DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-042
NDA 21-575/S-003

Merck & Co., Inc.
Attention: Michele Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 2000,
Mail Drop: RY 33-200
Rahway, NJ 07065

Dear Dr. Flicker:

Please refer to your supplemental new drug applications (NDAs) dated August 21, 2003, received August 22, 2003 (NDA 20-560), and December 15, 2003, received December 16, 2003 (NDA 21-575), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) Tablets (NDA 20-560) and for Fosamax (alendronate sodium) Oral Solution (NDA 21-575).

We acknowledge receipt of your submissions to the Fosamax Tablets NDA dated December 15, 2003, and February 13, 2004, and to the Oral Solution NDA dated February 13, 2004.

These supplemental new drug applications propose that the following paragraph be added to the *Pregnancy* subsection of the **PRECAUTIONS** section of the package insert:

> "Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominately skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been studied."

We have completed the review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted February 13, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-560/S-042, and NDA 21-575/S-003." Approval of these submissions by FDA is not required before the labeling is used.

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, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff

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