DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-051

Merck & Co., Inc.
Attention: Michael C. Elia, Ph.D., DABT
Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Elia:

Please refer to your supplemental new drug application dated May 14, 2001, received May 15, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We acknowledge receipt of your submissions dated December 18, 2001, and April 26, 2002. Your submission of April 26, 2002, constituted a complete response to our October 12, 2001, action letter.

This supplement proposes changes to the labeling regarding the risk of myopathy associated with simvastatin use alone or in combination with inhibitors of CYP3A4 or other drugs that can increase the risk of myopathy. This supplement provides for revisions to the **CLINICAL PHARMACOLOGY**, *Pharmacokinetics*; **WARNINGS,** *Myopathy/Rhabdomyolysis*; **PRECAUTIONS,** *Information for Patients*, and *Drug Interactions*; and **ADVERSE REACTIONS**; and **DOSAGE AND ADMINISTRATION,** *Dosage in Patients taking Amiodarone or Verapamil and Concomitant Lipid-Lowering Therapy*, subsections of the Package Insert. The specific changes are as follows:

To the **CLINICAL PHARMACOLOGY,** *Pharmacokinetics*, subsection, the eighth paragraph has been added:

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions).*

The **WARNINGS,** *Skeletal Muscle*, subsection has been changed to *Myopathy/Rhabdomyolysis* subsection. Additionally, the subsection has been changed to read:

Myopathy/Rhabdomyolysis
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

- **The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following:**

  Potent inhibitors of CYP3A4: Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily), particularly with higher doses of simvastatin (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, CYP3A4 Interactions*).

  Lipid-lowering drugs that can cause myopathy when given alone: Gemfibrozil, other fibrates, or lipid-lowering doses (≥1 g/day) of niacin, particularly with higher doses of simvastatin (see below; CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

  Other drugs: Amiodarone or verapamil with higher doses of simvastatin (see PRECAUTIONS, *Drug Interactions, Other drug interactions*). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13/21,224; 0.061%).

- **The risk of myopathy/rhabdomyolysis is dose related.** The incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.02% at 20 mg, 0.07% at 40 mg and 0.3% at 80 mg.

Consequently:

1. **Use of simvastatin concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided.** If treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

2. **The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine, gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin. The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination.** Addition of these drugs to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained.

3. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.

4. All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and/or a CK level >10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

5. Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

To the **PRECAUTIONS,** *Information for Patients* subsection, the language has been changed to:

Patients should be advised about substances they should not take concomitantly with simvastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking ZOCOR.

To the **PRECAUTIONS,** *Drug Interactions* and *Other drug interactions* subsections, the language has been changed to:

Drug Interactions
CYP3A4 Interactions

Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of simvastatin.

See WARNINGS, *Myopathy/Rhabdomyolysis*, and CLINICAL PHARMACOLOGY, *Pharmacokinetics.*

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
HIV protease inhibitors
Nefazodone
Cyclosporine
Large quantities of grapefruit juice (>1 quart daily)

Interactions with lipid-lowering drugs that can cause myopathy when given alone

The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent CYP3A inhibitors, but which can cause myopathy when given alone.

See WARNINGS, *Myopathy/Rhabdomyolysis.*

Gemfibrozil
Other fibrates
Niacin (nicotinic acid) (>1 g/day)

Other drug interactions

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil (see WARNINGS, *Myopathy/Rhabdomyolysis*).

The **ADVERSE REACTIONS,** *Concomitant Therapy* subsection has been changed to *Concomitant Lipid-Lowering Therapy* subsection. Additionally, the third sentence, has been changed to:

The combined use of simvastatin at doses exceeding 10 mg/day with gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin should be avoided (see WARNINGS, *Myopathy/Rhabdomyolysis*).

To the **DOSAGE AND ADMINISTRATION,** a new subsection, *Dosage in Patients taking Amiodarone or Verapamil,* has been added with the following information:

In patients taking amiodarone or verapamil concomitantly with ZOCOR, the dose should not exceed 20 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*, *Other drug interactions*).

To the **DOSAGE AND ADMINISTRATION,** *Concomitant Lipid-Lowering Therapy* subsection, the paragraph was changed to:

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. If ZOCOR is used in combination with gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin, the dose of ZOCOR should not exceed 10 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

We have completed the review of this supplemental application, 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, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted April 26, 2002).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar

material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-766/S-051." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit 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, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" 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, call Margaret Simoneau, 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

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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