CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022078Orig1s013

Trade Name: SIMCOR

Generic Name: Niacin extended-release/simvastatin

Sponsor: Abbott Laboratories

Approval Date: 02/28/2012

Indications: SIMCOR is a combination of simvastatin, an HMG-Co-A reductase inhibitor, and niacin extended-release (NIASPAN), nicotinic acid. SIMCOR is indicated to: Reduce elevated Total–C, LDL-C, Apo B, non-HDL-C, TG, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate; Reduce TG in patients with hypertriglyceridemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022078/S-013

SUPPLEMENT APPROVAL

Abbott Laboratories
Attention: Richard Leber
Manager, Regulatory Affairs-PPG
200 Abbott Park Road
Abbott Park, IL 60064

Dear Mr. Leber:

Please refer to your Supplemental New Drug Application (sNDA) dated September 28, 2011, received September 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Simcor (niacin ER/simvastatin) Tablets, 500 mg/20 mg, 500 mg/40 mg, 750 mg/20 mg, 1000 ng/20 mg and 1000 mg/40 mg.

We acknowledge receipt of your amendment dated December 29, 2011, and February 13, 2012, containing revised labeling.

This "Prior Approval" supplemental new drug application provides for revisions to the CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS sections of the HIGHLIGHTS OF PRESCRIBING INFORMATION page and the DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY, and PATIENT COUNSELING INFORMATION sections of the Full Prescribing Information of the SIMCOR package insert in response to our letter dated August 11, 2011. A version of this letter, based on the Agency's 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 co-administration, was issued to all statin drugs and combination products with a statin component.

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), with the addition of any labeling changes in pending "Changes Being Effected" (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).

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 Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

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(S):
Content of Labeling (tracked changes version and clean)

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
02/28/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SIMCOR (niacin extended-release/simvastatin) tablet, film coated for oral use.

Initial U.S. Approval: 2008

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

Dosage and Administration, Coadministration with Other Drugs (2.2) 06/2011
Dosage and Administration, Chinese Patients Taking SIMCOR (2.3) 06/2011
Contraindications (4) 06/2011
Warnings and Precautions, Myopathy/Rhabdomyolysis (5.1) 06/2011

-------INDICATIONS AND USAGE-------

SIMCOR is a combination of simvastatin, an HMG-Co-A reductase inhibitor, and niacin extended-release (NIASPAN), nicotinic acid. SIMCOR is indicated to:

- Reduce elevated Total–C, LDL-C, Apo B, non-HDL-C, TG, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate. (1.1)
- Reduce TG in patients with hypertriglyceridemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate. (1.1)

Limitations of use:

No incremental benefit of SIMCOR on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin monotherapy and niacin monotherapy has been established. (1.1)

-------DOSAGE AND ADMINISTRATION-------

- SIMCOR should be taken at bedtime with a low-fat snack. (2)
- Dose range: 500/20 mg to 2000/40 mg once daily. (2)
- Initial dose for patients naïve to or switching from immediate-release niacin: 500/20 mg once daily. (2)
- The initial dose for patients already receiving niacin extended-release should not exceed 2000/40 mg once daily. (2)
- Maintenance dose: 1000/20 mg to 2000/40 mg once daily. (2)
- Doses greater than 2000/40 mg daily are not recommended. (2)

-------DOSAGE FORMS AND STRENGTHS-------

- Unscored film-coated tablets:
  500 mg niacin extended-release/20 mg simvastatin (3)
  500 mg niacin extended-release/40 mg simvastatin (3)
  750 mg niacin extended-release/20 mg simvastatin (3)
  1000 mg niacin extended-release/20 mg simvastatin (3)
  1000 mg niacin extended-release/40 mg simvastatin (3)

-------CONTRAINDICATIONS-------

- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4, 5.2)
- Active peptic ulcer disease (4)
- Arterial bleeding (4)
- Concomitant administration of strong CYP3A4 inhibitors (4, 5.1)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol (4, 5.1)
- Concomitant administration of verapamil or diltiazem (4,5.1)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)
- Known hypersensitivity to product components (4, 6.1)

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

- 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, 8.7)
- Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzymes tests before initiating therapy and as clinically indicated thereafter. (5.2)
- Severe hepatic toxicity has occurred in patients substituting sustained-release niacin for immediate-release niacin at equivalent doses. If switching from niacin preparations other than niacin extended-release (NIASPAN), initiate with lowest SIMCOR dose; niacin extended-release can be converted at equivalent doses. (5.2)
- Niacin extended-release can increase serum glucose levels. Glucose levels should be closely monitored in diabetic or potentially diabetic patients particularly during the first few months of use. (5.3)

-------ADVERSE REACTIONS-------

The most common (incidence > 3%) adverse reactions with SIMCOR are flushing, headache, back pain, diarrhea, nausea, and pruritis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633–9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.2, 4, 5.1, 7.1, 7.2, 7.3, 7.4, 12.3)	
Interacting Agents	Prescribing Recommendations
Strong CYP3A4 inhibitors(e.g., itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nafazodone), gemfibrozil, cyclosporine, danazol, verapamil, diltiazem	Contraindicated with SIMCOR
Amiodarone, amlodipine, ranolazine	Do not exceed 1000/20 mg SIMCOR daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

- Fenofibrate: Combination with SIMCOR increases the risk of adverse skeletal muscle effects and should be avoided. (7.3)
- Coumarin anticoagulants: Combination prolongs INR. Achieve stable INR prior to starting SIMCOR. Monitor INR frequently until stable upon initiation or alteration of SIMCOR therapy. (7.7)

-------USE IN SPECIFIC POPULATIONS-------

- Severe renal impairment (not on dialysis): SIMCOR should be used with extreme caution. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 2/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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 Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles

SIMCOR

SIMCOR is indicated to reduce Total-C, LDL-C, Apo B, non-HDL-C, TG, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

SIMCOR is indicated to reduce TG in patients with hypertriglyceridemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

Limitations of use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

SIMCOR should be taken as a single daily dose at bedtime, with a low fat snack. Patients not currently on niacin extended-release and patients currently on niacin products other than niacin extended-release should start SIMCOR at a single 500/20 mg tablet daily at bedtime. Patients already taking simvastatin 20 to 40 mg who need additional management of their lipid levels may be started on a SIMCOR dose of 500/40 mg once daily at bedtime. *[See Warnings and Precautions (5.2)]*. The dose of niacin extended-release should not be increased by more than 500 mg daily every 4 weeks - see Table 1.

Table 1. Recommended niacin extended-release dosing

	Week(s)	**Daily dose of niacin extended-release**
Initial Titration Schedule	1 to 4	500 mg
	5 to 8	1000 mg
	*	1500 mg
	*	2000 mg

* After Week 8, titrate to patient response and tolerance. If response to 1000 mg daily is inadequate, increase dose to 1500 mg daily; may subsequently increase dose to 2000 mg daily. Daily dose should not be increased more than 500 mg in a 4-week period, and doses above 2000 mg daily are not recommended.

The recommended maintenance dose for SIMCOR is 1000/20 mg to 2000/40 mg (two 1000/20 mg tablets) once daily depending on patient tolerability and lipid levels. **The efficacy and safety of doses of SIMCOR greater than 2000/40 mg daily have not been studied and are therefore not recommended.**

If SIMCOR therapy is discontinued for an extended period of time (> 7 days), re-titration as tolerated is recommended. SIMCOR tablets should be taken whole and should not be broken, crushed, or chewed before swallowing.

Due to the increased risk of hepatotoxicity with other modified-release (sustained-release or time-release) niacin preparations or immediate-release (crystalline) niacin, SIMCOR should only be substituted for equivalent doses of niacin extended-release (NIASPAN).

Flushing *[See Adverse Reactions (6.1)]* may be reduced in frequency or severity by pretreatment with aspirin up to the recommended dose of 325 mg (taken approximately 30 minutes prior to SIMCOR dose). Flushing, pruritus, and gastrointestinal distress are also reduced by gradually increasing the dose of niacin (refer to Table 1) and avoiding administration on an empty stomach. Concomitant alcoholic, hot drinks or spicy foods may increase the side effects of flushing and pruritus and should be avoided around the time of SIMCOR ingestion.

2.2 Coadministration with Other Drugs

Patients taking Amiodarone, Amlodipine or Ranolazine

- The dose of SIMCOR should not exceed 1000/20 mg/day *[see Warnings and Precautions (5.1), Drug Interactions (7.4), and Clinical Pharmacology (12.3)]*.

2.3 Chinese Patients Taking SIMCOR

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 prescribing SIMCOR in doses that exceed 1000/20 mg/day to Chinese patients. 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

SIMCOR tablets are formulated for oral administration in the following strength combinations:

Table 2. SIMCOR Tablet Strengths

	500mg/20mg	500mg/40mg	750mg/20mg	1000mg/20mg	1000mg/40mg
Niacin extended-release equivalent (mg)	500	500	750	1000	1000
simvastatin equivalent (mg)	20	40	20	20	40

4 CONTRAINDICATIONS

SIMCOR is contraindicated in the following conditions:

- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels *[See Warnings and Precautions (5.2)]*
- Patients with active peptic ulcer disease
- Patients with arterial bleeding
- Concomitant administration of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) *[see Warnings and Precautions (5.1)]*
- Concomitant administration of gemfibrozil, cyclosporine, or danazol *[see Warnings and Precautions (5.1)]*
- Concomitant administration of verapamil or diltiazem *[see Warnings and Precautions (5.1)]*
- Women who are pregnant or may become pregnant. SIMCOR may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for 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 SIMCOR use during pregnancy; however in rare reports congenital anomalies were observed following intrauterine exposure to HMG-CoA reductase inhibitors. If SIMCOR 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. *[See Use In Specific Populations (8.1)]* In rat and rabbit animal reproduction studies, simvastatin revealed no evidence of teratogenicity. There are no animal reproductive studies conducted with niacin.
- Nursing mothers. SIMCOR contains simvastatin and nicotinic acid. Nicotinic acid is excreted into human milk and 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 of the potential for serious adverse reactions in nursing infants, women who require SIMCOR treatment should not breastfeed their infants. *[See Use In Specific Populations (8.3)]*
- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including one of more of the following adverse reactions have been reported for simvastatin and/or niacin extended-release: anaphylaxis, angioedema, urticaria, fever, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and flushing. *[See Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

SIMCOR should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to SIMCOR, therapy with SIMCOR should be initiated at 500/20 mg and appropriately titrated to the desired therapeutic response. Patients already taking simvastatin 20-40 mg who need additional management of their lipid levels may be started on a SIMCOR dose of 500/40 mg once daily at bedtime. Doses of SIMCOR greater than 2000/40 mg are not recommended.

5.1 Myopathy/Rhabdomyolysis

Simvastatin

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,413 patients were treated with simvastatin with 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 ZOCOR (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) was approximately 0.4% in patients on 80 mg/day 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.

All patients starting therapy with SIMCOR, or whose dose of SIMCOR is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report symptoms promptly. SIMCOR therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.
Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated

medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. SIMCOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. SIMCOR 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 which 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, boceprevir, telaprevir, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily), and combination of these drugs with SIMCOR is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with SIMCOR must be suspended during the course of treatment. *[See Contraindications (4) and Drug Interactions (7.1)]*. *In vitro* studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the SIMCOR dose may be needed to reduce the risk of myopathy/rhabdomyolysis if voriconazole must be used concomitantly with simvastatin. *[see Drug Interactions (7.1)]*.

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

The combined use of SIMCOR with verapamil or diltiazem is contraindicated, because dosages of simvastatin are not to exceed 10 mg when these drugs are co-administered and all doses of SIMCOR contain simvastatin in excess of 10 mg. *[See Contraindications (4) and Drug Interactions (7.2)]*.

The combined use of SIMCOR with drugs that cause myopathy/rhabdomyolysis when given alone, such as fibrates, should be avoided *[See Drug Interactions (7.3)]*.

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing SIMCOR with colchicine *[see Drug Interactions (7.8)]*.

The benefits of the combined use of SIMCOR with amlodipine or ranolazine should be carefully weighed against the potential risks of combination. *[See Drug Interactions (7.4)]*. Periodic CK determinations may be considered in patients starting therapy with or increasing the dose of these agents, but there is no assurance that such monitoring will prevent myopathy.

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 coadministered with lipid modifying doses of a niacin-containing product. Caution should be used when prescribing SIMCOR in doses that exceed 1000/20 mg/day to Chinese patients. 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 Dosage and Administration(2.3)]*.

Prescribing recommendations for interacting agents are summarized in Table 3 *[see also Dosage and Administration (2.2), Contraindications (4), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

TABLE 3
Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Strong CYP3A4 inhibitors, e.g., Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Gemfibrozil Cyclosporine Danazol Verapamil Diltiazem	Contraindicated with SIMCOR
Amiodarone Amlodipine Ranolazine	Do not exceed 1000/20 mg SIMCOR daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

SIMCOR

Myopathy and/or rhabdomyolysis have been reported when simvastatin is used in combination with lipid-altering doses (≥ 1 gram/day) of niacin. Physicians contemplating the use of SIMCOR, a combination of simvastatin and niacin extended-release (NIASPAN), should weigh the potential benefits and risks, and should carefully monitor for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial month of treatment or during any period of upward dosage titration of either drug. Periodic determination of serum creatine kinase (CK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

Patients starting therapy with SIMCOR should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness, or weakness. A CK level above ten times the upper limit of normal (ULN) in a patient with unexplained muscle symptoms indicates myopathy. SIMCOR therapy should be discontinued if myopathy is diagnosed or suspected.

In patients with complicated medical histories predisposing to rhabdomyolysis, such as renal insufficiency, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with SIMCOR should be stopped for a few days before elective major surgery and when any major acute medical or surgical condition supervenes (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).

5.2 Liver Dysfunction

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses. Patients previously receiving niacin products other than niacin extended-release (NIASPAN) should be started on SIMCOR at the lowest recommended starting dose. *[See Dosage and Administration (2)]*

SIMCOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of SIMCOR. *[See Contraindications (4)]*

Niacin extended-release (NIASPAN) and simvastatin can cause abnormal liver tests. In a simvastatin-controlled, 24 week study with SIMCOR in 641 patients, there were no persistent increases (to more than 3x the ULN) in serum transaminases. In three placebo-controlled clinical studies of niacin extended-release, patients with normal serum transaminases levels at baseline did not experience any transaminase elevations greater than 3x the ULN. Persistent increases (to more than 3x the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminases levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with SIMCOR and repeated as 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 SIMCOR, promptly interrupt therapy. If an alternate etiology is not found do not restart SIMCOR. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy *[see Warnings and Precautions (5.1)]*.

5.3 Laboratory Abnormalities

Increase in Blood Glucose: Niacin treatment can increase fasting blood glucose. In a simvastatin-controlled, 24-week study with SIMCOR the change from baseline in glycosylated hemoglobin levels was 0.2% for SIMCOR-treated patients and 0.2% for simvastatin-treated patients. Diabetic or potentially diabetic patients should be observed closely during treatment with SIMCOR, particularly during the first few months of therapy. Adjustment of diet and/or hypoglycemic therapy or discontinuation of SIMCOR may be necessary.

Reduction in platelet count: Niacin can reduce platelet count. In a simvastatin-controlled, 24-week study with SIMCOR the mean percent change from baseline for patients treated with 2000/40 mg daily was -5.6%.

Increase in ProthrombinTime (PT): Niacin can cause small increases in PT . In a simvastatin-controlled, 24-week study with SIMCOR this effect was not seen.

Increase in Uric Acid: Elevated uric acid levels have occurred with niacin therapy. In a simvastatin-controlled, 24-week study with SIMCOR this effect was not seen. Nevertheless, in patients predisposed to gout, SIMCOR therapy should be used with caution.

Decrease in Phosphorus: Small dose-related reductions in phosphorous levels were seen in clinical studies with niacin. In a simvastatin-controlled, 24-week study with SIMCOR this effect was not seen.

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

Overview

In a controlled clinical study, 14% of patients randomized to SIMCOR discontinued therapy due to an adverse event. Flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse reactions, occurring in up to 59% of patients treated with SIMCOR. Spontaneous reports with niacin extended-release and clinical studies of SIMCOR suggest that flushing may be accompanied by symptoms of dizziness or syncope, tachycardia, palpitations, shortness of breath, sweating, burning sensation/skin burning sensation, chills, and/or edema.

6.1 Clinical Studies Experience

SIMCOR

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.

The safety data described below reflect exposure to SIMCOR in 403 patients in a controlled study for a period of 6 months.

Flushing: Flushing (warmth, redness, itching and/or tingling) occurred in up to 59% of patients treated with SIMCOR. Flushing resulted in study discontinuation for 6.0% of patients.

More Common Adverse Reactions: In addition to flushing, adverse reactions occurring in ≥ 3% of patients (irrespective of investigator causality) treated with SIMCOR are shown in Table 4 below:

Table 4. Adverse Reactions Occurring in ≥ 3% of Patients in a Controlled Clinical Trial

Adverse Event	SIMCOR overall *	Simvastatin overall **
Total Number of Patients	N=403	N=238
Headache	18 (4.5%)	11 (4.6%)
Pruritus	13 (3.2%)	0 (0.0%)
Nausea	13 (3.2%)	10 (4.2%)
Back Pain	13 (3.2%)	5 (2.1%)
Diarrhea	12 (3.0%)	7 (2.9%)

* SIMCOR overall included all doses from 500/20 mg to 2000/40 mg
** Simvastatin overall included 20 mg, 40 mg, and 80 mg doses

Simvastatin

In pre-marketing controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months) 1.4% of patients discontinued due to adverse reactions. The most commonly reported adverse reactions (incidence > 1%) in simvastatin controlled clinical trials were: headache (3.5%), abdominal pain (3.5%), constipation (2.3%), upper respiratory infection (2.1%), diarrhea (1.9%), and flatulence (1.9%).

Other Clinical Studies

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.

Niacin Extended-Release

In placebo-controlled clinical trials (n=245), flushing episodes were the most common treatment-emergent adverse events (up to 88% of patients) for niacin extended-release. Other adverse events occurring in 5% or greater of patients treated with niacin extended-release are headache (9%), diarrhea (7%), nausea (5%), rhinitis (5%), and dyspepsia (4%) at a maintenance dose of 1000mg daily.

Clinical Laboratory Abnormalities:

SIMCOR

Chemistry

Elevations in serum transaminases *[See Warnings and Precautions (5.2)]*, CK, fasting glucose, uric acid, alkaline phosphatase, LDH, amylase, γ-glutamyl transpeptidase, bilirubin, and reductions in phosphorus, and abnormal thyroid function tests.

Hematology

Reductions in platelet counts and prolongation of PT. *[See Warnings and Precautions (5.3)]*

6.2 Postmarketing Experience

See also the full prescribing information for niacin extended release (Niaspan) and simvastatin products.

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.

Simvastatin

The following additional adverse reactions have been identified during postapproval use of simvastatin. Hypersensitivity reaction including one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, vasculitis, purpura, thrombocytopenia, leucopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, photosensitivity, chills, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, urticaria, fever, dyspnea, and arthralgia; pancreatitis, hepatitis, fatal and non-fatal hepatic failure, pruritus, cataracts, polymyositis, dermatomyositis, polymyalgia rheumatica, tendon rupture, peripheral neuropathy, erectile dysfunction, depression, interstitial lung disease, alopecia, a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails), muscle cramps, vomiting, malaise.

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).

NIASPAN

The following additional adverse reactions have been identified during post-approval use of NIASPAN. Hypersensitivity reaction including one or more of the following features: anaphylaxis, dyspnea, angioedema, tongue edema, larynx edema, face edema, laryngismus; tachycardia, atrial fibrillation, other cardiac arrhythmias, palpitations, hypotension, postural hypotension, dizziness, syncope, flushing, burning sensation/skin burning sensation, paresthesia, urticaria, vesiculobullous rash, maculopapular rash, sweating, dry skin, skin discoloration, blurred vision, macular edema, myalgia, myopathy, peptic ulcers, eructation, flatulence, hepatitis, jaundice, peripheral edema, asthenia, nervousness, insomnia, migraine, gout, and decreased glucose tolerance.

7 DRUG INTERACTIONS

No drug interaction studies were conducted with SIMCOR. However, the following interactions have been noted with the individual components of SIMCOR:

Simvastatin

7.1 Strong CYP3A4 Inhibitors, cyclosporine, or danazol

Strong CYP3A4 inhibitors: Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of CYP3A4. Simvastatin 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.

Elevated plasma levels of HMG-CoA reductase inhibitory activity increases the risk of myopathy and rhabdomyolysis, particularly with higher doses of SIMCOR. *[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 SIMCOR 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 SIMCOR be considered during concomitant use of voriconazole and SIMCOR 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 Verapamil or Diltiazem

The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of verapamil or diltiazem with doses of simvastatin exceeding 10 mg. Because all doses of SIMCOR contain simvastatin in excess of 10 mg, concomitant use of these drugs is contraindicated.*[see Contraindications (4),Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).]*

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

Gemfibrozil: Contraindicated with SIMCOR *[see Contraindications (4) and Warnings and Precautions (5.1)]*.
Other fibrates: Combined use with SIMCOR should be avoided. *[see Warnings and Precautions (5.1).]*

7.4 Amlodipine or Ranolazine

The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of amlodipine or ranolazine *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1) and Table 5 in Clinical Pharmacology (12.3)*].

7.5 Propranolol

In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

7.6 Digoxin

Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when SIMCOR is initiated.

7.7 Coumarin Anticoagulants

In normal volunteers and hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants since 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 the volunteers and patients, respectively. With other reductase inhibitors, 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 SIMCOR 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 SIMCOR is changed or discontinued, the same procedure should be repeated.

7.8 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing SIMCOR with colchicine.*[see Warnings and Precautions (5.1)*

Niacin

7.9 Aspirin

Concomitant use of aspirin may decrease the metabolic clearance of niacin. The clinical relevance of this finding is unclear.

7.10 Antihypertensive Therapy

Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

7.11 Bile Acid Sequestrants

An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of SIMCOR.

7.12 Other

Nutritional supplements containing large doses of niacin or related compounds may potentiate the adverse effects of SIMCOR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X – *[See Contraindications (4)]*

SIMCOR 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. Serum cholesterol and triglycerides increase during normal pregnancy. 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 SIMCOR use

during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to HMG-CoA reductase inhibitors *in utero*. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. SIMCOR may cause fetal harm when administered to a pregnant woman. If SIMCOR 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.

SIMCOR contains simvastatin (a HMG-CoA reductase inhibitor) and niacin (nicotinic acid). There are rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed those expected in the general population. However, the study was only able to exclude a 3- to 4-fold increased risk of congenital anomalies over the background rate. In 89% of these cases, drug treatment was initiated prior to pregnancy and was discontinued during the first trimester when pregnancy was identified. It is not known whether niacin at doses used for lipid disorders can cause fetal harm when administered to a pregnant woman.

Simvastatin was not teratogenic in rats or rabbits at doses that resulted in 3 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Animal reproduction studies have not been conducted with niacin.

Women of childbearing potential, who require SIMCOR treatment for a lipid disorder, should use effective contraception. Patients trying to conceive should contact their prescriber to discuss stopping SIMCOR treatment. If pregnancy occurs, SIMCOR should be immediately discontinued.

8.3 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. Niacin is excreted into human milk but the actual infant dose or infant dose as a percent of the maternal dose is not known. Because of the potential for serious adverse reactions in nursing infants, nursing mothers who require SIMCOR treatment should not breastfeed 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)]*.

8.4 Pediatric Use

The safety and effectiveness of SIMCOR in pediatric patients have not been established.

8.5 Geriatric Use

There were 281 (30.8%) patients aged 65 years and older treated with SIMCOR in Phase III clinical studies. No overall differences in safety and effectiveness were observed between these patients and younger patients, but

greater sensitivity of some older individuals cannot be ruled out. A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age.

Because advanced age (≥65 years) is a predisposing factor for myopathy, including rhabdomyolysis, SIMCOR 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 Gender

Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of niacin extended-release. No consistent gender differences in efficacy and safety were observed in SIMCOR studies.

8.7 Renal Impairment

No pharmacokinetic studies have been conducted in patients with renal impairment for SIMCOR. Caution should be exercised when SIMCOR is administered to patients with renal disease. For patients with severe renal insufficiency, SIMCOR should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 10 mg or higher. Caution should be exercised when SIMCOR is administered to these patients and they should be closely monitored.

8.8 Hepatic Impairment

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for SIMCOR. *[See Warnings and Precautions (5.2).]*

10 OVERDOSAGE

Supportive measures should be taken in the event of an overdose. The dialyzability of niacin, or of simvastatin and its metabolites, is not known.

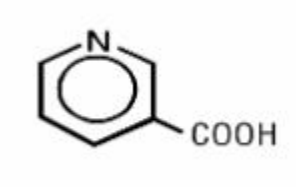
A few cases of overdosage with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

11 DESCRIPTION

SIMCOR tablets contain niacin extended-release (NIASPAN) and simvastatin in combination. Simvastatin, an inhibitor of HMG-CoA reductase, and niacin are both lipid-altering agents.

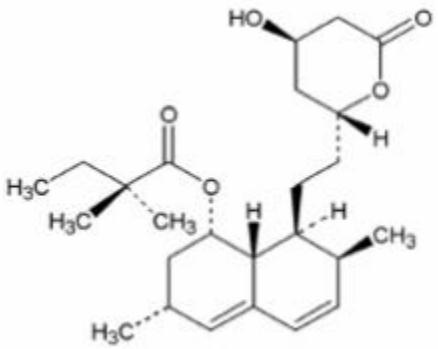
Niacin Extended-Release

Niacin is nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is a white, nonhygroscopic crystalline powder that is very soluble in water, boiling ethanol, and propylene glycol. It is insoluble in ethyl ether. The empirical formula of niacin is $C_6H_5NO_2$ and its molecular weight is 123.11. Niacin has the following structural formula:



Simvastatin

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]]. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in chloroform, methanol, and ethanol. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Simvastatin has the following structural formula:



SIMCOR is available for oral administration as tablets containing 500 mg of niacin extended-release (NIASPAN) and 20 mg simvastatin (SIMCOR 500/20 mg), 500 mg of niacin extended-release (NIASPAN) and 40 mg simvastatin (SIMCOR 500/40 mg), 750 mg of niacin extended-release (NIASPAN) and 20 mg simvastatin (SIMCOR 750/20 mg), 1000 mg of niacin extended-release (NIASPAN) and 20 mg simvastatin (SIMCOR 1000/20 mg) and 1000 mg of niacin extended-release (NIASPAN) and 40 mg simvastatin (SIMCOR 1000/40 mg). Each tablet contains the following inactive ingredients: hypromellose, povidone, stearic acid, polyethylene glycol, butylated hydroxyanisole, FD&C Blue #2, lactose monohydrate, titanium dioxide, triacetin. SIMCOR 500/20 mg, SIMCOR 750/20 mg, and SIMCOR 1000/20 mg also contain iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Niacin

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. The mechanism by which niacin alters lipid profiles is not completely understood and may involve several actions, including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity (which may increase the rate of chylomicron triglyceride removal from plasma). Niacin decreases the rate of hepatic synthesis of VLDL-C and LDL-C, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

Simvastatin

Simvastatin is a prodrug and is hydrolyzed to its active ß-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 VLDL and TG and increases HDL-C.

12.2 Pharmacodynamics

A variety of clinical studies have demonstrated that elevated levels of Total-C, LDL-C, and Apo B promote human atherosclerosis. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations 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 lipoprotein (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

SIMCOR

SIMCOR reduces Total-C, LDL-C, non-HDL-C, Apo B, TG, and Lp(a) levels and increases HDL-C in patients with primary hyperlipidemia, mixed dyslipidemia, or hypertriglyceridemia.

Niacin

Niacin (but not nicotinamide) in gram doses reduces LDL-C, Apo B, Lp(a), TG, and Total-C, and increases HDL-C. The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL2:HDL3 ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL-C particle containing only Apo A-I). Niacin treatment also decreases serum levels of apolipoprotein B-100 (Apo B), the major protein component of the very low-density lipoprotein (VLDL) and LDL fractions, and of Lp(a), a variant form of LDL independently associated with coronary risk. In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect requires further investigation.

Simvastatin

Simvastatin reduces elevated Total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with primary heterozygous familial and nonfamilial hypercholesterolemia and mixed dyslipidemia. Simvastatin reduces Total-C and LDL-C in patients with homozygous familial hypercholesterolemia. Simvastatin decreases VLDL, Total-C/HDL-C ratio, and LDL-C/HDL-C ratio.

12.3 Pharmacokinetics

Absorption and Bioavailability

SIMCOR

The relative bioavailability of niacin (Nicotinuric acid, NUA, C_{max} and total urinary excretion as the surrogate), simvastatin, and simvastatin acid was evaluated under a light snack conditions in healthy volunteers (n=42), following administration of two 1000/20 mg SIMCOR tablets. Niacin exposure (C_{max} and AUC) after SIMCOR was similar to that of a niacin extended-release formulation. However, simvastatin and simvastatin acid AUC after SIMCOR increased by 23% and 41%, respectively, compared to those of a simvastatin immediate release formulation. The mean time to Cmax (T_{max}) for niacin ranged from 4.6 to 4.9 hours and simvastatin from 1.9 to 2.0 hours. Following administration of 2 x 1000/20 mg SIMCOR, the mean C_{max}, T_{max} and $AUC_{(0-t)}$ for simvastatin acid, active metabolite of simvastatin, were 3.29 ng/mL, 6.56 hours and 30.81 ng.hr/mL respectively.

Bioequivalence has not been evaluated among different SIMCOR dosage strengths except between 1000/40 and 500/20 mg. SIMCOR tablets 1000/40 mg and 500/20 mg were bioequivalent following a single dose of 2000/80 mg. Therefore, dosage strengths of SIMCOR should not be considered exchangeable except between these two strengths.

Niacin

Due to extensive and saturable first-pass metabolism, niacin concentrations in the general circulation are dose dependent and highly variable. Peak steady-state niacin concentrations were 0.6, 4.9, and 15.5 mcg/mL after

doses of 1000, 1500, and 2000 mg NIASPAN once daily (given as two 500 mg, two 750 mg, and two 1000 mg tablets, respectively). To reduce the risk of gastrointestinal upset, administration of niacin extended-release with a low-fat meal or snack is recommended.

Simvastatin

Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%). Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. Following an oral dose of ^{14}C-labeled simvastatin in man, plasma concentration of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

Metabolism

SIMCOR

Following administration of SIMCOR, niacin and simvastatin undergo rapid and extensive first-pass metabolism as described in the following niacin and simvastatin sections. Following administration of 2 x 1000/20 mg SIMCOR in healthy volunteers, 10.2%, 10.7%, and 29.5% of the administered niacin dose was recovered in urine as niacin metabolites, NUA, N-methylnicotinamide (MNA), and N-methyl-2-pyridone-5-carboxamide (2PY), respectively. Following administration of 2 x 1000/20 mg SIMCOR, the mean C_{max}, T_{max}, and $AUC_{(0-t)}$ for the simvastatin metabolite, simvastatin acid were 3.29 ng/mL, 6.56hours, and 30.81ng·hr/mL respectively.

Niacin

Niacin undergoes rapid and extensive first-pass metabolism that is dose-rate specific and, at the doses used to treat dyslipidemia, saturable. In humans, one pathway is through a simple conjugation step with glycine to form NUA. NUA is then excreted, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least MNA and nicotinamide-N-oxide NNO. MNA is further metabolized to two other compounds, 2PY and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans.

Simvastatin

Simvastatin is a substrate of CYP3A4. Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. 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.

Elimination

SIMCOR

Following 2 x 1000/20 mg SIMCOR administration, approximately 54% of the niacin dose administered was recovered in urine in 96 hours as niacin and metabolites of which 3.6% was recovered as niacin.

After SIMCOR administration, the mean terminal plasma half-life for simvastatin was 4.2 to 4.9 hours and for simvastatin acid was 4.6 to 5.0 hours.

Niacin

Niacin and its metabolites are rapidly eliminated in the urine. Following single and multiple doses of 1500 to 2000 mg niacin, approximately 53 to 77% of the niacin dose administered as NIASPAN was recovered in urine as niacin and metabolites; up to 7.7% of the dose was recovered in urine as unchanged niacin after multiple dosing with 2 x 1000 mg NIASPAN. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Simvastatin

Simvastatin is excreted in urine, based on studies in humans. Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces.

Special Populations

A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age.

Steady-state plasma concentrations of niacin and metabolites after administration of niacin extended-release are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders. The gender differences observed in plasma levels of niacin and its metabolites may be due to gender-specific differences in metabolic rate or volume of distribution.

Pharmacokinetic studies with a 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 insufficiency (as measured by creatinine clearance).

Drug Interaction

Effect of other drugs on simvastatin:

Table 5
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 simvastatin, *[see Contraindications (4) and Warnings and Precautions (5.1)]*					
Telithromycin†	200 mg QD for 4 days	80 mg	simvastatin 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	simvastatin 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 simvastatin *[see Warnings and Precautions (5.1)]*					
Grapefruit Juice§ (high dose)	200 mL of double-strength TID¶	60 mg single dose	simvastatin acid simvastatin	7 16	
Grapefruit Juice§ (low dose)	8 oz (about 237 mL) of single-strength#	20 mg single dose	simvastatin acid simvastatin	1.3 1.9	
Avoid taking with >10 mg simvastatin, based on clinical and/or post-marketing 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 simvastatin	2.3 2.5	2.4 2.1
Diltiazem	120 mg BID for 10 days	80 mg on Day 10	simvastatin acid simvastatin	2.69 3.10	2.69 2.88
Diltiazem	120 mg BID for 14 days	20 mg on Day 14	simvastatin	4.6	3.6
Avoid taking with >20 mg simvastatin, based on clinical and/or post-marketing experience *[see Warnings and Precautions (5.1)]*					
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	Simvastatin acid simvastatin	1.75 1.76	1.72 1.79
Amlodipine	10 mg QD for 10 days	80 mg on Day 10	simvastatin acid simvastatin	1.58 1.77	1.56 1.47
Ranolazine SR	1000 mg BID for 7 days	80 mg on Day 1, and Day 6-9	simvastatin acid simvastatin	2.26 1.86	2.28 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 simvastatin	0.64 0.89	0.89 0.83
Niacin extended-release [Þ]	2 g single dose	20 mg single dose	simvastatin acid simvastatin	1.6 1.4	1.84 1.08
Propranolol	80 mg single dose	80 mg single dose	total inhibitor active inhibitor	0.79 0.79	↓ from 33.6 to 21.1 ng·eq/mL ↓ 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.
[Þ] Because Chinese patients have an increased risk for myopathy with simvastatin coadministered with lipid-modifying doses (≥1 gram/day niacin) of niacin-containing products, and the risk is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products *[see Warnings and Precautions (5.1)]*.

Simvastatin effect on other drugs:

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.

Coadministration of simvastatin (40 mg QD for 10 days) resulted in an increase in the maximum mean levels of cardioactive digoxin (given as a single 0.4 mg dose on day 10) by approximately 0.3 ng/mL.

Niacin effect on other drugs:

Niacin did not affect fluvastatin pharmacokinetics.

When NIASPAN 2000 mg and lovastatin 40 mg were co-administered, NIASPAN increased lovastatin C_{max} and AUC by 2% and 14%, respectively, and decreased lovastatin acid C_{max} and AUC by 22% and 2%, respectively. Lovastatin reduced NIASPAN bioavailability by 2-3%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with SIMCOR regarding carcinogenesis, mutagenesis, or impairment of fertility.

Niacin

Niacin, administered to mice for a lifetime as a 1% solution in drinking water, was not carcinogenic. The mice in this study received approximately 6 to 8 times a human dose of 3000 mg/day as determined on a mg/m^2 basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed.

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 HMG-CoA reductase inhibitors. 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 milligram 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/m^2), 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

SIMCOR

No animal toxicology or pharmacology studies were done with SIMCOR.

Niacin

No animal toxicology or pharmacology studies were done with niacin extended-release.

Simvastatin

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.

Central Nervous System (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 simvastatin 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).

Reproductive Toxicology Studies

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg/day. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

14 CLINICAL STUDIES

14.1 Modifications of Lipid Profiles

SIMCOR

In a double-blind, randomized, multicenter, multi-national, active-controlled, 24-week study, the lipid effects of SIMCOR were compared to simvastatin 20 mg and 80 mg in 641 patients with type II hyperlipidemia or mixed dyslipidemia. Following a lipid qualification phase, patients were eligible to enter one of two treatment groups. In Group A, patients on simvastatin 20 mg monotherapy with elevated non-HDL levels and LDL-C levels at goal, per the NCEP guidelines, were randomized to one of three treatment arms: SIMCOR 1000/20 mg, SIMCOR 2000/20 mg, or simvastatin 20 mg. In Group B, patients on simvastatin 40 mg monotherapy, with elevated non-HDL levels per the NCEP guidelines regardless of attainment of LDL-C goals, were randomized to one of three treatment arms: SIMCOR 1000/40 mg, SIMCOR 2000/40 mg, or simvastatin 80 mg. Therapy was initiated at the 500 mg dose of SIMCOR and increased by 500 mg every four weeks. Thus patients were titrated to the 1000 mg dose of SIMCOR after four weeks and to the 2000 mg dose of SIMCOR after 12 weeks. All patients randomized to simvastatin monotherapy received 50 mg immediate-release niacin daily in an attempt to keep the study from becoming unblinded due to flushing in the SIMCOR groups. Patients were instructed to take one 325 mg aspirin 30 minutes prior to taking the double-blind medication to help minimize flushing effects.

In Group A, the primary efficacy analysis was a comparison of the mean percent change in non-HDL levels between the SIMCOR 2000/20 mg and simvastatin 20 mg groups, and if statistically significant, then a comparison was conducted between the SIMCOR 1000/20 mg and simvastatin 20 mg groups. In Group B, the primary efficacy analysis was a determination of whether the mean percent change in non-HDL in the SIMCOR 2000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group, and if so, whether the mean percent change in non-HDL in the SIMCOR 1000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group.

In Group A, the non-HDL-C lowering with SIMCOR 2000/20 and SIMCOR 1000/20 was statistically significantly greater than that achieved with simvastatin 20 mg after 24 weeks ($p<0.05$; Table 6). The completion rate after 24 weeks was 72% for the SIMCOR arms and 88% for the simvastatin 20 mg arm. In Group B, the non-HDL-C lowering with SIMCOR 2000/40 and SIMCOR 1000/40 was non-inferior to that

achieved with simvastatin 80 mg after 24 weeks (Table 7). The completion rate after 24 weeks was 78% for the SIMCOR arms and 80% for the simvastatin 80 mg arm.

SIMCOR was not superior to simvastatin in lowering LDL-C in either Group A or Group B. However, SIMCOR was superior to simvastatin in both groups in lowering TG and raising HDL (Tables 8 and 9).

Table 6. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 20-mg Treated Baseline

Group A

	SIMCOR 2000/20			SIMCOR 1000/20			Simvastatin 20		
Week	n[a]	dose (mg/mg)	non-HDL[b]	n[a]	Dose (mg/mg)	non-HDL[b]	n[a]	Dose (mg/mg)	non-HDL[b]
Baseline	56	---	163.1 mg/dL	108	---	164.8 mg/dL	102	---	163.7 mg/dL
4	52	500/20	-12.9%	86	500/20	-12.8%	91	20	-8.3%
8	46	1000/20	-17.5%	91	1000/20	-15.5%	95	20	-8.3%
12	46	1500/20	-18.9%	90	1000/20	-14.8%	96	20	-6.4%
24	40	2000/20	-19.5%†	78	1000/20	-13.6%†	90	20	-5.0%
Dropouts by week 24:	28.6%			27.8%			11.8%		

[a] n=number of subjects with values in the analysis window at each timepoint

[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.

† significant vs. simvastatin 20 mg at the primary endpoint (Week 24), $p<0.05$

Table 7. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 40-mg Treated Baseline

Group B

	SIMCOR 2000/40			SIMCOR 1000/40			Simvastatin 80		
Week	n[a]	dose (mg/mg)	non-HDL[b]	n[a]	Dose (mg/mg)	non-HDL[b]	n[a]	Dose (mg/mg)	non-HDL[b]
Baseline	98	---	144.4 mg/dL	111	---	141.2 mg/dL	113	---	134.5 mg/dL
4	96	500/40	-6.0%	108	500/40	-5.9%	110	80	-11.3%
8	93	1000/40	-15.5%	100	1000/40	-16.2%	104	80	-13.7%
12	90	1500/40	-18.4%	97	1000/40	-12.6%	100	80	-9.5%
24	80	2000/40	-7.6%[c]	82	1000/40	-6.7%[d]	90	80	-6.0%
Dropouts by week 24:	18.4%			26.1%			20.4%		

[a] n=number of subjects with values in the analysis window at each timepoint

[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.

[c] non-inferior to Simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for SIMCOR 2000/40 vs. Simvastatin 80 is (-7.7%, 4.5%)

[d] non-inferior to Simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for SIMCOR 1000/40 vs. SIMCOR 80 is (-6.6%, 5.3%)

Table 8. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels

		Treatment Group A				
TREATMENT	**N**	**LDL-C**	**Total-C**	**HDL-C**	**TG[a]**	**Apo B**
Baseline (mg/dL)*	266	120	207	43	209	102
Simvastatin 20 mg	102	-6.7%	-4.5%	7.8%	-15.3%	-5.6%
SIMCOR 1000/20	108	-11.9%	-8.8%	20.7%	-26.5%	-13.2%
SIMCOR 2000/20	56	-14.3%	-11.1%	29.0%	-38.0%	-18.5%

* either treatment naïve or after receiving simvastatin 20 mg

[a] medians are reported for TG

Table 9. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels

		Treatment Group B				
TREATMENT	**N**	**LDL-C**	**Total-C**	**HDL-C**	**TG[a]**	**Apo B**
Baseline (mg/dL)*	322	108	187	47	145	93
Simvastatin 80 mg	113	-11.4%	-6.2%	0.1%	0.3%	-7.5%
SIMCOR 1000/40	111	-7.1%	-3.1%	15.4%	-22.8%	-7.7%
SIMCOR 2000/40	98	-5.1%	-1.6%	24.4%	-31.8%	-10.5%

* after receiving simvastatin 40 mg

[a] medians are reported for TG

Limitations of use

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

16 HOW SUPPLIED/STORAGE AND HANDLING

SIMCOR 500 mg/20 mg, 750 mg/20 mg and 1000 mg/20 mg tablets are available as blue, unscored, tablets, printed with black ink and packaged in bottles of 90 tablets. SIMCOR 500 mg/40 mg and 1000 mg/40 mg tablets are available as dark blue, unscored, tablets, printed with white ink and packaged in bottles of 90 tablets. Each tablet is printed on one side with the Abbott “A” and a code number specific to the tablet strength. Please see the table below:

SIMCOR Tablet Strength	Printed ID	NDC Number
500 mg/20 mg	A 500-20	0074-3312-90
500 mg/40 mg	A 500-40	0074-3459-90
750 mg/20 mg	A 750-20	0074-3315-90
1000 mg/20 mg	A 1000-20	0074-3455-90
1000 mg/40 mg	A 1000-40	0074-3457-90

Storage: Store at controlled room temperature 20º-25ºC (68º-77ºF).

17 PATIENT COUNSELING 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 simvastatin *[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 SIMCOR.

17.1 Muscle Pain

All patients starting therapy with SIMCOR should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. The risk of myopathy, including rhabdomyolysis, occurring with the use of SIMCOR 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 enzyme tests be performed before the initiation of SIMCOR, and if signs or symptoms of liver injury occur. All patients treated with SIMCOR 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 Dosing Time

SIMCOR tablets should be taken at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended.

17.4 Tablet Integrity

SIMCOR tablets should not be broken, crushed or chewed, but should be swallowed whole.

17.5 Dosing Interruption

If dosing is interrupted for any length of time, their physician should be contacted prior to re-starting therapy; re-titration is recommended.

17.6 Flushing

Flushing is a common side effect of niacin therapy that may subside after several weeks of consistent SIMCOR use. Flushing may vary in severity and is more likely to occur with initiation of therapy, or during dose increases. By dosing at bedtime, flushing will most likely occur during sleep. However, if awakened by flushing at night, the patient should get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications.

17.7 Use of Aspirin

Taking aspirin approximately 30 minutes before dosing can minimize flushing.

17.8 Diet

To avoid ingestion of alcohol, hot beverages and spicy foods around the time of taking SIMCOR to minimize flushing.

17.9 Supplements

To notify their physician if they are taking vitamins or other nutritional supplements containing niacin or nicotinamide.

17.10 Dizziness

To notify their physician if symptoms of dizziness occur.

17.11 Diabetics

If diabetic, to notify their physician of changes in blood glucose.

17.12 Pregnancy

Women of childbearing age should use an effective method of birth control to prevent pregnancy while using SIMCOR. Discuss future pregnancy plans with your healthcare professional, and discuss when to stop SIMCOR if you are trying to conceive. If you are pregnant, stop SIMCOR and call your healthcare professional.

17.13 Breastfeeding

Women who are breastfeeding should not use SIMCOR. If you have a lipid disorder and are breastfeeding, speak with your healthcare professionals about your lipid disorder and whether or not you should breastfeed your infant.

Manufactured by Abbott Pharmaceuticals PR Ltd., Barceloneta, PR 00617

for Abbott Laboratories North Chicago, IL 60064, U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022078Orig1s013

Tracked Changes Label

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SIMCOR (niacin extended-release/simvastatin) tablet, film coated for oral use.

Initial U.S. Approval: 2008

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

Dosage and Administration, Coadministration with Other Drugs (2.2) 06/2011
Dosage and Administration, Chinese Patients Taking SIMCOR (2.3) 06/2011
Contraindications (4) 06/2011
Warnings and Precautions, Myopathy/Rhabdomyolysis (5.1) 06/2011

-------INDICATIONS AND USAGE-------

SIMCOR is a combination of simvastatin, an HMG-Co-A reductase inhibitor, and niacin extended-release (NIASPAN), nicotinic acid. SIMCOR is indicated to:

- Reduce elevated Total–C, LDL-C, Apo B, non-HDL-C, TG, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate. (1.1)
- Reduce TG in patients with hypertriglyceridemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate. (1.1)

Limitations of use:

No incremental benefit of SIMCOR on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin monotherapy and niacin monotherapy has been established. (1.1)

-------DOSAGE AND ADMINISTRATION-------

- SIMCOR should be taken at bedtime with a low-fat snack. (2)
- Dose range: 500/20 mg to 2000/40 mg once daily. (2)
- Initial dose for patients naïve to or switching from immediate-release niacin: 500/20 mg once daily. (2)
- The initial dose for patients already receiving niacin extended-release should not exceed 2000/40 mg once daily. (2)
- Maintenance dose: 1000/20 mg to 2000/40 mg once daily. (2)
- Doses greater than 2000/40 mg daily are not recommended. (2)

-------DOSAGE FORMS AND STRENGTHS-------

- Unscored film-coated tablets:
  500 mg niacin extended-release/20 mg simvastatin (3)
  500 mg niacin extended-release/40 mg simvastatin (3)
  750 mg niacin extended-release/20 mg simvastatin (3)
  1000 mg niacin extended-release/20 mg simvastatin (3)
  1000 mg niacin extended-release/40 mg simvastatin (3)

-------CONTRAINDICATIONS-------

- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4, 5.2)
- Active peptic ulcer disease (4)
- Arterial bleeding (4)
- Concomitant administration of strong CYP3A4 inhibitors (4, 5.1)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol (4, 5.1)
- Concomitant administration of ~~amiodarone~~, verapamil~~,~~ or diltiazem (4,5.1)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)
- Known hypersensitivity to product components (4, 6.1)

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

- 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, 8.7)
- Liver enzyme abnormalities ~~and monitoring~~: Persistent elevations in hepatic transaminase~~s~~ can occur. ~~Monitor~~ Check liver enzyme~~s~~ tests before initiating therapy and ~~during treatment~~ as clinically indicated thereafter. (5.2)
- Severe hepatic toxicity has occurred in patients substituting sustained-release niacin for immediate-release niacin at equivalent doses. If switching from niacin preparations other than niacin extended-release (NIASPAN), initiate with lowest SIMCOR dose; niacin extended-release can be converted at equivalent doses. (5.2)
- Niacin extended-release can increase serum glucose levels. Glucose levels should be closely monitored in diabetic or potentially diabetic patients particularly during the first few months of use. (5.3)

-------ADVERSE REACTIONS-------

The most common (incidence > 3%) adverse reactions with SIMCOR are flushing, headache, back pain, diarrhea, nausea, and pruritis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633–9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.2, 4, 5.1, 7.1, 7.2, 7.3, 7.4, 12.3)	
Interacting Agents	Prescribing Recommendations
Strong CYP3A4 inhibitors(e.g., itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nafazodone), gemfibrozil, cyclosporine, danazol~~, amiodarone,~~ verapamil, diltiazem	Contraindicated with SIMCOR
Amiodarone, a~~A~~mlodipine, ranolazine	Do not exceed 1000/20 mg SIMCOR daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

- Fenofibrate: Combination with SIMCOR increases the risk of adverse skeletal muscle effects and should be avoided. (7.3)
- Coumarin anticoagulants: Combination prolongs INR. Achieve stable INR prior to starting SIMCOR. Monitor INR frequently until stable upon initiation or alteration of SIMCOR therapy. (7.7)

-------USE IN SPECIFIC POPULATIONS-------

- Severe renal impairment (not on dialysis): SIMCOR should be used with extreme caution. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 2/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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 Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles

SIMCOR

SIMCOR is indicated to reduce Total-C, LDL-C, Apo B, non-HDL-C, TG, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

SIMCOR is indicated to reduce TG in patients with hypertriglyceridemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

Limitations of use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

SIMCOR should be taken as a single daily dose at bedtime, with a low fat snack. Patients not currently on niacin extended-release and patients currently on niacin products other than niacin extended-release should start SIMCOR at a single 500/20 mg tablet daily at bedtime. Patients already taking simvastatin 20 to 40 mg who need additional management of their lipid levels may be started on a SIMCOR dose of 500/40 mg once daily at bedtime. *[See Warnings and Precautions (5.2)]*. The dose of niacin extended-release should not be increased by more than 500 mg daily every 4 weeks - see Table 1.

Table 1. Recommended niacin extended-release dosing

	Week(s)	**Daily dose of niacin extended-release**
Initial Titration Schedule	1 to 4	500 mg
	5 to 8	1000 mg
	*	1500 mg
	*	2000 mg

* After Week 8, titrate to patient response and tolerance. If response to 1000 mg daily is inadequate, increase dose to 1500 mg daily; may subsequently increase dose to 2000 mg daily. Daily dose should not be increased more than 500 mg in a 4-week period, and doses above 2000 mg daily are not recommended.

The recommended maintenance dose for SIMCOR is 1000/20 mg to 2000/40 mg (two 1000/20 mg tablets) once daily depending on patient tolerability and lipid levels. **The efficacy and safety of doses of SIMCOR greater than 2000/40 mg daily have not been studied and are therefore not recommended.**

If SIMCOR therapy is discontinued for an extended period of time (> 7 days), re-titration as tolerated is recommended. SIMCOR tablets should be taken whole and should not be broken, crushed, or chewed before swallowing.

Due to the increased risk of hepatotoxicity with other modified-release (sustained-release or time-release) niacin preparations or immediate-release (crystalline) niacin, SIMCOR should only be substituted for equivalent doses of niacin extended-release (NIASPAN).

Flushing *[See Adverse Reactions (6.1)]* may be reduced in frequency or severity by pretreatment with aspirin up to the recommended dose of 325 mg (taken approximately 30 minutes prior to SIMCOR dose). Flushing, pruritus, and gastrointestinal distress are also reduced by gradually increasing the dose of niacin (refer to Table 1) and avoiding administration on an empty stomach. Concomitant alcoholic, hot drinks or spicy foods may increase the side effects of flushing and pruritus and should be avoided around the time of SIMCOR ingestion.

2.2 Coadministration with Other Drugs

Patients taking Amiodarone, Amlodipine or Ranolazine

- The dose of SIMCOR should not exceed 1000/20 mg/day *[see Warnings and Precautions (5.1), Drug Interactions (7.4), and Clinical Pharmacology (12.3)]*.

2.3 Chinese Patients Taking SIMCOR

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 prescribing SIMCOR in doses that exceed 1000/20 mg/day to Chinese patients. 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

SIMCOR tablets are formulated for oral administration in the following strength combinations:

Table 2. SIMCOR Tablet Strengths

	500mg/20mg	500mg/40mg	750mg/20mg	1000mg/20mg	1000mg/40mg
Niacin extended-release equivalent (mg)	500	500	750	1000	1000
simvastatin equivalent (mg)	20	40	20	20	40

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4 CONTRAINDICATIONS

SIMCOR is contraindicated in the following conditions:

- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels *[See Warnings and Precautions (5.2)]*
- Patients with active peptic ulcer disease
- Patients with arterial bleeding
- Concomitant administration of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) *[see Warnings and Precautions (5.1)]*
- Concomitant administration of gemfibrozil, cyclosporine, or danazol *[see Warnings and Precautions (5.1)]*
- Concomitant administration of ~~amiodarone,~~ verapamil~~,~~ or diltiazem *[see Warnings and Precautions (5.1)]*
- Women who are pregnant or may become pregnant. SIMCOR may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for 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 SIMCOR use during pregnancy; however in rare reports congenital anomalies were observed following intrauterine exposure to HMG-CoA reductase inhibitors. If SIMCOR 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. *[See Use In Specific Populations (8.1)]* In rat and rabbit animal reproduction studies, simvastatin revealed no evidence of teratogenicity. There are no animal reproductive studies conducted with niacin.
- Nursing mothers. SIMCOR contains simvastatin and nicotinic acid. Nicotinic acid is excreted into human milk and 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 of the potential for serious adverse reactions in nursing infants, women who require SIMCOR treatment should not breastfeed their infants. *[See Use In Specific Populations (8.3)]*
- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including one of more of the following adverse reactions have been reported for simvastatin and/or niacin

extended-release: anaphylaxis, angioedema, urticaria, fever, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and flushing. *[See Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

SIMCOR should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to SIMCOR, therapy with SIMCOR should be initiated at 500/20 mg and appropriately titrated to the desired therapeutic response. Patients already taking simvastatin 20-40 mg who need additional management of their lipid levels may be started on a SIMCOR dose of 500/40 mg once daily at bedtime. Doses of SIMCOR greater than 2000/40 mg are not recommended.

5.1 Myopathy/Rhabdomyolysis

Simvastatin

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,413 patients were treated with simvastatin with 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 ZOCOR (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) was approximately 0.4% in patients on 80 mg/day 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.

All patients starting therapy with SIMCOR, or whose dose of SIMCOR is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report symptoms promptly. SIMCOR therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK

determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. ~~Therapy with SIMCOR should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.~~ SIMCOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. SIMCOR 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 which 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, boceprevir, telaprevir, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily), and combination of these drugs with SIMCOR is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with SIMCOR must be suspended during the course of treatment. *[See Contraindications (4) and Drug Interactions (7.1)]*. *In vitro* studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the SIMCOR dose may be needed to reduce the risk of myopathy/rhabdomyolysis if voriconazole must be used concomitantly with simvastatin. *[see Drug Interactions (7.1)]*.

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

The combined use of SIMCOR with ~~amiodarone,~~ verapamil~~,~~ or diltiazem is contraindicated, because dosages of simvastatin are not to exceed 10 mg when these drugs are co-administered and all doses of SIMCOR contain simvastatin in excess of 10 mg. *[See Contraindications (4) and Drug Interactions (7.2)]*.

The combined use of SIMCOR with drugs that cause myopathy/rhabdomyolysis when given alone, such as fibrates, should be avoided *[See Drug Interactions (7.3)]*.

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing SIMCOR with colchicine *[see Drug Interactions (7.8)]*.

The benefits of the combined use of SIMCOR with amlodipine or ranolazine should be carefully weighed against the potential risks of combination. *[See Drug Interactions (7.4)]*. Periodic CK determinations may be considered in patients starting therapy with or increasing the dose of these agents, but there is no assurance that such monitoring will prevent myopathy.

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 coadministered with lipid modifying doses of a niacin-containing product. Caution should be used when prescribing SIMCOR in doses that exceed 1000/20 mg/day to Chinese patients. 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 Dosage and Administration(2.3)]*.
Prescribing recommendations for interacting agents are summarized in Table 3 *[see also Dosage and Administration (2.2), Contraindications (4), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

TABLE 3
Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Strong CYP3A4 inhibitors, e.g., Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Gemfibrozil Cyclosporine Danazol ~~Amiodarone~~ Verapamil Diltiazem	Contraindicated with SIMCOR
Amiodarone Amlodipine Ranolazine	Do not exceed 1000/20 mg SIMCOR daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

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SIMCOR

Myopathy and/or rhabdomyolysis have been reported when simvastatin is used in combination with lipid-altering doses (≥ 1 gram/day) of niacin. Physicians contemplating the use of SIMCOR, a combination of simvastatin and niacin extended-release (NIASPAN), should weigh the potential benefits and risks, and should carefully monitor for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial month of treatment or during any period of upward dosage titration of either drug. Periodic determination of serum creatine kinase (CK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

Patients starting therapy with SIMCOR should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness, or weakness. A CK level above ten times the upper limit of normal (ULN) in a patient with unexplained muscle symptoms indicates myopathy. SIMCOR therapy should be discontinued if myopathy is diagnosed or suspected.

In patients with complicated medical histories predisposing to rhabdomyolysis, such as renal insufficiency, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with SIMCOR should be stopped for a few days before elective major surgery and when any major acute medical or surgical condition supervenes (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).

5.2 Liver Dysfunction

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses. Patients previously receiving niacin products other than niacin extended-release (NIASPAN) should be started on SIMCOR at the lowest recommended starting dose. *[See Dosage and Administration (2)]*

SIMCOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of SIMCOR. *[See Contraindications (4)]*

Niacin extended-release (NIASPAN) and simvastatin can cause abnormal liver tests. In a simvastatin-controlled, 24 week study with SIMCOR in 641 patients, there were no persistent increases (to more than 3x the ULN) in serum transaminases. In three placebo-controlled clinical studies of niacin extended-release, patients with normal serum transaminases levels at baseline did not experience any transaminase elevations greater than 3x the ULN. Persistent increases (to more than 3x the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminases levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

~~Liver function tests should be performed on all patients during therapy with SIMCOR. It is recommended that liver function tests be performed before treatment begins, every 12 weeks for the first 6 months, and periodically thereafter (e.g., at approximately 6-month intervals). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality returns to normal. Should an increase in transaminase levels of more than 3x ULN persist, or if transaminase elevations are associated with symptoms of nausea, fever, and/or malaise, withdrawal of SIMCOR therapy is recommended.~~ It is recommended that liver enzyme tests be obtained prior to initiating therapy with SIMCOR and repeated as 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 SIMCOR, promptly interrupt therapy. If an alternate etiology is not found do not restart SIMCOR. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy *[see Warnings and Precautions (5.1)]*.

5.3 Laboratory Abnormalities

Increase in Blood Glucose: Niacin treatment can increase fasting blood glucose. In a simvastatin-controlled, 24-week study with SIMCOR the change from baseline in glycosylated hemoglobin levels was 0.2% for SIMCOR-treated patients and 0.2% for simvastatin-treated patients. Diabetic or potentially diabetic patients should be observed closely during treatment with SIMCOR, particularly during the first few months of therapy. Adjustment of diet and/or hypoglycemic therapy or discontinuation of SIMCOR may be necessary.

Reduction in platelet count: Niacin can reduce platelet count. In a simvastatin-controlled, 24-week study with SIMCOR the mean percent change from baseline for patients treated with 2000/40 mg daily was -5.6%.

Increase in ProthrombinTime (PT): Niacin can cause small increases in PT . In a simvastatin-controlled, 24-week study with SIMCOR this effect was not seen.

Increase in Uric Acid: Elevated uric acid levels have occurred with niacin therapy. In a simvastatin-controlled, 24-week study with SIMCOR this effect was not seen. Nevertheless, in patients predisposed to gout, SIMCOR therapy should be used with caution.

Decrease in Phosphorus: Small dose-related reductions in phosphorous levels were seen in clinical studies with niacin. In a simvastatin-controlled, 24-week study with SIMCOR this effect was not seen.

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

Overview

In a controlled clinical study, 14% of patients randomized to SIMCOR discontinued therapy due to an adverse event. Flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse reactions, occurring in up to 59% of patients treated with SIMCOR. Spontaneous reports with niacin extended-release and clinical studies of SIMCOR suggest that flushing may be accompanied by symptoms of dizziness or syncope, tachycardia, palpitations, shortness of breath, sweating, burning sensation/skin burning sensation, chills, and/or edema.

6.1 Clinical Studies Experience

SIMCOR

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.

The safety data described below reflect exposure to SIMCOR in 403 patients in a controlled study for a period of 6 months.

Flushing: Flushing (warmth, redness, itching and/or tingling) occurred in up to 59% of patients treated with SIMCOR. Flushing resulted in study discontinuation for 6.0% of patients.

More Common Adverse Reactions: In addition to flushing, adverse reactions occurring in ≥ 3% of patients (irrespective of investigator causality) treated with SIMCOR are shown in Table 4 below:

Table 4. Adverse Reactions Occurring in ≥ 3% of Patients in a Controlled Clinical Trial

Adverse Event	SIMCOR overall *	Simvastatin overall **
Total Number of Patients	N=403	N=238
Headache	18 (4.5%)	11 (4.6%)
Pruritus	13 (3.2%)	0 (0.0%)
Nausea	13 (3.2%)	10 (4.2%)
Back Pain	13 (3.2%)	5 (2.1%)
Diarrhea	12 (3.0%)	7 (2.9%)

* SIMCOR overall included all doses from 500/20 mg to 2000/40 mg
** Simvastatin overall included 20 mg, 40 mg, and 80 mg doses

Simvastatin

In pre-marketing controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months) 1.4% of patients discontinued due to adverse reactions. The most commonly reported adverse reactions (incidence > 1%) in simvastatin controlled clinical trials were: headache (3.5%), abdominal pain (3.5%), constipation (2.3%), upper respiratory infection (2.1%), diarrhea (1.9%), and flatulence (1.9%).

Other Clinical Studies

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.

Niacin Extended-Release

In placebo-controlled clinical trials (n=245), flushing episodes were the most common treatment-emergent adverse events (up to 88% of patients) for niacin extended-release. Other adverse events occurring in 5% or greater of patients treated with niacin extended-release are headache (9%), diarrhea (7%), nausea (5%), rhinitis (5%), and dyspepsia (4%) at a maintenance dose of 1000mg daily.

Clinical Laboratory Abnormalities:

SIMCOR

Chemistry

Elevations in serum transaminases *[See Warnings and Precautions (5.2)]*, CK, fasting glucose, uric acid, alkaline phosphatase, LDH, amylase, γ-glutamyl transpeptidase, bilirubin, and reductions in phosphorus, and abnormal thyroid function tests.

Hematology

Reductions in platelet counts and prolongation of PT. *[See Warnings and Precautions (5.3)]*

6.2 Postmarketing Experience

See also the full prescribing information for niacin extended release (Niaspan) and simvastatin products.

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.

Simvastatin

The following additional adverse reactions have been identified during postapproval use of simvastatin. Hypersensitivity reaction including one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, vasculitis, purpura, thrombocytopenia, leucopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, photosensitivity, chills, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, urticaria, fever, dyspnea, and arthralgia; pancreatitis, hepatitis, fatal and non-fatal hepatic failure, pruritus, cataracts, polymyositis, dermatomyositis, polymyalgia rheumatica, ~~global amnesia~~, tendon rupture, peripheral neuropathy, ~~memory impairment~~, erectile dysfunction, depression, interstitial lung disease, alopecia, a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails), muscle cramps, vomiting, malaise.

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).

NIASPAN

The following additional adverse reactions have been identified during post-approval use of NIASPAN. Hypersensitivity reaction including one or more of the following features: anaphylaxis, dyspnea, angioedema, tongue edema, larynx edema, face edema, laryngismus; tachycardia, atrial fibrillation, other cardiac arrhythmias, palpitations, hypotension, postural hypotension, dizziness, syncope, flushing, burning sensation/skin burning sensation, paresthesia, urticaria, vesiculobullous rash, maculopapular rash, sweating, dry skin, skin discoloration, blurred vision, macular edema, myalgia, myopathy, peptic ulcers, eructation, flatulence, hepatitis, jaundice, peripheral edema, asthenia, nervousness, insomnia, migraine, gout, and decreased glucose tolerance.

7 DRUG INTERACTIONS

No drug interaction studies were conducted with SIMCOR. However, the following interactions have been noted with the individual components of SIMCOR:

Simvastatin

7.1 Strong CYP3A4 Inhibitors, cyclosporine, or danazol

Strong CYP3A4 inhibitors: Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of CYP3A4. Simvastatin 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.

Elevated plasma levels of HMG-CoA reductase inhibitory activity increases the risk of myopathy and rhabdomyolysis, particularly with higher doses of SIMCOR. *[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 SIMCOR 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 SIMCOR be considered during concomitant use of voriconazole and SIMCOR 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 ~~Amiodarone,~~ Verapamil~~,~~ or Diltiazem

The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of ~~amiodarone,~~ verapamil~~,~~ or diltiazem with doses of simvastatin exceeding 10 mg. Because all doses of SIMCOR contain simvastatin in excess of 10 mg, concomitant use of these drugs is contraindicated.*[see Contraindications (4),Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).]*

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

Gemfibrozil: Contraindicated with SIMCOR *[see Contraindications (4) and Warnings and Precautions (5.1)]*.
Other fibrates: Combined use with SIMCOR should be avoided. *[see Warnings and Precautions (5.1).]*

7.4 Amlodipine or Ranolazine

The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of amlodipine or ranolazine *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1) and Table 5 in Clinical Pharmacology (12.3)*].

7.5 Propranolol

In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

7.6 Digoxin

Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when SIMCOR is initiated.

7.7 Coumarin Anticoagulants

In normal volunteers and hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants since 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 the volunteers and patients, respectively. With other reductase inhibitors, 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 SIMCOR 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 SIMCOR is changed or discontinued, the same procedure should be repeated.

7.8 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing SIMCOR with colchicine.*[see Warnings and Precautions (5.1)*

Niacin

7.9 Aspirin

Concomitant use of aspirin may decrease the metabolic clearance of niacin. The clinical relevance of this finding is unclear.

7.10 Antihypertensive Therapy

Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

7.11 Bile Acid Sequestrants

An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of SIMCOR.

7.12 Other

Nutritional supplements containing large doses of niacin or related compounds may potentiate the adverse effects of SIMCOR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X – *[See Contraindications (4)]*

SIMCOR 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. Serum cholesterol and triglycerides increase during normal pregnancy. 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 SIMCOR use during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to HMG-CoA reductase inhibitors *in utero*. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. SIMCOR may cause fetal harm when administered to a pregnant woman. If SIMCOR 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.

SIMCOR contains simvastatin (a HMG-CoA reductase inhibitor) and niacin (nicotinic acid). There are rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed those expected in the general population. However, the study was only able to exclude a 3- to 4-fold increased risk of congenital anomalies over the background rate. In 89% of these cases, drug treatment was initiated prior to pregnancy and was discontinued during the first trimester when pregnancy was identified. It is not known whether niacin at doses used for lipid disorders can cause fetal harm when administered to a pregnant woman.

Simvastatin was not teratogenic in rats or rabbits at doses that resulted in 3 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Animal reproduction studies have not been conducted with niacin.

Women of childbearing potential, who require SIMCOR treatment for a lipid disorder, should use effective contraception. Patients trying to conceive should contact their prescriber to discuss stopping SIMCOR treatment. If pregnancy occurs, SIMCOR should be immediately discontinued.

8.3 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. Niacin is excreted into human milk but the actual infant dose or infant dose as a percent of the maternal dose is not known. Because of the potential for serious adverse reactions in nursing infants, nursing mothers who require SIMCOR treatment should not breastfeed 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)]*.

8.4 Pediatric Use

The safety and effectiveness of SIMCOR in pediatric patients have not been established.

8.5 Geriatric Use

There were 281 (30.8%) patients aged 65 years and older treated with SIMCOR in Phase III clinical studies. No overall differences in safety and effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age.

Because advanced age (≥65 years) is a predisposing factor for myopathy, including rhabdomyolysis, SIMCOR 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 Gender

Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of niacin extended-release. No consistent gender differences in efficacy and safety were observed in SIMCOR studies.

8.7 Renal Impairment

No pharmacokinetic studies have been conducted in patients with renal impairment for SIMCOR. Caution should be exercised when SIMCOR is administered to patients with renal disease. For patients with severe renal insufficiency, SIMCOR should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 10 mg or higher. Caution should be exercised when SIMCOR is administered to these patients and they should be closely monitored.

8.8 Hepatic Impairment

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for SIMCOR. *[See Warnings and Precautions (5.2).]*

10 OVERDOSAGE

Supportive measures should be taken in the event of an overdose. The dialyzability of niacin, or of simvastatin and its metabolites, is not known.

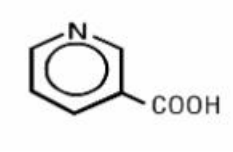
A few cases of overdosage with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

11 DESCRIPTION

SIMCOR tablets contain niacin extended-release (NIASPAN) and simvastatin in combination. Simvastatin, an inhibitor of HMG-CoA reductase, and niacin are both lipid-altering agents.

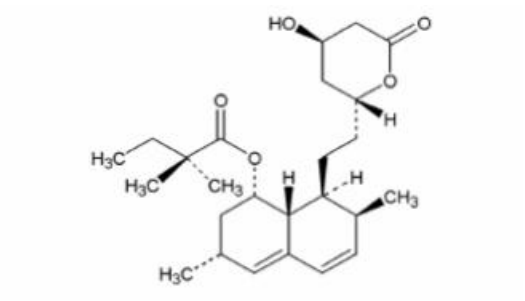
Niacin Extended-Release

Niacin is nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is a white, nonhygroscopic crystalline powder that is very soluble in water, boiling ethanol, and propylene glycol. It is insoluble in ethyl ether. The empirical formula of niacin is $C_6H_5NO_2$ and its molecular weight is 123.11. Niacin has the following structural formula:



Simvastatin

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]]. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in chloroform, methanol, and ethanol. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Simvastatin has the following structural formula:



SIMCOR is available for oral administration as tablets containing 500 mg of niacin extended-release (NIASPAN) and 20 mg simvastatin (SIMCOR 500/20 mg), 500 mg of niacin extended-release (NIASPAN) and 40 mg simvastatin (SIMCOR 500/40 mg), 750 mg of niacin extended-release (NIASPAN) and 20 mg simvastatin (SIMCOR 750/20 mg), 1000 mg of niacin extended-release (NIASPAN) and 20 mg simvastatin (SIMCOR 1000/20 mg) and 1000 mg of niacin extended-release (NIASPAN) and 40 mg simvastatin (SIMCOR 1000/40 mg). Each tablet contains the following inactive ingredients: hypromellose, povidone, stearic acid, polyethylene glycol, butylated hydroxyanisole, FD&C Blue #2, lactose monohydrate, titanium dioxide, triacetin. SIMCOR 500/20 mg, SIMCOR 750/20 mg, and SIMCOR 1000/20 mg also contain iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Niacin

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. The mechanism by which niacin alters lipid profiles is not completely understood and may involve several actions, including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity (which may increase the rate of chylomicron triglyceride removal from plasma). Niacin decreases the rate of hepatic synthesis of VLDL-C and LDL-C, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

Simvastatin

Simvastatin is a prodrug and is hydrolyzed to its active ß-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 VLDL and TG and increases HDL-C.

12.2 Pharmacodynamics

A variety of clinical studies have demonstrated that elevated levels of Total-C, LDL-C, and Apo B promote human atherosclerosis. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations 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 lipoprotein (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

SIMCOR

SIMCOR reduces Total-C, LDL-C, non-HDL-C, Apo B, TG, and Lp(a) levels and increases HDL-C in patients with primary hyperlipidemia, mixed dyslipidemia, or hypertriglyceridemia.

Niacin

Niacin (but not nicotinamide) in gram doses reduces LDL-C, Apo B, Lp(a), TG, and Total-C, and increases HDL-C. The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions. These shifts include an increase in the HDL2:HDL3 ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL-C particle containing only Apo A-I). Niacin treatment also decreases serum levels of apolipoprotein B-100 (Apo B), the major protein component of the very low-density lipoprotein (VLDL) and LDL fractions, and of Lp(a), a variant form of LDL independently associated with coronary risk. In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect requires further investigation.

Simvastatin

Simvastatin reduces elevated Total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with primary heterozygous familial and nonfamilial hypercholesterolemia and mixed dyslipidemia. Simvastatin reduces Total-C and LDL-C in patients with homozygous familial hypercholesterolemia. Simvastatin decreases VLDL, Total-C/HDL-C ratio, and LDL-C/HDL-C ratio.

12.3 Pharmacokinetics

Absorption and Bioavailability

SIMCOR

The relative bioavailability of niacin (Nicotinuric acid, NUA, C_{max} and total urinary excretion as the surrogate), simvastatin, and simvastatin acid was evaluated under a light snack conditions in healthy volunteers (n=42), following administration of two 1000/20 mg SIMCOR tablets. Niacin exposure (C_{max} and AUC) after SIMCOR was similar to that of a niacin extended-release formulation. However, simvastatin and simvastatin acid AUC after SIMCOR increased by 23% and 41%, respectively, compared to those of a simvastatin immediate release formulation. The mean time to Cmax (T_{max}) for niacin ranged from 4.6 to 4.9 hours and simvastatin from 1.9 to 2.0 hours. Following administration of 2 x 1000/20 mg SIMCOR, the mean C_{max}, T_{max} and $AUC_{(0-t)}$ for simvastatin acid, active metabolite of simvastatin, were 3.29 ng/mL, 6.56 hours and 30.81 ng.hr/mL respectively.

Bioequivalence has not been evaluated among different SIMCOR dosage strengths except between 1000/40 and 500/20 mg. SIMCOR tablets 1000/40 mg and 500/20 mg were bioequivalent following a single dose of 2000/80 mg. Therefore, dosage strengths of SIMCOR should not be considered exchangeable except between these two strengths.

Niacin

Due to extensive and saturable first-pass metabolism, niacin concentrations in the general circulation are dose dependent and highly variable. Peak steady-state niacin concentrations were 0.6, 4.9, and 15.5 mcg/mL after doses of 1000, 1500, and 2000 mg NIASPAN once daily (given as two 500 mg, two 750 mg, and two 1000 mg tablets, respectively). To reduce the risk of gastrointestinal upset, administration of niacin extended-release with a low-fat meal or snack is recommended.

Simvastatin

Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%). Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. Following an oral dose of ^{14}C-labeled simvastatin in man, plasma concentration of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

Metabolism

SIMCOR

Following administration of SIMCOR, niacin and simvastatin undergo rapid and extensive first-pass metabolism as described in the following niacin and simvastatin sections. Following administration of 2 x

1000/20 mg SIMCOR in healthy volunteers, 10.2%, 10.7%, and 29.5% of the administered niacin dose was recovered in urine as niacin metabolites, NUA, N-methylnicotinamide (MNA), and N-methyl-2-pyridone-5-carboxamide (2PY), respectively. Following administration of 2 x 1000/20 mg SIMCOR, the mean C_{max}, T_{max}, and $AUC_{(0-t)}$ for the simvastatin metabolite, simvastatin acid were 3.29 ng/mL, 6.56hours, and 30.81ng·hr/mL respectively.

Niacin

Niacin undergoes rapid and extensive first-pass metabolism that is dose-rate specific and, at the doses used to treat dyslipidemia, saturable. In humans, one pathway is through a simple conjugation step with glycine to form NUA. NUA is then excreted, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least MNA and nicotinamide-N-oxide NNO. MNA is further metabolized to two other compounds, 2PY and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans.

Simvastatin

Simvastatin is a substrate of CYP3A4. Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. 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.

Elimination

SIMCOR

Following 2 x 1000/20 mg SIMCOR administration, approximately 54% of the niacin dose administered was recovered in urine in 96 hours as niacin and metabolites of which 3.6% was recovered as niacin.

After SIMCOR administration, the mean terminal plasma half-life for simvastatin was 4.2 to 4.9 hours and for simvastatin acid was 4.6 to 5.0 hours.

Niacin

Niacin and its metabolites are rapidly eliminated in the urine. Following single and multiple doses of 1500 to 2000 mg niacin, approximately 53 to 77% of the niacin dose administered as NIASPAN was recovered in urine as niacin and metabolites; up to 7.7% of the dose was recovered in urine as unchanged niacin after multiple dosing with 2 x 1000 mg NIASPAN. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Simvastatin

Simvastatin is excreted in urine, based on studies in humans. Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces.

Special Populations

A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age.

Steady-state plasma concentrations of niacin and metabolites after administration of niacin extended-release are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders. The gender differences observed in plasma levels of niacin and its metabolites may be due to gender-specific differences in metabolic rate or volume of distribution.

Pharmacokinetic studies with a 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 insufficiency (as measured by creatinine clearance).

Drug Interaction

Effect of other drugs on simvastatin:

Table 5
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 simvastatin, *[see Contraindications (4) and Warnings and Precautions (5.1)]*					
Telithromycin†	200 mg QD for 4 days	80 mg	simvastatin 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	simvastatin 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 simvastatin *[see Warnings and Precautions (5.1)]*					
Grapefruit Juice[§] (high dose)	200 mL of double-strength TID[¶]	60 mg single dose	simvastatin acid simvastatin	7 16	
Grapefruit Juice[§] (low dose)	8 oz (about 237 mL) of single-strength[#]	20 mg single dose	simvastatin acid simvastatin	1.3 1.9	
Avoid taking with >10 mg simvastatin, based on clinical and/or post-marketing 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 simvastatin	2.3 2.5	2.4 2.1
Diltiazem	120 mg BID for 10 days	80 mg on Day 10	simvastatin acid simvastatin	2.69 3.10	2.69 2.88
Diltiazem	120 mg BID for 14 days	20 mg on Day 14	simvastatin	4.6	3.6
~~Amiodarone~~	~~400 mg QD for 3 days~~	~~40 mg on Day 3~~	~~simvastatin~~ ~~simvastatin acid~~	~~1.75~~ ~~1.76~~	~~1.72~~ ~~1.79~~
Avoid taking with >20 mg simvastatin, based on clinical and/or post-marketing experience *[see Warnings and Precautions (5.1)]*					
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	Simvastatin acid simvastatin	1.75 1.76	1.72 1.79
Amlodipine	10 mg QD for 10 days	80 mg on Day 10	simvastatin acid simvastatin	1.58 1.77	1.56 1.47
Ranolazine SR	1000 mg BID for 7 days	80 mg on Day 1, and Day 6-9	simvastatin acid simvastatin	2.26 1.86	2.28 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 simvastatin	0.64 0.89	0.89 0.83
Niacin extended-release[Þ]	2 g single dose	20 mg single dose	simvastatin acid simvastatin	1.6 1.4	1.84 1.08
Propranolol	80 mg single dose	80 mg single dose	total inhibitor active inhibitor	0.79 0.79	↓ from 33.6 to 21.1 ng·eq/mL ↓ 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.
[Þ] Because Chinese patients have an increased risk for myopathy with simvastatin coadministered with lipid-modifying doses (≥1 gram/day niacin) of niacin-containing products, and the risk is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products *[see Warnings and Precautions (5.1)]*.

Simvastatin effect on other drugs:

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.

Coadministration of simvastatin (40 mg QD for 10 days) resulted in an increase in the maximum mean levels of cardioactive digoxin (given as a single 0.4 mg dose on day 10) by approximately 0.3 ng/mL.

Niacin effect on other drugs:

Niacin did not affect fluvastatin pharmacokinetics.

When NIASPAN 2000 mg and lovastatin 40 mg were co-administered, NIASPAN increased lovastatin C_{max} and AUC by 2% and 14%, respectively, and decreased lovastatin acid C_{max} and AUC by 22% and 2%, respectively. Lovastatin reduced NIASPAN bioavailability by 2-3%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with SIMCOR regarding carcinogenesis, mutagenesis, or impairment of fertility.

Niacin

Niacin, administered to mice for a lifetime as a 1% solution in drinking water, was not carcinogenic. The mice in this study received approximately 6 to 8 times a human dose of 3000 mg/day as determined on a mg/m^2 basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed.

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 HMG-CoA reductase inhibitors. 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 milligram 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/m^2), 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

SIMCOR

No animal toxicology or pharmacology studies were done with SIMCOR.

Niacin

No animal toxicology or pharmacology studies were done with niacin extended-release.

Simvastatin

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.

Central Nervous System (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 simvastatin 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).

Reproductive Toxicology Studies

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg/day. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

14 CLINICAL STUDIES

14.1 Modifications of Lipid Profiles

SIMCOR

In a double-blind, randomized, multicenter, multi-national, active-controlled, 24-week study, the lipid effects of SIMCOR were compared to simvastatin 20 mg and 80 mg in 641 patients with type II hyperlipidemia or mixed dyslipidemia. Following a lipid qualification phase, patients were eligible to enter one of two treatment groups. In Group A, patients on simvastatin 20 mg monotherapy with elevated non-HDL levels and LDL-C levels at goal, per the NCEP guidelines, were randomized to one of three treatment arms: SIMCOR 1000/20 mg, SIMCOR 2000/20 mg, or simvastatin 20 mg. In Group B, patients on simvastatin 40 mg monotherapy, with elevated non-HDL levels per the NCEP guidelines regardless of attainment of LDL-C goals, were randomized to one of three treatment arms: SIMCOR 1000/40 mg, SIMCOR 2000/40 mg, or simvastatin 80 mg. Therapy was initiated at the 500 mg dose of SIMCOR and increased by 500 mg every four weeks. Thus patients were titrated to the 1000 mg dose of SIMCOR after four weeks and to the 2000 mg dose of SIMCOR after 12 weeks. All patients randomized to simvastatin monotherapy received 50 mg immediate-release niacin daily in an attempt to keep the study from becoming unblinded due to flushing in the SIMCOR groups. Patients were instructed to take one 325 mg aspirin 30 minutes prior to taking the double-blind medication to help minimize flushing effects.

In Group A, the primary efficacy analysis was a comparison of the mean percent change in non-HDL levels between the SIMCOR 2000/20 mg and simvastatin 20 mg groups, and if statistically significant, then a comparison was conducted between the SIMCOR 1000/20 mg and simvastatin 20 mg groups. In Group B, the primary efficacy analysis was a determination of whether the mean percent change in non-HDL in the SIMCOR 2000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group, and if so, whether the mean percent change in non-HDL in the SIMCOR 1000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group.

In Group A, the non-HDL-C lowering with SIMCOR 2000/20 and SIMCOR 1000/20 was statistically significantly greater than that achieved with simvastatin 20 mg after 24 weeks ($p<0.05$; Table 6). The completion rate after 24 weeks was 72% for the SIMCOR arms and 88% for the simvastatin 20 mg arm. In Group B, the non-HDL-C lowering with SIMCOR 2000/40 and SIMCOR 1000/40 was non-inferior to that achieved with simvastatin 80 mg after 24 weeks (Table 7). The completion rate after 24 weeks was 78% for the SIMCOR arms and 80% for the simvastatin 80 mg arm.

SIMCOR was not superior to simvastatin in lowering LDL-C in either Group A or Group B. However, SIMCOR was superior to simvastatin in both groups in lowering TG and raising HDL (Tables 8 and 9).

Table 6. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 20-mg Treated Baseline

Group A									
	SIMCOR 2000/20			SIMCOR 1000/20			Simvastatin 20		
Week	n[a]	dose (mg/mg)	non-HDL[b]	n[a]	Dose (mg/mg)	non-HDL[b]	n[a]	Dose (mg/mg)	non-HDL[b]
Baseline	56	---	163.1 mg/dL	108	---	164.8 mg/dL	102	---	163.7 mg/dL
4	52	500/20	-12.9%	86	500/20	-12.8%	91	20	-8.3%
8	46	1000/20	-17.5%	91	1000/20	-15.5%	95	20	-8.3%
12	46	1500/20	-18.9%	90	1000/20	-14.8%	96	20	-6.4%
24	40	2000/20	-19.5%[†]	78	1000/20	-13.6%[†]	90	20	-5.0%
Dropouts by week 24:	28.6%			27.8%			11.8%		

[a] n=number of subjects with values in the analysis window at each timepoint

[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.

[†] significant vs. simvastatin 20 mg at the primary endpoint (Week 24), $p<0.05$

Table 7. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 40-mg Treated Baseline

Group B									
	SIMCOR 2000/40			SIMCOR 1000/40			Simvastatin 80		
Week	n[a]	dose (mg/mg)	non-HDL[b]	n[a]	Dose (mg/mg)	non-HDL[b]	n[a]	Dose (mg/mg)	non-HDL[b]
Baseline	98	---	144.4 mg/dL	111	---	141.2 mg/dL	113	---	134.5 mg/dL
4	96	500/40	-6.0%	108	500/40	-5.9%	110	80	-11.3%
8	93	1000/40	-15.5%	100	1000/40	-16.2%	104	80	-13.7%
12	90	1500/40	-18.4%	97	1000/40	-12.6%	100	80	-9.5%
24	80	2000/40	-7.6%[c]	82	1000/40	-6.7%[d]	90	80	-6.0%
Dropouts by week 24:	18.4%			26.1%			20.4%		

[a] n=number of subjects with values in the analysis window at each timepoint

[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.

[c] non-inferior to Simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for SIMCOR 2000/40 vs. Simvastatin 80 is (-7.7%, 4.5%)

[d] non-inferior to Simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for SIMCOR 1000/40 vs. SIMCOR 80 is (-6.6%, 5.3%)

Table 8. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels

	Treatment Group A					
TREATMENT	**N**	**LDL-C**	**Total-C**	**HDL-C**	**TG[a]**	**Apo B**
Baseline (mg/dL)*	266	120	207	43	209	102
Simvastatin 20 mg	102	-6.7%	-4.5%	7.8%	-15.3%	-5.6%
SIMCOR 1000/20	108	-11.9%	-8.8%	20.7%	-26.5%	-13.2%
SIMCOR	56	-14.3%	-11.1%	29.0%	-38.0%	-18.5%

2000/20

* either treatment naïve or after receiving simvastatin 20 mg
[a] medians are reported for TG

Table 9. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels

		Treatment Group B				
TREATMENT	**N**	**LDL-C**	**Total-C**	**HDL-C**	**TG[a]**	**Apo B**
Baseline (mg/dL)*	322	108	187	47	145	93
Simvastatin 80 mg	113	-11.4%	-6.2%	0.1%	0.3%	-7.5%
SIMCOR 1000/40	111	-7.1%	-3.1%	15.4%	-22.8%	-7.7%
SIMCOR 2000/40	98	-5.1%	-1.6%	24.4%	-31.8%	-10.5%

* after receiving simvastatin 40 mg
[a] medians are reported for TG

Limitations of use

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

16 HOW SUPPLIED/STORAGE AND HANDLING

SIMCOR 500 mg/20 mg, 750 mg/20 mg and 1000 mg/20 mg tablets are available as blue, unscored, tablets, printed with black ink and packaged in bottles of 90 tablets. SIMCOR 500 mg/40 mg and 1000 mg/40 mg tablets are available as dark blue, unscored, tablets, printed with white ink and packaged in bottles of 90 tablets. Each tablet is printed on one side with the Abbott "A" and a code number specific to the tablet strength. Please see the table below:

SIMCOR Tablet Strength	Printed ID	NDC Number
500 mg/20 mg	A 500-20	0074-3312-90
500 mg/40 mg	A 500-40	0074-3459-90
750 mg/20 mg	A 750-20	0074-3315-90
1000 mg/20 mg	A 1000-20	0074-3455-90
1000 mg/40 mg	A 1000-40	0074-3457-90

Storage: Store at controlled room temperature 20º-25ºC (68º-77ºF).

17 PATIENT COUNSELING 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 simvastatin *[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 SIMCOR.

17.1 Muscle Pain

All patients starting therapy with SIMCOR should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. The risk of myopathy, including rhabdomyolysis, occurring with the use of SIMCOR 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 enzyme tests be performed before the initiation of SIMCOR, and if signs or symptoms of liver injury occur. All patients treated with SIMCOR should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

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17.3 Dosing Time

SIMCOR tablets should be taken at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended.

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17.4 Tablet Integrity

SIMCOR tablets should not be broken, crushed or chewed, but should be swallowed whole.

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17.5 Dosing Interruption

If dosing is interrupted for any length of time, their physician should be contacted prior to re-starting therapy; re-titration is recommended.

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17.6 Flushing

Flushing is a common side effect of niacin therapy that may subside after several weeks of consistent SIMCOR use. Flushing may vary in severity and is more likely to occur with initiation of therapy, or during dose increases. By dosing at bedtime, flushing will most likely occur during sleep. However, if awakened by flushing at night, the patient should get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications.

17.7 Use of Aspirin

Taking aspirin approximately 30 minutes before dosing can minimize flushing.

17.8 Diet

To avoid ingestion of alcohol, hot beverages and spicy foods around the time of taking SIMCOR to minimize flushing.

17.9 Supplements

To notify their physician if they are taking vitamins or other nutritional supplements containing niacin or nicotinamide.

17.10 Dizziness

To notify their physician if symptoms of dizziness occur.

17.11 Diabetics

If diabetic, to notify their physician of changes in blood glucose.

17.12 Pregnancy

Women of childbearing age should use an effective method of birth control to prevent pregnancy while using SIMCOR. Discuss future pregnancy plans with your healthcare professional, and discuss when to stop SIMCOR if you are trying to conceive. If you are pregnant, stop SIMCOR and call your healthcare professional.

17.13 Breastfeeding

Women who are breastfeeding should not use SIMCOR. If you have a lipid disorder and are breastfeeding, speak with your healthcare professionals about your lipid disorder and whether or not you should breastfeed your infant.

Manufactured by Abbott Pharmaceuticals PR Ltd., Barceloneta, PR 00617

for Abbott Laboratories North Chicago, IL 60064, U.S.A.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022078Orig1s013

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 as cases per (b) (4)
Lovastatin (Mevacor, Advicor, Altocor)	23		(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,** (b) (4)

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

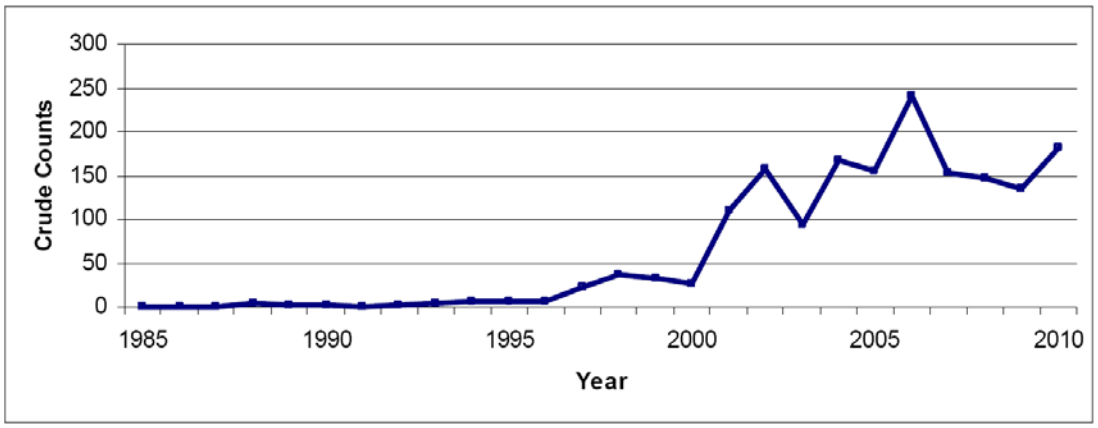
DMEP consulted OSE and requested that a review of AERS and the published literature be conducted to further assess the effect of statins on cognition. In 2002, OSE had performed a review of 279 statin reports associated with transient memory loss. This review had been requested by DMEP in response to 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)

[redacted]

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)

(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 ~~10 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, 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*, or ~~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

*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 inhibitor~~s~~ 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 Cmax
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓27%	↓18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

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}
Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 days	40 mg single dose	↑81%	↑63%
Kaletra 400 mg/100 mg BID for 14 days	20 mg OD for 4 days	↑33%	↑26%

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}
20 mg OD for 4 days	Kaletra 400 mg/100 mg BID for 14 days	No change	No change

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 Boceprevir Telaprevir Nefazodone	~~Avoid~~ Contraindicated 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 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)**~~

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.

Altoprev:

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 benzafibrate (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: Baker *et al.* (2004); Hsu *et al.* (2002)	Both are CYP3A4 and P-gp substrates; P-gp inhibition by simvastatin	Acute myopathy or rhabdomyolysis (could be attributed to either drug)
	Fluvastatin: Atasoyu *et al.* (2005)	Synergistic myotoxicity *via* PK & PD mechanism; fluvastatin is not a P-gp inhibitor	
	Pravastatin: Alayli *et al.* (2005)	Synergistic myotoxicity *via* PK & PD mechanism; pravastatin is not a P-gp inhibitor	
	Atorvastatin: Tufan *et al.* (2006)	Both are CYP3A4 substrates; P-gp inhibition by atorvastatin	
Fibrates	Gemfibrozil; Atmaca *et al.*, 2002	Synergistic toxic effect of both drugs	
	Fenofibrate & Diltiazem: Sinsawaiwong *et al.*, 1997	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 $AUC_{0\text{-last}}$, and simvastatin acid $AUC_{0\text{-last}}$ 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 d~~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 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 d~~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~~ Contraindicated with lovastatin
Gemfibrozil Cyclosporine	Avoid with lovastatin
~~Gembibrozil~~ ~~Other fibrates~~ ~~Lipid-lowering doses (≥1 g/day) of nicacin~~ ~~Cyclosporine~~ Danazol Diltiazem Verapamil	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., ~~below~~ 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 (≥ 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-strengthÞ for 4 days	40 mg single dose	1.94	1.57
Cyclosporine	16	Not describedß	10 mg QD for 10 days	5- to 8-fold	NDà
	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 acide	
Diltiazem	10	120 mg BID for 14 days	20 mg	3 57è	

* 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

Þ 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

ß 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.

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
02/27/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022078Orig1s013

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 22078/S-013
Name of Drug: Simcor (niacin ER/simvastatin)
Applicant: Abbott Laboratories

Labeling Reviewed:

Submission Date: February 21, 2012, Package Insert

Background and Summary Description:

Simcor was approved February 15, 2008, and is currently indicated to:

-Reduce elevated Total–C, LDL-C, Apo B, non-HDL-C, TG, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

-Reduce TG in patients with hypertriglyceridemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

Supplement -013 was submitted September 28, 2011, in response to our letter dated August 11, 2011 (attached to this review). This letter resulted following a comprehensive review of all of the statin labels.

On December 3, 2011, and February 3, 2012 we requested some revisions to our August 11, 2011, request (e-mails are attached to this review). The sponsor submitted revised labeling on December 29, 2011, and February 13, 2012 respectively.

Review

The proposed labeling was compared to the currently approved labeling (S-012, approved June 8, 2011). No other revisions were made other than those requested of the sponsor.

Recommendations

An approval letter should be issued.

Attachments: August 11, 2011 Supplement request letter
December 3, 2011 e-mail requesting further revisions
February 3, 2012 e-mail requesting further revisions

Review done by:
Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products

August 11, 2011 Supplement Request Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022078

PRIOR APPROVAL SUPPLEMENT REQUEST

Abbott Laboratories
Attention: Kelly Kaleck-Schlinsog
Associate Director, Dyslipidemia & Metabolism
Dept. PA76, Building AP-30-1NE
200 Abbott Park Road
Abbott Park, IL 60064

Dear Ms. Kaleck-Schlinsog:

Please refer to your new drug application (NDA) for Simcor (niacin extended-release/simvastatin) Tablets, 500 mg/20 mg, 500 mg/40 mg, 750 mg/20 mg, 1000 mg/20 mg and 1000 mg/40 mg.

FDA has completed a comprehensive review of the HMG-CoA reductase inhibitor (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. Based on the results of our review, you are requested to modify the Prescribing Information (PI) for Simcor.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

Under **5 WARNINGS AND PRECAUTIONS, 5.1 Myopathy/Rhabdomyolysis, Simvastatin**:

Delete the last sentence of paragraph 5:

~~Therapy with SIMCOR should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.~~

and replace it with:

SIMCOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. SIMCOR 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.

Under **5 WARNINGS AND PRECAUTIONS:**

Add the following:

Reference ID: 3090606

5.4 Endocrine Function:

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

Under **6 ADVERSE REACTIONS, 6.2 Postmarketing Experience, Simvastatin:**

From paragraph 1, delete:

~~memory impairment~~ and ~~global amnesia~~

and add the following paragraph 2:

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).

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

Modify the 2nd bullet as follows:

Liver enzyme abnormalities ~~and monitoring~~: Persistent elevations in hepatic transaminases can occur. ~~Monitor~~ Check liver enzymes ~~tests~~ before initiating therapy and ~~during treatment~~ as clinically indicated thereafter. (5.2)

Under **5 WARNINGS AND PRECAUTIONS, 5.2 Liver Dysfunction:**

Delete the following from the 4th paragraph:

~~Liver function tests should be performed on all patients during therapy with SIMCOR. It is recommended that liver function tests be performed before treatment begins, every 12 weeks for the first 6 months, and periodically thereafter (e.g., at approximately 6-month intervals). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3X ULN or greater persist, withdrawal of therapy with SIMCOR is recommended.~~

and replace it with:

It is recommended that liver enzyme tests be obtained prior to initiating therapy with SIMCOR and repeated as 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 SIMCOR, promptly interrupt therapy. If an alternate etiology is not found do not restart SIMCOR.

Under **6 ADVERSE REACTIONS, 6.2 Post-Marketing Experience, Simvastatin:**

Modify:

(b) (4)

to:

fatal and non-fatal hepatic failure

Under **17 PATIENT COUNSELING INFORMATION:**

Add the following:

17.2 Liver Enzymes:

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

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

Modify the first bullet as follows:

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines, (b) (4)
Predisposing factors include advanced age (≥65), female gender, uncontrolled hypothyroidism, and renal impairment. (4, 5.1, 8.5, 8.7)

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, **DRUG INTERACTIONS:**

Modify the first bullet as follows:

- Fenofibrate: Combination with SIMCOR increases the risk of adverse skeletal muscle effects and should be avoided. (7.3)

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, **CONTRAINDICATIONS:**

Modify as follows:

- Concomitant administration of ~~amiodarone,~~ verapamil~~,~~ or diltiazem (4, 5.1)

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, **DRUG INTERACTIONS, Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis** (2.2, 4, 5.1, 7.1, 7.2, 7.3, 7.4, 12.3):

Modify the table as follows:

Interacting Agents	Prescribing Recommendations
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol, ~~amiodarone,~~ verapamil, diltiazem	Contraindicated with SIMCOR
Amiodarone, ~~A~~amlodipine, ranolazine	Do not exceed 1000/20 mg SIMCOR daily

Under **DOSAGE AND ADMINISTRATION, 2.2 Coadministration with Other Drugs:**

Modify as follows:

Patients taking Amiodarone, Amlodipine, or Ranolazine
• The dose of SIMCOR should not exceed 1000/20 mg/day *[see Warnings and Precautions (5.1), Drug Interactions (7.4), and Clinical Pharmacology (12.3)].*

Under **CONTRAINDICATIONS:**

Modify as follows:

- Concomitant administration of ~~amiodarone,~~ verapamil~~,~~ or diltiazem *[see Warnings and Precautions (5.1)]*

Under **WARNINGS AND PRECAUTIONS, 5.1 Myopathy/Rhabdomyolysis, Simvastatin**, *Drug Interactions*:

Modify the second paragraph as follows:

The combined use of SIMCOR with ~~amiodarone,~~ verapamil~~,~~ or diltiazem is contraindicated, because dosages of simvastatin are not to exceed 10 mg when these drugs are co-administered and all doses of SIMCOR contain simvastatin in excess of 10 mg. *[see Contraindications (4) and Drug Interactions (7.2)]*.

and modify TABLE 3 as follows:

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Gemfibrozil Cyclosporine Danazol ~~Amiodarone~~ Verapamil Diltiazem	Contraindicated with SIMCOR
Amiodarone Amlodipine Ranolazine	Do not exceed 1000/20 mg SIMCOR daily

Under **DRUG INTERACTIONS, Simvastatin:**

Modify as follows:

7.2 ~~Amiodarone,~~ Verapamil~~,~~ or Diltiazem

The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of ~~amiodarone,~~ verapamil~~,~~ or diltiazem with doses of simvastatin exceeding 10 mg. Because all doses of SIMCOR contain simvastatin in excess of 10 mg, concomitant use of these drugs is contraindicated. *[see Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Under **CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, Drug Interaction:**

Modify Table 5 as follows:

Avoid taking with >10 mg simvastatin based on clinical and/or post-marketing experience *[see Warnings and Precautions (5.1)]*					
~~Amiodarone~~	~~400 mg QD for 3 days~~	~~40 mg on Day 3~~	~~simvastatin~~ ~~simvastatin acid~~	~~1.75~~ ~~1.76~~	~~1.72~~ ~~1.79~~
Avoid taking with >20 mg simvastatin, based on clinical and/or post-marketing experience *[see Warnings and Precautions (5.1)]*					
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	simvastatin acid simvastatin	1.75 1.76	1.72 1.79

Submit draft labeling as a prior approval supplement to this application, incorporating all revisions since the last approval of the package insert. 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. Your supplement must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Please submit this prior approval labeling supplement by September 30, 2011.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

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

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/s/

AMY G EGAN
08/11/2011

December 3, 2011 e-mail

Johnson, Kati

From: Johnson, Kati
Sent: Saturday, December 03, 2011 11:14 AM
To: Richard R Leber
Subject: NDA 22078/S-013, Simcor, revised labeling needed

Hi Richard,
Could you please amend this supplement, submitted 9/28/2011 to include the following revisions:

SIMCOR:

- Under HIGHLIGHTS OF PRESCRIBING INFORMATION, **WARNINGS AND PRECAUTIONS:**
  - [redacted] (b) (4)",
- Under **CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, Drug Interaction:**
  - Correct Table 5 as follows:

Avoid taking with >20 mg simvastatin, based on clinical and/or post-marketing experience *[see Warnings and Precautions (5.1)]*					
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	simvastatin acid simvastatin	1.75 1.76	1.72 1.79

Whenever you can get this in would be fine. It isn't due until 3/28/2012. We will get it done earlier than that, of course, but I certainly don't want any abbott folks working nights or weekends to get this labeling in.
This should be the only revision we will be requesting for this supplement.
Call me if you have any questions.
Hope you have a good weekend.
Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

February 3, 2012 e-mail

Johnson, Kati

From: Johnson, Kati
Sent: Friday, February 03, 2012 11:56 AM
To: Richard R Leber
Cc: Johnson, Kati
Subject: Simcor labeling supplement, 1 more revision

Attachments: SIMCORrevisions02032012.doc

Hi Richard,
Could you amend the Simcor labeling to include the following RED and underlined text?? Merck has OK'd this for their label.
I think this will be the end of this.
We are trying to finalize this by the 15th, so hopefully you can turn it around quickly.

SIMCORrevision
2032012.doc (5

When we approve this, there will be 2 labels attached to the AP letter-one will have underline/strikeout, and then there will be a clean version.
When you amend this supplement, send in the PI that is easiest for you to cobble together. I am just going to add this new text to the underline/strikeout and clean versions that I have already put together.

Sorry for all this trouble.
Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

HIGHLIGHTS:

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

Interacting Agents	Prescribing Recommendations
Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone), gemfibrozil, cyclosporine, danazol	Contraindicated with simvastatin
Verapamil, diltiazem	Do not exceed 10 mg simvastatin daily
Amiodarone, amlodipine, ranolazine	Do not exceed 20 mg simvastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

CONTRAINDICATIONS:

ZOCOR is contraindicated in the following conditions:

- Concomitant administration of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) *[see Warnings and Precautions (5.1)]*.

WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis, *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 which 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, boceprevir, telaprevir, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily). Combination of these drugs with simvastatin is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. *[See Contraindications (4) and Drug Interactions (7.1).]* *In vitro* studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the simvastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with simvastatin. *[See Drug Interactions (7.1).]*

WARNINGS AND PRECAUTIONS, Myopathy/Rhabdomyolysis, *Drug Interactions*:

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

Interacting Agents	Prescribing Recommendations
Strong CYP3A4 Inhibitors, e.g.: Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Gemfibrozil Cyclosporine Danazol	Contraindicated with simvastatin
Verapamil Diltiazem	Do not exceed 10 mg simvastatin daily
Amiodarone Amlodipine Ranolazine	Do not exceed 20 mg simvastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

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/s/

KATI JOHNSON
02/22/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022078Orig1s013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22078/S-013

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Abbott Laboratories
Attention: Richard Leber
Manager, Regulatory Affairs-PPG
200 Abbott Park Road
Abbott Park, IL 60064

Dear Mr. Leber:

We have received your September 28, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 22078

SUPPLEMENT NUMBER: S-013

PRODUCT NAME: Simcor (niacin extended-release/simvastatin) Tablets

DATE OF SUBMISSION: September 28, 2011

DATE OF RECEIPT: September 28, 2011

This supplemental application proposes to revise the WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS sections of the HIGHLIGHTS OF PRESCRIBING INFORMATION page and the DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACIONS, CLINICAL PHARMACOLOGY, and PATIENT COUNSELING INFORMATION sections of the Full Prescribing Information of the SIMCOR package insert in response to our letter dated August 11, 2011. A version of this letter, based on the Agency's 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 co-administration, was issued to all statin drugs and combination products with a statin component.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 27, 2011, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be March 28, 2012.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

KATI JOHNSON
10/20/2011