DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-687/S-010

Merck & Co., Inc., Agent for
MSP Singapore Company, LLC
Attention: Sandra Mackenzie, B.Sc., Director, Regulatory Affairs
126 E. Lincoln Avenue, PO Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Ms. Mackenzie:

Please refer to your supplemental new drug application dated October 27, 2005, received October 28, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vytorin (ezetimibe/simvastatin) Tablets.

We acknowledge receipt of your submissions dated May 4, and October 13, 2006 (email).

Your submission of May 4, 2006, constituted a complete response to our April 17, 2006 action letter.

This supplemental new drug application proposes labeling changes to the **CLINICAL PHARMACOLOGY**, **WARNINGS**, **PRECAUTIONS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION** sections of the Vytorin package insert (PI) and an additional change to the Patient Package Insert (PPI).

To the **CLINICAL PHARMACOLOGY,** Pharmacokinetics, Metabolism and Excretion, Simvastatin, after the first paragraph, the subsection has been changed to read:

> Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. Plasma concentrations of total radioactivity (simvastatin plus ^{14}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%).

To the **CLINICAL PHARMACOLOGY,** Pharmacokinetics, Drug Interactions, Cytochrome P450 subsection, a third new 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, Drug Interactions, Fenofibrate subsection, the following new second paragraph has been added:

Coadministration of fenofibrate (160 mg daily) with simvastatin (80 mg daily) for 7 days had no effect on plasma AUC (and C_{max}) 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,** Pharmacokinetics, Drug Interactions, Gemfibrozil subsection, the following new second paragraph has been added:

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_{max} (112%), possibly due to inhibition of simvastatin acid glucuronidation by gemfibrozil (see WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, Drug Interactions, DOSAGE AND ADMINISTRATION).

The **WARNINGS, Myopathy/Rhabdomyolysis** subsection, after the first two paragraphs, has been revised. Revisions include the removal of the text beginning with "Consequently" and followed by seven numbered paragraphs. A new Table 7, *Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolys,* was added with the subsequent renumbering of Table 8. 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 simvastatin 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 VYTORIN or whose dose of VYTORIN is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. VYTORIN therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when simvastatin 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 taking VYTORIN merit closer monitoring. Therapy with VYTORIN should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Because VYTORIN contains simvastatin, the risk of myopathy/rhabdomyolysis is increased by concomitant use of VYTORIN 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 VYTORIN 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 VYTORIN should be suspended during the course of treatment.

Other drugs:
Gemfibrozil, particularly with higher doses of VYTORIN: There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates (especially 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. The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with gemfibrozil. **Therefore, although not recommended, if VYTORIN is used in combination with gemfibrozil, the dose should not exceed 10/10 mg daily.** (See CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone, Other drug interactions*, and DOSAGE AND ADMINISTRATION.)

Other lipid-lowering drugs (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 VYTORIN, as these agents can cause myopathy when given alone. The safety and effectiveness of VYTORIN administered with other fibrates or (≥1 g/day) of niacin have not been established. **Therefore, the benefit of further alterations in lipid levels by the combined use of VYTORIN with other fibrates or niacin should be carefully weighed against the potential risks of these drug combinations.** (See CLINICAL PHARMACOLOGY, *Pharmacokinetics,* PRECAUTIONS, *Drug Interactions*, *Interactions with lipid-lowering drugs that can cause myopathy when given alone, Other drug interactions,* and DOSAGE AND ADMINISTRATION.)

Cyclosporine or danazol with higher doses of VYTORIN: The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving concomitant medication with cyclosporine or danazol. The benefits of the use of VYTORIN in patients receiving cyclosporine or danazol should be carefully weighed against the risks of these combinations. (See CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions, Other drug interactions*.)

Amiodarone or verapamil with higher doses of VYTORIN: The dose of VYTORIN should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of VYTORIN at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. (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%).

Prescribing recommendations for interacting agents are summarized in Table 7 (see also CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions*; DOSAGE AND ADMINISTRATION).

TABLE 7
Drug Interactions Associated with Increased
Risk of Myopathy/Rhabdomyolysis

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

*For additional information regarding gemfibrozil, see DOSAGE AND ADMINISTRATION.

To the **PRECAUTIONS,** *Drug Interactions, CYP3A4 Interactions* subsection, "Cyclosporine" was moved from the list of potent inhibitors of CYP3A4 and is now discussed in the *Other drug interactions* subsection under the new heading "Cyclosporine or Danazol."

To the **PRECAUTIONS,** *Other drug interactions* subsection, the first paragraph regarding "Danazol" was deleted and a new heading, "Cyclosporine or Danazol" was added to "Cyclosporine" with the following new paragraph:

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

To the **ADVERSE REACTIONS**, second Post-marketing Experience subsection, the word "myalgia" was added to the list of adverse reactions.

To the **DOSAGE AND ADMINISTRATION**, Patients taking other Concomitant Lipid-Lowering Therapy subsection, the first sentence was changed to read:

> The safety and effectiveness of VYTORIN administered with fibrates have not been established.

For the PPI, to section entitled, "**What are the possible side effects of Vytorin?**" the word "muscle pain" was added to the list of side effects.

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 by email on October 13, 2006. 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 21-687/S-010**." 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 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 insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
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
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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 H. Parks, 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 this page is the manifestation of the electronic signature.

/s/

Eric Colman

10/24/2006 02:08:27 PM

Eric Colman for Mary Parks