

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22-078/S006, S007

Trade Name: SIMCOR

Generic Name: (niacin ER/simvastatin)

Sponsor: Abbott Laboratories

Approval Date: July 28, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
22-078/S006, S007**

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-078/S006, S007

APPROVAL LETTER



NDA 22078/S-006, S-007

SUPPLEMENT APPROVAL

Abbott Laboratories
Attention: Tracy Verciglio
Associate Director, Regulatory Affairs, CMC
Dept. PA71, Bldg. AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Verciglio:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 30, 2009 (S-006) and November 20, 2009 (S-007), received September 30, 2009 (S-006) and November 20, 2009 (S-007), submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SIMCOR (Niacin ER/Simvastatin) Tablets, 500 mg/20 mg, 750 mg/20 mg, and 1000 mg/20 mg.

We acknowledge receipt of the following submissions to Supplement -007:

- December 17, 2009
- February 5, 2010
- June 29, 2010

These "Prior Approval" supplemental new drug applications provides for the following:

Supplement -006:

1. The Abbott Pharmaceuticals PR, Ltd (APL) site in Barceloneta, PR as a new manufacturing site for the Niacin Extended-Release (ER) core tablet and the final core tablet.;
2. Removal of the tablet debossing and the addition of the black printing.;
3. The Abbott Pharmaceuticals PR, Ltd (APL) site in Barceloneta, PR as an analytical testing site for the drug substance niacin.;
4. Removal of the following drug substance niacin analytical testing sites: [REDACTED] (b)(4)
5. Removal of [REDACTED] (b)(4) as a manufacturer of the drug substance simvastatin.;
6. Removal of the following drug substance simvastatin analytical testing sites: [REDACTED] (b)(4)
7. The removal of [REDACTED] (b)(4) as a drug product manufacturing and testing site.;

8. The removal to the two [REDACTED] (b)(4) packaging sites for the drug product.;
9. The removal of the [REDACTED] (b)(4) as a drug product analytical testing site.; and
10. Revision of the drug product Physical Examination Specification acceptance criteria to support the non-debossed, printed tablet.
11. Associated labeling revisions.

Supplement -007:

1. Addition of two dosage strengths: 500 mg/40 mg and 1000 mg/40 mg;
2. Reformulation of the 1000 mg/20 mg tablet to utilize a 1000 mg niacin ER [REDACTED] (b)(4) [REDACTED]
3. The Abbott Pharmaceuticals PR, Ltd (APL) site in Barceloneta, PR as a new manufacturing site for the Niacin Extended-Release (ER) core tablet and for the final product printing.;
4. Removal of the tablet debossing and the addition of white printing.;
5. The Abbott Pharmaceuticals PR, Ltd (APL) site in Barceloneta, PR as an analytical testing site for niacin. USP.
6. Associated labeling revisions.

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.

For future bioequivalence studies for the 500 mg/20 mg strength tablet, we recommend using 1000 mg/40 mg (2 X 500 mg/20 mg) instead of the 2000 mg/80 mg dose.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 pending "Changes Being Effected" (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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDA 22078/S-006, S-007". Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least

24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

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) 1234.

Sincerely,

{See appended electronic signature page}

Eric Colman, MD
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling: Package Insert

Carton and Container Labeling:

- 500 mg/20 mg, 3-count sample carton
- 500 mg/40 mg, 7-count sample bottle label
- 500 mg/40 mg, 7-count sample carton label
- Quick Answers for Patients (“Tips Card”)
- 500 mg/40 mg, 90-count bottle label
- 500 mg/20 mg, 90-count bottle label
- 750 mg/20 mg, 90-count bottle label
- 1000 mg/20 mg, 90-count bottle label
- 1000 mg/40 mg, 90-count bottle label

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22078	SUPPL-7	ABBOTT LABORATORIES	SIMCOR
NDA-22078	SUPPL-6	ABBOTT LABORATORIES	SIMCOR

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

/s/

ERIC C COLMAN
07/28/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-078/S006, S007

LABELING

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

Initial U.S. Approval: 2008

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)
- 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, advanced age (≥ 65), hypothyroidism, renal impairment, and concomitant use of cyclosporine, danazol, gemfibrozil, amiodarone, and verapamil and potent CYP3A4 inhibitors. (5.1)
- Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminase can occur. Monitor liver enzymes before and during treatment. (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

- Potent inhibitors of CYP 3A4: Combination increases simvastatin exposure. SIMCOR should not be used with potent inhibitors of CYP3A4. (7.1)
- Cyclosporine: Combination with SIMCOR should be avoided. (7.2)
- Danazol: Combination with SIMCOR should be avoided. (7.2)
- Amiodarone: Combination with SIMCOR should be limited to the 20 mg once daily dose of simvastatin. (7.3)
- Verapamil: Combination with SIMCOR should be limited to the 20 mg once daily dose of simvastatin. (7.3)
- Gemfibrozil: Combination with SIMCOR should be avoided. (7.4)
- Fenofibrate: Combination with SIMCOR should be avoided. (7.4)
- 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: 7/20/10

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

1.1 Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

5.2 Liver Dysfunction

5.3 Laboratory Abnormalities

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

7.2 Cyclosporine or Danazol

7.3 Amiodarone or Verapamil

7.4 Gemfibrozil and other Fibrates

7.5 Propranolol

7.6 Digoxin

7.7 Coumarin Anticoagulants

7.8 Aspirin

7.9 Antihypertensive Therapy

7.10 Bile Acid Sequestrants

7.11 Other

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Gender

8.7 Renal Impairment

8.8 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Modifications of Lipid Profiles

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Dosing Time

17.2 Tablet Integrity

17.3 Dosing Interruption

17.4 Muscle Pain

17.5 Flushing

17.6 Use of Aspirin

17.7 Diet

17.8 Supplements

17.9 Dizziness

17.10 Diabetics

17.11 Pregnancy

17.12 Breastfeeding

* 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

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 20-40 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. 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.

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.		

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.

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
- 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 or 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, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,050 patients were treated with simvastatin with 24,747 (approximately 60%) treated for at least 4 years, the incidence of myopathy was approximately

0.02%, 0.08%, and 0.53% at 20, 40, and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

Potent inhibitors of CYP3A4: The risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole, and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (> 1 quart daily).

The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin and, therefore, SIMCOR with the following:

Potent inhibitors of cytochrome P-450 isoform, 3A4 (CYP 3A4):

Itraconazole, ketoconazole, and other antifungal azoles

Macrolide antibiotics erythromycin, clarithromycin, and telithromycin

HIV protease inhibitors

Antidepressant nefazodone

Grapefruit juice in large quantities (> 1 quart daily)

The use of SIMCOR concomitantly with these potent CYP3A4 inhibitors should be avoided. [See *Drug Interactions (7.1)*]

Cyclosporine or Danazol: Simvastatin dose should not exceed 10 mg daily in combination with cyclosporine or danazol. Therefore, the combined use of SIMCOR with cyclosporine or danazol should be avoided. [See *Drug Interactions (7.2)*]

Gemfibrozil: Simvastatin dose should not exceed 10 mg daily when concomitantly used with gemfibrozil. Therefore, the combined use of SIMCOR with gemfibrozil should be avoided. [See *Drug Interactions (7.4)*]

Other Fibrates: Combined use of SIMCOR with drugs that cause myopathy/rhabdomyolysis when given alone, such as fibrates, should be avoided. [See *Drug Interactions (7.4)*]

Amiodarone or Verapamil: The dose of the simvastatin component of SIMCOR should not exceed 20 mg in patients receiving amiodarone or verapamil concomitantly. The combined use of the simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. [See *Drug Interactions (7.3)*]

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 10 times 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.

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 Prothrombin Time (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.

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 $\geq 3\%$ of patients (irrespective of investigator causality) treated with SIMCOR are shown in Table 3 below:

Table 3. Adverse Reactions Occurring in $\geq 3\%$ 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%).

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

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 erythematosus-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, hepatic failure, pruritus, cataracts, polymyositis, dermatomyositis, polymyalgia rheumatica, global amnesia, tendon rupture, peripheral neuropathy, memory impairment.

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 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.

Potent inhibitors of CYP3A4 include:

Itraconazole, ketoconazole, and other antifungal azoles,

Macrolide antibiotics erythromycin, clarithromycin, and telithromycin,

HIV protease inhibitors,

Antidepressant nefazodone,

Grapefruit juice in large quantities (> 1 quart daily).

Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of simvastatin. Hence when simvastatin is used with a potent inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin. *[See Warnings and Precautions (5.1)]*

Serious skeletal muscle disorder, e.g., rhabdomyolysis, have been reported during concomitant therapy of simvastatin or other HMG-CoA reductase inhibitors with cyclosporine, danazol, itraconazole, ketoconazole, gemfibrozil, niacin, erythromycin, clarithromycin, telithromycin, nefazodone or HIV protease inhibitors.

Concomitant use of drugs labeled as potent inhibitors of CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with SIMCOR should be suspended during the course of treatment.

7.2 Cyclosporine or Danazol

Although the mechanism is not fully understood, cyclosporine has been shown to increase the area under the curve (AUC) of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4. The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of simvastatin. *[See Warnings and Precautions (5.1)]*

7.3 Amiodarone or Verapamil

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin. *[See Warnings and Precautions (5.1)]*

7.4 Gemfibrozil and other Fibrates

Coadministration of gemfibrozil (600 mg twice daily for 3 days) with simvastatin (40 mg daily) resulted in clinically significant increases in simvastatin acid AUC (185%) and peak plasma concentration (C_{max} , 112%), possibly due to inhibition of simvastatin acid glucuronidation by gemfibrozil. The increase in simvastatin exposure increases the risk of myopathy when coadministered with gemfibrozil. The combined use of SIMCOR with gemfibrozil should be avoided *[See Warnings and Precautions (5.1)]*. The risk of myopathy also increases to a lesser extent when simvastatin is used in combination with other fibrates. Coadministration of 160 mg fenofibrate daily with 80 mg simvastatin daily for 7 days had no effect on plasma AUC (and C_{max}) of either total HMG-CoA reductase inhibitory activity or fenofibric acid; there was a modest reduction (approximately 35%) of simvastatin acid which was not considered clinically significant.

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.

Niacin

7.8 Aspirin

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

7.9 Antihypertensive Therapy

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

7.10 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.

7.11 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/m² 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.

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.

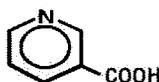
A few cases of overdosage with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

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

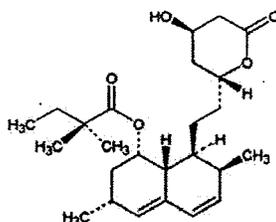
Niacin is nicotinic acid, or 3-pyridinecarboxylic acid. Niacin is a white, nonhygroscopic crystalline powder that is very soluble in water, boiling ethanol, and propylene glycol. It is insoluble in ethyl ether. The empirical formula of niacin is $C_6H_5NO_2$ and its molecular weight is 123.11. Niacin 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-[1 α ,3 α ,7 β ,8 β (2S*4S*),-8a β]].

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 β -hydroxyacid form, simvastatin acid, after administration. Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces 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 (Nicotinic 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 C_{max} (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, 6.56 hours, and 30.81 ng·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 ¹⁴C-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).

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/m² 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/m²), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

13.2 Animal Toxicology and/or Pharmacology

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/m² 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 5). 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 6). 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 7 and 8).

Table 4. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 20-mg Treated Baseline

Group A									
Week	SIMCOR 2000/20			SIMCOR 1000/20			Simvastatin 20		
	n ^a	dose (mg/mg)	non-HDL ^b (mg/dL)	n ^a	Dose (mg/mg)	non-HDL ^b (mg/dL)	n ^a	Dose (mg/mg)	non-HDL ^b (mg/dL)
Baseline	56	---	163.1	108	---	164.8	102	---	163.7
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 5. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 40-mg Treated Baseline

Group B									
Week	SIMCOR 2000/40			SIMCOR 1000/40			Simvastatin 80		
	n ^a	dose (mg/mg)	non-HDL ^b (mg/dL)	n ^a	Dose (mg/mg)	non-HDL ^b (mg/dL)	n ^a	Dose (mg/mg)	non-HDL ^b (mg/dL)
Baseline	98	---	144.4	111	---	141.2	113	---	134.5
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 18.4% 26.1% 20.4%

week 24:

- ^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 6. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels

TREATMENT	Treatment Group A					
	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 7. Mean Percent Change from Baseline to Week 24 in Lipoprotein Lipid Levels

TREATMENT	Treatment Group B					
	N	LDL-C	Total-C	HDL-C	TG ^a	Apo B
Baseline (mg/dL)*	322	108	187	47	145	93

Simvastatin	113	-11.4%	-6.2%	0.1%	0.3%	-7.5%
80 mg						
SIMCOR	111	-7.1%	-3.1%	15.4%	-22.8%	-7.7%
1000/40						
SIMCOR	98	-5.1%	-1.6%	24.4%	-31.8%	-10.5%
2000/40						

* 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 20°-25°C (68°-77°F).

17 PATIENT COUNSELING INFORMATION

The patient should be informed of the following:

17.1 Dosing Time

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

17.2 Tablet Integrity

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

17.3 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.

17.4 Muscle Pain

To notify their physician of any unexplained muscle pain, tenderness, or weakness promptly. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities of grapefruit juice. They should discuss all medication, both prescription and over the counter, with their physician.

17.5 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.

17.6 Use of Aspirin

Taking aspirin approximately 30 minutes before dosing can minimize flushing.

17.7 Diet

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

17.8 Supplements

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

17.9 Dizziness

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-078/S006, S007

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Metabolism and Endocrinology Products

Application Number and Name of Drug:

NDA 22078/S-006, S-007

Simcor (Niacin ER/Simvastatin) Tablets, 500 mg/20 mg, 760 mg/20 mg, 1000 mg/20 mg

Applicant: Abbott

Material Reviewed:

Submission Date(s): September 30, 2009 (S-006)

November 20, 2009 (S-007)

Labeling Reviewed: Package Insert (PI) and all container/bottle labeling (except the 3-count sample bottle label for the 500 mg/20 mg strength tablet)

Background and Summary

Simcor (niacin extended-release/simvastatin) Tablets were approved December 15, 2008 to:

1. 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.
2. Reduce TG in patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia) when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

Simcor was approved in the following strengths and presentations:

SIMCOR 500 mg/20 mg-sample bottle label and carton (3 tablets)

SIMCOR 500 mg/20 mg-90-count bottle

SIMCOR 750 mg/20 mg-90-count bottle

SIMCOR 1000 mg/20 mg-90-count bottle

Supplement -006, submitted September 30, 2009, provides for, among other things, Barceloneta, Puerto Rico as a new manufacturing site (replacing Edison, NJ) for Niacin ER cores, use in the production of Simcor Tablets. The supplement also provides for manufacturing process changes, including removal of the tablet debossing. The sponsor conducted studies to establish bioequivalence of Simcor manufactured in the two sites. A biowaiver was requested for the intermediate strength, 750 mg/20 mg. tablet. Reviewers involved in the review, and the results of those reviews are described below:

1. Chemistry, Manufacturing and Controls (CMC)-The January 29, 2010 review recommended APPROVAL.

2. Biopharm (CMC)-According to the January 25, 2010, the biowaiver request for the 750 mg/20 mg tablet is granted.
3. Clinical Pharmacology-The January 29, 2010 review stated that the 500 mg/20 mg tablets and the 1000 mg/20 mg tablets using the Niacin ER cores manufactured at the Puerto Rico site are bioequivalent to those manufactured at the Edison, NJ site.

Proposed container labeling for this supplement is in Appendix 1:

- 500 mg/20 mg, 3-count sample carton labels.
- 500 mg/20 mg, 90-count bottle label
- 750 mg/20 mg, 90-count bottle label

Following discussions with the Agency, it was agreed that the sponsor could submit the proposed PI and the labeling for the reformulated 1000 mg/20 mg strength presentation in S-007.

Supplement -007, submitted November 20, 2009, provides for, in addition to other things, the addition of two dosage strengths, 500 mg/40 mg and 1000 mg/40 mg tablets. The 1000 mg/20 mg dosage strength has also been reformulated to utilize a 1000 mg niacin ER (b) (4) (b) (4) The 500 mg/40 mg tablet will also use the (b) (4)

Disciplines involved in the review of this supplement include:

- Clinical Pharmacology-The March 25, 2010 review provided the following conclusions:
 - a. The new 1000 mg/40 mg tablet was bioequivalent to the approved reference product.
 - b. The reformulated 1000 mg/20 mg strength tablet (manufactured by (b) (4) (b) (4) was NOT bioequivalent to the tablet manufactured using (b) (4) See clinical review cited below.

-Biopharmaceutics (CMC)-In the March 5, 2010 review, the request for a waiver for the new strength 5000 mg/40 mg tablet was granted.

-CMC-The March 15, 2010 review recommended approval

-Microbiology-The February 16, 2010 review found the proposal to eliminate routine micro testing acceptable.

-Clinical-the firm is proposing to add 500 mg/40 mg as a starting dose, in addition to the already approved 500 mg/20 mg strength tablet. This was found acceptable in the July 13, 2010 review. In another July 13, 2010 review, the clinical reviewer agreed with the sponsor's justification as to why the 1000 mg/20 mg (b) (4) should be approved despite that it was found NOT bioequivalent to the (b) (4) (The Cmax is not bioequivalent, however the AUC is bioequivalent).

-Office of Surveillance and Epidemiology (OSE) provided comments on the proposed labeling in a review dated June 23, 2010. All of the OSE concerns have been adequately addressed with the revised labeling.

Labeling proposed in the supplement (excluding the PI) is in Appendix 2:

-500 mg/40 mg 7-count sample bottle and carton labeling

-“Quick Answers for Patients” (called “Tips Card”) to be included in the sample packages only

-500 mg/40 mg, 90-count bottle label

-1000 mg/20 mg, 90-count bottle label

-1000 mg/40 mg, 90-count bottle label

Note: THE ONLY CURRENTLY APPROVED LABELING THAT IS NOT REVISED IN EITHER S-006 OR S-007 IS THE 500 MG/20 MG BOTTLE LABEL FOR THE 3-COUNT SAMPLE.

Review

PACKAGE INSERT

The revisions requested by the firm that were found NOT acceptable are as follows:

-In the INDICATIONS AND USAGE section, in both the HIGHLIGHTS and FULL PRESCRIBING INFORMATION sections, “(Fredrickson types IIa and IIb)” were deleted, at the request of the Agency.

NOTE: this terminology is being removed from the lipid medications, starting with the recently approve fenofibrates. The firm had agreed to delete it in this supplement, but inadvertently forgot to remove it.

-FULL PRESCRIBING INFORMATION

-Under 3. DOSAGE FORMS AND STRENGTHS, following Table 2 (SIMCOR Tablet Strengths) there is a description of each of the tablets which is identical to that which is contained in 16. HOW SUPPLIED/STORAGE AND HANDLING section. This type of information is supposed to be in section 16 but not in section 3., so it was deleted.

-Under 5. WARNINGS AND PRECAUTIONS, SIMCOR, the underlined text has been deleted:

“Myopathy and/or rhabdomyolysis have been reported when simvastatin is used in combination with lipid-altering doses (≥ 1 gram/day) of niacin. (b) (4)

(b) (4)
(b) (4) Physicians contemplating the use of SIMCOR, a combination of simvastatin and niacin extended release (NIASPAN), should weight the potential benefits and risks....”

NOTE: This was deleted because there was insufficient detail (b) (4) In addition, we did not want this to be used for promotional purposes.

-Under 6.1 CLINICAL STUDIES EXPERIENCE, SIMCOR, the sponsor had proposed including information on a (b) (4)

NOTE: Information from (b) (4) is not useful information for inclusion in the labeling, so the proposed text was deleted.

- Under 12.3 PHARMACOKINETICS, Absorption and Bioavailability, SIMCOR: The following paragraph was retained as currently approved (b) (4)

(b) (4)
“The relative bioavailability of niacin (Nicotinuric acid, NUA, Cmax and total urinary excretion as the surrogate), simvastatin, and simvastatin acid was evaluated under a light snack conditions in healthy volunteers.....”

-Under 12.3 PHARMACOKINETICS, Metabolism, SIMCOR, the following paragraph was left unchanged (b) (4)

(b) (4)
“Following administration of SIMCOR, niacin and simvastatin undergo rapid and extensive first-pass metabolism as described in the following niacin and simvastatin sections...”

Under 12.3 PHARMACOKINETICS, Elimination, SIMCOR, the paragraph was retained as currently approved (b) (4)

(b) (4)
“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.”

CARTON/CONTAINER LABELING

NOTE: there was significant interaction between the review division and OSE regarding the bottle and carton labeling. The interaction and final labeling that was agreed upon by the Agency (OSE and the review division) and the sponsor, is described below for each piece of labeling.

500 mg/20 mg, 3-count sample carton label

The proposed labeling (13-A269-R2) was compared to the currently approved label (approved with the original NDA) (13-A0820R1, Final Printed Labeling (FPL) submitted March 6, 2008, Ack & Retained May 27, 2008). The following revisions have been made:

1. Under “Remember These Important Tips:”, the text:

- Take aspirin or a non-steroidal anti-inflammatory medication (e.g., ibuprofen) about 30 minutes before taking SIMCOR, with your doctor’s approval.” has been revised to:
- Take aspirin about 30 minutes before taking SIMCOR, with your doctor’s approval.

NOTE: This makes the labeling consistent with that approved for Niaspan (NDA 20-381/S-038, approved March 26, 2009). This is an acceptable revision.

2. **The Manufacturing information:**

“Manufactured for Abbott Laboratories
North Chicago, IL 60064” has been revised to the following:

“Manufactured by Abbott Pharmaceuticals PR Ltd.
Barceloneta, PR 00617
For Abbott Laboratories
North Chicago, IL 60064, U.S.A.”

NOTE: This is an appropriate revision for this supplement since the manufacturing site has been changed to the Puerto Rico facility.

Following discussions between the sponsor and the agency, the following further revisions were made and agreed upon by all:

· Moved "500mg/20mg" so that it is now located within the white box on front and top panels containing

Simcor
Niacin extended-release/simvastatin tablets

Note: This was done in response to the OSE review request

· Changed the part of the background color that was blue to all green (editorial)

· Removed Solvay logo (editorial)

· The statement “Take aspirin about 30 minutes before taking SIMCOR, with your doctor’s approval” has been changed to “Taking aspirin (up to the recommended dose of 325 mg) approximately 30 minutes prior to SIMCOR, as directed by your physician may minimize flushing.” (editorial and consistent with the approved NIASPAN labeling (20381/S-038, approved March 26, 2009).

-The following information has been added to a back panel (replacing a duplicate front panel):

“Join the SIMCOR Alliance patient support program to learn more about this medication and receive special offers and healthy lifestyle tips. Call 1-888-4-SIMCOR (1-888-474-6267) or visit www.simcortablets.com” (OSE had no objections to this proposed revision).

The final agreed-upon label is in Attachment 3

Quick Answers for Patients (Tips Card)(included with the sample packages only)

The proposed labeling (03A300) was compared to the approved labeling (03A082, approved with the original NDA, Acknowledged and Retained May 27, 2008). The following revisions have been made:

-Under “**What is SIMCOR Used For?**”, the first bullet has been revised to DELETE the underlined word: “SIMCOR is the combination of two cholesterol (b) (4) medications: niacin extended-release (NIASPAN)...”

NOTE: The firm said this was deleted because SIMCOR (b) (4) components of cholesterol. This revision was found acceptable by Eric Colman, MD, Deputy Division Director and Lipid Team Leader.

-At the end of the labeling, the following text:

“For more information,
Please call our Patient
Education Program at
1-888-4SIMCOR or visit
www.simcortablets.com”

has been revised to the following:

“Join the SIMCOR Alliance
Patient support program to
Learn more about this
Medication and receive
Special offers and healthy
Lifestyle tips.

Call 1-888-4SIMCOR
(1-888-474-6267) or visit
www.simcortablets.com”

NOTE: This revision was found acceptable by the review division and OSE.

-Under “Important Tips”, the first bullet has been revised from,

“Take aspirin or a non-steroidal anti-inflammatory medication (e.g. ibuprofen)
about 30 minutes before taking SIMCOR, with your doctor’s approval.”

to the following:

“Taking aspirin (up to the recommended dose of 325 mg) approximately 30
minutes prior to SIMCOR, as directed by your physician may minimize flushing.”

NOTE: This is an acceptable revision given that this change was approved for the NIASPAN
NDA 20-381/S-038 on March 26, 2009.

-Under “What is Flushing?”, the following bullet has been revised to include the underlined text:

•Flushing is mild to moderate for most patients....such as dizziness or fainting,
rapid or pronounced heartbeat, shortness of breath, sweating, burning sensation,
chills, and/or swelling...”

NOTE: This change was necessitated by a labeling change for Niaspan (NDA 20381/S-042,
approved February 24, 2010) and the firm and agency agreed to include this revision in this
labeling in lieu of issuing a supplement request letter requesting this small revision.

-The revision date has been revised (editorial).

The final agreed-upon label is in Attachment 3

500 mg/20 mg, 90-count bottle label

The propose label (04-A474-R2) was compared to the currently approved label (04-A116-R1, approved with the initial NDA, FPL submitted May 6, 2008, Ack and Retained May 27, 2008).

The following revisions have been made:

-Other than the revision date, the only change is that the following text:

“Manufactured for
Abbott Laboratories
North Chicago, Il 60064, U.S.A.” has been changed to the following:

“Manufactured by
Abbott Pharmaceuticals PR Ltd.
Barceloneta, PR 00617
For Abbott Laboratories
North Chicago, IL 60064, U.S.A.

NOTE: This is an appropriate revision for this supplement since the manufacturing site has been changed to the Puerto Rico facility.

Based on the OSE review, the labeling was further revised to include “Tablets” at the end of the generic name. The label now reads:

Simcor
Niacin Extended-Release/Simvastatin Tablets

The agreed upon labeling can be found in Appendix 3.

750 mg/20 mg, 90-count bottle label

The propose label (04-A475-R2) was compared to the currently approved label (04-A117-R1, approved with the initial NDA, FPL submitted May 6, 2008, Ack and Retained May 27, 20/08).

The following revisions have been made:

-Other than the revision date, the only change is that the following text:

“Manufactured for
Abbott Laboratories
North Chicago, Il 60064, U.S.A.” has been changed to the following:

“Manufactured by
Abbott Pharmaceuticals PR Ltd.
Barceloneta, PR 00617
For Abbott Laboratories
North Chicago, IL 60064, U.S.A.

NOTE: This is an appropriate revision for this supplement since the manufacturing site has been changed to the Puerto Rico facility.

Based on the OSE review, the labeling was further revised to include "Tablets" at the end of the generic name. The label now reads:

Simcor
Niacin Extended-Release/Simvastatin Tablets

The agreed upon labeling can be found in Appendix 3.

500 mg/40 mg, 90-count bottle label

The proposed labeling (04-A483-R1) was compared to the bottle labels that were approved with the original NDA. Other than the identifier, the changes necessitated by the different strength of ingredients, and the color of the box surrounding the tablet strength, the labeling is identical.

The (b) (4) that the sponsor proposed for the background color of the box surrounding the strength was similar to the (b) (4) strength tablet. Based on the comments from OSE, the following revisions were made to the proposed label:

- The background color of the box surrounding the strength was changed to a purple color.
- "Tablet" was added following the generic name such that the label now reads:

Simcor
Niacin Extended-Release/
Simvastatin Tablets

- A box with "NEW STRENGTH" has been added. This information will remain on the labeling for 6 months.

The agreed upon labeling can be found in Appendix 3.

500 mg/40 mg 7-count sample bottle label

The proposed sample bottle label (04-A485-R1) was compared to that approved for the 500 mg/20 mg. Other than the identifier and the changes necessitated by the different strengths of ingredients, and the background color of the label (500 mg/20 mg (b) (4) 500 mg/40 mg (b) (4) the labeling is identical.

Since the label for the 90-count bottle of this strength was revised such that the (b) (4) background surrounding the tablet strength was revised to purple, the sample bottle was changed such that the background was also purple.

The agreed upon labeling can be found in Appendix 3.

500 mg/40 mg 7-count sample carton

Other than changes necessitated by the different strengths, this label (identifier 13-A279-R1) is identical to the 500 mg/20 mg label that was reviewed above.

When the purple labeling was found acceptable by OSE for the 500 mg/40 mg 90-count bottle the firm decided to make the background on this label purple also.

The agreed upon labeling can be found in Appendix 3.

1000 mg/20 mg, 90-count bottle label

The proposed label (04-A486-R2) was compared to that which was approved with the original NDA.

-Other than the revision date, the only change is that the following text:

“Manufactured for
Abbott Laboratories
North Chicago, IL 60064, U.S.A.” has been changed to the following:

“Manufactured by
Abbott Pharmaceuticals PR Ltd.
Barceloneta, PR 00617
For Abbott Laboratories
North Chicago, IL 60064, U.S.A.

NOTE: This is an appropriate revision for this supplement since the manufacturing site has been changed to the Puerto Rico facility.

Based on the OSE review, the labeling was further revised to include “Tablets” at the end of the generic name. The label now reads:

Simcor
Niacin Extended-Release/Simvastatin Tablets

The agreed upon labeling can be found in Appendix 3.

1000 mg/40 mg, 90-count bottle label

The proposed labeling (04-A484-R1) was compared to the 1000 mg/20 mg tablet labeling. Other than the identifier and revisions necessitated by the change in strength, they are identical.

Based on the OSE review, the labeling was further revised to include "Tablets" at the end of the generic name. The label now reads:

Simcor

Niacin Extended-Release/Simvastatin Tablets

There was also an issue in that OSE thought that the color bar which surrounded this strength (b) (4) was too similar to that for the (b) (4) strength tablet (b) (4) and requested that it be changed.

In addition, a box with "NEW STRENGTH" has been added directly under the box containing the tablet strength information. This information will remain on the labeling for 6 months.

The agreed upon labeling can be found in Appendix 3.

Recommendations

An approval letter should be drafted.

Review done by:

Kati Johnson

Project Manager

Division of Metabolism and Endocrinology Products

PM LABELING REVIEW

~~//~~ Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

APPENDIX 3

3 Tablets
500 mg/20 mg
Simvastatin tablets
niacin extended-release/
SIMCOR[®]

NDC 0074-9312-03

SIMCOR[®]
niacin extended-release/
simvastatin tablets
500 mg/20 mg

Taking SIMCOR[®]
(niacin extended-release/
simvastatin tablets)

NDC 0074-9312-03

SIMCOR[®]
niacin extended-release/
simvastatin tablets
500 mg/20 mg

SIMCOR[®]
niacin extended-release/
simvastatin tablets
500 mg/20 mg

Do not accept if seal over bottle opening is broken or missing.

Each tablet contains 500 mg of niacin extended-release and 20 mg of simvastatin.

Dosage: See package insert for full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

See bottom of carton for expiration date and lot number.

Store at room temperature.
20-25°C (68-77°F).

Taking aspirin (up to the recommended dose of 325 mg) approximately 30 minutes prior to SIMCOR, as directed by your physician may minimize flushing.

Take SIMCOR with a low-fat snack.

Take SIMCOR at bedtime.

Avoid alcoholic beverages, hot beverages, and spicy foods around the time of taking SIMCOR.

Do not break, crush or chew SIMCOR tablets.

3 Tablets

PROFESSIONAL SAMPLE
NOT TO BE SOLD

Rx only

 Abbott

Manufactured by:
Abbott Pharmaceutical PR Ltd.
Banc Street, PR10 6B7
© Abbott Laboratories
North Chicago, IL 60064, U.S.A.
© 2010 Abbott Laboratories
Product Code: 890
10-AC09-P0

Lot:
Exp:



13A269

Quick Answers for Patients



03A300

SIMCOR[®]

niacin extended-release/
simvastatin tablets

What Is SIMCOR Used For?

- SIMCOR is the combination of two cholesterol medications: niacin extended-release (NIASPAN[®]) and simvastatin. SIMCOR is used along with diet to lower levels of cholesterol, LDL "bad" cholesterol, and triglycerides and to increase HDL "good" cholesterol.
- SIMCOR has not been shown to lower the risk of heart attacks or death any more than simvastatin or niacin when they are used alone.

When Taking SIMCOR

- You should take SIMCOR every night with a low-fat snack at bedtime as prescribed. If you miss a dose, take your usual SIMCOR dose the next evening; do not make up for missed doses by taking extra tablets.
- SIMCOR should be used with caution if you drink substantial amounts of alcohol or have a history of kidney problems.
- SIMCOR should not be used if you have liver problems, stomach ulcers, or serious bleeding problems.
- Other than flushing, additional side effects such as headache and rash have been observed.
- Do not break, crush, or chew SIMCOR tablets.
- Avoid taking SIMCOR with grapefruit or grapefruit juice.
- If you stop taking SIMCOR for a week or more, contact your doctor for instructions.

Other Important Information

- Your doctor will do routine blood tests to check the effects of SIMCOR on your liver function.
- Muscle pain, muscle weakness, or muscle tenderness can be a sign of a serious but rare muscle disorder, from which rare cases of death have occurred. Report any of these symptoms to your doctor immediately.

- SIMCOR may increase your fasting blood sugar levels. If you have diabetes, report any changes in blood sugar to your doctor.
- SIMCOR is not for women who are pregnant or nursing. If pregnancy is suspected, SIMCOR should be discontinued immediately.

What Is Flushing?

- The niacin ingredient in SIMCOR sometimes causes flushing, a redness, warmth, itching, and/or tingling sensation on the face, neck, chest, and/or back. It usually starts a few hours after dosing and may last a few hours.
- Most patients taking SIMCOR will experience flushing, usually at the start of therapy or when the dose is increased.
- Flushing may subside after several weeks of consistent SIMCOR use.
- Flushing is mild to moderate for most patients. For some, flushing may be more intense, and additional symptoms, such as dizziness or fainting, rapid or pronounced heartbeat, shortness of breath, sweating, chills, and/or swelling, may occur. Notify your doctor if dizziness or fainting occurs.
- If the flushing wakes you up and you wish to get out of bed, take your time and get up slowly — especially if you start to feel faint or dizzy, or if you take blood pressure medication.

Abbott Laboratories
Abbott Park, IL 60064
03-A300-R2
Revised September, 2009

Join the SIMCOR Alliance patient support program to learn more about this medication and receive special offers and healthy lifestyle tips.

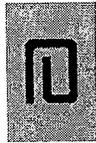
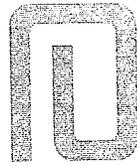
Call 1-888-4-SIMCOR
(1-888-474-6267) or visit
www.simcortablets.com.

Important Tips

Before starting SIMCOR (niacin extended-release/simvastatin tablets), remember these important tips:

- Taking aspirin (up to the recommended dose of 325 mg) approximately 30 minutes prior to SIMCOR, as directed by your physician may minimize flushing.
- Take SIMCOR with a low-fat snack.
- Take SIMCOR at bedtime.
- Avoid alcoholic beverages, hot beverages, and spicy foods around the time of taking SIMCOR.





NDC 0074-3312-90

Simcor[®]

Niacin Extended-Release/
Simvastatin Tablets

500 mg/20 mg



04-A474-R3

Exp.
Lot

90 Tablets



Abbott

Rx only

Do not accept if seal over bottle opening is broken or missing.

Each tablet contains 500 mg of niacin extended-release and 20 mg of simvastatin.

Do not break, crush or chew tablet.

Usual dosage: See package insert for full prescribing information.

Store at room temperature 20-25°C (68-77°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

Manufactured by
Abbott Pharmaceuticals PR Ltd.
Barcelona, PR 00617
for Abbott Laboratories
North Chicago, IL 60064, U.S.A.



Exp.
Lot
04-A475-R3



NDC 0074-3315-90

Simcor[®]

Niacin Extended-Release/
Simvastatin Tablets

750 mg/20 mg

90 Tablets

Rx only



Do not accept if seal over bottle opening is broken or missing.

Each tablet contains 750 mg of niacin extended-release and 20 mg of simvastatin.

Do not break, crush or chew tablet.

Usual dosage: See package insert for full prescribing information.

Store at room temperature 20-25°C (68-77°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

Manufactured by
Abbott Pharmaceuticals PR Ltd,
Barceloneta, PR 00617
for Abbott Laboratories
North Chicago, IL 60064, U.S.A.



NDC 0074-3459-90

Simcor[®]

Niacin Extended-Release/
Simvastatin Tablets

500 mg/40 mg

NEW STRENGTH

90 Tablets



Rx only



Exp.
Lot
04-A483-R2



Do not accept if seal over bottle opening is broken or missing.

Each tablet contains 500 mg of niacin extended-release and 40 mg of simvastatin.

Do not break, crush or chew tablet.

Usual dosage: See package insert for full prescribing information.

Store at room temperature 20-25°C (68-77°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

Manufactured by
Abbott Pharmaceuticals PR Ltd.
Barceloneta, PR 00617
for Abbott Laboratories
North Chicago, IL 60064, U.S.A.

NDC 0074-3459-03

SIMCOR[®]
niacin extended-release/
simvastatin tablets
500 mg/40 mg

7 Tablets Rx only

PROFESSIONAL SAMPLE
NOT TO BE SOLD

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



04-A485-R2

EXP
LOT

Do not accept if seal over bottle opening is broken or missing.

Each tablet contains 500 mg of niacin extended-release and 40 mg of simvastatin.

Do not break, crush or chew tablet.

Dosage: See package insert for full prescribing information.

Dispense in this tight, light-resistant container with a child-resistant closure.

Store at room temperature:
20-25°C (68-77°F).

7 Tablets
500 mg/40 mg
niacin extended-release/
simvastatin tablets
SIMCOR®

NDC 0074-3459-03

SIMCOR®
niacin extended-release/
simvastatin tablets
500 mg/40 mg

Join the SIMCOR Alliance patient support program to learn more about this medication and receive special offers and healthy lifestyle tips.

Call 1-888-4-SIMCOR (1-888-474-6267) or visit www.simcortablets.com.

Manufactured by
Abbott Pharmaceutical PR Ltd.
Barrington, PR 00617
for Abbott Laboratories
North Chicago, IL 60064 U.S.A.
©2010 Abbott Laboratories
Product Code: SE1
13-A279-R2

Taking SIMCOR®
(niacin extended-release/
simvastatin tablets)

Remember These Important Tips:

- Taking aspirin (up to the recommended dose of 325 mg) approximately 30 minutes prior to SIMCOR, as directed by your physician may minimize flushing.
- Take SIMCOR with a low-fat snack.
- Take SIMCOR at bedtime.
- Avoid alcoholic beverages, hot beverages, and spicy foods around the time of taking SIMCOR.
- Do not break, crush or chew SIMCOR tablets.

NDC 0074-3459-03

SIMCOR®
niacin extended-release/
simvastatin tablets
500 mg/40 mg

7 Tablets

PROFESSIONAL SAMPLE
NOT TO BE SOLD

Rx only

 Abbott

SIMCOR®
niacin extended-release/
simvastatin tablets
500 mg/40 mg

Do not accept if seal over bottle opening is broken or missing. Each tablet contains 500 mg of niacin extended-release and 40 mg of simvastatin.

Dosage: See package insert for full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

See bottom of carton for expiration date and lot number.

Store at room temperature;
20°-25°C (68°-77° F).

Lot:
Exp:



13A279



Exp.
Lot
04-A486-R3



3

NDC 0074-3455-90

Simcor[®]

Niacin Extended-Release/
Simvastatin Tablets

1000 mg/20 mg



90 Tablets



Abbott

Rx only

Do not accept if seal over bottle opening is broken or missing.

Each tablet contains 1000 mg of niacin extended-release and 20 mg of simvastatin.

Do not break, crush or chew tablet.

Usual dosage: See package insert for full prescribing information.

Store at room temperature 20-25°C (68-77°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

Manufactured by
Abbott Pharmaceuticals PR Ltd.
Barceloneta, PR 00617
for Abbott Laboratories
North Chicago, IL 60064, U.S.A.



Exp.
Lot
04-A484-R2



NDC 0074-3457-90

Simcor[®]
Niacin Extended-Release/
Simvastatin Tablets

1000 mg/40 mg

NEW STRENGTH



90 Tablets



Abbott

Rx only

Do not accept if seal over bottle opening is broken or missing.

Each tablet contains 1000 mg of niacin extended-release and 40 mg of simvastatin.

Do not break, crush or chew tablet.

Usual dosage: See package insert for full prescribing information.

Store at room temperature 20-25°C (68-77°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

Manufactured by
Abbott Pharmaceuticals PR Ltd.
Barceloneta, PR 00617
for Abbott Laboratories
North Chicago, IL 60064, U.S.A.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22078	SUPPL-6	ABBOTT LABORATORIES	SIMCOR
NDA-22078	SUPPL-7	ABBOTT LABORATORIES	SIMCOR

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
08/30/2010