NDA 20-560/S-015, S-018 24 November 1999

Merck Research Laboratories
Attention: Michelle Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box BLA-20
West Point, PA 19486-0004

Dear Dr. Flicker:

Please refer to your supplemental new drug applications dated September 18, 1998 (S-015), and January 28, 1999 (S-018), received September 21, 1998, and January 28, 1999, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) Tablets.

For Supplement-015, we acknowledge receipt of your submissions dated November 9, 19, 23, and 24, 1999. Your submission of November 9, 1999, constituted a complete response to our September 3, 1999, action letter.

For Supplement-018, we acknowledge receipt of your submissions dated February 5, March 1 and 24, May 3 and 5, October 1 and 27, and November 3, 16, 19, 23, and 24, 1999.

Supplemental new drug application -015 provides for the addition of clinical efficacy and safety information from the four-year Fracture Intervention Trial (FIT). The *Clinical Studies* subsection of the **CLINICAL PHARMACOLOGY** section of the Fosamax package insert was modified to reflect the results of the FIT trial.

Supplemental new drug application –018 provides for the addition to the Fosamax labeling of efficacy and safety information derived from two clinical studies in which Fosamax was used concomitantly with estrogen alone or with estrogen plus progestin. A new subsection titled "*Concomitant use with estrogen/hormone replacement therapy (HRT)"* is added to the *Clinical Studies* subsection of the **CLINICAL PHARMACOLOGY** section, and a new paragraph is inserted at the beginning of the *Drug Interactions* subsection of the **PRECAUTIONS** section of the package insert. This concomitant use information has been added to the patient package insert also.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is

safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and patient package insert submitted November 24, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-560/S-015, S-018." Approval of these submissions by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated November 23, 1999. These commitments, along with any completion dates agreed upon, are listed below.

1. You will submit the 3-year data from the Estrogen Combination/Comparison Study (Protocol 072) . This study was extended for a third year. In the third year extension, patients who had been receiving placebo, estrogen, or alendronate received placebo. Of the patients previously receiving combination (estrogen/alendronate) therapy, half cointued on the combination for one year and half were randomly and blindly switched to placebo. Estimated time frame for completion: June 30, 2000.

2. You will evaluate and submit the fracture experience in women who were taking concomitant conjugated estrogen in the Fracture Intervention Trial. Women who had taken HRT within six months prior to study participation had been excluded, but women were allowed to remain in the study if they started HRT after enrollment. You estimated that approximately 600 women used conjugated estrogen during FIT for unspecified durations of time. Estimated time frame for completeion: December 31, 2000.

3. You are exploring the possibility of using information from the Women's Health Initiative (WHI). A WHI investigator estimated that a recent survey indicated that approximately 700-800 women used alendronate. Despite the study's being blinded until the year 2004, you will continue to explore potential studies regarding fracture incidence and fracture healing in patients likely receiving treatment combination therapy. Estimated time frame to submit a progress report: February 28, 2000.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study,

expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632)(21 CFR 314.55 (or 601.27)). The Agency has not made a determination if a health benefit would be gained by studying alendronate in pediatric patients for its approved indications. FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations because pediatric studies should be delayed until additional safety or effectiveness data have been collected and reviewed. FDA will inform you on or before March 31, 2000, whether pediatric studies are required under the rule. If FDA determines at that time that pediatric studies are necessary, FDA will also set a specific time at which you must submit the required assessments.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely yours,

/s

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II
Center for Drug Evaluation and Research