Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
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August 3, 1998

MERCK
Research Laboratories

Solomon Sobel, M D., Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-560/S-012: FOSAMAX™ (Alendronate Sodium Tablets)
General Correspondence

Dear Dr. Sobel:

Reference is made to the supplemental new drug application cited above and to a May 26, 1998 Approvable Letter requesting additional information regarding this supplemental application. The purpose of this communication is to provide an overview of MRL's plans regarding responses to the items outlined in the Approvable Letter cited above and to obtain Agency concurrence with our proposed plans.

As detailed below, MRL's response to the Approvable Letter will consist of four main elements: (1) the complete Clinical Study Report of the (preplanned) combined results from both double-blind extensions of the Glucocorticoid-Induced Osteoporosis (GIOP) Studies (protocols 082/083) through 2 years; (2) revised draft labeling for supplemental application S-012, (3) a five-year CIOMS II report of the worldwide postmarketing experience with alendronate; and (4) a comprehensive review of safety information available from all Merck osteoporosis clinical trials with alendronate since the time of filing supplemental application S-012 on November 26, 1997.

The following are more detailed descriptions of MRL's proposed responses to each Agency request outlined in the Approvable Letter cited above.

FDA Request # 1:

Before this application may be approved, it will be necessary for you to submit:

1. **Additional information about the two-year double-blind extension studies. A more thorough and audited presentation of data from this recent submission should be provided to the Division. Please also include the following in the submission:**

   A. **Include time exposures (patient-months of treatment), drop-out rates, and the numbers of patients who remained at risk at the end of two years.**

   B. **Fracture results should be presented in terms of patient-months of therapy.**

2. **A database including both the initial treatment as presented in the one-year studies of the NDA, and the two-year, double-blind extensions. The following should be included with the database:**

   A. **Present an analysis of subgroups based on the underlying disease condition and its interaction with bone density endpoints and fractures.**

   B. **Provide an analysis of the NDA data that dissects out the contribution to efficacy results of postmenopausal patients who are, and are not on hormone replacement therapy. Provide similar analyses for premenopausal patients and for men.**

We request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. **Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the same time the NDA was submitted vs. now will certainly facilitate review.**

2. **Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.**

3. **Provide details of any significant changes or findings, if any.**

5. **Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.**

MRL Reply #1:

As detailed in the attached Data Analysis Plan (DAP; Attachment 1), a comprehensive Clinical Study Report (CSR) covering the full two-year experience (efficacy and safety) of the extension cohort of the alendronate glucocorticoid-induced osteoporosis studies (protocols 082 and 083) will be provided. This extension cohort is a subset of the original 1-year study cohort and baseline characteristics of the extension cohort were generally similar to those for the original cohort. As pre-defined in the original protocol, this extension cohort will be presented in one CSR for the combined Protocols 082 and 083. The data will be presented in a fashion consistent with the presentation in the original supplemental application CSRs, Special Endpoint Report, and Integrated Summary as well as the submissions provided in response to Agency requests for additional information regarding this supplemental application. The CSR will be accompanied by a database in a format similar to that which was used in the original supplemental application S-012. As requested, the following items will be included in the CSR:

1. Time exposures (patient-months of treatment), drop-out rates, and the numbers of patients who remained at risk at the end of two years.

2. An in-depth review of the fracture data will be provided. It will include a presentation of the data in patient-months of therapy and is described in detail in the DAP (Attachment 1).

3. Analyses of predefined subgroups as previously depicted in the original supplemental application S-012 will be provided, including an assessment of the underlying disease condition and its interaction with bone density endpoints (shown previously) and fractures (new). As done previously, an analysis of the effect of gender, menopausal status and estrogen use will be provided.

To facilitate review of safety information, the original 1-year safety data will be provided alongside the extension safety data. Where appropriate, narratives will be provided. Listings of serious and other adverse experiences will delineate events occurring in year 1 versus year 2. Upper gastrointestinal (GI) and fracture adverse experiences (AEs) will be divided into Year 1 and Year 2; event rates will be compared to those in the original supplemental application. As requested, the following will be provided in this CSR: retabulation of all safety data (including drop-outs during Year 1 versus Year 2 of the study), details of any significant findings, if any, and case report forms for each patient who died or did not complete the study because of an adverse event.

Request # 2:

Revision of the draft labeling submitted on November 26, 1998, will be required. The duration of treatment should be limited to one year reflective of the treatment period of the 560 patients in the studies presented in the original NDA.

MRL Reply #2:

Draft labeling previously submitted with supplemental application S-012 will be revised and provided. As the 2-year extension CSR described above will be submitted in response to items cited in the Approvable Letter, MRL proposes to incorporate any new information obtained from the two-year safety and efficacy analyses as appropriate in this revised draft labeling.

FDA Request #3:

Summarize worldwide experience on the safety of this drug.

MRL Reply # 3:

A 5-year CIOMS II report will be provided to the Agency. This report will summarize the 5-year postmarketing experience with alendronate worldwide and will also contain information on serious drug-related adverse experiences from clinical trials with alendronate conducted by Merck & Co., Inc.

FDA Request # 4:

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

MRL Reply # 4:

MRL will provide the Agency with a comprehensive review of safety information available from osteoporosis clinical trials with alendronate conducted by Merck. A proposed, draft table of contents for this report is provided in Attachment 2 The information contained within this review will be derived from alendronate osteoporosis clinical trials with the most currently available completed clinical study reports and audited safety data from case report forms. A listing of the studies that will be included in this report is provided in Attachment 3. MRL will comprehensively summarize the overall safety experience with alendronate across the entire clinical development program for osteoporosis. Information on patient exposure for each of these studies as well as a review of the design and/or special features of the studies and/or population studied will be included. Tabulations will be provided in a style similar to that presented in supplemental application S-012, those tabulations presented in the original supplemental application will also be shown to facilitate review of this updated safety information, although it is recognized that the studies and populations are different and statistical comparisons cannot therefore be made. An overview of clinical and laboratory adverse experiences across these studies will be provided in tabular format and this information will be accompanied by summaries of clinically relevant findings in the individual studies. Within this report, there will be separate sections providing a review of the latest information regarding upper gastrointestinal AEs and fractures in these alendronate osteoporosis clinical trials. To facilitate review, safety information previously submitted to the Agency will also be included in this report, in parallel with the presently submitted data, to allow for interpretation of the data in the context of the entire alendronate osteoporosis clinical development program.

For ongoing osteoporosis clinical studies with alendronate, the only safety information available is that from the Worldwide Adverse Experience System (WAES) database. However, most of the WAES data for these ongoing studies are blinded with regard to the patients' treatment (alendronate versus placebo) and MRL does not believe that inclusion of such blinded data will provide additional useful information for assessment of alendronate's safety profile, especially in light of the vast experience to be reported in the audited data described above.

A major issue discussed at the May 13, 1998 Advisory Committee Meeting was the need for accurate preclinical models for glucocorticoid-induced osteoporosis to support human bone safety data MRL would like to notify the Agency that we have recently completed additional studies with alendronate in combination with prednisolone in both male and female nine-month old rats. In male rats, there was no change in bone mineral density (BMD) with prednisolone treatment at

a relatively high dose (3.5 mg/kg twice weekly for 8 weeks). Combining alendronate at a dose of 35 mcg/kg twice weekly with prednisolone resulted in a statistically significant ($p<0.05$) increase in vertebral bone mineral content (29%) and bone strength (49%), demonstrating that alendronate produces bone of normal quality in the presence of glucocorticoids in this animal model. In female rats, the same dose of prednisolone resulted in a statistically significant reduction (7%; $p<0.05$) in lumbar spine BMD and alendronate treatment at 35 mcg/kg twice weekly fully restored lumbar spine BMD to control levels. As in male rats, the ratios of bone strength to BMD were not different among the groups, again consistent with the maintenance of bone of normal quality in the presence of combined glucocorticoid and alendronate treatment in this animal model. We conclude that alendronate, when combined with glucocorticoid treatment in the rat, produces bone of normal quality. We would be pleased to provide a detailed report of this preclinical information to the Agency upon request.

MRL believes that the clinical documents outlined above will be useful to the Agency in its review of supplemental application S-012 and we are confident that this approach will provide the information requested by the Agency in a comprehensive manner. We trust that the plans outlined above meet with the Agency's approval We look forward to the Agency's concurrence on our approach and to providing our complete response to the Approvable Letter as soon as possible. I will be contacting the Agency shortly to discuss these plans further and to obtain the Agency's concurrence on our approach; should the Agency desire additional discussions on these plans, we would be happy to discuss them further in either a face-to-face or teleconference meeting.

We look forward to reaching a rapid agreement with the Agency on our proposed plans. Please direct any questions to Michelle Kloss, Ph.D. (610-397-2905) or, in my absence, Larry P. Bell, M.D. (610-397-2310).

Sincerely, yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Q:RC\MK-0217\GIOP\PROP1

Attachments

Federal Express #1

APPEARS THIS WAY ON ORIGINAL

Desk Copies
Mr. Randy Hedin (5), HFD-510, Room 14B-04 Federal Express #1

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

DESK COPY

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May 27, 1998

MERCK
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Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-560/S-012: FOSAMAX™ (alendronate sodium tablets)

Dear Dr. Sobel:

Please refer to your letter dated May 26, 1998 indicating that the above-captioned supplement is approvable. With this letter, we wish to notify you of our intent to file an amendment to this application.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610) 397-2905 or, in my absence, Larry P. Bell, M.D. (610) 397-2310.

Sincerely,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Federal Express #1

(1) Desk copy: Mr. Randy Hedin, HFD-510, Room 14B-04
Federal Express #2

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Michelle W. Kloss, Ph D
Director
Regulatory Affairs

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May 22, 1998

Solomon Sobel, M.D. - Director
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Rockville, Maryland 20857

MERCK
Research Laboratories

NDA 20-560/S-012: FOSAMAX
(Alendronate Sodium Tablets)

Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to the pending supplemental application cited above submitted on November 26, 1997, to a May 21, 1998 telephone conversation between Drs. Solomon Sobel (FDA) and Bonnie Goldmann, Merck Research Laboratories (MRL), as well as a May 22, 1998 telephone conversation between Drs. Bilstad and Goldmann. The subject of these conversations was the status of supplement 012 and the outcome of the recent Endocrine and Metabolic Advisory Committee Meeting (May 13, 1998) concerning recommendations on the data necessary to support an indication for the treatment of glucocorticoid-induced osteoporosis (GIOP). By copy of this letter, Merck is providing additional information to address the Agency's concerns.

During these conversations, it was clear that MRL's understanding of the Advisory Committee Meeting recommendations differed on several points from that of the Division of Metabolism and Endocrine Products' interpretation. To that end, we are providing a copy of the May 18, 1998 F.D.C. Reports (Attachment 1) which relays an interpretation of the proceeding similar to MRL's, i.e., that for drugs previously approved for osteoporosis therapy, fracture data is not necessary for approval.

Dr. Sobel also commented that there was still concern among various members of the Division about the 1-year nonvertebral fracture data provided in the submission. As requested by the Division, we are providing preliminary 2-year fracture data from the GIOP studies. This report (Attachment 2) summarizes the fracture results, from Month 0 to Month 24, for the 203 patients enrolled in the double-blind GIOP Extension Studies. These patients represent the subset of patients from the initial 560 patients randomized into the alendronate GIOP studies who were taking prednisone at a dose of at least 7.5 mg/day (or equivalent) and were willing to enter the extension. Data for vertebral and nonvertebral fractures are presented, including categorization of the timing of the fractures (Month 0-12 or Month 12-24). It should be noted that this is a preliminary analysis, since the database has not been closed and the data have not been audited. However, any changes are likely to be small and are unlikely to affect the conclusions. Also included is a supportive analysis of the 2-year data for all patients randomized at month 0 to double-blind study therapy.

These data clearly demonstrate that there is no increase in the rate of vertebral or nonvertebral fractures during the second year in GIOP patients who continued to receive alendronate. This is entirely consistent with the data from our studies in postmenopausal osteoporosis, which now extend out to five years and show that the effects of alendronate to decrease fracture incidence is consistent over time. It is also consistent with the bone biopsy data previously submitted, as well as the fact that the rate of bone turnover in the GIOP population, as determined by biochemical markers, is only partially decreased to reach a new steady state for both bone formation and bone resorption with mean values well within the normal range for healthy premenopausal women.

We consider the information included in this submission to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

We trust you will find this information helpful. We would like to have the opportunity to discuss with you as soon as possible. We will be calling your office shortly in follow up

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Larry P. Bell, M.D. (610/397-2310).

Sincerely,

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Facsimile: Dr. Solomon Sobel
Dr. James Bilstad

Attachments
Q:\HEMMERLE\CARROLL\20560

APPEARS THIS WAY ON ORIGINAL

Federal Express #1

Desk Copy: Mr. Randy Hedin, HFD-510 Federal Express #2
Dr. Gloria Troendle, HFD-510 Federal Express #2
Dr. Solomon Sobel, HFD-510 Federal Express #2
Dr. James Bilstad, HFD-102 Federal Express #2

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Attachment 1

Pink Sheet

Date: 05/18/98

Title: Steroid-Induced Osteoporosis Claims For Approved Drugs Need One-Year Study

Source: PINK-SHEET, May 18, 1998, Page 9

One-year trials are sufficient for corticosteroid-induced osteoporosis therapies already approved for another osteoporosis indication, FDA's Endocrinologic and Metabolic Drugs Advisory Committee agreed May 13.

"We want to make it clear in the labeling that this has only been tested for a year," committee Chair Henry Bone, MD, Michigan Bone and Mineral Clinic, added.

FDA Division of Metabolic & Endocrine Drug Products Deputy Director Gloria Troendle, MD, observed that three-year studies are required for a postmenopausal osteoporosis indication. "To get an approval based on bone mineral density, it is necessary to have three-year data, but most of those interested in an indication for glucocorticoid-induced osteoporosis propose one-year studies."

"We are told that longer studies are impossible and that patients do not stay on glucocorticoids more than one year," Troendle said.

The committee did not deem fracture studies necessary for previously approved osteoporosis therapies. "If it hasn't been shown to have an anti-fracture effect, we'll say so" in labeling, Bone said. "It gives the company the opportunity to enhance the claim by having long-term studies that show anti-fracture data."

"Fracture endpoints...are particularly not necessary," Merck VP-Research Gideon Rodan, MD/PhD, asserted. "It would be extremely difficult [to get the necessary number of patients] of 5,000 or more...It would take over five years to recruit this number."

The committee suggested that endpoints for already approved drugs should include bone mineral density. "I would be satisfied with lack of evidence of toxic effect on remodeling and evidence of a positive effect on bone density without the necessity" of showing a fracture effect, committee guest expert Eric Orwoll, MD, Oregon Health Sciences University, said.

The committee agreed that a threshold for corticosteroid dosage should be 5 mg/day but that a sponsor could increase that level.

The committee suggested that corticosteroid induced osteoporosis study populations should include patients with polymyalgia rheumatica, chronic obstructive pulmonary disease, rheumatoid arthritis, renal

transplant and postmenopausal women with chronic steroid-dependent asthma.

Bone commented that FDA "would probably want to see a sufficient number of people with at least two or three different underlying diseases to be assured that the effects or benefits that were seen from a drug were consistently experienced." 11 of 16 Drugs that are not approved for another osteoporosis indication should require more rigorous studies, the committee agreed. Committee member Charles Turner, PhD, Indiana University School of Medicine, cautioned that "corticosteroid-induced osteoporosis shouldn't be an easy way to get around postmenopausal osteoporosis."

A study for a non-approved drug "clearly has to include fracture evidence and clearly has to go on for...a couple of years," committee member Robert Marcus, MD, Palo Alto VA Medical Center, added.

"Certainly, for a drug with an indication of a bone quality problem in either preclinical studies, or demonstration of a problem in clinical trials, it's hard to imagine that we could recommend approval without demonstration of antifracture efficacy," Bone commented. "I would say that would have to be antifracture evidence over a period of time."

"I think endpoints would be relatively short-term and would be centered around some animal demonstration that there wasn't a mineralization defect," Orwoll said. In addition, sponsors could do "biopsy studies in humans that showed that there weren't abnormalities in bone."

Although guest expert Lawrence Raisz, MD, Weicker General Clinical Research Center, suggested that two biopsy studies should be done, Bone said that one would be acceptable. "We might settle for a biopsy at the end as a compromise and see if you had mineralization defects," the chairman proposed.

FDA's Troendle noted that the agency is concerned that "no [animal] models have been identified" for corticosteroid-induced osteoporosis. Bone said that a good "animal model should have suppressed bone formation, increased bone resorption, and it should respond to something like fluoride similar to humans."

Attachment 2

FOSAMAX®

MERCK RESEARCH LABORATORIES (MRL)

RESPONSE TO REGULATORY AGENCY CONCERNS:

THE FOOD AND DRUG ADMINISTRATION, USA

The Food and Drug Administration has requested the following documentation concerning NDA 20-560/S-012, in a telephone conversation with Dr. Bonnie Goldmann, Vice President, Regulatory Affairs, on May 21, 1998:

Preliminary Analysis of the GIOP Extension Fracture Data - Protocols 082/083

As requested by the Agency, this report summarizes the fracture results, from Month 0 to Month 24, for the 203 patients enrolled in the double-blind Glucocorticoid-Induced Osteoporosis (GIOP) Extension Studies. These patients represent the subset of patients from the initial 560 patients randomized into the alendronate GIOP studies who were taking prednisone at a dose of at least 7.5 mg/day (or equivalent) and were willing to enter the extension. Data for vertebral and nonvertebral fractures are presented, including categorization of the timing of fractures (Month 0-12 or Month 12-24). It should be noted that this is a preliminary analysis, since the database has not been closed and the data have not been audited. However, any changes are likely to be small and are unlikely to affect the conclusions.

1. Study Design

Of the 560 patients enrolled in the original 1-year studies, a total of 217 entered the extension studies (Table 1). However, 14 patients (8 placebo and 6 alendronate) who were declared "fast bone losers" based on spine bone mineral density (BMD) data from Month 9 were given open-label alendronate 10 mg from Month 12 to Month 24. Other patients did not enter the extension study either because they did not complete the original study, their study site decided not to participate in the study extensions, they were ineligible due to a Month 12 steroid dose below 7.5 mg/day prednisone (or equivalent) or they did not provide consent (Table 1). The primary focus of this report is the 203 patients who entered into the blinded extension study.