DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-766/S-065, S-066

Merck & Co., Inc.
Attention: Andrew M. Tershakovec, M.D.
Director, Regulatory Affairs
Sumneytown Pike, P.O.Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tershakovec:

Please refer to your supplemental new drug applications, S-065, dated March 18, 2003, received March 19, 2003, and S-066, dated April 24, 2003, received April 25, 2003, submitted under under 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We acknowledge receipt of your submission dated September 12, 2003.

Supplement-065 provides for revisions to the **WARNINGS, Myopathy/Rhabdomyolysis** subsection, **PRECAUTIONS,** *Interactions with lipid-lowering drugs that can cause myopathy when given alone* subsection**, ADVERSE REACTIONS,** *Concomitant Lipid Lowering Therapy* subsection, **OVERDOSAGE** section, and **DOSAGE AND ADMINISTRATION**, *Concomitant Lipid-Lowering Therapy* subsections of the package insert.

To the **WARNINGS; *Myopathy/Rhabdomyolysis*** subsection, the first bullet, second item, *lipid-lowering drugs that can cause myopathy when given alone,* has been changed to read:

Other drugs:
Gemfibrozil particularly with higher doses of simvastatin (see below; PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone*; DOSAGE AND ADMINISTRATION).

Other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin) that can cause myopathy when given alone (see below; PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

To the **WARNINGS; *Myopathy/Rhabdomyolysis*** subsection, items two and three have been changed to read:

2. The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with gemfibrozil. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. Caution should be used when prescribing other lipid-lowering drugs (other fibrates or lipid-

lowering doses (≥1 g/day) of niacin) with simvastatin, as these agents can cause myopathy when given alone. The benefit of further alterations in lipid levels by the combined use of simvastatin with fibrates or niacin should be carefully weighed against the potential risks of these combinations. Addition of fibrates or niacin 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 10 mg daily in patients receiving concomitant medication with cyclosporine. The benefits of the use of simvastatin in patients receiving cyclosporine should be carefully weighed against the risks of this combination.

To the **PRECAUTIONS;** *Drug Interactions*; *Interactions with lipid-lowering drugs that can cause myopathy when given alone* subsection, has been changed to read:

Interactions with lipid-lowering drugs that can cause myopathy when given alone
See WARNINGS, *Myopathy/Rhabdomyolysis.*
The risk of myopathy is increased by gemfibrozil **(see DOSAGE AND ADMINISTRATION)** and to a lesser extent by other fibrates and niacin (nicotinic acid) (≥1 g/day).

To the **ADVERSE REACTIONS;** *Concomitant Lipid-Lowering Therapy* subsection, third sentence has been changed to read:

The combined use of simvastatin at doses exceeding 10 mg/day with gemfibrozil should be avoided (see WARNINGS, *Myopathy/Rhabdomyolysis*).

To the **OVERDOSAGE** section, second paragraph, the first two sentences have been changed to read:

A few cases of overdosage with ZOCOR have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

To the **DOSAGE AND ADMINISTRATION;** *Concomitant Lipid-Lowering Therapy* subsection, the second sentence has been changed to read:

If ZOCOR is used in combination with gemfibrozil, the dose of ZOCOR should not exceed 10 mg/day (see WARNINGS, *Myopathy/Rhabdomyolysis* and PRECAUTIONS, *Drug Interactions*).

Supplement-066 provides for a correction of the computational error in the **CLINICAL PHARMACOLOGY,** *Reductions in Risk of CHD Mortality and Cardiovascular Events* subsection of labeling in supplement S-058.

To the **CLINICAL PHARMACOLOGY;** *Reductions in Risk of CHD Mortality and Cardiovascular Events* subsection, second paragraph, last sentence (percentage correction from 9% to 5%) to read:

At baseline, 3,421 patients (17%) had LDL-C levels below 100 mg/dL, of whom 953 (5%) had LDL-C levels below 80 mg/dL; 7,068 patients (34%) had levels between 100 and 130 mg/dL; and 10,047 patients (49%) had levels greater than 130 mg/dL.

We completed our 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 draft labeling (package insert submitted September 12, 2003)(copy enclosed).

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 supplement NDA 19-766 /S-065, S-066." Approval of these submissions by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. 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 inserts 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 reporting requirements for an approved NDA (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

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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