



NDA 19-766/S-069

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 March 29, 2004, received March 29, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We acknowledge receipt of your submissions dated October 6, 2004, and March 18, August 17 and 23, 2005. Your submission of March 18, 2005, constituted a complete response to our September 29, 2004 action letter.

This supplemental new drug application provides for multiple changes including deletions to the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, and PRECAUTIONS** sections of the Zocor package insert.

To the **CLINICAL PHARMACOLOGY**, the first four paragraphs have been changed to read:

*“Epidemiological studies have demonstrated that elevated levels of total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), as well as decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis and increased cardiovascular risk. Lowering LDL-C decreases this risk. However, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.”*

To the **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* subsection, the second and third paragraphs have been changed to read:

*“Following an oral dose of <sup>14</sup>C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. Plasma concentrations of total radioactivity (simvastatin plus <sup>14</sup>C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%).*

*Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Rat studies indicate that when radiolabeled simvastatin was administered, simvastatin-derived radioactivity crossed the blood-brain barrier.”*

To the **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* subsection, a new eighth paragraph has been added to read:

*“Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.”*

To the **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* subsection, a new tenth and eleventh paragraph has been added to read:

*“Gemfibrozil: Coadministration of gemfibrozil (600 mg twice daily for 3 days) with simvastatin (40 mg daily) resulted in clinically significant increases in simvastatin acid AUC (185%) and C<sub>max</sub> (112%), possibly due to inhibition of simvastatin acid glucuronidation by gemfibrozil (see WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, Drug Interactions, DOSAGE AND ADMINISTRATION).*

*Fenofibrate: Coadministration of fenofibrate (160 mg daily) with ZOCOR (80 mg daily) for 7 days had no effect on plasma AUC (and C<sub>max</sub>) of either total HMG-CoA reductase inhibitory activity or fenofibric acid; there was a modest reduction (approximately 35%) of simvastatin acid which was not considered clinically significant (see WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, Drug Interactions).”*

To the **CLINICAL PHARMACOLOGY**, *Primary Hypercholesterolemia (Fredrickson type Ila and I Ib)* subsection, the last paragraph was deleted and the first three paragraphs have been changed to read:

*“ZOCOR has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during chronic therapy. ZOCOR consistently and significantly decreased total-C, LDL-C, total-C/HDL-C ratio, and LDL-C/HDL-C ratio; ZOCOR also decreased TG and increased HDL-C (see Table 2).”*

To Table 2, *Mean Response in Patients with Primary Hypercholesterolemia and Combined (mixed) Hyperlipidemia (Mean Percent Change from Baseline After 6 to 24 Weeks)*, the following footnote was added to read:

‡ mean baseline LDL-C 244 mg/dL and median baseline TG 168 mg/dL

§ mean baseline LDL-C 188 mg/dL and median baseline TG 128 mg/dL

|| mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL

¶ mean baseline LDL-C 156 mg/dL and median baseline TG 391 mg/dL

To the **CLINICAL PHARMACOLOGY**, *Hypertriglyceridemia (Fredrickson type IV)* subsection, first paragraph, the second sentence was deleted.

To Table 3, *Six-week, Lipid-lowering Effects of Simvastatin in Type IV Hyperlipidemia Median Percent Change (25<sup>th</sup> and 75<sup>th</sup> percentile) from Baseline*<sup>†</sup> the following footnote was added to read:

<sup>†</sup> The median baseline values (mg/dL) for the patients in this study were: total-C = 254, LDL-C = 135, HDL-C = 36, TG = 404, VLDL-C = 83, and non-HDL-C = 215.

To the **INDICATIONS AND USAGE**, *General Recommendations* subsection, the fifth paragraph was changed to read:

*“At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge.”*

The **WARNINGS, Myopathy/Rhabdomyolysis** subsection has been completely changed. In the first paragraph, “creatine kinase (CK) above 10X...” was changed to read “creatine kinase (CK) above ten times...” was the only change and the remainder of the paragraph stayed the same. A new Table 8, *Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis*, was added with the subsequent renumbering of Tables 9 and 10. This new section reads as follows:

“As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,050 patients were treated with ZOCOR with 24,747 (approximately 60%) treated for at least 4 years, the incidence of myopathy was approximately 0.02%, 0.08% and 0.53% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

**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.** In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. 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.

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.

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

**Potent inhibitors of CYP3A4:** Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). When simvastatin is used with a potent inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin.

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

**Gemfibrozil, particularly with higher doses of simvastatin:** 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.

**Other lipid-lowering drugs (other fibrates or  $\geq 1$  g/day of niacin):** Caution should be used when prescribing other fibrates or lipid-lowering doses ( $\geq 1$  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 other fibrates or niacin should be carefully weighed against the potential risks of these combinations.**

**Cyclosporine or danazol, with higher doses of simvastatin:** 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.

**Amiodarone or verapamil, with higher doses of simvastatin:** 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. 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%).

Prescribing recommendations for interacting agents are summarized in Table 8 (see also CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions*; DOSAGE AND ADMINISTRATION).”

TABLE 8  
Drug Interactions Associated with Increased  
Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	Avoid simvastatin
Gemfibrozil Cyclosporine Danazol	Do not exceed 10 mg simvastatin daily
Amiodarone Verapamil	Do not exceed 20 mg simvastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

To the **PRECAUTIONS, Drug Interactions, CYP3A4 Interactions** subsection, “Cyclosporine” was moved from the list of potent inhibitors of CYP3A4 and discussed under the *Other drug interactions* subsection noted below.

To the **PRECAUTIONS, Other drug interactions** subsection, the first paragraph was changed to read:

“*Cyclosporine or Danazol*: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of simvastatin (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*; WARNINGS, *Myopathy/Rhabdomyolysis*).”

We completed our review of this supplemental new drug application, as amended. It is 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 August 17, 2005)(copy enclosed).

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:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Mary Parks  
8/31/2005 09:52:22 AM  
for Dr. Orloff