

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022687Orig1s041

Trade Name: Vytorin Tablets

Generic Name: Ezetimibe/simvastatin

Sponsor: MSP Singapore Company, LLC

Approval Date: October 6, 2011

Indications: HMG-CoA reductase inhibitor (statin) drugs, labeling modification.

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APPROVAL LETTER



NDA 21687/S-041

SUPPLEMENT APPROVAL

MSP Singapore Company, LLC
Attention: Jeffrey R. Tucker, M.D., Agent
Senior Director, Regulatory Affairs
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099

Dear Dr. Tucker:

Please refer to your Supplemental New Drug Application (sNDA) dated September 20, 2011, received September 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vytorin (ezetimibe/simvastatin) Tablets.

We acknowledge receipt of your amendment dated October 3, 2011 (email).

We also refer to our letter dated August 11, 2011, requesting that sponsors of HMG-CoA reductase inhibitor (statin) drugs, modify their labeling based on our comprehensive review of clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin coadministration.

This "Prior Approval" supplemental new drug application provides for revisions to the **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS** sections of the Highlights of Prescribing Information section and changes to the **DOSAGE AND ADMINISTRATION**, **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, **CLINICAL PHARMACOLOGY**, and **PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the Vytorin package insert. Additional changes have been made to the Vytorin Patient Package Insert under the section entitled "What are the possible side effects of Vytorin?"

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content

of labeling must be identical to the enclosed labeling (text for the package insert and patient package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) 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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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. RPh, Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
10/06/2011

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYTORIN safely and effectively. See full prescribing information for VYTORIN.

VYTORIN (ezetimibe/simvastatin) Tablets

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Dosage and Administration	
Recommended Dosing (2.1)	06/2011
Restricted Dosing for 10/80 mg (2.2)	06/2011
Coadministration with Other Drugs (2.3)	10/2011
Patients with Homozygous Familial Hypercholesterolemia (2.4)	06/2011
Chinese Patients Taking Lipid-Modifying Doses (≥ 1 g/day) of Niacin-Containing Products (2.8)	06/2011
Contraindications (4)	06/2011
Warnings and Precautions	
Myopathy/Rhabdomyolysis (5.1)	10/2011
Liver Enzymes (5.2)	10/2011
Endocrine Function (5.4)	10/2011

INDICATIONS AND USAGE

VYTORIN[®], which contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet to:

- reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia. (1.1)
- reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments. (1.2)

Limitations of Use (1.3)

- No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.
- VYTORIN has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias.

DOSAGE AND ADMINISTRATION

- Dose range is 10/10 mg/day to 10/40 mg/day. (2.1)
- Recommended usual starting dose is 10/10 or 10/20 mg/day. (2.1)
- Due to the increased risk of myopathy, including rhabdomyolysis, use of the 10/80-mg dose of VYTORIN should be restricted to patients who have been taking VYTORIN 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. (2.2)
- Patients who are currently tolerating the 10/80-mg dose of VYTORIN who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin or statin-based regimen with less potential for the drug-drug interaction. (2.2)
- Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 10/80-mg dose of VYTORIN, patients unable to achieve their LDL-C goal utilizing the 10/40-mg dose of VYTORIN should not be titrated to the 10/80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering. (2.2)
- Dosing of VYTORIN should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant. (2.3, 7.5)

DOSAGE FORMS AND STRENGTHS

- Tablets (ezetimibe mg/simvastatin mg): 10/10, 10/20, 10/40, 10/80 (3)

CONTRAINDICATIONS

- Concomitant administration of strong CYP3A4 inhibitors. (4, 5.1)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol. (4, 5.1)
- Hypersensitivity to any component of this medication (4, 6.2)
- Active liver disease or unexplained persistent elevations of hepatic transaminase levels (4, 5.2)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)

WARNINGS AND PRECAUTIONS

- Patients should be advised of the increased risk of myopathy, including rhabdomyolysis, with the 10/80-mg dose. (5.1)
- Patients should be advised to report promptly any symptoms of myopathy. VYTORIN should be discontinued immediately if myopathy is diagnosed or suspected. (5.1)
- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥ 65), female gender, uncontrolled hypothyroidism, and renal impairment. (4, 5.1, 8.5, 8.6)
- Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter. (5.2)
- VYTORIN is not recommended in patients with moderate or severe hepatic impairment. (5.3, 12.3)

ADVERSE REACTIONS

- Common (incidence $\geq 2\%$ and greater than placebo) adverse reactions in clinical trials: headache, increased ALT, myalgia, upper respiratory tract infection, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck/Schering-Plough Pharmaceuticals at 1-866-637-2501 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.3, 4, 5.1, 7.1, 7.2, 7.3, 7.6, 7.8, 12.3)

Interacting Agents	Prescribing Recommendations
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol	Contraindicated with VYTORIN
Verapamil, diltiazem	Do not exceed 10/10 mg VYTORIN daily
Amiodarone, amlodipine, ranolazine	Do not exceed 10/20 mg VYTORIN daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

- Coumarin anticoagulants: simvastatin prolongs INR. Achieve stable INR prior to starting VYTORIN. Monitor INR frequently until stable upon initiation or alteration of VYTORIN therapy. (7.8)
- Cholestyramine: Combination decreases exposure of ezetimibe. (2.3, 7.5)
- Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with VYTORIN. (5.1, 7.2, 7.4).

USE IN SPECIFIC POPULATIONS

- Severe renal impairment: Caution should be exercised and the patient should be closely monitored. (2.6, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2011

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

1.1 Primary Hyperlipidemia

VYTORIN is indicated for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia.

1.2 Homozygous Familial Hypercholesterolemia (HoFH)

VYTORIN is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

1.3 Limitations of Use

No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

VYTORIN has not been studied in Fredrickson type I, III, IV, and V dyslipidemias.

2 DOSAGE AND ADMINISTRATION**2.1 Recommended Dosing**

The usual dosage range is 10/10 mg/day to 10/40 mg/day. The recommended usual starting dose is 10/10 mg/day or 10/20 mg/day. VYTORIN should be taken as a single daily dose in the evening, with or

without food. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day. After initiation or titration of VYTORIN, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed.

2.2 Restricted Dosing for 10/80 mg

Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 10/80-mg dose of VYTORIN should be restricted to patients who have been taking VYTORIN 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity [see *Warnings and Precautions (5.1)*].

Patients who are currently tolerating the 10/80-mg dose of VYTORIN who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin or statin-based regimen with less potential for the drug-drug interaction.

Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 10/80-mg dose of VYTORIN, patients unable to achieve their LDL-C goal utilizing the 10/40-mg dose of VYTORIN should not be titrated to the 10/80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering.

2.3 Coadministration with Other Drugs

Patients taking Verapamil or Diltiazem

- The dose of VYTORIN should not exceed 10/10 mg/day [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.3)*, and *Clinical Pharmacology (12.3)*].

Patients taking Amiodarone, Amlodipine or Ranolazine

- The dose of VYTORIN should not exceed 10/20 mg/day [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.3)*, and *Clinical Pharmacology (12.3)*].

Patients taking Bile Acid Sequestrants

- Dosing of VYTORIN should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant [see *Drug Interactions (7.5)*].

2.4 Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is VYTORIN 10/40 mg/day in the evening [see *Dosage and Administration, Restricted Dosing for 10/80 mg (2.2)*]. VYTORIN should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.5 Patients with Hepatic Impairment

No dosage adjustment is necessary in patients with mild hepatic impairment [see *Warnings and Precautions (5.3)*].

2.6 Patients with Renal Impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment. However, for patients with severe renal insufficiency, VYTORIN should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. Caution should be exercised when VYTORIN is administered to these patients, and they should be closely monitored [see *Warnings and Precautions (5.1)*; *Clinical Pharmacology (12.3)*].

2.7 Geriatric Patients

No dosage adjustment is necessary in geriatric patients [see *Clinical Pharmacology (12.3)*].

2.8 Chinese Patients Taking Lipid-Modifying Doses (≥ 1 g/day Niacin) of Niacin-Containing Products

Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with VYTORIN doses exceeding 10/20 mg/day coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive VYTORIN 10/80 mg coadministered with lipid-modifying doses of niacin-containing products. The cause of the increased risk of myopathy is not known. It is also unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients. [See *Warnings and Precautions (5.1)*.]

3 DOSAGE FORMS AND STRENGTHS

- VYTORIN® 10/10, (ezetimibe 10 mg/simvastatin 10 mg tablets) are white to off-white capsule-shaped tablets with code “311” on one side.
- VYTORIN® 10/20, (ezetimibe 10 mg/simvastatin 20 mg tablets) are white to off-white capsule-shaped tablets with code “312” on one side.
- VYTORIN® 10/40, (ezetimibe 10 mg/simvastatin 40 mg tablets) are white to off-white capsule-shaped tablets with code “313” on one side.
- VYTORIN® 10/80, (ezetimibe 10 mg/simvastatin 80 mg tablets) are white to off-white capsule-shaped tablets with code “315” on one side.

4 CONTRAINDICATIONS

VYTORIN is contraindicated in the following conditions:

- Concomitant administration of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) [see *Warnings and Precautions* (5.1)].
- Concomitant administration of gemfibrozil, cyclosporine, or danazol [see *Warnings and Precautions* (5.1)].
- Hypersensitivity to any component of this medication [see *Adverse Reactions* (6.2)].
- Active liver disease or unexplained persistent elevations in hepatic transaminase levels [see *Warnings and Precautions* (5.2)].
- Women who are pregnant or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because HMG-CoA reductase inhibitors (statins), such as simvastatin, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, VYTORIN may cause fetal harm when administered to a pregnant woman. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of VYTORIN use during pregnancy; however, in rare reports congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, simvastatin revealed no evidence of teratogenicity. **VYTORIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, VYTORIN should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations* (8.1)].
- Nursing mothers. It is not known whether simvastatin is excreted into human milk; however, a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require VYTORIN treatment should not breast-feed their infants [see *Use in Specific Populations* (8.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase 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 statin activity in plasma. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy, including rhabdomyolysis, is dose related. In a clinical trial database in which 41,413 patients were treated with simvastatin, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03% and 0.08% at 20 and 40 mg/day, respectively. The incidence of myopathy with 80 mg (0.61%) was disproportionately higher than that observed at the lower doses. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with simvastatin (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

The risk of myopathy, including rhabdomyolysis, is greater in patients on simvastatin 80 mg compared with other statin therapies with similar or greater LDL-C-lowering efficacy and compared with lower doses of simvastatin. Therefore, the 10/80-mg dose of VYTORIN should be used only in patients who have been taking VYTORIN 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity [see *Dosage and Administration, Restricted Dosing for 10/80 mg (2.2)*]. If, however, a patient who is currently tolerating the 10/80-mg dose of VYTORIN needs to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin, that patient should be switched to an alternative statin or statin-based regimen with less potential for the drug-drug interaction. Patients should be advised of the increased risk of myopathy, including rhabdomyolysis, and to report promptly any unexplained muscle pain, tenderness or weakness. If symptoms occur, treatment should be discontinued immediately [see *Warnings and Precautions (5.2)*].

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates.

All patients starting therapy with VYTORIN or whose dose of VYTORIN is being increased should be advised of the risk of myopathy, including rhabdomyolysis, 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.

VYTORIN therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. VYTORIN therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

Drug Interactions

The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs that inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily). Combination of these drugs with VYTORIN is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with VYTORIN must be suspended during the course of treatment. [See *Contraindications (4) and Drug Interactions (7)*.] *In vitro* studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the VYTORIN dose may be needed to reduce the risk of myopathy/rhabdomyolysis if voriconazole must be used concomitantly with VYTORIN. [See *Drug Interactions (7.1)*.]

The combined use of VYTORIN with gemfibrozil, cyclosporine, or danazol is contraindicated [see *Contraindications (4) and Drug Interactions (7.1 and 7.2)*].

Caution should be used when prescribing other fibrates with VYTORIN, as these agents can cause myopathy when given alone and the risk is increased when they are co-administered [see *Drug Interactions (7.2, 7.7)*].

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing VYTORIN with colchicine [see *Drug Interactions (7.9)*].

The benefits of the combined use of VYTORIN with the following drugs should be carefully weighed against the potential risks of combinations: other lipid-lowering drugs (other fibrates or ≥ 1 g/day of niacin), amiodarone, verapamil, diltiazem, amlodipine, or ranolazine [see *Drug Interactions (7.3)* and *Table 6 in Clinical Pharmacology (12.3)*].

Cases of myopathy, including rhabdomyolysis, have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products. In an ongoing, double-blind, randomized cardiovascular outcomes trial, an independent safety monitoring committee identified that the incidence of myopathy is higher in Chinese compared with non-Chinese patients taking simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg coadministered with lipid-modifying doses of a niacin-containing product. Caution should be used when treating Chinese patients with VYTORIN in doses exceeding 10/20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive VYTORIN 10/80 mg coadministered with lipid-modifying doses of niacin-containing products. It is unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients [see *Drug Interactions (7.4)*].

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.3)*, *Drug Interactions (7)*, and *Clinical Pharmacology (12.3)*].

Table 1
Drug Interactions Associated with Increased
Risk of Myopathy/Rhabdomyolysis

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

5.2 Liver Enzymes

In three placebo-controlled, 12-week trials, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.7% overall for patients treated with VYTORIN and appeared to be dose-related with an incidence of 2.6% for patients treated with VYTORIN 10/80. In controlled long-term (48-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with VYTORIN 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

It is recommended that liver function tests be performed before the initiation of treatment with VYTORIN, and thereafter when clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with VYTORIN, promptly interrupt therapy. If an alternate etiology is not found do not restart VYTORIN. Note that ALT may

emanate from muscle, therefore ALT rising with CK may indicate myopathy [see *Warnings and Precautions* (5.1)].

VYTORIN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of VYTORIN.

5.3 Hepatic Impairment

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, VYTORIN is not recommended in these patients. [See *Clinical Pharmacology* (12.3).]

5.4 Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including simvastatin.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Rhabdomyolysis and myopathy [see *Warnings and Precautions* (5.1)]
- Liver enzyme abnormalities [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

VYTORIN

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In the VYTORIN (ezetimibe/simvastatin) placebo-controlled clinical trials database of 1420 patients (age range 20-83 years, 52% women, 87% Caucasians, 3% Blacks, 5% Hispanics, 3% Asians) with a median treatment duration of 27 weeks, 5% of patients on VYTORIN and 2.2% of patients on placebo discontinued due to adverse reactions.

The most common adverse reactions in the group treated with VYTORIN that led to treatment discontinuation and occurred at a rate greater than placebo were:

- Increased ALT (0.9%)
- Myalgia (0.6%)
- Increased AST (0.4%)
- Back pain (0.4%)

The most commonly reported adverse reactions (incidence $\geq 2\%$ and greater than placebo) in controlled clinical trials were: headache (5.8%), increased ALT (3.7%), myalgia (3.6%), upper respiratory tract infection (3.6%), and diarrhea (2.8%).

VYTORIN has been evaluated for safety in more than 10,189 patients in clinical trials.

Table 2 summarizes the frequency of clinical adverse reactions reported in $\geq 2\%$ of patients treated with VYTORIN (n=1420) and at an incidence greater than placebo, regardless of causality assessment, from four placebo-controlled trials.

Table 2*
Clinical Adverse Reactions Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Reaction	Placebo (%) n=371	Ezetimibe 10 mg (%) n=302	Simvastatin** (%) n=1234	VYTORIN** (%) n=1420
<i>Body as a whole – general disorders</i>				
Headache	5.4	6.0	5.9	5.8
<i>Gastrointestinal system disorders</i>				
Diarrhea	2.2	5.0	3.7	2.8
<i>Infections and infestations</i>				
Influenza	0.8	1.0	1.9	2.3
Upper respiratory tract infection	2.7	5.0	5.0	3.6
<i>Musculoskeletal and connective tissue disorders</i>				
Myalgia	2.4	2.3	2.6	3.6
Pain in extremity	1.3	3.0	2.0	2.3

*Includes two placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and two placebo-controlled studies in which VYTORIN was administered.

**All doses.

Ezetimibe

Other adverse reactions reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: *Musculoskeletal system disorders*: arthralgia; *Infections and infestations*: sinusitis; *Body as a whole – general disorders*: fatigue.

Simvastatin

In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with simvastatin (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

Other adverse reactions reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: *Cardiac disorders*: atrial fibrillation; *Ear and labyrinth disorders*: vertigo; *Gastrointestinal disorders*: abdominal pain, constipation, dyspepsia, flatulence, gastritis; *Skin and subcutaneous tissue disorders*: eczema, rash; *Endocrine disorders*: diabetes mellitus; *Infections and infestations*: bronchitis, sinusitis, urinary tract infections; *Body as a whole – general disorders*: asthenia, edema/swelling; *Psychiatric disorders*: insomnia.

Laboratory Tests

Marked persistent increases of hepatic serum transaminases have been noted [see *Warnings and Precautions* (5.2)]. Elevated alkaline phosphatase and γ -glutamyl transpeptidase have been reported. About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK [see *Warnings and Precautions* (5.1)].

6.2 Post-Marketing Experience

Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been reported in post-marketing experience for VYTORIN or ezetimibe or simvastatin: pruritus; alopecia; erythema multiforme; a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails); dizziness; muscle cramps; myalgia; arthralgia; pancreatitis; paresthesia; peripheral neuropathy; vomiting; nausea; anemia; erectile dysfunction; interstitial lung disease; myopathy/rhabdomyolysis [see *Warnings and Precautions* (5.1)]; hepatitis/jaundice; fatal and non-fatal hepatic failure; depression; cholelithiasis; cholecystitis; thrombocytopenia; elevations in liver transaminases; elevated creatine phosphokinase.

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria have been reported.

In addition, an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

7 DRUG INTERACTIONS

[See *Clinical Pharmacology* (12.3).]

VYTORIN

7.1 Strong CYP3A4 Inhibitors, cyclosporine, or danazol

Strong CYP3A4 inhibitors: The risk of myopathy is increased by reducing the elimination of the simvastatin component of VYTORIN. Hence when VYTORIN is used with an inhibitor of CYP3A4 (e.g., as listed below), elevated plasma levels of HMG-CoA reductase inhibitory activity increases the risk of myopathy and rhabdomyolysis, particularly with higher doses of VYTORIN. [See *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3).] Concomitant use of drugs labeled as having a strong inhibitory effect on CYP3A4 is contraindicated [see *Contraindications* (4)]. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with VYTORIN must be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of simvastatin. It is recommended that dose adjustment of VYTORIN be considered during concomitant use of voriconazole and VYTORIN to reduce the risk of myopathy, including rhabdomyolysis. [see *Warnings and Precautions* (5.1)].

Cyclosporine or Danazol: The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol. Therefore, concomitant use of these drugs is contraindicated. [see *Contraindications* (4), *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

7.2 Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: Contraindicated with VYTORIN [see *Contraindications* (4) and *Warnings and Precautions* (5.1)].

Other fibrates: Caution should be used when prescribing with VYTORIN [see *Warnings and Precautions* (5.1)].

7.3 Amiodarone, Ranolazine, or Calcium Channel Blockers

The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of amiodarone, ranolazine, or calcium channel blockers such as verapamil, diltiazem or amlodipine [see *Dosage and Administration* (2.3) and *Warnings and Precautions* (5.1) and *Table 6 in Clinical Pharmacology* (12.3)].

7.4 Niacin

Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with VYTORIN doses exceeding 10/20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive VYTORIN 10/80 mg coadministered with lipid-modifying doses of niacin-containing products. [See *Warnings and Precautions* (5.1).]

7.5 Cholestyramine

Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding VYTORIN to cholestyramine may be reduced by this interaction.

7.6 Digoxin

In one study, concomitant administration of digoxin with simvastatin resulted in a slight elevation in plasma digoxin concentrations. Patients taking digoxin should be monitored appropriately when VYTORIN is initiated.

7.7 Fibrates

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

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile [see *Animal Toxicology and/or Pharmacology* (13.2)]. Coadministration of VYTORIN with fibrates is not recommended until use in patients is studied. [See *Warnings and Precautions* (5.1).]

7.8 Coumarin Anticoagulants

Simvastatin 20–40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in a normal volunteer study and in a hypercholesterolemic patient study, respectively. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting VYTORIN and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of VYTORIN is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. There have been post-marketing reports of increased INR in patients who had ezetimibe added to warfarin. Most of these patients were also on other medications.

The effect of VYTORIN on the prothrombin time has not been studied.

7.9 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing VYTORIN with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X.

[See *Contraindications* (4).]

VYTORIN

VYTORIN is contraindicated in women who are or may become pregnant. Lipid-lowering drugs offer no benefit during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy. There are no adequate and well-controlled studies of VYTORIN use during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to statins *in utero*. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because statins, such as simvastatin, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, VYTORIN may cause fetal harm when administered to a pregnant woman. If VYTORIN is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Women of childbearing potential, who require VYTORIN treatment for a lipid disorder, should be advised to use effective contraception. For women trying to conceive, discontinuation of VYTORIN should be considered. If pregnancy occurs, VYTORIN should be immediately discontinued.

Ezetimibe

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryo-lethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple-dose studies of ezetimibe coadministered with statins in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in coadministration therapy compared to monotherapy.

Simvastatin

Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m² surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice.

There are rare reports of congenital anomalies following intrauterine exposure to statins. In a review¹ of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally-related statin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

8.3 Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants. A decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother [see *Contraindications (4)*].

In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe or simvastatin are excreted into human breast milk. Because a small amount of another drug in the same class as simvastatin is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women who are nursing should not take VYTORIN [see *Contraindications (4)*].

8.4 Pediatric Use

The effects of ezetimibe coadministered with simvastatin (n=126) compared to simvastatin monotherapy (n=122) have been evaluated in adolescent boys and girls with heterozygous familial hypercholesterolemia (HeFH). In a multicenter, double-blind, controlled study followed by an open-label phase, 142 boys and 106 postmenarchal girls, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% Caucasians, 4% Asian, 2% Blacks, 13% multi-racial) with HeFH were randomized to receive either ezetimibe coadministered with simvastatin or simvastatin monotherapy. Inclusion in the study required 1) a baseline LDL-C level between 160 and 400 mg/dL and 2) a medical history and clinical presentation consistent with HeFH. The mean baseline LDL-C value was 225 mg/dL (range: 161-351 mg/dL) in the ezetimibe coadministered with simvastatin group compared to 219 mg/dL (range: 149-336 mg/dL) in the simvastatin monotherapy group. The patients received coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, coadministered ezetimibe and 40 mg simvastatin or 40 mg simvastatin monotherapy for the next 27 weeks, and open-label coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

The results of the study at Week 6 are summarized in Table 3. Results at Week 33 were consistent with those at Week 6.

¹ Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6):439-446, 1996.

Table 3
Mean Percent Difference at Week 6 Between the Pooled Ezetimibe Coadministered with Simvastatin Group and the Pooled Simvastatin Monotherapy Group in Adolescent Patients with Heterozygous Familial Hypercholesterolemia

	Total-C	LDL-C	Apo B	Non-HDL-C	TG ^a	HDL-C
Mean percent difference between treatment groups	-12%	-15%	-12%	-14%	-2%	+0.1%
95% Confidence Interval	(-15%, -9%)	(-18%, -12%)	(-15%, -9%)	(-17%, -11%)	(-9, +4)	(-3, +3)

^a For triglycerides, median % change from baseline

From the start of the trial to the end of Week 33, discontinuations due to an adverse reaction occurred in 7 (6%) patients in the ezetimibe coadministered with simvastatin group and in 2 (2%) patients in the simvastatin monotherapy group.

During the trial, hepatic transaminase elevations (two consecutive measurements for ALT and/or AST ≥ 3 X ULN) occurred in four (3%) individuals in the ezetimibe coadministered with simvastatin group and in two (2%) individuals in the simvastatin monotherapy group. Elevations of CPK (≥ 10 X ULN) occurred in two (2%) individuals in the ezetimibe coadministered with simvastatin group and in zero individuals in the simvastatin monotherapy group.

In this limited controlled study, there was no significant effect on growth or sexual maturation in the adolescent boys or girls, or on menstrual cycle length in girls.

Coadministration of ezetimibe with simvastatin at doses greater than 40 mg/day has not been studied in adolescents. Also, VYTORIN has not been studied in patients younger than 10 years of age or in premenarchal girls.

Ezetimibe

Based on total ezetimibe (ezetimibe + ezetimibe-glucuronide) there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Simvastatin

The pharmacokinetics of simvastatin has not been studied in the pediatric population.

8.5 Geriatric Use

Of the 10,189 patients who received VYTORIN in clinical studies, 3242 (32%) were 65 and older (this included 844 (8%) who were 75 and older). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients but greater sensitivity of some older individuals cannot be ruled out. Since advanced age (≥ 65 years) is a predisposing factor for myopathy, VYTORIN should be prescribed with caution in the elderly. [See *Clinical Pharmacology* (12.3).]

Because advanced age (≥ 65 years) is a predisposing factor for myopathy, including rhabdomyolysis, VYTORIN should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy, including rhabdomyolysis, compared to patients <65 years of age. [See *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3).]

8.6 Renal Impairment

Caution should be exercised when VYTORIN is administered to patients with severe renal impairment. [See *Dosage and Administration* (2.6).]

8.7 Hepatic Impairment

VYTORIN is contraindicated in patients with active liver disease or unexplained persistent elevations of hepatic transaminases. VYTORIN is not recommended in patients with moderate to severe hepatic impairment. [See *Contraindications* (4) and *Warnings and Precautions* (5.2).]

10 OVERDOSAGE

VYTORIN

No specific treatment of overdosage with VYTORIN can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hyperlipidemia for up to 56 days, was generally well tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Simvastatin

Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

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

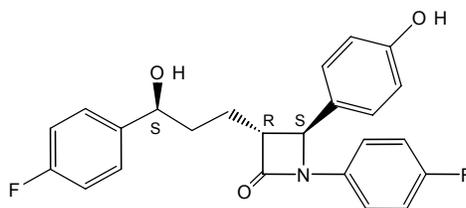
The dialyzability of simvastatin and its metabolites in man is not known at present.

11 DESCRIPTION

VYTORIN contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, an HMG-CoA reductase inhibitor.

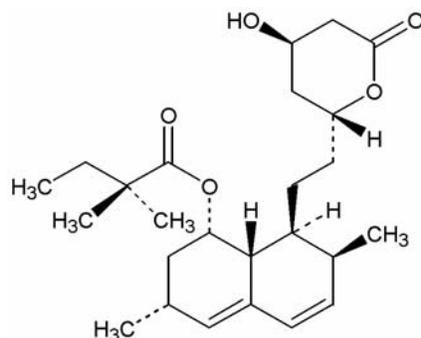
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is C₂₄H₂₁F₂NO₃ and its molecular weight is 409.4.

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Its structural formula is:



Simvastatin, an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form, which is an inhibitor of HMG-CoA reductase. Simvastatin is butanoic acid, 2,2-dimethyl-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),-8aβ]]. The empirical formula of simvastatin is C₂₅H₃₈O₅ and its molecular weight is 418.57.

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in chloroform, methanol and ethanol. Its structural formula is:



VYTORIN is available for oral use as tablets containing 10 mg of ezetimibe, and 10 mg of simvastatin (VYTORIN 10/10), 20 mg of simvastatin (VYTORIN 10/20), 40 mg of simvastatin (VYTORIN 10/40), or 80 mg of simvastatin (VYTORIN 10/80). Each tablet contains the following inactive ingredients: butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hypromellose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VYTORIN

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. VYTORIN contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. VYTORIN reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.

Ezetimibe

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo. Ezetimibe had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E and did not impair adrenocortical steroid hormone production.

Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of statins [see *Clinical Studies (14)*].

Simvastatin

Simvastatin is a prodrug and is hydrolyzed to its active β -hydroxyacid form, simvastatin acid, after administration. Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces very-low-density lipoproteins (VLDL) and TG and increases HDL-C.

12.2 Pharmacodynamics

Clinical studies have demonstrated that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.3 Pharmacokinetics

The results of a bioequivalence study in healthy subjects demonstrated that the VYTORIN (ezetimibe/simvastatin) 10 mg/10 mg to 10 mg/80 mg combination tablets are bioequivalent to coadministration of corresponding doses of ezetimibe (ZETIA®) and simvastatin (ZOCOR®) as individual tablets.

Absorption

Ezetimibe

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide).

Simvastatin

The availability of the β -hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose, consistent with extensive hepatic first-pass extraction.

Effect of Food on Oral Absorption

Ezetimibe

Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as 10-mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high-fat meals.

Simvastatin

Relative to the fasting state, the plasma profiles of both active and total inhibitors of HMG-CoA reductase were not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

Distribution

Ezetimibe

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Simvastatin

Both simvastatin and its β -hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. When radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

Metabolism and Excretion

Ezetimibe

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ^{14}C -ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Simvastatin

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β -hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is a basis for an assay in pharmacokinetic studies of the β -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin. The major active metabolites of simvastatin present in human plasma are the β -hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives.

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.

Specific Populations

Geriatric Patients

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥ 65 years) healthy subjects compared to younger subjects.

Simvastatin

In a study including 16 elderly patients between 70 and 78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age.

Pediatric Patients: [See Pediatric Use (8.4).]

Gender

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Ezetimibe

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Black and Caucasian subjects. Studies in Asian subjects indicated that the pharmacokinetics of ezetimibe was similar to those seen in Caucasian subjects.

Hepatic Impairment

Ezetimibe

After a single 10-mg dose of ezetimibe, the mean exposure (based on area under the curve [AUC]) to total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment, the mean AUC for total ezetimibe and ezetimibe increased approximately 4-fold compared to healthy subjects.

Renal Impairment

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl \leq 30 mL/min/1.73 m²), the mean AUC for total ezetimibe and ezetimibe increased approximately 1.5-fold, compared to healthy subjects (n=9).

Simvastatin

Pharmacokinetic studies with another statin having a similar principal route of elimination to that of simvastatin have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal impairment (as measured by creatinine clearance).

Drug Interactions [See also Drug Interactions (7).]

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin. No specific pharmacokinetic drug interaction studies with VYTORIN have been conducted other than the following study with NIASPAN (Niacin extended-release tablets).

Niacin: The effect of VYTORIN (10/20 mg daily for 7 days) on the pharmacokinetics of NIASPAN extended-release tablets (1000 mg for 2 days and 2000 mg for 5 days following a low-fat breakfast) was studied in healthy subjects. The mean C_{max} and AUC of niacin increased 9% and 22%, respectively. The mean C_{max} and AUC of nicotinic acid increased 10% and 19%, respectively (N=13). In the same study, the effect of NIASPAN on the pharmacokinetics of VYTORIN was evaluated (N=15). While concomitant NIASPAN decreased the mean C_{max} of total ezetimibe (1%), and simvastatin (2%), it increased the mean C_{max} of simvastatin acid (18%). In addition, concomitant NIASPAN increased the mean AUC of total ezetimibe (26%), simvastatin (20%), and simvastatin acid (35%).

Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (\geq 1 g/day niacin) of niacin-containing products. [See Warnings and Precautions (5.1) and Drug Interactions (7.4).]

Cytochrome P450: Ezetimibe had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4 and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of statins. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

Simvastatin is a substrate for CYP3A4. Inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy. [See *Warnings and Precautions (5.1); Drug Interactions (7.1).*]

Ezetimibe

Table 4
Effect of Coadministered Drugs on Total Ezetimibe

Coadministered Drug and Dosing Regimen	Total Ezetimibe*	
	Change in AUC	Change in C _{max}
Cyclosporine-stable dose required (75-150 mg BID) ^{†, **}	↑240%	↑290%
Fenofibrate, 200 mg QD, 14 days [†]	↑48%	↑64%
Gemfibrozil, 600 mg BID, 7 days [†]	↑64%	↑91%
Cholestyramine, 4 g BID, 14 days [†]	↓55%	↓4%
Aluminum & magnesium hydroxide combination antacid, single dose [§]	↓4%	↓30%
Cimetidine, 400 mg BID, 7 days	↑6%	↑22%
Glipizide, 10 mg, single dose	↑4%	↓8%
Statins		
Lovasta in 20 mg QD, 7 days	↑9%	↑3%
Pravastatin 20 mg QD, 14 days	↑7%	↑23%
Atorvastatin 10 mg QD, 14 days	↓2%	↑12%
Rosuvastatin 10 mg QD, 14 days	↑13%	↑18%
Fluvastatin 20 mg QD, 14 days	↓19%	↑7%

* Based on 10 mg-dose of ezetimibe

** Post-renal transplant patients with mild impaired or normal renal function. In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m²) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects.

[†] See 7. Drug Interactions

[§] Supralox®, 20 mL

Table 5
Effect of Ezetimibe Coadministration on Systemic Exposure to Other Drugs

Coadministered Drug and its Dosage Regimen	Ezetimibe Dosage Regimen	Change in AUC of Coadministered Drug	Change in C _{max} of Coadministered Drug
Warfarin, 25 mg single dose on Day 7	10 mg QD, 11 days	↓2% (R-warfarin)	↑3% (R-warfarin)
		↓4% (S-warfarin)	↑1% (S-warfarin)
Digoxin, 0.5 mg single dose	10 mg QD, 8 days	↑2%	↓7%
Gemfibrozil, 600 mg BID, 7 days [†]	10 mg QD, 7 days	↓1%	↓11%
Ethinyl estradiol & Levonorgestrel, QD, 21 days	10 mg QD, Days 8-14 of 21 day oral contraceptive cycle	Ethinyl estradiol	Ethinyl estradiol
		0%	↓9%
Levonorgestrel	10 mg QD, Days 8-14 of 21 day oral contraceptive cycle	Levonorgestrel	Levonorgestrel
		0%	↓5%
Glipizide, 10 mg on Days 1 and 9	10 mg QD, Days 2-9	↓3%	↓5%
Fenofibrate, 200 mg QD, 14 days [†]	10 mg QD, 14 days	↑11%	↑7%
Cyclosporine, 100 mg single dose Day 7 [†]	20 mg QD, 8 days	↑15%	↑10%
Statins			
Lovasta in 20 mg QD, 7 days	10 mg QD, 7 days	↑19%	↑3%
Pravastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓20%	↓24%
Atorvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↓4%	↑7%
Rosuvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↑19%	↑17%
Fluvastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓39%	↓27%

[†] See 7. Drug Interactions

Simvastatin

Table 6
Effect of Coadministered Drugs or Grapefruit Juice on Simvastatin Systemic Exposure

Coadministered Drug or Grapefruit Juice	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Simvastatin	Geometric Mean Ratio (Ratio* with / without coadministered drug) No Effect = 1.00		
				AUC	C _{max}
Contraindicated with VYTORIN [see Contraindications (4) and Warnings and Precautions (5.1)]					
Telithromycin [†]	200 mg QD for 4 days	80 mg	simvasta in acid [‡] simvastatin	12 8.9	15 5.3
Nelfinavir [†]	1250 mg BID for 14 days	20 mg QD for 28 days	simvastatin acid [‡] simvastatin	6	6.2
Itraconazole [†]	200 mg QD for 4 days	80 mg	simvasta in acid [‡] simvastatin		13.1 13.1
Posaconazole	100 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid [‡] simvastatin	7.3 10.3	9.2 9.4
	200 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid [‡] simvastatin	8.5 10.6	9.5 11.4
Gemfibrozil	600 mg BID for 3 days	40 mg	simvastatin acid [‡] simvastatin	2.85 1.35	2.18 0.91
Avoid >1 quart of grapefruit juice with VYTORIN [see Warnings and Precautions (5.1)]					
Grapefruit Juice [§] (high dose)	200 mL of double-strength TID [¶]	60 mg single dose	simvastatin acid	7	
			simvastatin	16	
Grapefruit Juice [§] (low dose)	8 oz (about 237 mL) of single-strength [#]	20 mg single dose	simvastatin acid	1.3	
			simvastatin	1.9	
Avoid taking with >10/10 mg VYTORIN, based on clinical and/or post-marketing simvastatin experience [see Warnings and Precautions (5.1)]					
Verapamil SR	240 mg QD Days 1-7 then 240 mg BID on Days 8-10	80 mg on Day 10	simvastatin acid	2.3	2.4
			simvastatin	2.5	2.1
Diltiazem	120 mg BID for 10 days	80 mg on Day 10	simvastatin acid	2.69	2.69
			simvastatin	3.10	2.88
Diltiazem	120 mg BID for 14 days	20 mg on Day 14	simvastatin	4.6	3.6
Avoid taking with >10/20 mg VYTORIN, based on clinical and/or post-marketing simvastatin experience [see Warnings and Precautions (5.1)]					
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	simvastatin acid	1.75	1.72
			simvastatin	1.76	1.79
Amlodipine	10 mg QD for 10 days	80 mg on Day 10	simvastatin acid	1.58	1.56
			simvastatin	1.77	1.47
Ranolazine SR	1000 mg BID for 7 days	80 mg on Day 1 and Days 6-9	simvastatin acid	2.26	2.28
			simvastatin	1.86	1.75
No dosing adjustments required for the following:					
Fenofibrate	160 mg QD for 14 days	80 mg QD on Days 8-14	simvastatin acid	0.64	0.89
			simvastatin	0.89	0.83
Propranolol	80 mg single dose	80 mg single dose	total inhibitor	0.79	↓ from 33.6 to 21.1 ng-eq/mL
			active inhibitor	0.79	↓ from 7.0 to 4.7 ng-eq/mL

* Results based on a chemical assay except results with propranolol as indicated.

† Results could be representative of the following CYP3A4 inhibitors: ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone.

‡ Simvastatin acid refers to the β-hydroxyacid of simvastatin.

§ The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

¶ Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose simvastatin and 30 and 90 minutes following single dose simvastatin on Day 3.

Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and simvastatin was administered in the evening on Day 3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VYTORIN

No animal carcinogenicity or fertility studies have been conducted with the combination of ezetimibe and simvastatin. The combination of ezetimibe with simvastatin did not show evidence of mutagenicity *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with ezetimibe and simvastatin with or without

metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin (1:1) in the *in vivo* mouse micronucleus test.

Ezetimibe

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe).

Simvastatin

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively, (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80-mg daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m²), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day (approximately

2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

13.2 Animal Toxicology and/or Pharmacology

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

Ezetimibe

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED₅₀ value of 0.5 µg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED₅₀ values in dogs, rats, and mice were 7, 30, and 700 µg/kg/day, respectively. These results are consistent with ezetimibe being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (ezetimibe-glucuronide) was administered intraduodenally, the metabolite was as potent as ezetimibe in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03 to 300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of ¹⁴C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat-soluble vitamins A and D.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug-metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with statins (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

VYTORIN

VYTORIN reduces total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C in patients with hyperlipidemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

VYTORIN is effective in men and women with hyperlipidemia. Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of VYTORIN.

Five multicenter, double-blind studies conducted with either VYTORIN or coadministered ezetimibe and simvastatin equivalent to VYTORIN in patients with primary hyperlipidemia are reported: two were

comparisons with simvastatin, two were comparisons with atorvastatin, and one was a comparison with rosuvastatin.

In a multicenter, double-blind, placebo-controlled, 12-week trial, 1528 hyperlipidemic patients were randomized to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or VYTORIN (10/10, 10/20, 10/40, or 10/80).

When patients receiving VYTORIN were compared to those receiving all doses of simvastatin, VYTORIN significantly lowered total-C, LDL-C, Apo B, TG, and non-HDL-C. The effects of VYTORIN on HDL-C were similar to the effects seen with simvastatin. Further analysis showed VYTORIN significantly increased HDL-C compared with placebo. (See Table 7.) The lipid response to VYTORIN was similar in patients with TG levels greater than or less than 200 mg/dL.

Table 7
Response to VYTORIN in Patients with Primary Hyperlipidemia
(Mean^a % Change from Untreated Baseline^b)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG ^a	Non-HDL-C
Pooled data (All VYTORIN doses) ^c	609	-38	-53	-42	+7	-24	-49
Pooled data (All simvastatin doses) ^c	622	-28	-39	-32	+7	-21	-36
Ezetimibe 10 mg	149	-13	-19	-15	+5	-11	-18
Placebo	148	-1	-2	0	0	-2	-2
VYTORIN by dose							
10/10	152	-31	-45	-35	+8	-23	-41
10/20	156	-36	-52	-41	+10	-24	-47
10/40	147	-39	-55	-44	+6	-23	-51
10/80	154	-43	-60	-49	+6	-31	-56
Simvastatin by dose							
10 mg	158	-23	-33	-26	+5	-17	-30
20 mg	150	-24	-34	-28	+7	-18	-32
40 mg	156	-29	-41	-33	+8	-21	-38
80 mg	158	-35	-49	-39	+7	-27	-45

^a For triglycerides, median % change from baseline

^b Baseline - on no lipid-lowering drug

^c VYTORIN doses pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, and non-HDL-C compared to simvastatin and significantly increased HDL-C compared to placebo.

In a multicenter, double-blind, controlled, 23-week study, 710 patients with known CHD or CHD risk equivalents, as defined by the NCEP ATP III guidelines, and an LDL-C \geq 130 mg/dL were randomized to one of four treatment groups: coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10, 10/20, and 10/40) or simvastatin 20 mg. Patients not reaching an LDL-C <100 mg/dL had their simvastatin dose titrated at 6-week intervals to a maximal dose of 80 mg.

At Week 5, the LDL-C reductions with VYTORIN 10/10, 10/20, or 10/40 were significantly larger than with simvastatin 20 mg (see Table 8).

Table 8
Response to VYTORIN after 5 Weeks in Patients with CHD or CHD Risk Equivalents and an LDL-C \geq 130 mg/dL

	Simvastatin 20 mg	VYTORIN 10/10	VYTORIN 10/20	VYTORIN 10/40
N	253	251	109	97
Mean baseline LDL-C	174	165	167	171
Percent change LDL-C	-38	-47	-53	-59

In a multicenter, double-blind, 6-week study, 1902 patients with primary hyperlipidemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of eight treatment groups: VYTORIN (10/10, 10/20, 10/40, or 10/80) or atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg).

Across the dosage range, when patients receiving VYTORIN were compared to those receiving milligram-equivalent statin doses of atorvastatin, VYTORIN lowered total-C, LDL-C, Apo B, and non-HDL-C significantly more than atorvastatin. Only the 10/40 mg and 10/80 mg VYTORIN doses increased HDL-C significantly more than the corresponding milligram-equivalent statin dose of atorvastatin. The effects of VYTORIN on TG were similar to the effects seen with atorvastatin. (See Table 9.)

Table 9
Response to VYTORIN and Atorvastatin in Patients with Primary Hyperlipidemia (Mean^a % Change from Untreated Baseline^b)

Treatment (Daily Dose)	N	Total-C ^c	LDL-C ^c	Apo B ^c	HDL-C	TG ^a	Non-HDL-C ^c
VYTORIN by dose							
10/10	230	-34 ^d	-47 ^d	-37 ^d	+8	-26	-43 ^d
10/20	233	-37 ^d	-51 ^d	-40 ^d	+7	-25	-46 ^d
10/40	236	-41 ^d	-57 ^d	-46 ^d	+9 ^d	-27	-52 ^d
10/80	224	-43 ^d	-59 ^d	-48 ^d	+8 ^d	-31	-54 ^d
Atorvastatin by dose							
10 mg	235	-27	-36	-31	+7	-21	-34
20 mg	230	-32	-44	-37	+5	-25	-41
40 mg	232	-36	-48	-40	+4	-24	-45
80 mg	230	-40	-53	-44	+1	-32	-50

^a For triglycerides, median % change from baseline

^b Baseline - on no lipid-lowering drug

^c VYTORIN doses pooled (10/10-10/80) provided significantly greater reductions in total-C, LDL-C, Apo B, and non-HDL-C compared to atorvastatin doses pooled (10-80).

^d p<0.05 for difference with atorvastatin at equal mg doses of the simvastatin component

In a multicenter, double-blind, 24-week, forced-titration study, 788 patients with primary hyperlipidemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to receive coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/10 and 10/20) or atorvastatin 10 mg. For all three treatment groups, the dose of the statin was titrated at 6-week intervals to 80 mg. At each pre-specified dose comparison, VYTORIN lowered LDL-C to a greater degree than atorvastatin (see Table 10).

Table 10
Response to VYTORIN and Atorvastatin in Patients with Primary Hyperlipidemia
(Mean^a % Change from Untreated Baseline^b)

Treatment	N	Total-C	LDL-C	Apo B	HDL-C	TG ^a	Non-HDL-C
Week 6							
Atorvastatin 10 mg ^c	262	-28	-37	-32	+5	-23	-35
VYTORIN 10/10 ^d	263	-34 ^f	-46 ^f	-38 ^f	+8 ^f	-26	-43 ^f
VYTORIN 10/20 ^e	263	-36 ^f	-50 ^f	-41 ^f	+10 ^f	-25	-46 ^f
Week 12							
Atorvastatin 20 mg	246	-33	-44	-38	+7	-28	-42
VYTORIN 10/20	250	-37 ^f	-50 ^f	-41 ^f	+9	-28	-46 ^f
VYTORIN 10/40	252	-39 ^f	-54 ^f	-45 ^f	+12 ^f	-31	-50 ^f
Week 18							
Atorvastatin 40 mg	237	-37	-49	-42	+8	-31	-47
VYTORIN 10/40 ^g	482	-40 ^f	-56 ^f	-45 ^f	+11 ^f	-32	-52 ^f
Week 24							
Atorvastatin 80 mg	228	-40	-53	-45	+6	-35	-50
VYTORIN 10/80 ^g	459	-43 ^f	-59 ^f	-49 ^f	+12 ^f	-35	-55 ^f

^a For triglycerides, median % change from baseline

^b Baseline - on no lipid-lowering drug

^c Atorvastatin: 10 mg start dose titrated to 20 mg, 40 mg, and 80 mg through Weeks 6, 12, 18, and 24

^d VYTORIN: 10/10 start dose titrated to 10/20, 10/40, and 10/80 through Weeks 6, 12, 18, and 24

^e VYTORIN: 10/20 start dose titrated to 10/40, 10/40, and 10/80 through Weeks 6, 12, 18, and 24

^f p≤0.05 for difference with atorvastatin in the specified week

^g Data pooled for common doses of VYTORIN at Weeks 18 and 24.

In a multicenter, double-blind, 6-week study, 2959 patients with primary hyperlipidemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of six treatment groups: VYTORIN (10/20, 10/40, or 10/80) or rosuvastatin (10 mg, 20 mg, or 40 mg).

The effects of VYTORIN and rosuvastatin on total-C, LDL-C, Apo B, TG, non-HDL-C and HDL-C are shown in Table 11.

Table 11
Response to VYTORIN and Rosuvastatin in Patients with Primary Hyperlipidemia
(Mean^a % Change from Untreated Baseline^b)

Treatment (Daily Dose)	N	Total-C ^c	LDL-C ^c	Apo B ^c	HDL-C	TG ^a	Non-HDL-C ^c
VYTORIN by dose							
10/20	476	-37 ^d	-52 ^d	-42 ^d	+7	-23 ^d	-47 ^d
10/40	477	-39 ^e	-55 ^e	-44 ^e	+8	-27	-50 ^e
10/80	474	-44 ^f	-61 ^f	-50 ^f	+8	-30 ^f	-56 ^f
Rosuvasta in by dose							
10 mg	475	-32	-46	-37	+7	-20	-42
20 mg	478	-37	-52	-43	+8	-26	-48
40 mg	475	-41	-57	-47	+8	-28	-52

^a For triglycerides, median % change from baseline

^b Baseline - on no lipid-lowering drug

^c VYTORIN doses pooled (10/20-10/80) provided significantly greater reductions in total-C, LDL-C, Apo B, and non-HDL-C compared to rosuvastatin doses pooled (10-40 mg).

^d p<0.05 vs. rosuvastatin 10 mg

^e p<0.05 vs. rosuvastatin 20 mg

^f p<0.05 vs. rosuvastatin 40 mg

In a multicenter, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks were randomized to receive either simvastatin 40 mg or the coadministered active ingredients equivalent to VYTORIN 10/20. The median LDL-C and HbA1c levels at baseline were 89 mg/dL and 7.1%, respectively.

VYTORIN 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg. The median percent changes from baseline for VYTORIN vs. simvastatin were: LDL-C -25% and -5%; total-C -16% and -5%; Apo B -19% and -5%; and non-HDL-C -23% and -5%. Results for HDL-C and TG between the two treatment groups were not significantly different.

Ezetimibe

In two multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hyperlipidemia, ezetimibe significantly lowered total-C (-13%), LDL-C (-19%), Apo B (-14%), and TG (-8%), and increased HDL-C (+3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

Simvastatin

In two large, placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (N=4,444 patients) and the Heart Protection Study (N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths; the risk of non-fatal myocardial infarction and stroke; and the need for coronary and non-coronary revascularization procedures.

No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

14.2 Homozygous Familial Hypercholesterolemia (HoFH)

A double-blind, randomized, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analyzed from a subgroup of patients (n=14) receiving simvastatin 40 mg at baseline. Increasing the dose of simvastatin from 40 to 80 mg (n=5) produced a reduction of LDL-C of 13% from baseline on simvastatin 40 mg. Coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/40 and 10/80 pooled, n=9), produced a reduction of LDL-C of 23% from baseline on simvastatin 40 mg. In those patients coadministered ezetimibe and simvastatin equivalent to VYTORIN (10/80, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3873 — Tablets VYTORIN 10/10 are white to off-white capsule-shaped tablets with code “311” on one side.

They are supplied as follows:

NDC 66582-311-31 bottles of 30

NDC 66582-311-54 bottles of 90

NDC 66582-311-82 bottles of 1000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-311-87 bottles of 10,000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-311-28 unit dose packages of 100.

No. 3874 — Tablets VYTORIN 10/20 are white to off-white capsule-shaped tablets with code “312” on one side.

They are supplied as follows:

NDC 66582-312-31 bottles of 30

NDC 66582-312-54 bottles of 90

NDC 66582-312-82 bottles of 1000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-312-87 bottles of 10,000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-312-28 unit dose packages of 100.

No. 3875 — Tablets VYTORIN 10/40 are white to off-white capsule-shaped tablets with code “313” on one side.

They are supplied as follows:

NDC 66582-313-31 bottles of 30

NDC 66582-313-54 bottles of 90

NDC 66582-313-74 bottles of 500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-313-86 bottles of 5000 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-313-52 unit dose packages of 50.

No. 3876 — Tablets VYTORIN 10/80 are white to off-white capsule-shaped tablets with code “315” on one side.

They are supplied as follows:

NDC 66582-315-31 bottles of 30

NDC 66582-315-54 bottles of 90

NDC 66582-315-74 bottles of 500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-315-66 bottles of 2500 (If repackaged in blisters, then opaque or light-resistant blisters should be used.)

NDC 66582-315-52 unit dose packages of 50.

Storage

Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Keep container tightly closed.

Storage of 10,000, 5000, and 2500 count bottles

Store bottle of 10,000 VYTORIN 10/10 and 10/20, 5000 VYTORIN 10/40, and 2500 VYTORIN 10/80 capsule-shaped tablets at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Store in original container until time of use. When product container is subdivided, repackage into a tightly-closed, light-resistant container. Entire contents must be repackaged immediately upon opening.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

Patients should be advised about substances they should not take concomitantly with VYTORIN [see Contraindications (4) and Warnings and Precautions (5.1)]. Patients should also be advised to inform other healthcare professionals prescribing a new medication or increasing the dose of an existing medication that they are taking VYTORIN.

17.1 Muscle Pain

All patients starting therapy with VYTORIN should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. **Patients using the 10/80-mg dose should be informed that the risk of myopathy, including rhabdomyolysis, is increased with the use of the 10/80-mg dose.** The risk of myopathy, including rhabdomyolysis, occurring with use of VYTORIN is increased when taking certain types of medication or consuming larger quantities of grapefruit juice. Patients should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes

It is recommended that liver function tests be performed before the initiation of VYTORIN, and thereafter when clinically indicated. All patients treated with VYTORIN should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using VYTORIN. Discuss future pregnancy plans with your patients, and discuss when to stop taking VYTORIN if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking VYTORIN and call their healthcare professional.

17.4 Breast-feeding

Women who are breast-feeding should be advised to not use VYTORIN. Patients who have a lipid disorder and are breast-feeding should be advised to discuss the options with their healthcare professional.



MERCK/Schering-Plough Pharmaceuticals

Manufactured for:
MERCK/Schering-Plough Pharmaceuticals
North Wales, PA 19454, USA

By:
MSD Technology Singapore Pte. Ltd.
Singapore 637766

Or

Merck Sharp & Dohme (Italia) S.p.A.
Via Emilia, 21
27100 – Pavia, Italy

Or

Merck Sharp & Dohme Ltd.
Cramlington, Northumberland, UK NE23 3JU

Or

Jointly manufactured by:
Merck Sharp & Dohme (Italia) S.p.A.
Via Emilia, 21

VYTORIN® (ezetimibe/simvastatin) Tablets

9619519

27100 – Pavia, Italy
and
MSD Technology Singapore Pte. Ltd.
Singapore 637766

U.S. Patent Nos. 5,846,966 and RE37,721

Revised: 10/2011

9619519

VYTORIN® (ezetimibe/simvastatin) Tablets

Patient Information about VYTORIN (VI-tor-in)

Generic name: ezetimibe/simvastatin tablets

Read this information carefully before you start taking VYTORIN. Review this information each time you refill your prescription for VYTORIN as there may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about VYTORIN, ask your doctor. Only your doctor can determine if VYTORIN is right for you.

What is VYTORIN?

VYTORIN contains two cholesterol-lowering medications, ezetimibe and simvastatin. VYTORIN is a prescription medicine used to lower levels of total cholesterol, LDL (bad) cholesterol, and fatty substances called triglycerides in the blood. In addition, VYTORIN raises levels of HDL (good) cholesterol. VYTORIN is for patients who cannot control their cholesterol levels by diet and exercise alone. You should stay on a cholesterol-lowering diet while taking this medicine.

VYTORIN works to reduce your cholesterol in two ways. It reduces the cholesterol absorbed in your digestive tract, as well as the cholesterol your body makes by itself. VYTORIN does not help you lose weight.

VYTORIN has not been shown to reduce heart attacks or strokes more than simvastatin alone.

The usual dose of VYTORIN is 10/10 mg to 10/40 mg 1 time each day.

VYTORIN 10/80 mg increases your chance of developing muscle damage. The 10/80 mg dose should only be used by people who:

- have been taking VYTORIN 10/80 mg chronically (such as 12 months or more) without having muscle damage
- do not need to take certain other medicines with VYTORIN that would increase your chance of getting muscle damage.

If you are unable to reach your LDL-cholesterol goal using VYTORIN 10/40 mg, your doctor should switch you to another cholesterol-lowering medicine.

For more information about cholesterol, see the section called “What should I know about high cholesterol?”

Who should not take VYTORIN?

Do not take VYTORIN if you take:

- Certain anti-fungal medicines including:
 - itraconazole
 - ketoconazole
 - posaconazole
- HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir, tipranavir, or atazanavir),
- Certain antibiotics, including:
 - erythromycin
 - clarithromycin
 - telithromycin
- nefazodone
- A fibric acid medicine for lowering cholesterol called gemfibrozil
- cyclosporine

- danazol

Ask your doctor if you are not sure if your medicine is listed above.

Also do not take VYTORIN:

- If you are allergic to ezetimibe or simvastatin, the active ingredients in VYTORIN, or to the inactive ingredients. For a list of inactive ingredients, see the “Inactive ingredients” section at the end of this information sheet.
- If you have active liver disease or repeated blood tests indicating possible liver problems.
- If you are pregnant, or think you may be pregnant, or planning to become pregnant or breast-feeding.
- If you are a woman of childbearing age, you should use an effective method of birth control to prevent pregnancy while using VYTORIN.

VYTORIN has not been studied in children under 10 years of age.

What should I tell my doctor before and while taking VYTORIN?

Tell your doctor right away if you have unexplained muscle pain, tenderness, or weakness while you take VYTORIN. Muscle problems, including muscle breakdown, can be serious in some people and rarely cause kidney damage that can lead to death.

The risk of muscle breakdown is greater at higher doses of VYTORIN, particularly the 10/80 mg dose.

The risk of muscle breakdown is greater in people 65 years of age and older, females, and people with kidney or thyroid problems.

Taking VYTORIN with certain substances can increase the risk of muscle problems. It is especially important to tell your doctor if you take:

- fibric acid derivatives (such as fenofibrate)
- amiodarone (a drug used to treat an irregular heartbeat)
- verapamil, diltiazem, amlodipine, or ranolazine (drugs used to treat high blood pressure, chest pain associated with heart disease, or other heart conditions)
- large quantities of grapefruit juice (more than 1 quart daily)
- colchicine (a medicine used to treat gout)
- voriconazole (an anti-fungal medicine)
- large doses of niacin or nicotinic acid

Tell your doctor if you are taking niacin or a niacin-containing product, as this may increase your risk of muscle problems, especially if you are Chinese.

It is also important to tell your doctor if you are taking coumarin anticoagulants (drugs that prevent blood clots, such as warfarin).

Tell your doctor about all the medicines you take, including any prescription and nonprescription medicines, vitamins, and herbal supplements.

If you have more than 1 doctor, tell all of your doctors that you take VYTORIN. This is especially important when they prescribe a new medicine or increase the dose of your other medicines.

Tell your doctor about all your medical conditions including allergies.

Tell your doctor if you:

- drink substantial quantities of alcohol or ever had liver problems. VYTORIN may not be right for you.
- are pregnant or plan to become pregnant. Do not use VYTORIN if you are pregnant, trying to become pregnant or suspect that you are pregnant. If you become pregnant while taking VYTORIN, stop taking it and contact your doctor immediately.
- are breast-feeding. Do not use VYTORIN if you are breast-feeding.

Tell other doctors prescribing a new medication that you are taking VYTORIN.

How should I take VYTORIN?

- Take VYTORIN exactly as your doctor tells you to take it.
- Take VYTORIN once a day, in the evening, with or without food.
- If you miss a dose, do not take an extra dose. Just resume your usual schedule.
- Continue to follow a cholesterol-lowering diet while taking VYTORIN. Ask your doctor if you need diet information.
- Keep taking VYTORIN unless your doctor tells you to stop. If you stop taking VYTORIN, your cholesterol may rise again.

What should I do in case of an overdose?

Contact your doctor immediately.

What are the possible side effects of VYTORIN?

See your doctor regularly to check your cholesterol level and to check for side effects. Your doctor should do blood tests to check your liver before you start taking VYTORIN and if you have any symptoms of liver problems while you take VYTORIN. Call your doctor right away if you have the following symptoms of liver problems:

- feel tired or weak
- loss of appetite
- upper belly pain
- dark urine
- yellowing of your skin or the whites of your eyes

In clinical studies patients reported the following common side effects while taking VYTORIN: headache, muscle pain, and diarrhea (see What should I tell my doctor before and while taking VYTORIN?).

The following side effects have been reported in general use with VYTORIN or with ezetimibe or simvastatin tablets (tablets that contain the active ingredients of VYTORIN):

- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (which may require treatment right away), rash, hives; raised red rash, sometimes with target-shaped lesions; joint pain; muscle pain; alterations in some laboratory blood tests; liver problems (sometimes serious); inflammation of the pancreas; nausea; dizziness; tingling sensation; depression; gallstones; inflammation of the gallbladder; trouble sleeping; poor memory; erectile dysfunction; breathing problems including persistent cough and/or shortness of breath or fever.

Tell your doctor if you are having these or any other medical problems while on VYTORIN. This is not a complete list of side effects. For a complete list, ask your doctor or pharmacist.

What should I know about high cholesterol?

Cholesterol is a type of fat found in your blood. Cholesterol comes from two sources. It is produced by your body and it comes from the food you eat. Your total cholesterol is made up of both LDL and HDL cholesterol.

LDL cholesterol is called “bad” cholesterol because it can build up in the wall of your arteries and form plaque. Over time, plaque build-up can cause a narrowing of the arteries. This narrowing can slow or block blood flow to your heart, brain, and other organs. High LDL cholesterol is a major cause of heart disease and one of the causes for stroke.

HDL cholesterol is called “good” cholesterol because it keeps the bad cholesterol from building up in the arteries.

Triglycerides also are fats found in your body.

General Information about VYTORIN

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use VYTORIN for a condition for which it was not prescribed. Do not give VYTORIN to other people, even if they have the same condition you have. It may harm them.

This summarizes the most important information about VYTORIN. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about VYTORIN that is written for health professionals. For additional information, visit the following web site: vytorin.com.

Inactive ingredients:

Butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hypromellose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.



Manufactured for:
Merck/Schering-Plough Pharmaceuticals
North Wales, PA 19454, USA

This patient information has been approved by the U.S. Food and Drug Administration

Revised: 10/2011

9619519

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
10/06/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022687Orig1s041

MEDICAL REVIEW(S)

Clinical Review for Statin Class Labeling Changes

February 15, 2012

Amy G. Egan, M.D., M.P.H.

On August 11, 2011 the Division of Metabolism and Endocrinology Products (DMEP) issued supplement request letters to the sponsors of all HMG-CoA reductase inhibitor (statin) drugs requesting changes to the labeling so as to furnish adequate information for the safe and effective use of their statin. These labeling changes were based on FDA's comprehensive review of the statin class of drugs, including clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin co-administration. This review will serve to summarize the safety issues and the sources and reviews of the data.

1. Liver enzyme abnormalities – TSI #57

On March 19, 2007 DMEP opened Tracked Safety Issue (TSI) #57 to evaluate hepatotoxicity associated with the statin class of drugs. This was based on articles in the published literature which suggested that FDA should re-evaluate current recommendations in statin labeling for routine periodic monitoring of liver enzyme tests.

In March 2008, DMEP issued Information Request letters to the statin sponsors requesting the following:

- a. Does <<APPLICANT>> have an opinion or recommendation regarding the utility of baseline and/or periodic monitoring of serum aminotransferase activity prior to and/or during treatment with <<STATIN>>? Please address this question for subjects with normal liver function and for those with asymptomatic liver disease (e.g., NAFLD, hepatitis C).
- b. Upon what clinical evidence or other consideration are these opinions or recommendations based?
- c. Please provide the number of phase 2 and 3 trials conducted with <<STATIN>> for which you have access to the raw data.

The table below summarizes the sponsors' responses to the first question:

Table 10. Overview of Industry responses to FDA questions on hepatotoxicity of statins			
Sponsor	Product	Text suggests interest in withdrawal of monitoring	caveats
Andrx	Lovastatin ER	No	none
AstraZeneca	rosuvastatin	Yes	none
Bristol-Myers Squibb	pravastatin	N/A	No text to delete
Merck	lovastatin	No	None
Merck	simvastatin	No	None
Novartis	fluvastatin	No	None
Pfizer	atorvastatin	Yes	10 mg dose only

In general, most sponsors agreed that liver enzyme testing prior to initiation of statin therapy was appropriate, but acknowledged that there appeared to be limited utility to routine liver biochemistry monitoring during treatment. One sponsor commented on the recommendations of the Liver Expert Panel convened by the National Lipid Association which stated that “because there is no evidence that a relation exists between elevated serum aminotransferase levels and significant liver injury, or that routine monitoring of liver biochemistries will identify individuals likely to develop rare cases of idiosyncratic liver failure, the requirement for routine liver biochemistry monitoring in patients receiving any of the currently marketed statin therapies should be re-examined.” Another sponsor noted that “nearly 50% of hyperlipidemic patients have coexisting non-alcoholic fatty liver disease (NAFLD) and it is well known that LFT levels fluctuate in NAFLD.”

In conjunction with the request to statin sponsors, DMEP requested that the Office of Surveillance and Epidemiology (OSE) conduct a review to characterize the risk of clinically serious hepatotoxicity in association with statins and assist in a determination if the statin class labeling for liver enzyme monitoring should be retained, revised, or removed. OSE had conducted 5 postmarket reviews of statins and hepatotoxicity between 2000 and 2009. Those reviews had consistently noted that reporting of statin-associated serious liver injury to AERS was extremely low (reporting rate of ≤ 2 per one million patient-years).

The OSE review of AERS was completed May 13, 2011. The review focused on cases of severe liver injury, defined as a 4 (severe liver injury) or a 5 (death or liver transplant) using the Drug Induced Liver Injury Network (DILIN) liver injury severity scale. Cases meeting those criteria were further assessed for causality. Seventy-five cases (27 with a severity score of 4 and 48 with a severity score of 5 [37 deaths and 11 liver transplants]) were assessed for causality, 30 of which (14 deaths, 7 liver transplantations, and 9 severe liver injury) were assessed as possibly (25-49% likelihood) or probably (50-74% likelihood) associated with

statin therapy. No cases were assessed as highly likely (75-95% likelihood) or definitely (>95% likelihood) associated with statin therapy. OSE noted that “despite rising use of statins as a class since the late 1990s, there has not been a detectable uptick in the annual rates of fatal (deaths or liver transplant) or severe liver injury possibly or probably causally associated cases.” The cases are summarized in the table below:

Table 6. Characteristics of U.S. AERS Cases With A Liver Injury Severity Score of 4 (Severe) or 5 (Death or Transplant) and Causally Associated* With Statin Therapy. Source: AERS, marketing through January 1, 2009			
Liver Injury Severity Score	5 (Death)	5 (Transplant)	4 (Severe)
# of Cases	14	7	9
Median Age in Years (range)	66 (51-89)	48 (40-71)	58 (47-71)
Percent Female	79% (11/14)	71% (5/7)	67% (6/9)
Statin at the Time of Event Median Daily Dose in mg (range [n])			
Atorvastatin	4 -- (10, 10 [n=2])	3 10 (10-20 [n=3])	4 10 (10-20 [n=3])
Cerivastatin	--	--	--
Fluvastatin	--	--	1 -- (20 [n=1])
Lovastatin	1 -- (20 [n=1])	1 -- (-- [n=0])	--
Pravastatin	3 -- (20, 40 [n=2])	--	1 -- (10 [n=1])
Rosuvastatin	--	--	--
Simvastatin	6 20 (10-40 [n=5])	3 20 (20-40 [n=3])	3 -- (40 [n=1])
Time to Onset in Months**, Median (range)	2.5 (3 wk – 12 mo)	1.5 (2.4 wk - 6 mo)	2 (5 wk – 8 mo)
Peak Serum Total Bilirubin Level in mg/dL, Median (range [n])	23 (2.9-51 [n=12])	27 (22-32 [n=4])	10 (1.2-25 [n=9])
Peak Serum ALT Level in units/L, Median (range[n]) reference range: 6-41 units/L	1,127 (148-4,300 [n=10])	2,912 (2,037-13,531[n=4])	1,319 (538-3,000 [n=9])
Peak Serum AST Level in units/L, Median (range[n]) reference range: 9-34 units/L	1,497 (81-7,200 [n=11])	2,294 (1,755-6,815 [n=4])	1,260 (853-3,000 [n=9])
Peak Serum ALP Level in units/L, Median (range[n]) reference range: 37-116 units/L	206 (155-623 [n=9])	-- (290, 602 [n=2])	307 (131-800 [n=4])

*Defined as probably associated (supported by the evidence as implicating the drug but not definite or highly likely) or possibly associated (causality is not supported by the preponderance of evidence, but one cannot definitively exclude the possibility)

**Time to onset defined as the interval between exposure time or time after dose increased to reported liver injury event

OSE also looked at cases from the DILIN and Acute Liver Failure Study Group (ALFSG), organizations which have been systematically submitting reports to FDA of drug associated liver injury referred to their respective liver injury outcome studies. For statin associated liver injury, DILIN has submitted 25 reports to FDA as of January 1, 2011, twelve of which resulted in an outcome of hospitalization. In the ALFSG database, there were 9 reports of drug-induced liver injury (DILI) associated with statin therapy. OSE cited a 2010 article from

ALFSG that included 133 prospectively identified cases of idiopathic DILI resulting in acute liver failure. Fifteen patients were taking statins and in 6 of these 15 individuals a statin was identified as the only potential DILI agent. The authors noted that statin hepatotoxicity is “generally benign” and the identification of these 6 cases represents a “provocative observation”.

Using the AERS and drug utilization databases, reporting rates were calculated for U.S. statin cases associated with liver injury and an outcome of death or liver transplant, from the time of initial marketing approval through January 1, 2009. It should be noted that reporting rates are subject to secular reporting trends which normally preclude generation of reporting rates between products with initial marketing dates greater than 2-4 years apart. Despite the limitations of the analysis, it appears that reporting levels for serious liver injury in association with currently marketed statins are generally similar.

Table 9. Number of U.S. Statin Cases Associated with Liver Injury and an Outcome of Death or Liver Transplant (Severity Score 5). Initial Marketing Approval Through January 1, 2009

Generic Name (Brand)	Number of cases	Total Number of Prescriptions (TRxs) Dispensed by U.S. Retail Pharmacies, 1991-2008† (in millions)	Observed reporting rate (b) (4)
Lovastatin (Mevacor, Advicor, Altocor)	23	(b) (4)	(b) (4)
Pravastatin (Pravachol)	11		
Simvastatin (Zocor, Vytorin, Simcor)	51		
Fluvastatin (Lescol)	4		
Atorvastatin (Lipitor)	64		
Rosuvastatin (Crestor)	3		
Total	156		

OSE also reviewed current monitoring guidelines including the National Lipid Association’s Liver Expert Panel, which state:

The Liver Expert Panel does not believe that the available scientific evidence supports the routine monitoring of liver biochemistries in asymptomatic patients receiving statins. The Panel makes this recommendation because (1) irreversible liver damage resulting from statins is exceptionally rare and is likely idiosyncratic in nature, and (2) no data exist to show that routine monitoring of liver biochemistries is effective in identifying the very rare individual who may develop significant liver injury from ongoing statin therapy. In the view of the Panel, routine monitoring will instead identify patients with isolated

increased aminotransferase levels, which could motivate physicians to alter or discontinue statin therapy, thereby placing patients at increased risk for cardiovascular events.

OSE further noted that the NLA's Statin Safety Task Force had a slightly divergent opinion and made the following recommendation:

Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.

The OSE review concluded:

Serious, hepatocellular DILI can be caused by statins. Although the routine monitoring of serum ALT and other markers for liver injury is vital for drug development, it does not appear to be useful in a post-marketing, non-study, ambulatory setting to routinely detect and prevent serious liver injury in association with statins. In place of current recommendations for serum enzyme monitoring, labeling for statins should focus on an alert to identify serious liver injury and clinical symptoms of liver injury, interruption of therapy, physician interactions, and emphasize the importance of appropriate diagnostic work-up.

OSE further recommended:

It is justified that the recommendation to perform routine periodic serum ALT monitoring in all treated patients at prespecified intervals currently in place for some marketed statins be removed.

Based on these recommendations, DMEP requested the following changes to statin labeling:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, under **WARNINGS AND PRECAUTIONS**:

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter.

Under **5 WARNINGS AND PRECAUTIONS**, [REDACTED] (b) (4) :

It is recommended that liver enzyme tests be performed before the initiation of <<STATIN>> [REDACTED] (b) (4).

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including <<STATIN>>. If serious liver injury with clinical symptoms and/or

hyperbilirubinemia or jaundice occurs during treatment with <<STATIN>>, promptly interrupt therapy. If an alternate etiology is not found do not restart <<STATIN>>.

Under **6 ADVERSE REACTIONS, Post-Marketing Experience:**

(b) (4)

Under **17 PATIENT COUNSELING INFORMATION, Liver Enzymes:**

It is recommended that liver enzyme tests be (b) (4) before the initiation of <<STATIN>> and if signs or symptoms of liver injury occur. All patients treated with <<STATIN>> should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

(b) (4)

2. Cognitive effects – TSI #772

On September 2, 2009 DMEP opened TSI #772 to evaluate the effect of statins on cognition. This was based on a complaint received from Joe Graedon of the People’s Pharmacy, and an unpublished study by Duane Graveline, M.D., M.P.H. and Jay S. Cohen, M.D. entitled “Lipitor-associated memory loss: analysis of 662 cases of cognitive damage”, as well as other articles from the published literature.

In attempting to assess this risk, DMEP looked initially at pre-clinical data. Several of the statin drug sponsors had performed pre-clinical cognition studies; however, those studies only address the issue of dementia syndromes, and are less helpful in addressing the issue of acute confusional states or memory impairment. Therefore, it was determined that there was no value added to re-assessing the pre-clinical data.

DMEP sent information request letters to those statin sponsors who had conducted clinical trials in which some form of neurocognitive assessment had been conducted as part of the study protocol. Those trials included: Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Heart Protection Study (HPS), and Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

The findings were as follows:

- **PROSPER:** Subjects were screened with a Mini Mental Status Exam (MMSE) and excluded if their score was <24. Cognitive function was assessed in all 5,804 participants at six different time points during the study.

Four neuropsychological tests were performed, two of which tested executive function (attention and speed) and two of which tested memory (immediate and delayed). All tests showed a significant decline over time (3-year follow-up); however, there was no difference between treatment groups, pravastatin 40 mg versus placebo.

- **HPS:** A modified Telephone Interview for Cognitive Status (TICS-m) questionnaire was administered to participants during their final follow-up, either face-to-face in the clinic or over the telephone. Data were available on 8086/10269 (79%) of simvastatin-allocated subjects and 7834/10267 (76%) of placebo-allocated subjects. No significant differences were observed between the treatment groups in the percentages of participants classified as cognitively impaired (defined as a TICS-m score below 22 out of 39), either overall (23.7% simvastatin 40 mg-allocated vs. 24.2% placebo-allocated) or in subgroups defined with respect to their age at study entry (<65 years: 17.1% vs. 17.8%; 65-69 years: 25.8% vs. 25.4%; 70-80 years: 34.6% vs. 36.2%) or their previous history of cerebrovascular disease (no prior stroke: 22.8% vs. 23.3%; prior stroke: 31.9% vs. 33.3%). Nor was there any significant difference between the groups in mean TICS-m score (24.08 vs. 24.06). Similar numbers of participants in each treatment group were reported to have developed dementia during follow-up (31 [0.3%] vs. 31 [0.3%]).

There was a slightly higher frequency of cases of Alzheimer's disease or Alzheimer's type dementia in patients on simvastatin (n=6) compared to placebo (n=3). When looking at all patients with potential diagnoses of dementia including Alzheimer's disease, confusion, disorientation, dementia or cognitive impairment, there was no difference in the frequency of patients in the simvastatin group (n=35; 0.34%) compared to placebo (n=33; 0.32%).

- **SEARCH:** Assessment of cognitive function, using the TICS-m score, was a tertiary endpoint for the folate arm of the trial. It was performed in 8891 subjects – 4473 on simvastatin 80 mg and 4418 on simvastatin 20 mg – at the final visit. There was no difference in mean TICS-m score between treatment groups (24.3 ± 4.1 for simvastatin 80 mg vs. 24.3 ± 4.3 for simvastatin 20 mg), and no difference in percentages of patients with scores <20, ≥ 20 , <22, ≥ 22 , <25, ≥ 25 , <30, ≥ 30 between treatment groups. The TICS-m score reflects memorizing ability in large part. Verbal fluency scores also did not differ among patients allocated to simvastatin 80 mg and simvastatin 20 mg. Hearing thresholds were assessed at final follow-up and did not differ between the simvastatin groups.

The incidence of memory loss attributed to study treatment was 17 (0.3%) in patients allocated to simvastatin 80 mg, and 8 (0.1%) in patients allocated to simvastatin 20 mg.

It should also be noted that while no formal neurocognitive assessment was performed in the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), there was noted a

statistically significant increase in the reported adverse event of confusional state in subjects allocated to rosuvastatin 20 mg (n=8 [0.2%]) versus subjects allocated to placebo (n=4 [0.04%]).

DMEP was aware of a Phase III efficacy study of atorvastatin that had been conducted in patients with mild to moderate Alzheimer's Disease. The clinical study report for this study (Study A2581078) was requested from the sponsor and consulted to the Division of Neurology Products (DNP) for review. DNP's findings were as follows:

The results of Study A2581078, an adequately-designed Phase III efficacy and safety study of atorvastatin (Lipitor) in patients with mild to moderate Probable Alzheimer's Disease, provide no evidence that the administration of Lipitor results in cognitive worsening in this population; neither was there any evidence of a worsening of global function in those treated with atorvastatin in this study.

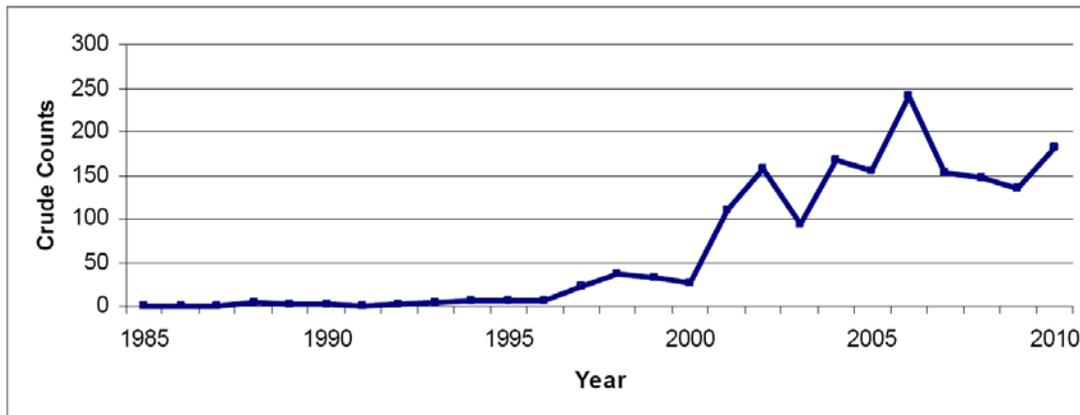
DMEP consulted OSE and requested that a review of AERS and the published literature be conducted to further assess the effect of statins on cognition. In 2002, OSE had performed a review of 279 statin reports associated with transient memory loss. This review had been requested by DMEP in response to a consumer report of transient global amnesia (TGA) with atorvastatin. At that time, OSE determined that the calculated reporting rate for statin-associated TGA (0.12-0.55 per 100,000 patient years) was well below the background incidence rate (3.4-32/100,000 population per year). As memory loss was already included in the statin labels, no labeling change was recommended at that time.

OSE's updated review of AERS focused on reports of serious cases of memory impairment, using the following High Level Terms (HLT):

- Mental Impairment (excluding dementia and memory loss)
- Memory Loss (excluding dementia)
- Amnestic Symptoms
- Confusion and Disorientation

Through January 1, 2011 there were 1,698 U.S. serious reports (crude counts) in AERS.

Figure 1. Number of U.S. Serious Statin* Reports (Crude Counts) Associated with Cognitive Change†, by Year Received. Source: AERS, Initial Marketing Approval Through January 1, 2011 (n=1,698)



*Includes single ingredient and combination statin products approved by FDA.

†Reports identified in AERS using four HLTs: Mental Impairment (excluding dementia & memory loss), Memory Loss (excluding dementia), Amnestic Symptoms, and Confusion and Disorientation

Further case review was limited to 182 reports received by FDA in 2010. Of those reports, 57 unique cases described transient cognitive change as the primary adverse event. Sixty-nine percent (n=125) of the cases were excluded because they reported multiple events such as rhabdomyolysis, renal failure, and confusion (n=81), were duplicates (n=18), hearsay (n=3), reported by attorneys (n=5), or solicited reports (n=16).

Characteristics of the 57 cases included:

- Age: median of 62 years (30-85)
- Sex: 62% male
- Exposure time: median of 3 years (1 month-12 years)

The literature review included case series of transient cognitive impairment associated with statin use, as well as observational studies on the association between statin use and the incidence of dementia. The observational evidence was summarized based on a meta-analysis by Zhou and colleagues:

After conducting a systematic review, the authors identified four cohort studies and three case-control studies which examined the association between statin use and dementia. The average observation period ranged from three to nine years. Three case-control studies suggested statin use may lower the incidence of dementia; while the remaining four cohort studies failed to demonstrate an association between statin use and incident dementia. A pooled analysis also failed to demonstrate an association between statin use and incident dementia.

OSE further noted:

Results from three prospective cohort studies published within the last year provide similar conflicting results. Analyses of Baltimore Longitudinal Study of Aging and the Ginkgo Evaluation of Memory Study suggested that statin use is associated with a lower risk of dementia. A nested-case control study in the Neurological Disorders in Central Spain cohort failed to detect an association between statin use and cross-sectional performance on a neuropsychological test battery.

Table 5. Observational Studies Summary: Statin Use and Cognition				
Author (Publication Date)	Study Design	Total Sample Size (% Exposed to Statins)	Outcome	Key Result
Zhou (2007)	Meta-Analysis – Observational Studies	10523 (12%)	Incident Dementia	Adjusted OR=0.77 (95%: 0.45-1.30)
Beydoun (2010)	Cohort Study	1604 (7%)	Incident Dementia	Adjusted HR=0.21 (95%: 0.09-0.48)
Betterman (2011)	Cohort Study	3069 (25%)	Incident Dementia	Adjusted HR=0.79 (95%: 0.65-0.96)
Benito-Leon (2010)	Nested Case-Control	548 (25%)	Neuropsychological Test Performance	No treatment effect observed in any test neuropsychological test administered (global cognition, verbal fluency, psychomotor speed, confrontational naming, verbal memory, logical memory)

OSE concluded:

The postmarket statin reports associated with transient cognitive change generally describe individuals over the age of 50 years who experience notable (sometimes described as “dramatic”), but ill-defined memory loss or impairment (e.g., “lost my mind”) that is reversible upon discontinuation of statin therapy. The statin exposure time to onset of the event is highly variable (1 day to years). These cases do not appear to be associated with fixed or progressive dementia, such as Alzheimer’s disease.

Like the previous (2002) OSE review, the analyzed data in this review did not reveal any discernible dose-event or age (the reported age at the time of event is similar to the age of the population using statins) trends or effects between statins and other drugs; few reports described neurologic follow-up or standardized testing results. Findings from this review (and the 2002 OSE review) are also similar to patient survey results recently published by the University of California San Diego (UCSD) Statin Effects Study investigators. Cognitive issues were reported for all statins, with atorvastatin and simvastatin most frequently reported. The time to onset was variable (1 day to 10 years). Ninety percent reported symptom improvement after the statin was discontinued. Complete recovery time varied from 1 day to several years (median time to first noted improvement was 2.5 weeks). Of 29 participants who underwent rechallenge, 19 reported recurrence of events.

An analysis of the epidemiologic evidence and clinical trials did not provide evidence that chronic statin use is associated with cognitive decline at the population level. Two studies demonstrated that exposure to statins for up to six months may prevent the acquisition of a practice effect on select neuropsychological measures. However, the clinical significance of an absent practice effect in the context of normal cognitive performance is questionable. Furthermore, no study systematically assessed patients who experienced statin-associated cognitive impairment during both dechallenge and rechallenge. Such systematic studies would provide additional evidence to support a causal association and better characterize the clinical phenotype.

OSE recommended that DMEP consider statin class labeling that would characterize the nature of the cognitive changes. In response, DMEP requested that the following be added to the **Adverse Reactions, Postmarketing Experience** sub-section of all statin labels:

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

(b) (4)

3. Drug-drug interaction with protease inhibitors – TSI #756

On July 23, 2009 TSI #756 was opened to examine the drug-drug interaction between statins and protease inhibitors.

In July 2009, the sponsor for rosuvastatin (CRESTOR) submitted a prior approval supplement (PAS) proposing to include information on increased rosuvastatin exposure when CRESTOR was co-administered with the combinations of protease inhibitors tipranavir/ritonavir, atazanavir/ritonavir or fosamprenavir/ritonavir, based on studies in the published literature. Previous CRESTOR labeling had noted a DDI with lopinavir/ritonavir (KALETRA) resulting in a dose cap of 10 mg of CRESTOR when co-administered with KALETRA.

In a January 2010 review of the PAS, it was noted that there were inconsistencies between the statin labels and the protease inhibitor labels regarding recommendations for co-administration of these products. It was therefore determined that the Office of Clinical Pharmacology (OCP) would review the relevant data on DDIs between statins and HIV and HCV protease inhibitors.

On August 3, 2011 OCP completed its review of the cross labeling initiative for drug interaction updates between protease inhibitors and statins. DMEP was requested to make changes to the atorvastatin and pravastatin labels to provide the results of DDI studies conducted with certain protease inhibitors, and in the case of atorvastatin, to provide dose caps where appropriate, based on the results of the following DDI studies:

- Tipranavir/ritonavir increases atorvastatin AUC and C_{max} 9.4-fold and 8.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and “Avoid atorvastatin” was recommended for labeling.
- Telaprevir increases atorvastatin AUC and C_{max} 7.88-fold and 10.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and “Avoid atorvastatin” was recommended for labeling.
- Darunavir/ritonavir increases atorvastatin AUC and C_{max} 3.4-fold and 2.25-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.
- Fosamprenavir increases atorvastatin AUC and C_{max} 2.3-fold and 4.04-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.

(b) (4)

Based on OCP's recommendation, DMEP requested the following changes to the atorvastatin and pravastatin labels:

Atorvastatin:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, **DRUG INTERACTIONS**, Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)	
Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Do not exceed 10 mg atorvastatin daily Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (ritonavir plus saquinavir plus ritonavir, lopinavir plus ritonavir darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Caution when exceeding doses >20mg atorvastatin daily. The lowest dose necessary should be used. Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

Under **DOSAGE AND ADMINISTRATION**:

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the Hepatitis C protease inhibitor (telaprevir), therapy ~~should be limited to with LIPITOR 40 mg once daily~~ should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of ~~ritonavir plus saquinavir plus ritonavir, or lopinavir plus ritonavir~~ darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir ~~for doses of therapy with LIPITOR should be limited to exceeding 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed.~~ In patients with HIV taking nelfinavir, therapy with LIPITOR should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed.

Under **5 WARNINGS AND PRECAUTIONS, 5.1 Skeletal Muscle**:

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including ritonavir plus saquinavir plus ritonavir, or lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with LIPITOR and fibric acid derivatives, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir plus ritonavir, or lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.

Under **Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:**

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine, <u>HIV protease inhibitors (tipranavir plus ritonavir)</u> , hepatitis C protease inhibitor (<u>telaprevir</u>)	<u>Do not exceed 10 mg atorvastatin daily</u> <u>Avoid atorvastatin</u>
<u>HIV protease inhibitor (lopinavir plus ritonavir)</u>	<u>Use with caution and lowest dose necessary</u>
Clarithromycin, itraconazole, HIV protease inhibitors (<u>ritonavir plus saquinavir plus ritonavir*</u> , or <u>lopinavir plus ritonavir</u> , <u>darunavir plus ritonavir</u> , <u>fosamprenavir</u> , <u>fosamprenavir plus ritonavir</u>)	<u>Caution when exceeding doses >20mg atorvastatin daily. The lowest dose necessary should be used.</u> <u>Do not exceed 20 mg atorvastatin daily</u>
<u>HIV protease inhibitor (nelfinavir)</u>	<u>Do not exceed 40 mg atorvastatin daily</u>

*Use with caution and with the lowest dose necessary

Under **DRUG INTERACTIONS, Combination of Protease Inhibitors, 7.1 Strong Inhibitors of CYP 3A4:**

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 40 mg with several combinations of HIV protease inhibitors, as well as with the Hepatitis C protease inhibitor telaprevir, ritonavir plus saquinavir (400 mg twice daily) or LIPITOR 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) compared to that of LIPITOR alone [see *Clinical Pharmacology* (12.3)]. Therefore, in patients taking the HIV protease inhibitors tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of LIPITOR should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the

dose of LIPITOR should not exceed 20 mg and should be used with caution. ~~caution should be used when the LIPITOR dose exceeds 20 mg.~~

Under 12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 3. Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin:

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑9.4 fold	↑8.6 fold
Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑74%	↑2.2-fold
Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑2.3-fold	↑4.04-fold
Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑2.53-fold	↑2.84-fold
Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑3.4-fold	↑2.25-fold
Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑7.88-fold	↑10.6-fold

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
^{#, ‡} Ritonavir Saquinavir 400 mg BID/saquinavir ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑3.9-fold	↑4.3-fold

[‡]The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be applied and the lowest dose necessary should be used.

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC ^{&}	Change in Cmax ^{&}
[#] Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days	20 mg QD for 4 days	⊖5.9 fold	⊖4.7 fold

Under 12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs:

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in C _{max}
<u>10 mg, SD</u>	<u>Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days</u>	<u>No change</u>	<u>No change</u>
<u>10 mg QD for 4 days</u>	<u>Fosamprenavir 1400 mg BID, 14 days</u>	<u>↓27%</u>	<u>↓18%</u>
<u>10 mg QD for 4 days</u>	<u>Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days</u>	<u>No change</u>	<u>No change</u>

Pravastatin:

**Under 12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 3:
Effect of Coadministered Drugs on the Pharmacokinetics of Pravastatin:**

Coadministered Drug and Dosing Regimen	Pravastatin		
	Dose (mg)	Change in AUC	Change in C _{max}
<u>Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 days</u>	<u>40 mg single dose</u>	<u>↑81%</u>	<u>↑63%</u>
<u>Kaletra 400 mg/100 mg BID for 14 days</u>	<u>20 mg OD for 4 days</u>	<u>↑33%</u>	<u>↑26%</u>

**Under 12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 4:
Effect of Pravastatin on the Pharmacokinetics of Coadministered Drugs**

Pravastatin Dosing Regimen	Name and Dose	Change in AUC	Change in C _{max}
<u>20 mg OD for 4 days</u>	<u>Kaletra 400 mg/100 mg BID for 14 days</u>	<u>No change</u>	<u>No change</u>

A December 6, 2011 OCP review of DDI's with lovastatin noted that available data support a contraindication with strong CYP3A4 inhibitors, such as the HIV protease inhibitors. The data were summarized as follows:

- *According to the Guidance for Industry Drug Interaction Studies, lovastatin is listed as one of the sensitive in vivo CYP3A4 substrates. Therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure because lovastatin is extensively metabolized by CYP3A4 isozyme.*
- *Literature survey indicates that itraconazole increases lovastatin exposure up to 15- to 20-fold and the drug interaction seems to result in rhabdomyolysis. Itraconazole is the representative strong CYP3A4 inhibitor and therefore, the effect of itraconazole on lovastatin exposure can be extrapolated to other strong CYP3A4 inhibitors listed in the Guidance as well as the FDA website.*

- *Strong CYP3A4 inhibitors are contraindicated for simvastatin because of the significant drug interaction and its potential for the increased risk on the rhabdomyolysis. Physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Meanwhile, itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.*

Therefore, concomitant use of lovastatin with HIV protease inhibitors, as well as the HCV protease inhibitors boceprevir and telaprevir, will be contraindicated.

Lovastatin:

Under **CONTRAINDICATIONS:**

Concomitant administration with strong CYP3A4 inhibitors, e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone)

Under **WARNINGS, Myopathy/Rhabdomyolysis, Strong 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 strong 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. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

Under **WARNINGS, Myopathy/Rhabdomyolysis, Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:**

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors <u>Boceprevir</u> <u>Telaprevir</u> Nefazodone	<u>Avoid-Contraindicated</u> with lovastatin

Under **PRECAUTIONS, Drug Interactions, CYP3A4 Interactions:**

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Strong inhibitors of CYP3A4 (e.g., below itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, bocprevir, telaprevir, nefazodone), and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin.

Itraconazole

Ketoconazole

Erythromycin

Clarithromycin

Telithromycin

HIV protease inhibitors

Nefazodone

Large quantities of grapefruit juice (>1 quart daily)

4. Increases in HbA1c and fasting plasma glucose – TSI #891

On April 8, 2010 TSI #891 was opened to evaluate the effect of statins on increases in HbA1c and fasting plasma glucose. This was based on findings from the JUPITER trial, which reported a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-exposed subjects compared to placebo-exposed subjects. High-dose atorvastatin had previously been associated with worsening glycemic control in the PROVE-IT TIMI 22 substudy.

Several articles from the published literature were also considered, including:

- Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. *Lancet*.2010;375:735-742
- Sukhija R et al. Effect of Statins on Fasting Plasma Glucose in Diabetic and Nondiabetic Patients. *Journal of Investigative Medicine*.2009;57(3): 495-499
- Rajpathak SN et al. Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis. *Diabetes Care*.2009;32:1924-1929
- Koh KK et al. Atorvastatin Causes Insulin Resistance and Increases Ambient Glycemia in Hypercholesterolemic Patients. *JACC*.2010;55(12):1209-1216
- Thongtang N et al. Effects of Maximal Atorvastatin and Rosuvastatin Treatment on Markers of Glucose Homeostasis and Inflammation. *Am J Cardiol*.2011;107:387-392
- Kostapanos MS et al. Do Statins Beneficially or Adversely Affect Glucose Homeostasis? *Current Vascular Pharmacology*.2010;8:612-631
- Mills EJ et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170255 patients from 76 randomized trials. *Q J Med*.2011;104:109-124

- Culver AL et al. Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women’s Health Initiative. *Arch Intern Med*. Published online January 9, 2012.

The Sattar meta-analysis, which looked at 13 statin trials with 91,140 participants, reported that “statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity ($I^2=11%$) between trials.”

The Rajpathak meta-analysis, which looked at 6 statin trials with 57,593 participants, reported a “small increase in diabetes risk” (relative risk [RR] 1.13; 95% CI 1.03-1.23), with “no evidence of heterogeneity across trials”.

The Mills meta-analysis, which looked at 76 randomized clinical trials (RCTs) with 170,255 participants, reported that 17 RCTs reported on increased risk of development of incident diabetes (Odds ratio [OR] 1.09; 95% CI 1.02-1.17, $p=0.001$, $I^2=11%$).

Culver et al looked at postmenopausal women participating in the Women’s Health Initiative (WHI) to investigate whether the incidence of new-onset diabetes mellitus is associated with statin use. The study involved 153,840 women. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83); the multivariate-adjusted HR was 1.48; 95% CI, 1.38-1.59. The association was observed for all types of statin medications.

At the time of approval of the JUPITER supplement, the following labeling was required for CRESTOR:

5.5 Endocrine Effects

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR.

The data for an effect of statins on incident diabetes, and increases in HbA1c and/or fasting plasma glucose seem to indicate a class effect; however, given the limitations of epidemiological data, and the findings from the West of Scotland Coronary Prevention Study (WOSCOPS) clinical trial, which suggested that pravastatin may decrease the incidence of diabetes by 30%, the division did not seek a labeling change for pravastatin.

Therefore, based on clinical trial data, epidemiological data, and the published literature, the following labeling change was requested for all statins except pravastatin:

5.X Endocrine Function:

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including <<STATIN>>.

5. Drug-drug interaction with ranolazine – TSI #988

TSI #988 was opened by the Division of Cardiovascular and Renal Products (DCRP) in July 2010 when during routine data monitoring of the AERS database for cases of ranolazine and torsades de pointes, a signal was identified for rhabdomyolysis in patients receiving ranolazine and statins.

Nine cases of drug interaction were related to concomitant use of ranolazine and a statin. Of those nine cases, seven (all male) involved the statin associated adverse events of rhabdomyolysis (6) and myalgia (1). Four of those six patients were stable on long-term statin therapy prior to the initiation of ranolazine. Most cases involved the use of simvastatin.

According to the OCP review:

Ranolazine and SV are both cleared via CYP3A metabolism. Hence, concomitant administration of the two may lead to pharmacokinetic DDI. Administration of ranolazine (1000 mg twice daily) with SV (80 mg once daily) resulted in a ~2-fold increase in C_{max} and ~1.5-fold increase in AUC of SV and SVA, at steady state. Increased systemic exposure to SV and SVA has been associated with increased risk of myopathy and rhabdomyolysis. The 80 mg dose of SV has been shown to be associated with increased incidence of myopathy and rhabdomyolysis. In addition, there is little gain in effectiveness of the 80 mg over 40 mg dose. The DMEP regulatory briefing held on 6/4/2010 suggested progressive removal of 80 mg dose of simvastatin from the market, leaving 40 mg as the highest available dose. Therefore, given the 2-fold increase in systemic exposure expected on concomitant administration of ranolazine and SV, limiting the dose of SV to 20 mg will avoid exposures similar or greater to that observed with 80 mg.

In addition, for other statins which are primarily metabolized by CYP3A (e.g., lovastatin and atorvastatin), concomitant medications which are CYP3A inhibitors are expected to elevate statin exposure, and risk of myopathy. However, at present, definitive data (such as available with simvastatin) is not available for other statins, in order to recommend dose-adjustments.

On June 8, 2011, in conjunction with the approval of new dosing restrictions with the 80 mg dose of simvastatin, DMEP approved a dose cap of simvastatin 20 mg when simvastatin is coadministered with ranolazine.

In addition, the current ranolazine label recommends a dose adjustment of sensitive CYP3A4 substrates such as lovastatin based on the 2-fold simvastatin exposure increase by ranolazine.

Based on the information above, the following recommendations for labeling changes were made:

Mevacor:

Under **WARNINGS, *Myopathy/Rhabdomyolysis***:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Dose adjustment of lovastatin may be considered during co-administration.

Under **PRECAUTIONS, *Other Drug Interactions***:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine.

Altprev:



Advicor:



6. Myopathy with concomitant administration with colchicine

In June 2010, a Regulatory Briefing was conducted to discuss the increased risk of myopathy, including rhabdomyolysis, associated with the use of simvastatin 80

mg, based on DMEP's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) clinical trial. In preparation for the briefing, OSE noted an interaction between statins and colchicine resulting in an increased risk of myopathy. Colchicine, a substrate of P-glycoprotein and CYP3A4, carried the following information in its label:

5.4 Neuromuscular Toxicity

Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or bezafibrate (themselves associated with myotoxicity) or cyclosporine may potentiate the development of myopathy. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

This was based on reports from the literature as summarized in the table below, and adapted from a 2008 OCP review of NDA 22-352 (Colstat [colchicine tablets]).

Lipid Lowering Agents			
HMG-CoA Reductase Inhibitors	Simvastatin: <u>Baker et al. (2004)</u> ; <u>Hsu et al. (2002)</u>	Both are CYP3A4 and P-gp substrates; P-gp inhibition by simvastatin	Acute myopathy or rhabdomyolysis (could be attributed to either drug)
	Fluvastatin: <u>Atasoyu et al. (2005)</u>	Synergistic myotoxicity via PK & PD mechanism; fluvastatin is not a P-gp inhibitor	
	Pravastatin: <u>Alayli et al. (2005)</u>	Synergistic myotoxicity via PK & PD mechanism; pravastatin is not a P-gp inhibitor	
	Atorvastatin: <u>Tufan et al. (2006)</u>	Both are CYP3A4 substrates; P-gp inhibition by atorvastatin	
Fibrates	Gemfibrozil: <u>Atmaca et al., 2002</u>	Synergistic toxic effect of both drugs	
	Fenofibrate & Diltiazem: <u>Sinsawaiwong et al., 1997</u>	Mechanism-based inhibition of CYP3A4 by diltiazem.	

On June 8, 2011, the following changes were approved for the simvastatin-containing drugs:

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

7 DRUG INTERACTIONS

7.7 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

In order to harmonize and update the appropriate statin labels, similar labeling changes were requested for atorvastatin, pravastatin, and fluvastatin. Furthermore, because of physicochemical and pharmacokinetic similarities between lovastatin and simvastatin, similar labeling changes were requested for lovastatin.

7. Myopathy with concomitant administration with fibrates

A National Institutes of Health (NIH) funded trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial, was reviewed by DMEP and discussed at an Advisory Committee meeting on May 19, 2011. ACCORD-Lipid evaluated the occurrence of major adverse cardiovascular events (MACE), a composite of nonfatal heart attack, nonfatal stroke, and cardiovascular death in patients receiving simvastatin plus fenofibrate, compared to simvastatin alone. The trial found that there was no difference in cardiovascular outcomes between the two groups (Hazard Ratio = 0.92; 95% Confidence Interval: 0.79-1.08; p=0.32).

This was the second failed cardiovascular outcome trial for fenofibrate. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (Hazard Ratio = 0.89; 95% Confidence Interval: 0.75-1.05; p=0.04) versus placebo.

The absence to date of proven cardiovascular benefit with fenofibrates must be viewed in the context of observational data showing an increase in the risk of myopathy with fenofibrates, especially when co-administered with a statin. In 2011, OSE conducted a review of observational data on rhabdomyolysis with fenofibrates and gemfibrozil in combination with statins. Their review looked at 3 studies:

- Graham DJ, Staffa JA, Shatin D et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-2590.
- Amend KL, Landon J, Thyagarajan V, Niemcryk S, McAfee A. Incidence of hospitalized rhabdomyolysis with statin and fibrate use in an insured US population. *Ann Pharmacother* 2011;45:1230-1239.
- Enger C, Gately R, Ming EE, Niemcryk SJ, Williams L, McAfee AT. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. *Am J Cardiol* 2010;106:1594-1601.

According to the OSE review, the best available evidence suggests that fenofibrate-statin combination is associated with an increased hazard rate for rhabdomyolysis (HR, 3.26, 95% CI, 1.21-8.80) relative to statin monotherapy. There also appears to be a differential risk associated with the gemfibrozil-statin combination therapy versus the fenofibrate-statin combination therapy, with a

numerically higher rate of rhabdomyolysis observed with gemfibrozil-statin combination therapy (HR, 11.93, 95% CI, 3.96-35.93) compared to statin monotherapy.

Most statin labels contain language in the FPI (Warnings and Precautions and Drug Interactions sections) regarding the increased risk of myopathy, including rhabdomyolysis, when statins and fibrates are co-administered. In order to highlight this increased risk, as well as to note the differential risk between gemfibrozil-statin combination therapy and fenofibrate-statin combination therapy, all sponsors of statin drugs with labels in the PLR format (i.e., all except the lovastatin products) were requested to add the following information to the Highlights page. The following language was also provided in the Drug Interactions section of the PI's, depending on the level of risk determined for each statin product:

-----**DRUG INTERACTIONS**-----

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with <<STATIN>>.

7.X Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: <<Contraindicated or Avoid>> with <<STATIN>>

Other fibrates: Caution should be used when prescribing with <<STATIN>>

7.X Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of <<STATIN>> with gemfibrozil should be avoided.

7.X Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, <<STATIN>> should be administered with caution when used concomitantly with other fibrates.

8. Myopathy with concomitant administration with lipid-modifying doses of niacin

In March 2010, DMEP approved a labeling revision for simvastatin based on interim results from an ongoing clinical trial - the Heart Protection Study 2 (HPS2) – Treatment of HDL to Reduce the Incidence of Vascular Events (THRIVE), a cardiovascular outcome trial being conducted in 20,000 patients with vascular disease from the UK, China and Scandinavia to investigate whether combining niacin with a new drug (laropiprant) that minimizes niacin's flushing effect can reduce the risk of serious heart attacks and strokes among people already taking treatment to lower their LDL-cholesterol. The interim HPS2 – THRIVE results showed that the incidence of myopathy was higher in patients of

Chinese descent (0.43%) compared with patients not of Chinese descent (0.03%) taking 40 mg simvastatin plus cholesterol-modifying doses (≥ 1 g/day) of a niacin-containing product. The exact mechanism of this drug interaction is not fully understood.

Drug-drug interaction studies report an increase in simvastatin exposure of 41-64% with co-administration of simvastatin and ER niacin. According to OCP, the cause of the observed changes in exposure of simvastatin due to ER niacin is not well established as this is not due to changes in the known pathways (e.g., via CYP3A4 or OATP1B1). Furthermore, a PK study of simvastatin in Chinese subjects showed no significant differences in Chinese and non-Asian subjects in simvastatin C_{max} and AUC_{0-last} , and simvastatin acid AUC_{0-last} or C_{max} .

The OCP Genomics Group further noted that the SLCO1B1 genotype that has been associated with statin-induced myopathy, is less prevalent in Asian populations than European populations and, therefore, does not seem to explain the higher myopathy risk rates among Chinese subjects in HPS2-THRIVE.

So, it remains unclear if this increased risk of myopathy with statin and niacin co-administration is unique to Chinese subjects, or applies to other Asians and non-Asians as well.

Furthermore, in the AIM-HIGH study, which compared ER-niacin with simvastatin to simvastatin alone in reducing the residual cardiovascular risk in patients with established cardiovascular disease, “there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels”.

The lack of clear benefit in conjunction with uncertainty as to the nature of the increased risk of myopathy in patients treated with niacin plus a statin led FDA to believe that this risk needed to be highlighted in statin labeling.

The labeling approved for simvastatin in March 2010 noted that patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products.

In June 2011, in conjunction with labeling revisions required based on the Agency’s review of the SEARCH trial, this language was modified to note that “caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products.”

Most statin labels contain information in the FPI (Warnings and Precautions and Drug Interactions sections) noting that “The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with niacin; a reduction in

<<STATIN>> dosage should be considered in this setting.” All sponsors of statin drugs with labels in the PLR format were requested to modify the HIGHLIGHTS page, with corresponding changes to the FPI if indicated, as follows:

-----DRUG INTERACTIONS-----

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with <<STATIN>>.

7.X Niacin

The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with lipid-modifying doses (≥ 1 g/day) of niacin; a reduction in <<STATIN>> dosage should be considered in this setting.

9. Update to lovastatin drug-drug interactions and dose caps

Subsequent to the June 2011 labeling revisions to the simvastatin-containing products which were largely based on the SEARCH clinical trial data and the increased risk of myopathy associated with the 80 mg dose of simvastatin, a review of drug-drug interactions with lovastatin was conducted. The physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Lovastatin is a sensitive *in vivo* CYP3A4 substrate; therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure. According to OCP:

Itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.

Based on available studies from the literature, as well as extrapolation from simvastatin data, the following changes to the lovastatin label were recommended:

Under **CONTRAINDICATIONS:**

Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone).

Under **WARNINGS, Myopathy/Rhabdomyolysis, Strong 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. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

~~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 strong inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of lovastatin. It is recommended that dose adjustment of lovastatin be considered during coadministration. Increased lovastatin concentration in plasma has been associated with an increased risk of myopathy/rhabdomyolysis.

Under **WARNINGS, Myopathy/Rhabdomyolysis:**

~~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: The use of lovastatin with cyclosporine should be avoided.

~~Cyclosporine or dDanazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine or danazol, diltiazem, or verapamil.~~ The benefits of the use of lovastatin in patients receiving cyclosporine or danazol, diltiazem, or verapamil 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.

Under **WARNINGS, Myopathy/Rhabdomyolysis:**

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

~~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.

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

Under **WARNINGS, Myopathy/Rhabdomyolysis, Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:**

Interacting Agents	Prescribing Recommendations
Ketoconazole Itraconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	Avoid <u>Contraindicated</u> with lovastatin
<u>Gemfibrozil</u> Cyclosporine	<u>Avoid with lovastatin</u>
Gemfibrozil Other fibrates Lipid lowering doses (≥1 g/day) of niacin Cyclosporine Danazol <u>Diltiazem</u> <u>Verapamil</u>	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)

Under **PRECAUTIONS, Drug Interactions, CYP3A4 Interactions:**

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. ~~Potent~~ Strong inhibitors of CYP3A4 (e.g., itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone and erythromycin), and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors
Nefazodone
Large quantities of grapefruit juice (>1 quart daily)

In vitro studies have demonstrated that voriconazole inhibits the metabolism of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with lovastatin.

Under **PRECAUTIONS**, *Other Drug Interactions*:

~~*Cyclosporine* or *Danazol*~~: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine ~~or danazol~~ particularly with higher doses of lovastatin.

Danazol, Diltiazem, or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, diltiazem, or verapamil particularly with higher doses of lovastatin.

~~*Amiodarone* or *Verapamil*~~: The risk of myopathy/rhabdomyolysis is increased when either amiodarone ~~or verapamil~~ is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class.

Under **PRECAUTIONS**, *Endocrine Function*:

Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ~~ketoconazole~~, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

Under **DOSAGE AND ADMINISTRATION**:

Dosage in Patients taking ~~Cyclosporine~~, or Danazol, Diltiazem, or Verapamil
In patients taking ~~cyclosporine~~, or danazol, diltiazem, or verapamil concomitantly with lovastatin, therapy should begin with 10 mg of lovastatin and should not exceed 20 mg/day.

Dosage in Patients taking ~~Amiodarone~~ or Verapamil
In patients taking ~~amiodarone~~ or verapamil concomitantly with MEVACOR, the dose should not exceed 40 mg/day.

Concomitant Lipid-Lowering Therapy

MEVACOR is effective alone or when used concomitantly with bile-acid sequestrants. ~~If MEVACOR is used in combination with gemfibrozil, other fibrates or lipid lowering doses (\geq 1g/day) of niacin, the dose of MEVACOR should not exceed 20 mg/day.~~

Under **CLINICAL PHARMACOLOGY**:

	Number of Subjects	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio* (with / without coadministered drug) No Effect = 1.00	
				Lovastatin	Lovastatin acid [†]
Gemfibrozil	11	600 mg BID for 3 days	40 mg	0.96	2.80
Itraconazole [‡]	12	200 mg QD for 4 days	40 mg on Day 4	> 36 [§]	22
	10	100 mg QD for 4 days	40 mg on Day 4	> 14.8 [§]	15.4
Grapefruit Juice [¶] (high dose)	10	200 mL of double-strength TID [#]	80 mg single dose	15.3	5.0
Grapefruit Juice [¶] (low dose)	16	8 oz (about 250 mL) of single-strength [‡] for 4 days	40 mg single dose	1.94	1.57
Cyclosporine	16	Not described ^β	10 mg QD for 10 days	5- to 8-fold	ND ^α
	Number of Subjects	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio* (with / without coadministered drug) No Effect = 1.00 Total Lovastatin acid [‡]	
Diltiazem	10	120 mg BID for 14 days	20 mg	3.57 [‡]	

* Results based on a chemical assay

[†] Lovastatin acid refers to the β-hydroxyacid of lovastatin

[‡] The mean total AUC of lovastatin without itraconazole phase could not be determined accurately. Results could be representative of strong CYP3A4 inhibitors such as ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone

[§] Estimated minimum change

[¶] The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied

[#] Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose lovastatin and 30 and 90 minutes following single dose lovastatin on Day 3

[‡] Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and lovastatin was administered in the evening on Day 3

^β Cyclosporine-treated patients with psoriasis or post kidney or heart transplant patients with stable graft function, transplanted at least 9 months prior to study

10. Update to simvastatin and lovastatin drug-drug interaction:

In May 2011, the hepatitis C protease inhibitors boceprevir and telaprevir were approved. These protease inhibitors have been characterized as being strong CYP3A4 inhibitors. Because simvastatin is contraindicated with strong CYP3A4 inhibitors, and because the simvastatin label individually lists strong CYP3A4 inhibitors with which simvastatin is contraindicated, these two recently approved protease inhibitors will be added to the list in all simvastatin-containing products (Zocor, Vytorin, and Simcor).

Because of the physicochemical and pharmacokinetic similarities between simvastatin and lovastatin, and consistent with changes being made to the lovastatin labeling which include a new contraindication with strong CYP3A4 inhibitors, the labeling for lovastatin will be modified to add boceprevir and telaprevir to the list of strong CYP3A4 inhibitors with which lovastatin is contraindicated.

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/s/

AMY G EGAN
06/04/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022687Orig1s041

OTHER REVIEW(S)

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: 21-687/S-041

Name of Drug: Vytorin (ezetimibe/simvastatin)

Sponsor: MSP Singapore Company, LLC

Submission Date: October 3, 2011

Background and Summary:

Vytorin is indicated for:

Primary Hypercholesterolemia

As adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)

For the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

It is supplied in the tablet dose strengths of 10/10, 10/20, 10/40 and 10/80mg.

The last approved labeling supplement was S-033 and S-040, which was a supplemental new drug application that provided changes to the **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, and CLINICAL PHARMACOLOGY** sections of the VYTORIN (ezetimibe/simvastatin) package insert informing patients and prescribers about the increased risk of myopathy, including rhabdomyolysis, in patients treated with 80 mg of simvastatin versus those treated with 20 mg.

Supplement, S-041, is a supplemental new drug application that provides for a number of revisions and additions to the **WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS** sections of the Highlights of Prescribing Information section and changes to the **DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY, and PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the Vytorin package insert. Additional changes have been

made to the Vytorin Patient Package Insert under the section entitled “What are the possible side effects of Vytorin?” The modifications were based on a comprehensive review of clinical trial data, Adverse Event Reporting System (AERS) reports, published literature, and the labels of other approved drugs containing information on statin coadministration. For completeness, a copy of the approved labeling is attached.

Cross-reference: NDA 19766/S-083 Zocor approved October 6, 2011

REVIEW:

WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS sections of the Highlights of Prescribing Information section

----- **RECENT MAJOR CHANGES** -----

Dosage and Administration	
Recommended Dosing (2.1)	06/2011
Restricted Dosing for 80 mg (2.2)	06/2011
Coadministration with Other Drugs (2.3)	10/2011
Patients with Homozygous Familial Hypercholesterolemia (2.4)	06/2011
Chinese Patients Taking Lipid-Modifying Doses (≥1 g/day Niacin) of Niacin-Containing Products (2.7)	06/2011
Contraindications (4)	
Warnings and Precautions	
Myopathy/Rhabdomyolysis (5.1)	10/2011
Liver Dysfunction (5.2)	10/2011
Endocrine Function (5) ^(b) ₍₄₎	10/2011

----- **WARNINGS AND PRECAUTIONS** -----

- Liver enzyme abnormalities: Persistent elevations in hepatic **transaminases** can occur. **Check** liver **enzyme tests** before **initiating therapy and as clinically indicated thereafter.** (5.2)

----- **DRUG INTERACTIONS** -----

Interacting Agents	
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemf brozil, cyclosporine, danazol	Contraindicated with VYTORIN
Verapamil , diltiazem	Do not exceed 10/10 mg VYTORIN daily
Amiodarone , amlodipine, ranolazine	Do not exceed 10/20 mg VYTORIN daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)
Interacting Agents	Prescribing Recommendations

- Coumarin anticoagulants: simvastatin prolongs INR. Achieve stable INR prior to starting VYTORIN. Monitor INR frequently until stable upon initiation or alteration of VYTORIN therapy. (7.8)
- Cholestyramine: Combination decreases exposure of ezetimibe. (2.3, 7.5)
- Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with VYTORIN. (5.1, 7.2, 7.4).

2 DOSAGE AND ADMINISTRATION

2.3 Coadministration with Other Drugs

Patients taking Verapamil or Diltiazem

- The dose of VYTORIN should not exceed 10/10 mg/day [see Warnings and Precautions (5.1), Drug Interactions (7.3), and Clinical Pharmacology (12.3)].

Patients taking Amiodarone, Amlodipine or Ranolazine

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

VYTORIN therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. VYTORIN therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

5.2 Liver Enzymes

It is recommended that liver function tests be performed before the initiation of treatment with VYTORIN, and thereafter when clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with VYTORIN, promptly interrupt therapy. If an alternate etiology is not found do not restart VYTORIN. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy [see Warnings and Precautions (5.1)].

5.4 Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG CoA reductase inhibitors, including simvastatin

6 ADVERSE REACTIONS

6.2 Post-Marketing Experience

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

17 PATIENT COUNSELING INFORMATION

17.2 Liver Enzymes

It is recommended that liver function tests be performed before the initiation of VYTORIN, and thereafter when clinically indicated. All patients treated with VYTORIN should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

Patient Information

What are the possible side effects of VYTORIN?

See your doctor regularly to check your cholesterol level and to check for side effects. Your doctor should do blood tests to check your liver before you start taking VYTORIN and if you have any symptoms of liver problems while you take VYTORIN. Call your doctor right away if you have the following symptoms of liver problems:

- feel tired or weak
- loss of appetite
- upper belly pain
- dark urine
- yellowing of your skin or the whites of your eyes

The Agency will issue an approval action on this supplement. The PI and PPI submitted on October 3, 2011, (Package Identification # 9619519) were accepted by the reviewing team (Drs. Amy Egan, Eric Colman, and Eileen Craig). A manual labeling review was completed using the last approved labeling supplement, S-033 and S-040, approved on June 8, 2011.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager/10/6/11
(See appended electronic signature page)

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARGARET A SIMONEAU
10/18/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022687Orig1s041

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

From: [Chiang, Raymond](#)
To: ["Swanson, Richard John";](#)
cc: ["carl_sparrow@merck.com"; Simoneau, Margaret A;](#)
Subject: RE: NDA 19766/S-083 (Zocor), NDA 21687/S-041 (Vytorin), and NDA 202343 (Juvisynd) labeling comments
Date: Thursday, September 29, 2011 2:19:55 PM

Hello Dr. Swanson and Dr. Sparrow,

As per our phone conversation, see the Division's comments below (in black font) regarding proposed labeling for NDA 19766/S-083 (Zocor), NDA 21687/S-041 (Vytorin), and NDA 202343 (Juvisynd).

We disagree with your modification under **5 Warnings and Precautions, 5.1 Myopathy/Rhabdomyolysis**. The first sentence of the proposed new paragraph should state: "ZOCOR/JUVISYND/VYTORIN therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected." The use of the word "and" implies that one must await the results of blood tests documenting an elevation in CPK levels before stopping simvastatin therapy, even if myopathy is suspected based on clinical presentation. Also, as was noted in SEARCH, myopathy was diagnosed in patients who had markedly elevated CPK levels detected in routine lab monitoring, but had not complained of muscle symptoms until queried after the lab abnormality was noted.

We agree with your deletion of [REDACTED] ^{(b) (4)}
[REDACTED] from the HIGHLIGHTS OF PRESCRIBING INFORMATION, **WARNINGS AND PRECAUTIONS** section.

We disagree with your modification to the language under HIGHLIGHTS OF PRESCRIBING INFORMATION, **DRUG INTERACTIONS** section. We will consider modification of this section upon review of the final study report for HPS2-THRIVE.

If you have any questions, please do not hesitate to call or email.

thanks,

ray and margaret

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/s/

RAYMOND S CHIANG
09/29/2011