



NDA 19-643/S-076

Merck & Co., Inc.
Attention: Kenneth A. Kramer
Manager, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Mr. Kramer:

Please refer to your supplemental new drug application dated July 1, 2004, received July 2, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor (lovastatin) Tablets.

We acknowledge receipt of your submissions dated May 12, and October 28, 2005. The May 12, 2005, submission constituted a complete response to our December 15, 2004, action letter.

This supplemental new drug application provides for changes to the **CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS** sections of the Mevacor package insert.

To the **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* subsection, a new seventh 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 lovastatin and lovastatin acid is presumably due, in part, to inhibition of CYP3A4.

The **WARNINGS, Myopathy/Rhabdomyolysis** subsection has been completely changed. A new Table VI, *Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis*, was added. This new section reads as follows:

WARNINGS

Myopathy/Rhabdomyolysis

Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times 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.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical study (EXCEL) in which patients were carefully monitored and some interacting drugs were excluded, there was one case of myopathy among 4933 patients randomized to lovastatin 20-40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily.

All patients starting therapy with lovastatin, or whose dose of lovastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Lovastatin 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 lovastatin 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 lovastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with lovastatin 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 lovastatin with the following:

Potent inhibitors of CYP3A4: Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). When lovastatin 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 lovastatin.

The use of lovastatin 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 lovastatin should be suspended during the course of treatment.

Gemfibrozil, particularly with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with gemfibrozil. The combined use of lovastatin 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 ≥ 1 g/day of niacin): The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with other fibrates or ≥ 1 g/day of niacin. Caution should be used when prescribing other fibrates or lipid-lowering doses (≥ 1 g/day) of niacin with lovastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of lovastatin with other fibrates or niacin should be carefully weighed against the potential risks of these combinations.**

Cyclosporine or danazol, with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine or danazol. The benefits of the use of lovastatin in patients receiving cyclosporine or danazol should be carefully weighed against the risks of these combinations.

Amiodarone or verapamil: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

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

Table VI
Drug Interactions Associated with Increased
Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone	Avoid lovastatin
Gemfibrozil Other fibrates Lipid-lowering doses (≥ 1 g/day) of niacin Cyclosporine Danazol	Do not exceed 20 mg lovastatin daily
Amiodarone Verapamil	Do not exceed 40 mg lovastatin 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 lovastatin (see **WARNINGS**, *Myopathy/Rhabdomyolysis*; **CLINICAL PHARMACOLOGY**, *Pharmacokinetics*).

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 October 28, 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) 796-1295.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolism and Endocrinology 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
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/s/

Mary Parks
11/4/2005 10:36:36 AM
for Dr. Orloff