



NDA 19-643/S-061

Merck & Co., Inc.  
Attention: Kenneth A. Kramer  
Associate Director, Regulatory Affairs  
P.O. Box 1000, UG2CD-48  
North Wales, PA 19454-1099

Dear Mr. Kramer:

Please refer to your supplemental new drug application dated June 6, 2000, received June 7, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor (lovastatin) Tablets.

We acknowledge receipt of your submissions dated November 10, 2006 and April 11, 2007.

Your submission of November 10, 2006, constituted a complete response to our December 4, 2000, action letter.

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

To the **CONTRAINDICATIONS** section, a cross-reference was added to the *Pregnancy and lactation* subsection.

The **PRECAUTIONS**, *Pregnancy, Pregnancy Category X* subsection has been changed to read:

*Pregnancy*

*Pregnancy Category X*

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Lovastatin has been shown to produce skeletal malformations in offspring of pregnant mice and rats dosed during gestation at 80 mg/kg/day (affected mouse fetuses/total: 8/307 compared to 4/289 in the control group; affected rat fetuses/total: 6/324 compared to 2/308 in the control group). Female rats dosed before mating through gestation at 80 mg/kg/day also had fetuses with skeletal malformations (affected fetuses/total: 1/152 compared to 0/171 in the control group). The 80 mg/kg/day dose in mice is 7 times the human dose based on body surface area and in rats results in 5 times the human exposure based on AUC. In pregnant rats given doses of 2, 20, or 200 mg/kg/day and treated through lactation, the following effects were observed: neonatal mortality (4.1%, 3.5%, and 46%, respectively, compared to 0.6% in the control group), decreased pup body weights throughout lactation (up to 5%, 8%, and 38%,

respectively, below control), supernumerary ribs in dead pups (affected fetuses/total: 0/7, 1/17, and 11/79, respectively, compared to 0/5 in the control group), delays in ossification in dead pups (affected fetuses/total: 0/7, 0/17, and 1/79, respectively, compared to 0/5 in the control group) and delays in pup development (delays in the appearance of an auditory startle response at 200 mg/kg/day and free-fall righting reflexes at 20 and 200 mg/kg/day).

Direct dosing of neonatal rats by subcutaneous injection with 10 mg/kg/day of the open hydroxyacid form of lovastatin resulted in delayed passive avoidance learning in female rats (mean of 8.3 trials to criterion, compared to 7.3 and 6.4 in untreated and vehicle-treated controls; no effects on retention 1 week later) at exposures 4 times the human systemic exposure at 80 mg/day based on AUC. No effect was seen in male rats. No evidence of malformations was observed when pregnant rabbits were given 5 mg/kg/day (doses equivalent to a human dose of 80 mg/day based on body surface area) or a maternally toxic dose of 15 mg/kg/day (3 times the human dose of 80 mg/day based on body surface area).

Rare clinical reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of greater than 200 prospectively followed pregnancies exposed during the first trimester to MEVACOR or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was sufficient to exclude a 3-fold or greater increase in congenital anomalies over the background incidence.

Maternal treatment with MEVACOR may reduce the fetal levels of mevalonate, which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia. For these reasons, MEVACOR should not be used in women who are pregnant, or can become pregnant (see CONTRAINDICATIONS). MEVACOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. Treatment should be immediately discontinued as soon as pregnancy is recognized.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text which you submitted April 11, 2007. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

The final printed labeling (FPL) must be identical to the enclosed draft labeling.

Please submit either an electronic version or 20 paper copies of the FPL as soon as it is available (no more than 30 days after it is printed). If paper copies are submitted, individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 19-643/S-61.**" Approval of this submission 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 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  
Food and Drug Administration  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

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, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
(DMEP)  
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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Eric Colman  
4/17/2007 01:09:54 PM  
Eric Colman for Mary Parks