- bone biopsy samples from postmenopausal women treated with Optinate 5 mg daily for 2 to 3 years, showed an expected moderate decrease in bone turnover. Bone formed during Optinate treatment was of normal lamellar structure and bone mineralisation.
- endoscopic findings from a number of patients with a number of moderate to severe GI complaints in both Optinate and control patients indicated no evidence of treatment related gastric, duodenal or oesophageal ulcers in either group, although duodenitis was uncommonly observed in the Optinate group.

Corticosteroid Induced Osteoporosis: The clinical programme included patients initiating corticosteroid therapy (≥ 7.5 mg/day prednisone or equivalent) within the previous 3 months or patients who had been taking corticosteroids for more than 6 months. Results of these studies demonstrate that:

- Optinate 5 mg daily given for one year maintains or increases BMD relative to control at the lumbar spine, femoral neck, and trochanter.
- Optinate 5 mg daily reduced the incidence of vertebral fractures, monitored for safety, relative to control at 1 year in pooled studies.
- histological examination of bone biopsies from patients taking corticosteroids and Optinate 5 mg daily did not show signs of disturbed mineralisation process.

5.2 Pharmacokinetic properties

Absorption: Absorption after an oral dose is relatively rapid (t_{max} ~1 hour) and is independent of dose over the range studied (2.5 to 30 mg). Mean oral bioavailability of the tablet is 0.63% and is decreased when risedronate sodium is administered with food. Bioavailability was similar in men and women.

Distribution: The mean steady state volume of distribution is 6.3 l/kg in humans. Plasma protein binding is about 24%.

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

Elimination: Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine after 28 days. Mean renal clearance is 105 ml/min and mean total clearance is 122 ml/min, with the difference probably attributed to clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in faeces. After intravenous administration the concentration-time profile shows three elimination phases with a terminal half-life of 480 hours.

Special populations:

Elderly : no dosage adjustment is necessary.

Renal impairment: no dosage adjustment is necessary in patients with creatinine clearance ≥ 30 ml/min. No dosage recommendation can be made for patients with severe renal impairment (creatinine clearance < 30 ml/min).

5.3 Preclinical safety data

In toxicological studies in rat and dog dose dependent liver toxic effects of risedronate sodium were seen, primarily as enzyme increases. The clinical relevance of these observations is unknown. In reproduction toxicity studies at exposures close to clinical exposure ossification changes were seen in sternum and/or skull of foetuses from treated rats and hypocalcemia and mortality in pregnant females allowed to deliver. Current studies on genotoxicity and carcinogenesis did not show any particular risks for humans.

6. Pharmaceutical Particulars

6.1 List of excipients

Tablet core: lactose monohydrate, microcrystalline cellulose, crospovidone, magnesium stearate.

Film coating: ferric oxide yellow E172, hypromellose, macrogol 400, hydroxypropyl cellulose, polyethylene glycol, silicon dioxide, titanium dioxide E171.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No specific storage conditions.

6.5 Nature and contents of container

Opaque PVC/aluminium foil blister cards of 14 tablets in a cardboard carton, tablet count 14, 28 (2 x 14), 84 (6 x 14) or 10 x 14* (hospital bundle).

2 x 10 * count perforated blister strip (hospital unit dose)

** Not intended for sale in Sweden.*

6.6 Instructions for use/handling

None.

7. Marketing authorisation Holder:

Hoechst Marion Roussel AB
Bryggvägen 16-18
117 68 Stockholm

8. Marketing Authorization Number

15296

9. Date of first authorisation / renewal of the authorisation

1999-10-07

10. Date of first revision of the text

1999-10-07

APPEARS THIS WAY
ON ORIGINAL

Procter&Gamble

The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

October 22, 1999

Solomon Sobel, M.D., Director
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

Response to Approvable Letter

Dear Dr. Sobel:

The purpose of this submission to NDA #20-835/S-001, S-002, S-003, S-004, ACTONEL (risedronate sodium) is to notify you, in accordance with 21 CFR 314.110(a)(1), that Procter & Gamble Pharmaceuticals (P&GP) intends to file an amendment to address the deficiencies noted in the approvable letter received from the Division on October 18, 1999. Work is currently underway to provide the requested information and it will be forwarded to you as soon as it is available.

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

Sincerely,

Linda W. Manning

Linda W. Manning, Pharm.D.
Senior Scientist, Regulatory Affairs
Phone: (513) 622-1114
FAX: (513) 622-5369

Desk Copy: Randy Hedin, R.Ph.

Procter&Gamble
PHARMACEUTICALS

Mail: The Procter & Gamble Company
Health Care Research Center
P O Box 8006
Mason, Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

October 8, 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, ACTONEL (risedronate sodium)

Dear Dr. Sobel:

Thank you for the opportunity to meet with the Division and with Drs. Jenkins and Temple on September 23 to discuss the circumstances related to the Approvable Letter we received on August 20 for our Corticosteroid-Induced Osteoprorosis (CIO) supplemental application. We were disappointed that Drs. Woodcock and O'Neill were not able to attend. This correspondence summarizes our notes from this meeting.

The following individuals attended the meeting:

FDA: Robert Temple, M.D., Director, Office of Medical Policy (by telephone)
John Jenkins, M.D., Director, Office of Drug Evaluation II
Solomon Sobel, M.D., Division Director, DMEDP
Gloria Troendle, M.D., Deputy Division Director, DMEDP
Bruce Stadel, M.D., M.P.H., Medical Officer, DMEDP
Eric Colman M.D., Medical Reviewer, DMEDP
Leo Lutwak, M.D.,Ph.D., Medical Reviewer, DMEDP
Bruce Schneider, M.D., Medical Reviewer, DMEDP
Joanna Zawadzki, M.D., Medical Reviewer, DMEDP
Sue-Jane Wang, Ph.D, Statistician, DMEDP
Randy Hedin, R. Ph. CSO , DMEDP
Julie Beitz, M.D., Medical Team Leader, Division of Oncology
Charles Anello, Ph.D., Deputy Director, Office of Epidemiology and Biostatistics
Ed Nevius, Ph.D., Supervisor, Division of Biometrics II
Todd Sahlroot, Ph.D., Team Leader, Division of Biometrics II

Procter and Gamble Pharmaceuticals (P&GP):

Larry R. Versteegh, Ph.D., Vice President Global Regulatory and Clinical Development
Nora L. Zorich, M.D., Ph.D., Director, Actonel Product Development
Bruce R. DeMark, Ph.D., Section Head, Regulatory Affairs
John D. Taulbee, Ph.D., Director Epidemiology and Biometrics
J. Michael Sprafka, Ph.D, M.P.H., Associate Director, Global Pharmacovigilance, Epidemiology and Pharmacoeconomics
Arkadi Chines, M. D., Senior Medical Monitor, Risedronate

Hoechst Marion Roussel (HMR):

Gillian Ivers-Read, Vice President, Strategic Regulatory Development

Four topics for discussion had been forwarded to the Agency prior to the meeting. A copy of these topics is provided in **Attachment 1**.

A summary of the key outcomes from the meeting are provided immediately below. Detailed meeting minutes follow the key outcomes section.

Key Meeting Outcomes/Agreements

1. The Agency expressed no real concern about a causal association between risedronate and lung cancer observations. However, since this is an unexpected AE signal, additional data are needed to resolve.

2. The Agency agreed all-cause mortality rates through 12/31/98, all-cancer mortality rates through 12/31/97, and lung cancer mortality rates through 12/31/97 could provide sufficient additional data to make an approval decision.

3. P&GP will provide a written mortality study proposal to the Agency. The Agency asked whether it would be possible to include data from European studies and stated that we should provide a justification if we decide to use only North American data.

4. The Agency does not feel it is reasonable to expect 12/18/99 approval if new mortality follow-up data are submitted 12/01/99. It is likely that an Action letter will be issued for the PMO indication on 10/18/99. The most likely approval date for the PMO and CIO indications is six months from the CIO resubmission which was sent to the Agency on August 27, 1999. This assumes a favorable outcome of the mortality data and the available of these data in December, 1999.

5. The approval decision on Actonel will be dependent only on the risedronate data. Mortality data from other class members are irrelevant.

6. The Agency does not feel the need for [redacted] but this will ultimately depend on the outcome of the mortality study.

7. [redacted]

8. The Agency stated that the lung cancer signal from the risedronate data is significantly greater than with other bisphosphonates. Dr. Stadel stated the relative risk to patients in studies where the average age at enrollment is less than 65 years is much higher in the risedronate data.

P&GP/HMR Statement of Position

The meeting began with a short presentation by Dr. Nora Zorich, stating the position of P&GP and HMR on the lung cancer issue. Dr. Zorich stated that consistent with the conclusions of our expert Safety Panel, we believed strongly that there was no basis to conclude that risedronate could be causally associated with lung cancer, either as a direct carcinogenic effect or as a tumor growth enhancer. She stated that we understood that the Agency felt they needed additional data and that we planned to discuss the mortality follow-up study later in the meeting as something which could provide further evidence that risedronate is not causally associated with lung cancer. Dr. Jenkins asked if we intended to do the mortality follow-up study prior to approval. Dr. Zorich responded that we would.

Dr. Zorich then proceeded to summarize the clinical and nonclinical evidence. During this presentation, Dr. Zorich presented the specific case data for one of the 8 trials (Study RVN008993) which illustrated the imbalance from the original sNDA submission. This study had one lung cancer case in placebo, 5 cases in the 2.5-mg treatment group and 3 cases in the 5-mg treatment group. Dr. Zorich stated that when evaluating the individual case data from this trial, 6 of the 8 cases were either evident prior to randomization, or were diagnosed less than six months into the trial. She showed that if all cases evident <6 months into the trials are considered unrelated to risedronate use, there is only one trial, Study RHN009193, which shows an obvious imbalance in lung cancers, but only in the 2.5 mg treatment group: 6 cases in placebo, 12 cases in the 2.5-mg group, and 3 cases in the 5-mg treatment group.
Dr. Temple asked if we had shared the individual patient information with the Division.
Dr. Zorich stated that we had made submissions to the Division on this and that we had presented this information to the Division in earlier meetings. A copy of Dr. Zorich's transparencies is provided in **Attachment 2.**

Dr. Jenkins asked about detection bias and what we felt about this as an explanation for the observed lung cancer data. Dr. Zorich stated that there were no specific data to support this hypothesis, although it cannot be ruled out that treatment caused some signs or symptoms resulting in a differential search for a cause and the incidental discovery of lung tumors. Another possible explanation is ascertainment bias which would result from placebo patients dropping from the studies early before being diagnosed. There is evidence for earlier discontinuations of placebo patients from some of the risedronate trials. Dr. Zorich then stated that a third, and perhaps even more likely possibility, is that the imbalance in lung cancer (against risedronate) and in GI cancers (in favor of risedronate) was due to the inaccuracy of a clinical diagnosis with respect to primary cancer site. She cited a review article by Lee on the accuracy of the clinical diagnosis of lung cancer, which concludes that autopsy findings fail to

confirm lung cancer as the primary site approximately 40% of the time.[1] She added that this is very likely a particular problem in the elderly population we studied since many times the patients do not get a complete work up.

Dr. Zorich also mentioned that we still felt that chance could explain the results. Dr. Temple stated that he had not ruled out chance as an explanation, given the multiplicity of adverse event observations. Dr. DeMark commented that we had prepared a document on this and sent it to the Division and we would be happy to provide a copy to him. (A copy was forwarded to Dr. Temple on September 29, 1999.)

Dr. Julie Beitz from Oncology asked about the primary lung cancer cases and if we had sorted primary cases according to those which were evident >6 months after the start of the studies. We stated that we had not specifically done this but would provide it to the Agency. (This has been provided in a subsequent submission dated September 29, 1999).

Mortality Study Design

Dr. DeMark presented an overview of the mortality study design. He stated that the purpose of the study is to evaluate all-cause mortality and lung-specific mortality in order to provide additional evidence that risedronate does not cause or promote lung cancer. He stated that the anticipated additional follow-up data through 1997 for the three North American trials (RHN, RVN, and RON) would increase the total follow-up to ~27,000 person-years, a 76% increase over what is currently available in the risedronate database. Based on this 1997 data, and the US National mortality rates, the follow-up study would have a 70% power to detect a 20% difference in all-cause mortality between placebo and treatment and an 80% power to detect a two-fold difference in lung cancer mortality. A copy of this presentation is provided in **Attachment 3.**

During the presentation, Dr. DeMark presented the incident cases of lung cancer during the three trials, the deaths due to lung cancer during these trials, and the expected number of lung cancer deaths for the entire follow-up period, based on US National mortality data and assuming all incident lung cancer cases would die in the follow-up study period. These data are summarized in the table on the next page.

[1] Lee PN. Comparison of autopsy, clinical and death certificate diagnosis with particular reference to lung cancer: a review of the published data. APMIS Suppl 1994;45:1-42.

Anticipated Deaths Due to Lung Cancer in Mortality Follow-up Studies RVN, RON, and RHN				
	Placebo	2.5 mg Risedronate	5 mg Risedronate	RR*
Incident lung cancer cases expected to die during follow-up	9# 1.64/1000	23# 5.05/1000	10# 1.81/1000	2.0
Additional follow-up deaths expected**	8.3 2.25/1000	10.1 2.25/1000	8.1 2.25/1000	
Total deaths through 12/31/97, assuming all incident cases die during follow-up	17.3 1.89/1000	33.1 3.67/1000	18.1 1.99/1000	1.5

* Relative risk based on pooled treatment groups.
** Based on US National mortality rates for white women age 70-79.
# Of these cases, 5 placebo, seven 2.5 mg, and three 5.0 mg patients died during the trials.

Dr. DeMark pointed out that if one assumes the incident lung cancer cases will all become lung cancer deaths during follow-up, there will be an imbalance in lung cancer deaths which is not likely to be overcome during follow-up. The relative risk of death based on pooled treatment groups for these incident cases alone would be 2.0.

Dr. DeMark stated that for the follow-up study, the distribution of new lung cancer deaths (excluding the incident cases) should be evaluated as an independent data set. Two scenarios were presented. In the first scenario, the independent data set would show no difference in lung cancer deaths between treatment groups (relative risk 1.0). This lack of replication of the original data set would result in an overall relative risk of 1.5 when this data set is combined with the deaths expected from the incident cases. However, in a second scenario, the overall relative risk would remain at 2.0 if the deaths for the independent data set replicated the deaths expected based on the incident lung cancer cases.

There was general agreement that if the new dataset showed an overall flat response relative to lung cancer deaths, this would provide comfort to the Agency, especially if all-cause mortality remained flat as well. However, Dr. Jenkins indicated that he was not sure if the expected number of new lung cancer cases would be large enough to draw conclusions. He asked what it would take to get 1998 data. Dr. Sprafka responded that the NDI database was updated annually and we could likely get 1998 all-cause mortality by November of this year. However, cause-specific 1998 mortality data will not be available until ~March 2000.

Dr. Zorich again mentioned the difficulty in getting accurate diagnosis of primary lung cancers. Dr. Temple then stated that given the uncertainty associated with lung cancer cases, it made sense and would help to look at all-cancer mortality as well. He concluded that the Agency would be comfortable if (1) the complete 1997 and 1998 all-cause mortality data is flat, (2) the 1997 all cancer mortality data are flat and (3) the 1997 lung cancer mortality is going down from the relative risk of 2.0.

Dr. Jenkins asked why we did not plan to collect follow-up mortality data from our European trials. Dr. Sprafka responded most of the cases were in the North American trials and that it was more difficult to obtain this type of information in Europe. Drs. Stadel and Temple indicated they thought this should not be difficult in some countries. Dr. Jenkins said it could

help the evaluation and might be beneficial to P&GP's cause if additional data were available. He said P&GP should include a justification in the proposal for the Mortality Study if we decided we would not collect European data.

Dr. Sobel asked that when the mortality data are analyzed, the data be presented from the time the patients started in the studies, in order to help evaluate any possibility that a tumor promoter mechanism is evident. He added that he did not believe this was the case. Dr. Sprafka indicated we would do this and Dr. Stadel commented that the data presentation of survival curves would take care of this.

Discussion of Timing Implications for PMO Indications

Dr. DeMark asked the Agency if they would work with P&GP to complete all labeling prior to receipt of the mortality data so that if the mortality data are available December 1 and look good, we can proceed to approvals by the 12-month action date for the PMO supplement, December 18. Dr. Jenkins responded that if the Agency received the data in early December, they would not have time to approve the product by December 18, as the data would need to be reviewed and thoroughly discussed.

Dr. Jenkins then asked for clarification of the PDUFA review timings for the PMO and CIO supplements. Mr. Hedin summarized the situation explaining that the PMO and CIO supplements had been submitted together but that only the CIO supplement was given priority review and the August approvable letter related to the CIO supplement. The PMO supplement has an Action Date goal of 10 months (October 18, 1999). Dr. DeMark stated that since the receipt of the CIO approvable letter, we had discussed with the Division that it made sense to combine the supplements so that labeling negotiations and approvals would occur at the same time with only one label negotiation. This was possible since all reviews would be complete. Mr. Hedin confirmed that the only outstanding review at this time was the Statistical review which was expected in a couple weeks. Mr. Hedin also said that since the CIO review was "back on the clock", the Division would continue the process, including providing labeling comments. Dr. Jenkins then asked if P&GP had responded to the CIO approvable letter. Mr. Hedin indicated that we had. Dr. DeMark stated that we had submitted a complete response on August 27. Dr. Jenkins then said that if we submit the mortality data in December and the data show a favorable outcome, it should be possible to complete the process on all indications within six months of the August 27 complete response. However, he stated there were no guarantees. He also indicated the Agency would likely issue an action letter on our PMO Supplement on October 18, since the review would be complete and it will not be possible to get an approval on December 18.

Other Comments

Response to Sponsor Questions

Dr. DeMark stated that most of the questions asked by P&GP had been answered during the discussion. Dr. Stadel said he wished to respond to Question 1 as to why our supplement was being held up while another bisphosphonate sponsor was approved this summer. He presented one data slide which showed the number of lung cancer cases by study where the clinical studies were grouped according to mean age at enrollment. Five of the ten studies (RBL, RCT, RCP, RON, and RPE) enrolled patients with a mean age at enrollment of <65 years, while the other 5 studies (ROE, RVE, RVN, RHN, and RHE) enrolled patients with an mean age at enrollment of >65 years. Dr. Stadel's slide showed the number of lung cancer cases in the studies with a mean age at enrollment < 65 years was 8 in treatment and 0 in placebo. He mentioned he had only looked at the reported numbers and not at the nature of the cases in terms of when they occurred. He then commented that the distribution of lung cancer cases in the older patient population were similar across bisphosphonate databases, but the observation of this lung cancer imbalance in the risedronate studies with younger patients was not seen in any other bisphosphonate database. Dr. Temple then commented that the risedronate data was a lot stronger or worse compared to the other databases.

> Note: Following the meeting, P&GP looked at the 8 cases from the studies with a mean age at enrollment less <65 years. Based on our review of these cases, (5 of the 8 cases were not <65 years of age) we disagree with the conclusion that risedronate is associated with lung cancer in younger patients. Please refer to NDA #20-835 S-001, S-002, S-003, correspondence dated September 29, 1999 for a further discussion of this issue.

Please contact me at (513) 622-5022 if you have any questions on these meeting minutes. We look forward to continuing to work through this issue with the Agency.

Sincerely,

Bruce R. DeMark Ph.D.
Section Head
US Regulatory Affairs

Desk Copies: Solomon Sobel, M.D.
Robert Temple, M.D.
Murray Lumpkin, M.D.
John Jenkins, M.D.
Eric Colman, M.D.
Bruce Stadel, M.D., MPH
Julie Beitz, M.D.
Randy Hedin, R.Ph.

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The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

SE1-CE1-GH

September 29, 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, Maryland 20857

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

Dear Dr. Sobel:

This submission is a follow-up to our September 23 meeting to discuss the status of the lung cancer issue. In addition to yourself and others from DMEDP and the Oncology Division, Dr. Jenkins and Dr. Temple also participated in this meeting. The purpose of this submission is the following:

1. To provide a response to the data regarding lung cancer seen in younger patients, which was presented for the first time to us by Dr. Stadel at the meeting.

2. To provide responses to questions raised at the meeting by Drs. Jenkins and Beitz and to provide our characterization of the individual patient data for the cases where an assignment of lung cancer was made. Although most of this information has been provided to the Division in earlier submissions, it appeared from his comments that Dr. Temple may have been unaware of this information.

Lung Cancer in Younger Patients

Dr. Stadel reported a data breakout of risedronate clinical studies that suggested a differentiation from other products due to an apparent excess of lung cancers in younger patients. This analysis was restricted to patients enrolled in risedronate clinical studies where the mean age of the study population at enrollment was <65 years (5 of the 10 studies). Using this approach, the incident cases in those studies were assigned to the <65 year category, regardless of their actual age at time of diagnosis. Thus, eight treatment cases were compared to none in placebo. Dr. Stadel then stated that this effect in younger patients was not seen in the other bisphosphonate databases, and Dr. Temple added that the lung cancer signal in the risedronate data was much worse than any of the other databases. The actual ages of these patients from these studies in provided in **Table A** on the next page.

Table A Lung Cancer Cases in Studies with mean Age at Enrollment <65			
Study	**Mean Age of Study Population at Enrollment**	**Lung Cancer Cases (Treatment Grp.)**	**Patient Age (yr) at Diagnosis of Lung Cancer**
RBL	53	2 cases (2.5 mg; 5 mg)	54 54
RCT	58	2 cases (2.5 mg; 2.5 mg)	79 64
RCP	60	1 case (5 mg)	70
RPE	59	1 case (5 mg)	74
RON	63	2 cases (2.5 mg; 5mg)	69 67

This is a perplexing and misleading way to display the data since only 3 of the 8 people reported to have lung cancer in these studies were <65 years when diagnosed. As shown in Table A, the other 5 patients ranged in age from 67 to 79 years. In order to draw any conclusions regarding the risk to patients <65 years, the lung cancer incidence in these younger patients should be evaluated within the entire database, and the strength of the cases should be assessed individually from a medical perspective.

Examination of the entire Phase III database of 15,797 patients, including studies with a mean age at enrollment ≥65, only 5 of the 69 patients with cases coded to lung cancer were <65 years of age at the time of diagnosis. **Table B** on the next page shows each of these cases and provides a brief synopsis of what was known about each case.

Table B
Database Cases Coded to Lung Cancer
Risedronate Studies in Study
Subjects < 65 Years of Age

Treatment	Placebo	2.5 mg Risedronate	5 mg Risedronate
Number of Cases	1	3	1
Case Summaries	RVN 43070628 F/62 16 months into study Lung primary documented. Pathology Report and Discharge Summary.	ROE 33800801 F/47 2 months into study Question in records of primary. Mass in lung and adrenal; large cell cancer. Well-documented hospital records. Advanced symptoms (Horner's) at 2 months.	RBL 43232414 F/54 21 months into study Metastatic Small Cell (clear cell). Lung Primary presumed had bone metastases. No path report or other records.
		RBL 43232416 F/54 6 months into study Diagnosis of widely metastatic adenocarcinoma of unknown primary. No history of smoking. Symptoms near time of diagnosis. Died 1 month after diagnosis.	
		RCT 44492119 F/64 Diagnosis 6 months after study over. Bronchoscopy showed obstruction in left main bronchus. Only squamous metaplasia noted on biopsy. Had multiple hepatic lesions suggestive of metastasis. Cancer not documented in hospital path report.	

The existence of just these 5 cases, with 1 in the placebo group, 3 in the 2.5-mg risedronate group, and 1 in the 5-mg risedronate group, cannot be considered evidence that risedronate is associated with lung cancer in patients <65 years of age.

Very relevant to this discussion is an examination of the case summaries. These data do not support a causal association between risedronate and lung cancer in patients <65 years of age. Further, there is substantial reason to question whether any or all of the 3 patients in the 2.5-mg group, in fact, had lung cancer. The patient in ROE had advanced symptoms 2 months into the study and had a concurrent finding of an adrenal lesion. The case in RBL was a patient who had no smoking history and was suggested in the hospital records to have spancreatic cancer as the primary site. The evidence for lung cancer was not confirmed by pathology in the patient in the RCT trial. Overall, there is no evidence to support that risedronate is associated with lung cancer in people <65 years of age.

Individual Lung Cancer Patient Data

During the September 23 meeting, Dr. Nora Zorich discussed the strength and quality of the individual patient data, which led to the assignment of lung cancer in the risedronate clinical studies, and there was a good discussion of the difficulties in making an accurate diagnosis of lung cancer, especially in elderly osteoporotic women with a history of past or current smoking. She also discussed the fact that many of the cases were observed early in the studies and if the cases which were evident ≤6 months after randomization were excluded, then only 1 of the 10 studies showed an imbalance in lung cancer.

During the discussion, several points were raised with respect to Dr. Zorich's presentation. Dr. Temple asked if this individual patient information and break-outs had been shared with the Division and we responded that it had. Dr. Temple also indicated that he felt chance was still a possible explanation for the outcome. We indicated that we had submitted a document discussing chance as a possible explanation. A copy of this document is provided in **Attachment I**.

Dr. Jenkins asked for our thoughts on detection bias as an explanation for the observations. We indicated that we believe a more likely explanation is the inaccuracy of a clinical diagnosis with respect to primary cancer site. Dr. Julie Beitz from Oncology asked about the primary lung cancer cases and if we had sorted primary cases according to those which were evident >6 months after the start of the studies. We stated that we had not specifically done this but would provide it to the Agency.

The discussion beginning on the next page provides a summary of some of the analyses of the data which we have provided previously to the Division. This information and associated attachments are provided again here for easy access/review by Drs. Temple, Lumpkin, and Jenkins. Also included within this discussion is a response to the questions from Dr. Beitz and our additional thoughts on detection bias and the potential for misclassification of lung cancer in our trials.

Quality of the Evidence for Lung Cancer

Attached **Tables 1a, 1b, and 1c** summarize the type of documentation that is available for the placebo, 2.5-mg risedronate, and 5-mg risedronate groups, respectively, for each of the 69 cases where a Lung Cancer COSTART assignment was made during the risedronate Phase III studies. The quality of the evidence for a clinical determination of lung cancer varied across the following categories, presented in order from strongest to weakest: (1) pathology report, (2) pathology mentioned (no report), (3) radiographic reports, (4) hospital records, (5) investigator notes/memo, (6) verbatim patient reports, (7) death certificate, or (8) case report form only. Most cases had several sources of evidence which led to the assignment of the Lung Cancer COSTART. The best available evidence for each case is provided in the far right hand column of the tables. Pathology information is available for 35 of the cases (49%). Thirty-two cases had pathology reports. After pathology report, the most frequent best evidence available was hospital records (25%). The distribution of best evidence is shown in **Table C** below for each treatment group and for all treatment groups combined across the 10 trials. This distribution varied across treatment groups with a greater proportion of the best evidence (pathology report) in the two risedronate treatment groups (47% and 60%) compared to placebo (23%).

Table C
Distribution of Best Evidence for Diagnosis of Lung Cancer

Best Evidence Categories	Placebo N (%)	2.5-mg Risedronate N (%)	5-mg Risedronate N (%)	All Treatment Groups N (%)
Pathology Report	3 (23%)	17 (47%)	12 (60%)	32 (46%)
Pathology Mentioned	2 (15%)	0 (0%)	0 (0%)	2 (3%)
Radiographic Reports	3 (23%)	2 (6%)	1 (5%)	6 (9%)
Hospital Records	4 (31%)	8 (22%)	5 (25%)	17 (25%)
Investigator Notes/Memo	0 (0%)	3 (8%)	2 (10%)	5 (7%)
Verbatim Patient Reports	0 (0%)	2 (6%)	0 (0%)	2 (3%)
Death Certificate	1 (8%)	1 (2%)	0 (0%)	2 (3%)
Case Report Form Only	0 (0%)	3 (8%)	0 (0%)	3 (4%)
Totals	13 (100%)	36 (100%)	20 (100%)	69 (100%)

Attached **Table 2** summarizes the available information on each of the 69 cases coded as lung cancer in the risedronate Phase III database. These data were compiled from all available source documents listed in Table C. The data are sorted according to treatment group and within each treatment group, by time when "symptoms or evidence" which led to work-up for lung cancer was evident. Also displayed is the time when the actual diagnosis of lung cancer was made, patient numbers, sex/age of each patient, smoking status, method of detection, available pathology, pulmonary history, and the best available evidence which led to the diagnosis. The table also includes a categorization (categories not mutually exclusive) of each case as follows on the next page:

A1 good clinical/pathological evidence to support the diagnosis of primary lung cancer

A2 suggestive of primary lung cancer but clinical/pathological evidence is insufficient

B unable to assign as primary or metastatic

C pre-existing lesion (evident before any study drug taken)

D not considered lung cancer (mesothelioma, pleural carcinomatosis)

E less than 6 months into the study when lung lesion found (actual diagnostic work-up may have taken several additional months)

F found on post-mortem exam (all in the 5-mg group) as incidental finding (not listed as cause of death)

G reported during post-study follow-up

Primary Lung Cancers

As only 3 patients had an autopsy and only 50% of the diagnoses were supported by actual pathology reports, the classification of primary cancer was difficult for many cases. Using the categorization discussed above, the number of primary lung cancers by treatment is shown in **Table D**, including whether these cases were noted prior to drug exposure or in the first 6 months of exposure.

Table D
Cases Categorized as Well-Supported Lung Primary (A1)

Treatment	Placebo	2.5 mg Risedronate	5 mg Risedronate.
Cases Prior to Drug Exposure	0	1	3
Cases in First 6 Months	1	4	2
Cases After 6 Months	**8**	**14**	**8**
Total	9	19	13

Excluding those cases with documented evidence of lung lesions prior to study as well as those diagnosed within the first 6 months of study yields 8 placebo cases, fourteen 2.5-mg cases, and eight 5-mg cases. The relative risk of the combined treatment groups compared to placebo is 1.47 (0.6,3.8).

Categorization of Lung Cancer Cases

Our independent Safety Advisory Panel advised that the cases which were evident within the first 6 months of study entry could not be associated with risedronate use. (See **Attachment II** for a copy of this report.) This Panel also indicated that 2 cases, a case of mesothelioma and a case of pleural carcinomatosis, should not be included in the assessment since these are not cancers of the lung parenchyma. **Table E** on the next page categorizes the lung cancer cases showing those which were not considered lung cancer, those that were evident prior to dosing, and cases which were evident within 6 months of study randomization.

Table E
Categorization of Lung Cancer Data

	Number of Patients		
	Placebo	**2.5 mg Risedronate**	**5 mg Risedronate**
Total coded as lung cancer in the database	13	36	20
Dataset Categorization			
D: Not lung cancer	–	**1** (RHE mesothelioma)	**1** (ROE pleural carcinomatosis)
C: Lung lesion prior to taking any risedronate	–	**4** (2 RVN, 2 RHN)	**4** (2 RHN, RHE, RON)
E: Additional cases found within first 6 months of study	**2** (RHN)	**9** (1 RBL, 1 RVN, 1 ROE, 1 RON, 2 RHE, 3 RHN)	**4** (2 RVN, 1 RHN, 1 RVE)

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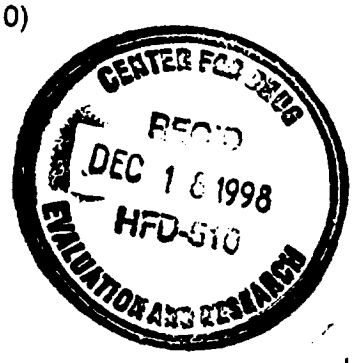
The Procter & Gamble Company
Sharon Woods Technical Center
11450 Grooms Road, Cincinnati, Ohio 45242-1434

NDA NO. 20-835 REF NO. 001

NDA SUPPL FOR SE1

December 18, 1998

Solomon Sobel, M.D., Director
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, ACTONEL (risedronate sodium)
Treatment of Postmenopausal Osteoporosis
Prevention of Postmenopausal Osteoporosis
Corticosteroid-Induced Osteoporosis

/S/ 1/4/99

Dear Dr. Sobel:

Pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, Procter & Gamble Pharmaceuticals (P&GP) is submitting Supplement 001 to NDA #20-835 for the use of ACTONEL (risedronate sodium) in the treatment of postmenopausal osteoporosis; prevention of postmenopausal osteoporosis; and corticosteroid-induced osteoporosis.

The archival copy of this submission contains sections in paper and electronic format. Sections 1 through 10 are paper. Section 11 (case report tabulations) and Section 12 (case report forms) are electronic. The case report tabulations and case report forms are PDF files (approximately — gigabytes in size) on one DLT tape. Norton AntiVirus 2.0.1 was used to assure the electronic portion of the submission is free of viruses.

A summary of key meetings and agreements between the Division and P&GP related to the overall structure and content of this NDA is provided for the reviewers in Attachment A.

Manufacturing facilities for the production and testing of ACTONEL tablets are prepared for a Pre-Approval Inspection as of the date of submission of this application. Field copies of the Chemistry, Manufacturing, and Controls section of this application have been sent to the District Offices of the FDA in Buffalo, New York, Chicago, Illinois, and Cincinnati, Ohio.

P&GP has been assigned User Fee identification number 3595 and has remitted a check for three supplemental NDA fees to the Food and Drug Administration through the Mellon Bank in Pittsburgh, Pennsylvania.

Arrangements have been made with Mr. Ken Edmunds, Office of Information Technology, to deliver the electronic review tool for this submission in two pieces. The electronic PDF files for this submission will be delivered on December, 23 1998 for installation. The query tool with

the SAS datasets and programs will be delivered on January 12, 1999 for installation. Training on use of the electronic review tool will occur during January 1999, as needed.

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

Sincerely,

Linda W Manning

Linda W. Manning, Pharm.D.
Senior Scientist, Regulatory Affairs
Phone: (513) 626-1114
FAX: (513) 626-3033

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REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

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The Procter & Gamble Company
Health Care Research Center
P.O. Box 8006
Mason, Ohio 45040-8006-

Shipping The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐
CSO INITIALS

July 28, 1999

NDA SUPP A...
SE1-001-BM

Solomon Sobel, M.D., Director
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

/S/ 8/12/99

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 29 1999
HFD-510

/S/ 8/12/99

RE: NDA #20-835/S-001 ACTONEL (risedronate sodium)

Dear Dr. Sobel:

We have received the FAX dated July 16, 1999 with the first draft of the Medical Officers' (Drs. Colman and Troendle) comments on the draft ACTONEL® Package Insert for corticosteroid-induced osteoporosis (CIO).

Attachment 1 presents a table showing the Medical Officers' proposed modifications, P&GP's proposal in response, and the rationale for our proposed modifications. In some cases, additional attachments are referred to in the rationale. Two of the comments are also addressed in greater detail here, related to the following:

- Class Statements Related to Esophageal Complications
- Vertebral Fracture Efficacy in Phase III CIO Studies

Class Labeling Statements Related to Esophageal Complications

There are several areas of the labeling (**Contraindications, Warnings, Precautions**, and **Overdosage**) where additional statements have been proposed by Dr. Colman or Dr. Troendle relative to potential esophageal adverse events. These statements are virtually identical to those that have been included in the FOSAMAX® label as a result of esophageal adverse events that occurred during Phase III clinical studies and post-marketing experience with FOSAMAX. In their labeling comments, the Medical Officers asked [redacted] While we believe it is appropriate to include some general labeling statements related to esophageal events for the bisphosphonate class, [redacted] Our rationale for this is presented below.

Comparison of FOSAMAX and ACTONEL Experience: "Evidence of the potential for severe esophageal adverse experiences with FOSAMAX was first observed in their Phase III

osteoporosis treatment studies, in which the drug-related incidences of esophageal ulcers and dysphagia were 1.5% and 1%, respectively, in the FOSAMAX 10-mg group, compared with a 0% incidence for each event in the placebo group (FOSAMAX package insert). This observation was substantiated in post-marketing experience with FOSAMAX, leading to further changes to the FOSAMAX label in the **Contraindications, Warnings, Precautions** and **Overdosage** sections.

Similar effects have not been observed with the commercial dose form of ACTONEL. While an increase in esophageal inflammation but not ulceration was observed in the ACTONEL 2-year Phase II osteoporosis trials **(Vs1.251/p295-298)**, these studies were conducted with the [redacted] dose form, which has been shown to have slower esophageal transit time and more adhesion to the mucosa than the cellulose film-coated tablet that is the commercial dose form. In contrast, ACTONEL has a very clean esophageal safety record in controlled Phase III clinical trials of over 15,000 patients using the commercial dose form.

Complete upper gastrointestinal (GI) adverse event data were provided in the supplemental NDA for both the PMO studies (RVE, RVN, ROE, RON, RBL) and the CIO studies (RCT and RCP). Additional data from the large Hip fracture studies (RHE and RHN) were provided in the 180-Day Safety Update, extending the Phase III database to more than 15,000 patients with 30,000 patient-years of exposure. Across this entire database, which is far larger than that available for FOSAMAX at the time of its approval, we have not observed any increase in esophageal adverse events with ACTONEL treatment compared with placebo. (See **Attachment 2** for a detailed summary of GI adverse events in the combined PMO studies, including the Hip studies.) These data provide strong evidence of the absence of significant esophageal effects of ACTONEL.

While the pivotal FOSAMAX clinical studies excluded patients on the basis of recent or current treatment with agents known to have the potential to irritate the GI mucosa, active peptic ulcer disease, or dyspepsia requiring daily treatment,[1,2] the ACTONEL clinical trials did not specifically exclude these patients. As a result of broad enrollment criteria, the population in the placebo-controlled ACTONEL PMO, CIO, and Hip studies included many patients with GI disorders at baseline (38%) or who were users of NSAIDs and/or aspirin (62%). We believe that the GI safety data from these ACTONEL studies is very robust based upon the inclusion of this high percentage of at-risk patients.

The upper GI adverse event profile in regular users of NSAIDs and aspirin has been presented in the sNDA (**Vs1.261/p219-222**), and shows that among these regular users (three or more times per week for the length of the study) the incidence of upper GI adverse experiences in ACTONEL-treated patients was similar to placebo-treated patients.

Patients with ongoing GI disease were enrolled in all ACTONEL PMO, CIO, and Hip trials. To further evaluate the upper GI safety of ACTONEL, we have reviewed the adverse event profile in patients with ongoing GI diseases at baseline (see **Attachment 3**). In our PMO, CIO, and Hip studies, the baseline incidence of upper GI adverse events was similar across treatments for these patients. The analysis of upper GI adverse events in those patients who entered the

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1. Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995;333:1437-96.
2. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41.

study with an active upper GI diagnosis demonstrates that ACTONEL did not result in worsening of their underlying condition, nor did ACTONEL use cause these patients to experience more upper GI adverse events overall.

In addition to the collection of upper GI adverse event data, the Phase III trials prospectively included a program for endoscopic evaluation of patients reporting moderate-to-severe upper GI adverse events. Endoscopic assessment of almost 500 patients across all of the placebo-controlled osteoporosis studies revealed no overall differences between ACTONEL-treated patients and those who received placebo at the endoscopic level, consistent with the favorable adverse event profile reported in the trials (see **Attachment 4**).

Comparison of GI Mucosal Irritation Potential of ACTONEL to FOSAMAX: In addition to our Phase III clinical study database, we have data from specific endoscopy studies, which are very similar in design to studies used to monitor irritant potential for NSAIDs. One of these studies, a recently completed, randomized, investigator-blinded 2-week GI endoscopy study in 500 patients (Protocol 1998054), indicated that ACTONEL is less irritating to the GI mucosa than FOSAMAX. This study compared the esophageal and gastroduodenal effects of ACTONEL 5 mg versus FOSAMAX 10 mg in healthy postmenopausal women (~250 patients in each treatment group, FOSAMAX or ACTONEL). ACTONEL-treated patients were instructed to take one tablet with 4 or more ounces of plain water at least 30 minutes before breakfast. FOSAMAX-treated patients were instructed to take the tablet according to approved labeling (at least 30 minutes before breakfast with 6-8 ounces of plain water). An interim summary of the data from this study is available and included in **Attachment 5**. We have also provided a copy of the protocol and the statistical analysis plans in **Attachments 6** and **7**, respectively.

The primary endpoint of this study (incidence of gastric ulcers over the 2-week treatment period) showed statistically significantly fewer patients with gastric ulcers in the ACTONEL group (6.3%) compared to patients treated with FOSAMAX (15.0%, p=0.002). Therefore, this study demonstrated significant differences between ACTONEL and FOSAMAX in their potential to damage the upper GI mucosa. In addition, this study revealed no esophageal ulcers among ACTONEL-treated patients compared with three patients with esophageal ulcers in the FOSAMAX 10-mg treatment group. This incidence of esophageal ulcer of 1.2% is similar to the incidence of esophageal ulceration reported in the FOSAMAX Package Insert (1.5%) and is higher than the incidence observed in ACTONEL clinical trials (0.3%, ACTONEL 5 mg; 0.5%, placebo; see **Attachment 2**).

These findings corroborate earlier findings in similar or identical clinical endoscopy models. With respect to gastric ulcers, a consistent 8-15% gastric ulceration rate has been observed for FOSAMAX 10 mg.[3,4,5,6] In a 2-week endoscopy study conducted in a small number of postmenopausal women, no gastric or esophageal ulcers were observed in ACTONEL-treated subjects, compared to one gastric ulcer in the placebo group (Study 1998013 in the 180-Day Safety Update).

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[3] Graham DY, Malaty HM. Drug-induced gastric ulcers are caused by more than just NSAIDs: alendronate gastric ulcers [abstract]. Gastroenterology 1998;114:A138.

[4] Graham DY, Malaty HM. Alendronate gastric ulcers. Ailment Pharmacol Ther 1999;13:515-9.

[5] Lanza F, Rack MF, Simon TJ, Lombardi A, Reyes R, Suryawanshi S. Effects of alendronate on gastric and duodenal mucosa. Am J Gastroenterol 1998;93:753-7.

[6] Marshall JK, Rainsford KD, James C, Hunt RH. Bisphosphonate-induced gastric ulcers not associated with reduced mucosal prostaglandin E_2 (PGE_2): results of a randomized controlled trial. Am J Gastroenterol. In press 1999.

Further support for differentiation among nitrogen-containing bisphosphonates, with respect to potential GI irritation, has been shown in a rat indomethacin gastric damage model. (See **Attachment 8** for summary and associated publications.) In several experiments with this model, the pyridynyl bisphosphonate risedronate was significantly less irritating than either of the primary amino bisphosphonates tested, with a rank order of gastric antral damage consistently showing pamidronate > alendronate > risedronate.

Conclusions: The Medical Officers' proposal has suggested that many of the FOSAMAX labeling statements be included in the ACTONEL package insert. We strongly object to any [redacted] While we believe it is appropriate to include some general labeling statements related to esophageal events for the bisphosphonate class, [redacted] Our clinical experience with ACTONEL in a database of more than 15,000 patients does not indicate that its use will be associated with significant esophageal events, and head-to- head comparisons with FOSAMAX indicate the potential to cause upper GI mucosal damage, including damage at the esophagus, is less for ACTONEL than it is for FOSAMAX.

We note that the tetracycline class of antibiotic drugs contains statements in the **Adverse Reactions** section of labeling stating that rare instances of esophagitis and esophageal ulcerations have been reported. Examination of the product labeling of drugs in this class, e.g., Vibramycin® (doxycycline hyclate) shows no contraindications or warnings related to this concern. The only additional mentioning of this in product labeling appears in **Precautions, Information for Patients** and the **Dosage and Administration** sections, where patients are advised to drink adequate amounts of fluids with the drug to reduce the risk of esophageal irritation and ulceration.

Given the lack of evidence that ACTONEL is expected to cause the same type of esophageal problems as FOSAMAX, we have proposed modifications in **Attachment 1** to the language proposed by the Medical Officers, primarily removing [redacted]

Vertebral Fracture Efficacy in Phase III CIO Studies

The Medical Officers' review of the proposed ACTONEL package insert has resulted in the deletion of our reference to a statistically significant vertebral fracture reduction for ACTONEL 5 mg compared to placebo when our two 1-year Phase III CIO studies were pooled. We contend that the pooled analysis should be sufficient support for the fracture claim. We base this contention on 1) the technical case made in our sNDA and 2) the Agency's approval on June 16, 1999 of fracture claims for FOSAMAX, which are based upon not only pooled studies, but on pooled doses as well. Discussion comparing the FOSAMAX and ACTONEL vertebral fracture data in CIO is provided below.

ACTONEL and FOSAMAX in Corticosteroid-Induced Osteoporosis (CIO): Data Comparison

The current FOSAMAX label related to CIO reads that FOSAMAX "significantly reduced the incidence of patients with a new vertebral fracture (FOSAMAX 0.7% vs. placebo 6.8%)".

The following presents data that have supported a FOSAMAX claim related to vertebral fracture risk reduction in CIO, and a comparison is made with data supporting a similar claim for ACTONEL. It is not our intention to disparage the data supporting the efficacy of FOSAMAX in the reduction of vertebral fractures, but to show that our data are more robust and strongly support the significant clinical efficacy of ACTONEL in the reduction of vertebral fracture incidence.

While the FOSAMAX trials employed two separate studies that each enrolled both patients on chronic corticosteroids and those just initiating therapy, the ACTONEL studies employed two separate protocols, one for each group of patients. Both programs enrolled approximately 500 patients in the trials. For practical purposes the study designs and intent are reasonably comparable.

A careful analysis of the FOSAMAX trials in prevention and treatment of corticosteroid-induced osteoporosis was undertaken using information from the publication of these studies.[7,8] Copies of these publications are provided in **Attachment 9**. The following discussion describes this analysis:

First, the two FOSAMAX studies of 1-year duration, enrolling 477 men and women, failed to demonstrate a statistically significant reduction in the incidence of new vertebral fractures with FOSAMAX treatment relative to placebo (2.3% vs. 3.7%). The relative risk of about 0.62 was seen in only one of the study subgroups, i.e., postmenopausal women, while not seen for men or premenopausal women. This lack of efficacy was observed even when combining the data across two studies and combining two doses (5 and 10 mg). In addition, the analysis was performed only in patients who received prednisone doses of 7.5 mg/day or greater (not a true intent-to-treat analysis).

Second, the two FOSAMAX studies that were originally planned for 1 year were extended for an additional year. In the population studied for 2 years, there was a significant ($p \leq 0.05$) reduction in vertebral fracture risk (FOSAMAX 0.7% vs. placebo 6.8%) in women when doses and studies are pooled. The results were based on pooling the two studies and combining now three doses of FOSAMAX (5 mg, 10 mg, and the patients who had been on 2.5 mg for the first year who were crossed-over to 10 mg for Year 2). It seems likely that an important bias was introduced during the study extension: only 37% (208 patients) of the original cohort continued throughout the second year, and thus the patients that entered the extension phase were likely to be different from the original cohort. For example, 0.7% of patients in the FOSAMAX group had new vertebral fractures after 2 years, while by the end of the first year the

---

[7] Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998;339:292-9.

[8] Saag K, Emkey R, Cividino A, Brown J, Goemaere S, Dumortier T, et al. Effects of alendronate for two years on BMD and fractures in patients receiving glucocorticoids [abstract]. Bone 1998;23:S182.

incidence was 2.3% in the FOSAMAX group. Thus the rate of vertebral fractures in the FOSAMAX group was more than three-fold different (lower) in those patients who participated in the extension study compared to patients that completed the first year of the original protocol. In addition, again no effect was observed in either study alone or in men after 2 years of treatment with FOSAMAX.

ACTONEL treatment demonstrated a fracture risk reduction of 70% with ACTONEL 5 mg relative to placebo after 1 year. This effect was consistently demonstrated in each study, and in both subgroups at risk of fracture, i.e., men (66% reduction) and postmenopausal women (73% reduction).

When compared to data related to FOSAMAX, it is worth noting that this result did not depend on combinations of the two doses nor were patients excluded who took prednisone less than 7.5 mg/day.

Our ACTONEL data share two limitations with FOSAMAX data: vertebral fracture incidence was not a primary endpoint, and because of the size of the studies, only pooled analysis (doses and/or studies) were statistically significant.

In conclusion, our data supporting labeling statements that ACTONEL 5 mg daily significantly reduces the risk of new vertebral fractures relative to placebo in men and women after 1 year of treatment are at least as strong, and we contend considerably stronger, than the data upon which the recently approved FOSAMAX labeling was based. We therefore maintain that ACTONEL is entitled to comparable labeling statements with respect to vertebral fractures.

Please call me at (513) 622-5022 or Linda Manning at (513) 622-1114 if you have questions on the information provided in this submission.

Sincerely,

Bruce R. DeMark/LMM

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

Desk Copies: Gloria Troendle, M.D.
Eric Colman, M.D.
Randy Hedin, R.Ph.

APPEARS THIS WAY
ON ORIGINAL

NDA 20-835/S-001, 002, and 003
Actonel (risedronate sodium) Tablets

Dear Dr. Manning:

Please refer to your pending December 18, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actonel (risedronate sodium) ———

We are reviewing the clinical section of your submission and have the following comments and information requests:

Study RCP

1. Refer to panel 7 (vol. 1.220/pg77), within the 3 stratum, are the baseline LS BMDs significantly different between the placebo and risedronate 5.0 mg groups? If so, are these differences taken into account in the statistical analyses reported in panel 18 of the same volume?

2. Please provide the median dose of steroid for the placebo and risedronate 5.0 mg groups shown in panels 11 and 12 (vol. 1.220/pg82).

3. The reported numbers of patients included in the EV population is confusing. Panel 15 (vol. 1.220) states that the EV population for the LS includes 60 patients in both the placebo and risedronate 5.0 mg groups; yet, in panel 16 it states that a total of 35 and 36 patients from the placebo and risedronate 5.0 mg groups, respectively, were excluded. Can you clarify this?

4. Please clarify an apparent discrepancy; in panel 37 (vol. 1.220/pg134) no rib fractures are listed for the risedronate 5.0-mg group. However, in the text above the panel a 5.0-mg subject is described as having suffered a rib fracture.

Study RCT

1. How many subjects were excluded from the study because of the presence of more than two fractured lumbar vertebrae?

2. Please provide the median daily dose of steroid for the placebo and risedronate 5.0 mg subjects shown in panel 11 (vol. 1.203/pg82).

3. Please refer to panel 18 (vol. 1.203/pg95). Is the LS mean between placebo and risedronate 5.0 mg at Month 12 really 5.10?

4. Please refer to panel 30 (vol. 1.203/pg117). Are the adverse events that were not coded as

related to study drug eliminated from this tally?

5. For those patients who had follow-up midshaft radius BMDs, what is the correlation between the change from baseline to Month 12 in LS BMD with the change in midshaft radius BMD?

For Both Studies

1. For all subjects in the placebo and risedronate 5.0 mg groups who developed, at any time during the studies, a high or markedly high value for ALT, AST, and/or GGT, please plot all of their values from baseline to endpoint. Also mention whether the abnormal value resolved spontaneously or required specific intervention.

2. For all subjects in the placebo and risedronate 5.0 mg groups who developed, at any time during the studies, a high or markedly high value for serum creatinine, please plot all of their values from baseline to endpoint. Also mention whether the abnormal value resolved spontaneously or required specific intervention.

3. For all subjects in the placebo and risedronate 5.0 mg groups who developed, at any time during the studies, a high or markedly high value for 24-hour urinary calcium, please plot all of their values from baseline to endpoint. Also mention whether the abnormal value resolved spontaneously or required specific intervention.

4. For each study, please provide a table that compares the number and percentage of patients in the placebo and risedronate 5.0 mg groups with adverse events occurring at a frequency > 2% and where the incidence is higher in the risedronate 5.0 mg–treated group than in placebo-treated group.

5. For the primary endpoint – percent change in LS BMD at Month 12 – please provide a completers analysis comparing the placebo and risedronate 5.0 mg groups. This analysis should include all patients with a baseline LS BMD measurement and a 12-month LS BMD assessment. Please include all patients excluded for any reason (i.e., EV population) and also include any patient who had a Month 12 BMD measurement regardless of whether on or off-study drug. This should be done separately for the two studies.

6. For all the placebo and risedronate 5.0 mg patients recorded as developing an incident vertebral deformity, please identify, by study and dose of study drug, if male, premenopausal or postmenopausal. Please also provide for each of these patients the percent change in LS BMD from baseline to Month 12.

7. When the data from the two studies are pooled, is there any evidence of a meaningful correlation between the increase or decrease in LS BMD at Month 12 and the risk for developing a vertebral deformity?

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely,

/S/

Dr. Gloria Troendle
Deputy Division Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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ON ORIGINAL

Table F below summarizes the cases which remain when the two cases which are not lung cancer (Category D) and the 23 cases which were evident within 6 months of study randomization (Categories C and E) are excluded.

Table F
Lung Cancers Excluding C, D, and E Cases

	Placebo				2.5 mg Risedronate				5 mg Risedronate			
Study	# rand.	pyrs	# cases	# / 1000 pyrs	# rand.	pyrs	# cases	# / 1000 pyrs	# rand.	pyrs	# cases	# / 1000 pyrs
RBL004494	126	214	0	0.0	128	220	0	0.0	129	234	1	4.3
RCP009993	77	78	0	0.0	75	64	0	0.0	76	78	1	12.8
RCT009893	96	96	0	0.0	94	98	2	20.4	100	108	0	0.0
ROE009493	180	322	0	0.0	184	281	1	3.6	179	307	0	0.0
RON009393	220	272	0	0.0	212	275	0	0.0	216	276	0	0.0
RPE002494	261	223	0	0.0	NA	NA	NA	—	263	234	1	4.3
RVE009093	408	952	1	1.1	410	867	1	1.2	408	967	1	1.0
RVN008993	820	1850	1	0.5	817	1021	2	2.0	821	1906	1	0.5
RHE009293	1520	3124	3	1.0	1518	3087	4	1.3	1511	3084	3	1.0
RHN009193	1664	3357	6	1.8	1633	3250	12	3.7	1651	3331	3	0.9
Total	5372	10488	11	1.0	5071	9163	22	2.4	5354	10525	11	1.0

When the remaining cases presented in Table F are examined, the lack of dose response is again evident; the 5-mg and the placebo treatment groups have the same exposure adjusted incidence of 1.0 case per 1000 patient years, while the 2.5-mg group has 2.4 cases per 1000 patient-years of exposure. In addition, there is only one study (RHN009193) which has a clear imbalance in the number of lung cancers across treatment groups with 6 cases in placebo, 12 cases in the 2.5-mg treatment group, and 3 cases in the 5-mg treatment group.

Detection Bias

It has been hypothesized that the difference in lung cancer incidence in the risedronate trials may be attributable to detection bias. That is, the treatment caused some signs or symptoms that resulted in a differential search for a cause and resulted in the incidental discovery of lung tumors. Despite efforts to identify and quantitate this potential bias, there are no data to support this hypothesis within the context of these trials. While this does not rule out detection bias as a potential explanation, we believe a more likely explanation is the inaccuracy of a clinical diagnosis with respect to primary cancer site.

A recent review on the accuracy of the clinical diagnosis of lung cancer concludes that autopsy findings fail to confirm lung cancer as the primary site approximately 40% of the time.[1] (Copies of references are provided in **Attachment III.**) Trinidad reported that of 317 cancer autopsies, 41% had pulmonary metastases.[2] The authors conclude that the predilection for pulmonary metastases among carcinomas that are difficult to detect clinically suggests that many erroneous diagnoses of lung cancer are made in the absence of autopsy. Rosenblatt studied 380 autopsy cases of extrathoracic carcinoma at Doctors Hospital in New York and reported that 49.7% of cases were metastatic from other sites, the most frequent being colon, breast, and pancreas.[3] Cechner reported that in a group of 415 clinically and pathologically diagnosed cases of lung cancer, only 63% were accurate.[4] Erroneous clinical/pathological diagnosis of lung cancer was attributable to metastatic lesions originating in the pancreas, kidney, stomach, adrenal, breast, or thyroid. They concluded that lung biopsies cannot be used to identify the site of the primary lesion with certainty. LeChevalier reported that of 184 abnormal chest x-rays among 302 cancer patients, 96 were thought to represent a primary tumor.[5] However, autopsy results confirmed only 31 (32%) of these cases. Cancers of the pancreas and digestive system were the most frequent primary site among those with cancer in the lung.

Given the inaccuracy of a clinical/pathological diagnosis of lung cancer as a primary site, as well as the fact that GI (colon, pancreas, stomach, and kidney) and breast cancer are commonly missed as the primary site in lung cancer diagnoses, it is reasonable to assume that if there is a risedronate effect on carcinogenesis it would manifest itself in the combination of these sites. In fact, the incidence of these tumors based solely on the COSTART term without any clinical or epidemiological interpretation shows no difference (**Table G** on the next page). The relative risk of lung, GI, and breast cancer in the risedronate treatment groups (2.5 and 5 mg) compared to placebo is 1.04 (0.8, 1.4).

1 Lee PN. Comparison of autopsy, clinical and death certificate diagnosis with particular reference to lung cancer: a review of the published data. APMIS Suppl 1994;45:1-42.

2 Trinidad S, Lisa JR, Rosenblatt MB. Bronchogenic carcinoma simulated by metastatic tumors. Cancer 1963;16:1521-9.

3 Rosenblatt MB, Lisa JR, Trinidad S. Pitfalls in the clinical and histologic diagnosis of bronchogenic carcinoma. Dis Chest 1966;49:396-404.

4 Cechner RL, Chamberlain W, Carter JR, Milojkovic-Mirceta L, Nash NP. Misdiagnosis of bronchogenic carcinoma: the role of cigarette smoking, surveillance bias, and other factors. Cancer 1980;46:190-9.

5 LeChevalier T, Cvitkovic E, Caille P, Harvey J, Contesso G, Spielmann M, et al. Early metastatic cancer of unknown primary origin at presentation: a clinical study of 302 consecutive autopsied patients. Arch Intern Med 1988;148:2035-9.

Table G Cancer Cases by Site						
Cancer Site	Placebo	2.5 mg Risedronate	5 mg Risedronate	RR*	95% CI	P-value
Lung, Breast, GI	89	99	75	1.04	(0.8, 1.4)	0.8
Others**	55	52	58	1.07	(0.8, 1.5)	0.8
Total	144	151	133	1.05	(0.9, 1.3)	0.7
* Treatment groups combined relative to placebo ** Excludes non-melanoma skin cancers						

In addition, all cancer sites combined shows no difference among treatments. This is a reasonable surrogate of the effect given that the clinical diagnosis of primary site is suspect. In the risedronate trials, there were only 3 autopsy reports among the lung cancer cases; all in the 5-mg group. In all 3 cases there was no pre-morbid diagnosis of lung cancer and lung cancer was discovered at autopsy (false negative findings). All other cases were defined as primary lung cancer based on clinical/pathological diagnosis only.

Unlike breast cancer (orlistat issue) which is a primary neoplasm, cancer of the lung is more often a result of metastatic growth. Both carcinomas and sarcomas arising from a variety of other sites may spread to the lungs via the blood, lymphatics, or by direct continuity.[6] Numerous studies over the last 3 decades show that clinical/pathologic evidence of lung cancer as the primary site, without autopsy evidence, is subject to substantial misclassification. The available evidence from the risedronate database cannot distinguish between cancer of the lung and cancer in the lung. This provides a plausible explanation for the apparent increased risk of lung cancer and a decreased risk of gastrointestinal cancers within the treatment groups and the lack of any effect of treatment on either breast, lung, and GI cancers taken together or on cancers overall. In addition, most of the lung cancers (40%) were adenocarcinomas which can arise from sites other than the lung. Typically, patients with adenocarcinoma of unknown primary site are elderly, and the primary site becomes obvious in only 15% to 20% of patients during life.[7] This leads to the conclusion that the clinical/pathological diagnosis of primary site is inaccurate and that assigning causality to site-specific findings untenable. The least biased assessment is all cancers combined, which, in the risedronate clinical studies, showed no difference in incidence by treatment group.

6 Cotran RS, Kumar V, Robbins SL. Robbins pathologic basis of disease. 4th ed. Philadelphia (PA): W.B. Saunders Company; 1989. p. 803-5.

7 Greco AF, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT, Jr., Hellman S, Rosenberg SA, editors. Cancer: principles & practice of oncology. 5th ed. Philadelphia (PA): Lippincott-Raven Publishers; 1997. p. 2423, 2426, 2442.

Based upon all available evidence we maintain that there is no basis to conclude that risedronate causes lung cancer. We also believe that the available data are sufficient to support an approval decision.

Consistent with our discussion on September 23, we are in the process of moving forward to collect follow-up mortality data. We ask, based on the information presented here, that you reconsider whether it is necessary to delay approval while these data are being collected. After your careful review of this information, please let me know if you have any other questions or if I can provide any additional information. We would be very happy to meet again with Dr. Jenkins and others from the Center-level at your convenience to further discuss this material.

Sincerely,

Bruce R DeMark

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

Desk Copies: Randy Hedin, R.Ph.
Solomon Sobel, M.D.
Robert Temple, M.D.
Murray Lumpkin, M.D.
John Jenkins, M.D.
Julie Beitz, M.D.

Enclosures

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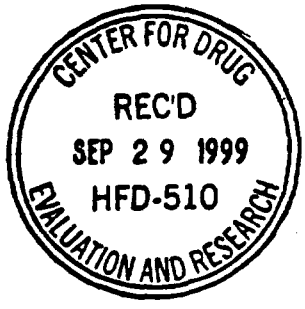
he Procter & Gamble Company
Health Care Research Center
P O. Box 8006
Mason Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

September 28, 1999

Lee Pian, Ph.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-003; ACTONEL (risedronate sodium)
Treatment of Postmenopausal Osteoporosis

Dear Dr. Pian:

Included with this letter is a copy of volume s1.122 from our sNDA which contains the text of the RVE009093 final study report, as you requested.

Please call me if you need any additional information.

Sincerely,

Linda W. Manning

Linda W. Manning, Pharm.D.
Senior Scientist
Regulatory Affairs
(513) 622-1114
(513) 622-5369 FAX

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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Procter&Gamble ORIGINAL
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Procter & Gamble Company
lth Care Research Center
Box 8006
on, Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

September 22, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
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SEP 23 1999
HFD-510

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
5600 Fishers Lane
Rockville, Maryland 20857

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

Dear Dr. Colman:

Included with this submission is the final report for Study 1998054. This risedronate trial was a randomized, investigator-blinded 2-week GI endoscopy study in 500 patients which compared ACTONEL 5 mg versus FOSAMAX 10 mg in healthy postmenopausal women. An interim summary of the data from this study was provided to you in a submission dated July 28, 1999 (response to Medical Officers' comments on draft ACTONEL Package Insert for CIO). The full report for this study is now complete. The text and end-of-text tables are included in this submission, for your information. If you would like to review the report appendices, I refer you to IND ——— Serial No. 453 for access to this information.

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

Sincerely,

Linda W Manning

Linda W. Manning, Pharm.D.
Senior Scientist
Regulatory Affairs
(513) 622-1114
(513) 622-5369 FAX

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ E-MAIL ☐ FAXED
CSO INITIALS DATE

/S/ 9/27/99

Contact to
GI. Please ask
if the data warrant
any change to the proposed
'SI

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SUPPL NEW CORRESP

The Procter & Gamble Company
Health Care Research Center
P O Box 8006
Mason, Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

September 21, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
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SEP 22 1999
HFD-510

Noted
/S/
10/2/99

Randy Hedin, R.Ph., CSO
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, ACTONEL (risedronate sodium)
Corticosteroid-Induced Osteoporosis

/S/ 9/24/99

Dear Mr. Hedin:

Representatives of Procter and Gamble Pharmaceuticals (P&GP) and its development partner, Hoechst Marion Roussel (HMR), will be meeting with the Agency on Thursday, September 23 at 4:00 p.m. The purpose of this meeting is to discuss the circumstances related to the Approvable Letter we received on August 20. A final list of discussion topics is provided in the **Attachment**.

The probable attendees at this meeting from P&GP and HMR are:

Larry R. Versteegh, Ph.D., Vice President Global Regulatory and Clinical Development, P&GP
Nora L. Zorich, M.D., Ph.D., Director, Actonel Product Development, P&GP
Bruce R. DeMark, Ph.D., Section Head, Regulatory Affairs, P&GP
John D. Taulbee, Ph.D., Director of Epidemiology and Biometrics, P&GP
J. Michael Sprafka, Ph.D, M.P.H., Associate Director, Global Pharmacovigilance, Epidemiology and Pharmacoeconomics, P&GP
Arkadi Chines, M.D., Senior Medical Monitor, P&GP
Gillian Ivers-Read, Vice President, Strategic Regulatory Development, HMR
Iris Loew-Friedrich, M.D., Vice President, Clinical Development, HMR

Thank you for your help.

/S/
9-27-99

Sincerely,

Bruce R. DeMark

Bruce R. DeMark, Ph.D.
Section Head
US Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
DATE
CSO INITIALS

Attachment

Attachment

Discussion Topics for FDA Meeting on Actonel Approvable Letter

1. **Delayed approval of Actonel efficacy supplements**

   We do not understand why approval of our Actonel efficacy supplements are being delayed. We have been told that this issue is seen with other members of the bisphosphonate class, and we note that one of these other members recently received approval of its efficacy supplement with no mention of this issue in product labeling or in the SBA documents.

2. **Mortality Study as a condition for approval**

   [redacted] The Agency has now recommended follow-up mortality data prior to approval. Why the change in position, what are your expectations for this study, and how will you use this information for decision making?

3. **Review timing for Actonel efficacy supplements**

   What are the Agency's plans for completion of the review of our pending efficacy supplements (PMO and CIO), including labeling, relative to the PDUFA action date of October 18, 1999 (PMO) and relative to resolution of the lung cancer issue?

4. **Benefit:Risk**

   We wish to discuss the benefit side of the benefit:risk ratio for bisphosphonates generally, and Actonel specifically, in connection with the Agency's current thinking and potential future actions on the lung cancer issue.

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NDA SUPPLEMENT

...e Procter & Gamble Company
...ealth Care Research Center
P O Box 8006
Mason, Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

September 3, 1999

Joy D. Mele, M.S.
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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP - 9 1999
HFD-510

RE: NDA #20-835/ S-002; ACTONEL (risedronate sodium)
Prevention of Postmenopausal Osteoporosis

Dear Ms Mele:

Enclosed with this submission are the electronic datasets you requested in your fax dated August 20, 1999. The datasets are provided on two diskettes (1 for the RBL004494 study; 1 for the RPE002494 study). Included in hard copy with this submission are listings of the derived variables and decodes for the coded variables in the SAS datasets for the RBL and RPE studies. Also included are the PROC CONTENTS for the SAS datasets and printouts of observations for each dataset.

Please call me at (513) 622-1114, if you have any questions on the information provided.

Sincerely,

Linda W. Manning

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

Reviewer's Copy /S/

REVIEWS COMPLETED
CSO ACTION
LETTER N.A.I. MEMO
DATE
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SNC

The Procter & Gamble Company
Health Care Research Center
P O Box 8006
Mason, Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

August 30, 1999

Randy Hedin, R.Ph., CSO
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, ACTONEL (risedronate sodium)
Corticosteroid-Induced Osteoporosis

Dear Mr. Hedin:

Representatives of Procter and Gamble Pharmaceuticals (P&GP) and its development partner, Hoechst Marion Roussel (HMR), wish to meet with the Agency for 90 minutes during the week of September 7-10 or September 13-17. The purpose of this meeting is to discuss the circumstances related to the Approvable Letter we received on August 20 and the decision to discuss the issue of lung cancer in the bisphosphonate class. A proposed Agenda for the meeting is provided in the **Attachment**.

Attendees at this meeting from P&GP and HMR would be:

Larry R. Versteegh, Ph.D., Vice President Global Regulatory and Clinical Development
Gillian Ivers-Read, Vice President, Strategic Regulatory Development, HMR
Nora L. Zorich, M.D., Ph.D., Director, Actonel Product Development, P&GP
Bruce R. DeMark, Ph.D., Section Head, Regulatory Affairs, P&GP

We request that Dr. Sobel, Dr. Jenkins, Dr. Lumpkin, and Mr. Hedin attend this meeting.

As I will be out of the office from August 27-September 2, please contact Linda Manning at 513-622-1114 to finalize the dates for this meeting.

Thank you for your help.

Sincerely,

Bruce R. DeMark

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

Attachment

Attachment

Proposed Agenda:

1. Discuss the Agency's decisions to (1) issue an Approvable Letter for Actonel-CIO pending resolution of the lung cancer issue and (2) approve Merck's Fosamax-CIO indication a few weeks earlier, in the face of similar lung cancer observations and knowledge of the lung cancer data on other drugs in the class.

2. [ ]

3. Discuss the impact of these decisions on the approval timing for pending Actonel-PMO supplement, which has a current PDUFA goal date of October 18, 1999.

4. [ ]

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

Procter&Gamble
PHARMACEUTICALS

Health Care Research Center
8700 Mason-Montgomery Road
P.O. Box 8006
Mason, Ohio 45040-9462

March 1, 2000

Eric Colman, MD
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) Tablets

Dear Dr. Colman:

In the labeling comments received from the Division yesterday, there was a suggestion that reference to secondary endpoints be removed from the labeling. During our telephone conversation earlier today, we pointed out that this request was inconsistent with Fosamax product labeling, which contains numerous references to data based on secondary endpoints. Mr. Hedin suggested that we provide a list of these examples from the Fosamax label for consideration by your team.

Attached Table 1 provides this information. The table lists the primary and secondary outcomes of the major clinical studies together with the labeling statements which relate to primary and secondary endpoints. It is clear that there are a substantial number of secondary endpoints included in the labeling, including data related to hip fracture from the FIT study. These data led to inclusion of a hip fracture claim in the *Indications* section of the Fosamax product labeling.

Separately, over the next few days, we will provide additional rationale for inclusion of key secondary endpoints from our pivotal studies.

Thank you for your consideration. We look forward to working through the labeling with you.

Sincerely,

B R DeMark

Bruce R. DeMark, PhD
Section Head
US Regulatory Affairs

Desk Copies: Randy Hedin
Attachments

Table 1

Outcomes in Approved Product Labeling
FOSAMAX

Study	Primary Outcome	Secondary Outcome	Labeling Statement	Date in Label	Background on Data Included that Were Secondary Endpoints
035 and 037	BMD Results were significant	Vertebral fractures from pooled studies and doses	Initial treatment indication: "treatment of osteoporosis in postmenopausal women" Clinical Studies Section: • There was a significant 48% reduction in vertebral fractures (**secondary endpoint**). • A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was observed (**secondary endpoint**). • There was significant smaller loss in stature than those who received placebo (-3mm vs. -4.6mm) (**secondary endpoint**). • There was less height loss in those who experienced a vertebral fracture (5.9mm vs. 23.3mm) (**secondary endpoint**).	Sept. 1995	Vert Fractures: Pooled studies, pooled doses (5, 10, and 20 mg), based upon a total of 39 fractures (22 vs. 17) Height loss: Pooled studies, pooled doses, subgroup analysis

Table 1

Outcomes in Approved Product Labeling
FOSAMAX

Study	Primary Outcome	Secondary Outcome	Labeling Statement	Date in Label	Background on Data Included that Were Secondary Endpoints
Vertebral fracture arm of FIT	Vertebral Fractures Results were significant	• Overall non-vertebral fracture not significant • Hip and wrist individually reached significance	Treatment indication: "...increase bone mass and prevents fractures; including those of hip, wrist, and spine (vertebral compression fractures)." Clinical Studies Section: • 47% reduction in vertebral fractures (primary endpoint) • 90% reduction in multiple vertebral fractures (**secondary endpoint**) • 55% reduction in symptomatic vertebral fractures (**secondary endpoint**) • 51% reduction in hip fractures (**secondary endpoint**), time to event figure added • 48% reduction in wrist fractures (**secondary endpoint**), time to event figure added • proportionally similar reductions of hip and wrist were seen in pooled earlier osteoporosis treatment studies • Significantly reduced the incidence of total hospitalizations (secondary endpoint)	Nov. 1996	Multiple fractures: One study to support, pooled doses, based upon a total of 52 fractures (47 vs. 5) Symptomatic Fractures: One study to support, based upon 73 fractures (50 vs. 23) Hip fractures: One study to support, pooled doses, based upon 33 fractures (22 vs. 11) Wrist Fractures: One study to support, pooled doses, based upon 63 fractures (41vs. 22) meta analysis of all doses > 1mg/day Hospitalizations: One study, pooled doses

Table 1

Outcomes in Approved Product Labeling
FOSAMAX

Study	Primary Outcome	Secondary Outcome	Labeling Statement	Date in Label	Background or Data Included that Were Secondary Endpoints
GIO Pre-marketing Studies (U.S. and European study)	BMD	Vertebral Fractures	GIO treatment indication added: "Treatment of GIO in men and women receiving glucocorticoids in a daily dosing...and who have low bone mineral density" Clinical Studies Section: • Significant increases in BMD (primary endpoint) • Significant reduction in vertebral fractures in pooled studies and pooled doses (**secondary endpoint**)	June 1999	Vert Fractures: Pooled studies, pooled doses, subgroup analysis (excluded patients on 2.5 for the first year, excluded patients who fractured during the first year and did not continue into the second year)

Procter&Gamble PHARMACEUTICALS

NDA NO. 20-835 REF. NO. 004

NDA SUPPL FOR SE8-0

1. The Procter & Gamble Company
Health Care Research Center
P O Box 8006
Mason, Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

August 27, 1999

ORIGINAL

Solomon Sobel, M.D., Director
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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 30 1999
HFD-510

RE: NDA 20-835/S-001, ACTONEL (risedronate sodium)
Corticosteroid-Induced Osteoporosis
NDA Amendment 7: Complete Response Letter

Dear Dr. Sobel:

The purpose of this amendment to NDA #20-835/S-001, ACTONEL (risedronate sodium) is to submit a complete response to the deficiencies addressed in the approvable letter received from the Division on August 20, 1999. The deficiencies noted in the letter dealt with the following: the safety issue surrounding the lung cancer cases seen in the risedronate Phase III clinical trials, revisions to the draft labeling, and an additional supplement for the prevention of corticosteroid-induced osteoporosis indication. Procter & Gamble Pharmaceuticals (P&GP) clarified in a telephone conversation with Mr. Randy Hedin (August 20, 1999) that the need for a GMP inspection of the Longjumeau, France facility is not an approvability issue and, therefore, is not addressed in this complete response letter.

In response to the Division's request for additional safety information concerning the lung cancer cases seen in the risedronate Phase III clinical trials, we have no new information on the lung cancer issue to provide to the Division. Instead, we refer you to our submission dated June 10, 1999, which contained a report from the Safety Advisory Panel that was convened by P&GP to evaluate the lung cancer cases.

Please refer to our submission dated August 20, 1999, which contained proposed labeling for the corticosteroid-induced osteoporosis indication. At the time of that submission, the proposed package insert did not fully address the comments received from the pharmacology reviewer. This amendment contains additional revisions to the label which completely address the comments received from Dr. Steigerwalt. (**Attachment 1**). The revised label (**Attachment 2**) now addresses the comments received from all of the reviewers at the Division (Medical, Biopharm, and Pharmacology).

/S/
9-21-99

Lastly, as requested, P&GP is submitting another user fee for the additional supplement for the indication of prevention of corticosteroid-induced osteoporosis. User Fee identification number 3789 has been assigned for this supplement (S-004). A check for the supplemental NDA fee ——— is being submitted to the Food and Drug Administration through the Mellon Bank in Pittsburgh, Pennsylvania. The data in support of the prevention of corticosteroid-induced osteoporosis indication was previously submitted in its entirety in S-001 to NDA #20-835.

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

Sincerely,

Linda W. Manning

Linda W. Manning, Pharm.D.
Senior Scientist, Regulatory Affairs
Phone: (513) 622-1114
FAX: (513) 622-5369

Desk Copy: Randy Hedin, R.Ph.
Ronald Steigerwalt, Ph.D.

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The Procter & Gamble Company
Health Care Research Center
P.O Box 8006
Mason Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

August 20, 1999

Solomon Sobel, M.D., Director
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; ACTONEL (risedronate sodium)
Corticosteroid-Induced Osteoporosis

Dear Dr. Sobel:

Included with this submission is the revised draft package insert for ACTONEL® (risedronate sodium) containing the additional indication of corticosteroid-induced osteoporosis. The insert is provided both with and without revision marks. Please note that the comments which were recently received from Dr. Steigerwalt, the Pharmacology reviewer, have been incorporated into the insert in the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section, but have not yet been addressed in the **ANIMAL PHARMACOLOGY AND/OR TOXICOLOGY** section.

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

Sincerely,

Linda W. Manning

Linda W. Manning, Pharm.D.
Senior Scientist
Regulatory Affairs
(513) 622-1114
(513) 622-5369 FAX

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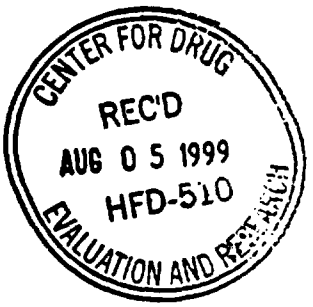
'ie Procter & Gamble Company
ealth Care Research Center
P O Box 8006
Mason, Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

August 3, 1999

ORIGINAL

SEI-001 B
NDA SUPPLEMENT



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 ACTONEL (risedronate sodium)

Dear Dr. Colman:

This responds to your e-mail request of August 2, 1999 for a tabular presentation of total esophageal related adverse events (Drug-related, Serious, Drop-out Due to AEs) for the following three groups of studies:

- Studies RVN, RVE, RON, ROE, and RBL
- Studies RHE and RHN
- Studies RCP and RCT

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I. ☐ MEMO

/S/ 8/19/99
CSO INITIALS DATE

The five esophageal COSTART terms used in the calculation of "total esophageal" adverse events are as follows:

CARDIOSPASM, DYSPHAGIA, ESOPHAGITIS, ESOPHAGEAL ULCER, ESOPHAGEAL STENOSIS

The data are presented in the tables attached and show a similar incidence of esophageal related AEs across treatment groups and studies. While there was a slight increase in drug-related esophageal AEs in the 5-mg risedronate group compared to placebo in the Hip studies, there were more Serious esophageal AEs in the placebo group compared to the treatment groups. There was no noted differences in the AE categories in the five PMO studies, and there were too few events in the CIO studies to draw any conclusions.

These data further support the esophageal safety of ACTONEL® 5 mg.

/S/
8/30/99

/S/ 8/19/99

Please let me know if you need any additional information related to this issue.

Sincerely,

Bruce R. DeMark

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

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

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Patients with Esophageal Related Adverse Events in Risedronate Phase III Clinical Studies

PMO Studies (RVN, RVE, RON, ROE, and RBL)			
Adverse Event Category	**Placebo N = 1744 n (%)**	**2.5 mg Risedronate N = 1740 n (%)**	**5 mg Risedronate N = 1742 n (%)**
Total Esophageal	56 (3.2)	44 (2.5)	59 (3.4)
Drug-related[a]	23 (1.32)	14 (0.80)	23 (1.32)
Serious	5 (0.29)	3 (0.17)	6 (0.34)
Drop-out Due to AE	7 (0.40)	6 (0.34)	6 (0.34)
[a] Drug-related includes causality assessment of possible or probable by the investigator.			

Hip Studies (RHN, RHE)			
Adverse Event Category	**Placebo N = 3134 n (%)**	**2.5 mg Risedronate N = 3093 n (%)**	**5 mg Risedronate N = 3104 n (%)**
Total Esophageal	107 (3.4)	90 (2.9)	96 (3.1)
Drug-related[a]	35 (1.12)	35 (1.13)	45 (1.45)
Serious	17 (0.54)	13 (0.42)	11 (0.35)
Drop-out Due to AE	14 (0.45)	14 (0.45)	16 (0.52)
[a] Drug-related includes causality assessment of possible or probable by the investigator.			

CIO Studies (RCT, RCP)			
Adverse Event Category	**Placebo N = 170 n (%)**	**2.5 mg Risedronate N = 165 n (%)**	**5 mg Risedronate N = 174 n (%)**
Total Esophageal	5 (2.9)	2 (1.2)	5 (2.9)
Drug-related[a]	0	2 (1.21)	2 (1.15)
Serious	2 (1.18)	0	2 (1.15)
Drop-out Due to AE	0	0	0
[a] Drug-related includes causality assessment of possible or probable by the investigator.			

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The Procter & Gamble Company
Health Care Research Center
P O Box 8006
Mason Ohio 45040-8006

Shipping: The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

August 3, 1999

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 ACTONEL (risedronate sodium)

Dear Dr Stadel:

In response to your email message of July 27, which was forwarded to me by Mr. Randy Hedin, we have included with this submission the Kaplan-Meier (K-M) plots for the cumulative incidence of lung and gastrointestinal (GI) cancers for the eight osteoporosis trials and for the two Hip fracture trials in the same format as previously supplied. As we have discussed previously with you, these data include all cases from our database with a COSTART code to these cancers, regardless of actual diagnosis or onset time. **Figures I** and **II** provide the plots for the eight osteoporosis trials for lung cancer and GI cancer, respectively. **Figures III** and **IV** provide the plots for the two Hip fracture trials for lung cancer and GI cancer, respectively.

When comparing the two plots of lung cancer incidence data (**Figure I**, eight PMO/CIO studies, 6300 patients; **Figure III**, two Hip studies, 9497 patients), it is notable that while the lung cancer cases in the 2.5-mg risedronate group are similarly increased within 6 months in both plots compared to placebo, the pattern of cases is not replicated for the 5-mg risedronate group versus placebo or the combined 2.5-mg & 5-mg risedronate group versus placebo. In the Hip studies (**Figure III**), the cumulative incidence of lung cancer cases in the placebo group tracks with that for the 5-mg risedronate group for the duration of the study and with the 2.5-mg & 5-mg risedronate combined group for up to 2 years. This does not support a causal association of lung cancer with risedronate treatment.

Another major difference in the two datasets is the incidence of cases of lung cancer in the placebo groups. There is an approximately three-fold lower cumulative incidence of lung cancers in the placebo group in the eight PMO/CIO studies, which represent a database of approximately 2200 placebo patients compared to the Hip studies (~3200 placebo patients). At 1 year, the cumulative incidence (%) of lung cancer cases in the placebo group in the eight PMO/CIO studies is 0.06% compared to the two Hip studies at 0.19%.

The incidence of placebo cases is also considerably lower than expected based on the most recent 1992-1996 SEER database. Based on this database and the patient-years exposure in our clinical trials, the observed-to-expected ratio of lung cancer cases for the eight PMO/CIO

studies would be 2/11.4 = 0.18, while the observed/expected ratio for the placebo group in the two Hip studies would be 11/18.4 = 0.60. This again illustrates the approximately three-fold difference between the incidence rates for lung cancer in the placebo groups for the eight PMO/CIO studies compared to the Hip studies and the overall lower than expected incidence compared to SEER. Please refer to **Attachment** 1 for an analysis of the 1992-96 SEER cancer data with respect to our studies.

We would also like to point out that it seems unusual that no additional lung cancer cases occurred in the placebo group in the eight PMO/CIO studies after 1.5 years and none in the two Hip studies after 2.25 years. As we discussed earlier, there are data to support a positive association between risk of lung cancer and the likelihood of study discontinuation.

In response to your request for the calendar time intervals of patient enrollment for the three studies [redacted] the intervals are provided below for each study:

Study	First Patient Enrolled	Last Patient Enrolled
RVN008993	03-December-93	02-March-95
RHN009193	18-November-93	06-March-95
RON009393	08-March-94	24-February-95

Please call me if there are questions or if you need any additional information.

Sincerely,

Linda W Manning

Linda W. Manning, Pharm.D.
Senior Scientist
Regulatory Affairs
(513) 622-1114
(513) 622-5369 FAX

Desk Copies: Bruce Stadel, M.D.
Eric Colman, M.D.
Randy Hedin, R.Ph.

Attachment

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Figure 1

Cumulative Incidence of Lung Cancer
RBL RVN RVE RON ROE RPE RCP & RCT Studies
Time Based on AE Onset Date

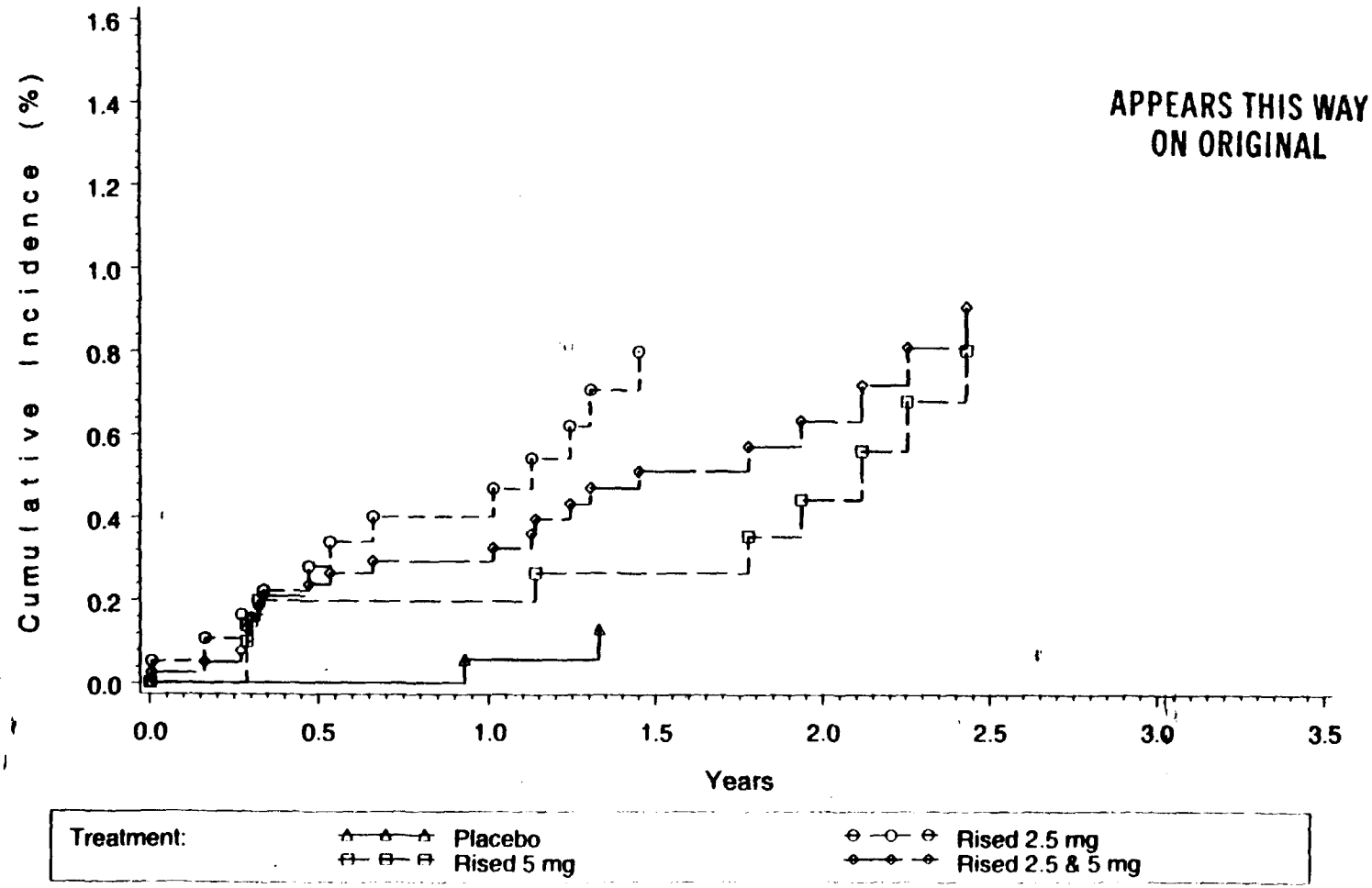

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Figure II

Cumulative Incidence of GI Cancer
RBL RVN RVE RON ROE RPE RCP & RCT Studies
Time Based on AE Onset Date

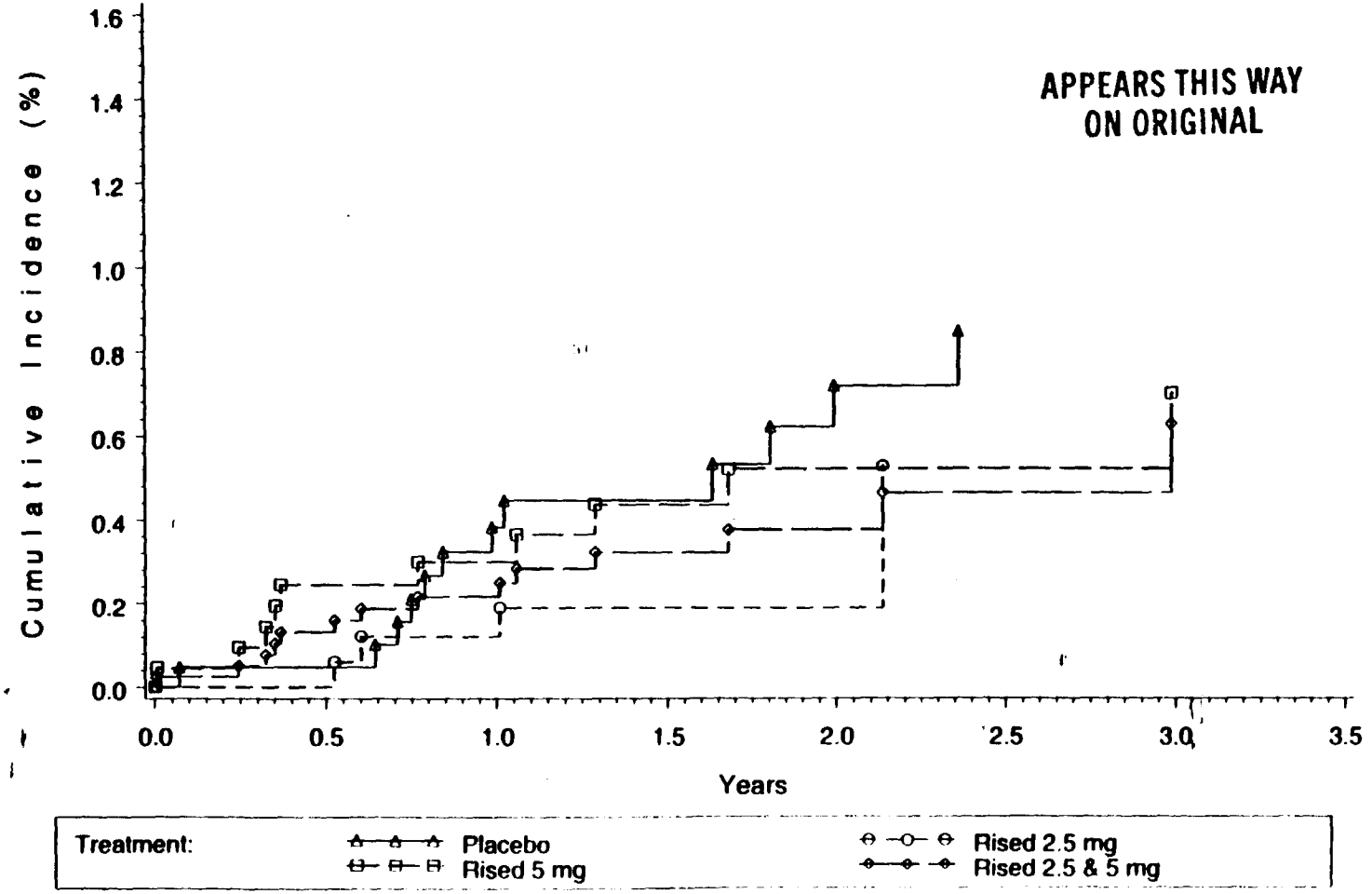

Figure III

Cumulative Incidence of Lung Cancer
RHN & RHE Studies
Time Based on AE Onset Date

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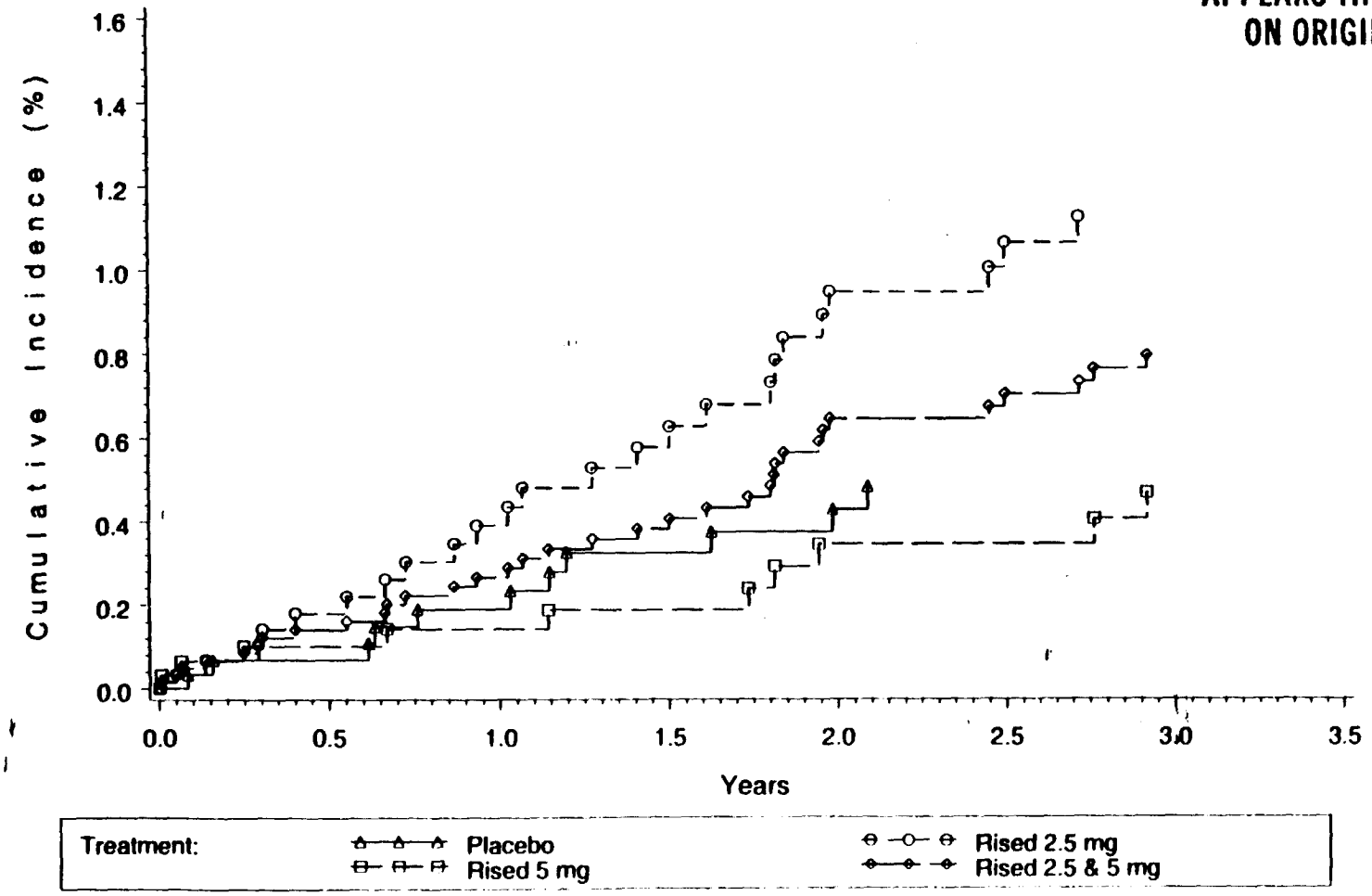

Figure IV

Cumulative Incidence of GI Cancer
RHN & RHE Studies
Time Based on AE Onset Date

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