DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-766/S-070

Merck & Co., Inc.
Attention: Vijay K. Tammara, Ph.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tammara:

Please refer to your supplemental new drug application dated November 18, 2004, received November 19, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

This "Changes Being Effected" supplemental new drug application provides for changes to the **WARNINGS, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections of the package insert to add information on the drug interactions with telithromycin and danazol.

To the **WARNINGS,** ***Myopathy/Rhabdomyolysis*** subsection, the following changes were made to the cited subsection:

- Potent inhibitors of CYP3A4, telithromycin was added to the list.
- Other drugs, a new paragraph was added to read:
  "Danazol particularly with higher doses of simvastatin (see below: PRECAUTIONS, Drug Interactions, Other drug interactions)."
- To the paragraph that begins with "Consequently," under number 1, telithromycin was added to the list of potent CYP3A4 inhibitors. Number 3 was changed to read:
  "The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine or danazol. The benefits of the use of simvastatin in patients receiving cyclosporine or danazol should be carefully weighed against the risks of these combinations."

To the **PRECAUTIONS**, *Drug Interactions*, subsection, the following changes were made:

- *CYP3A4 Interactions,* telithromycin was added to the list of potent inhibitors of CYP3A4.
- *Other drug interactions*, the following new sentence was added to the list to read:
  "Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol particularly with higher doses of simvastatin (see WARNINGS, Myopathy/Rhabdomyolysis."

- *Other drug interactions; Amiodarone or Verapamil,* the sentence was changed to add the underlined text:

  "The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see WARNINGS, Myopathy/Rhabdomyolysis)."

To the **DOSAGE AND ADMINISTRATION** section,

- Under the second paragraph, last sentence, danazol was added after the word "cyclosporine" to the list of medications for patients receiving concomitant therapy.
- *Patients taking Cyclosporine* subsection title has been changed to *Patients taking Cyclosporine or Danazol.* The paragraph was changed to read:

  "In patients taking cyclosporine or danazol concomitantly with ZOCOR (see WARNINGS, *Myopathy/Rhabdomyolysis*), therapy should begin with 5 mg/day and should not exceed 10 mg/day."

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on November 18, 2004.

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. We note that you have fulfilled the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
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, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 827-6411.

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/

Mary Parks
5/17/05 03:42:36 PM
for Dr. Orloff