HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

Warnings and Precautions, Myopathy/Rhabdomyolysis (5.2)	10/2012
Adverse Reactions, Postmarketing Experience (6.2)	10/2012
Indications and Usage, Limitations of Use (1.1)	02/2013
Warnings and Precautions, Mortality and Coronary Heart Disease Morbidity (5.1)	02/2013
Adverse Reactions, Clinical Studies Experience (6.1)	02/2013

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)

Niacin extended-release, one of the components of SIMCOR, at doses of 1,500 – 2,000 mg/day, in combination with simvastatin, did not reduce the incidence of cardiovascular events more than simvastatin in a randomized controlled trial of patients with cardiovascular disease and mean baseline LDL-C levels of 74 mg per deciliter (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, 5.3)
- Active peptic ulcer disease (4)
- Arterial bleeding (4)
- Concomitant administration of strong CYP3A4 inhibitors (4, 5.2)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol (4, 5.2)
- Concomitant administration of verapamil or diltiazem (4, 5.2)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)
- Known hypersensitivity to product components (4, 6.1)

WARNINGS AND PRECAUTIONS

- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥ 65), female gender, uncontrolled hypothyroidism, and renal impairment. Patients should be advised to report promptly any unexplained and/or persistent muscle pain, tenderness, or weakness. SIMCOR therapy should be discontinued immediately if myopathy is diagnosed or suspected. (4, 5.2, 8.5, 8.7)
- Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter. (5.3)
- 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. (5.3)
- 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. (5.4)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.2, 4, 5.2, 7.1, 7.2, 7.3, 7.4, 12.3)

Interacting Agents	Prescribing Recommendations
Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone), gemfibrozil, cyclosporine, danazol, verapamil, diltiazem	Contraindicated with SIMCOR
Amiodarone, amlodipine, ranolazine	Do not exceed 1000/20 mg SIMCOR daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles

SIMCOR

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

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

Limitations of use

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

Niacin extended-release, one of the components of SIMCOR, at doses of 1,500 – 2,000 mg/day, in combination with simvastatin, did not reduce the incidence of cardiovascular events more than simvastatin in a randomized controlled trial of patients with cardiovascular disease and mean baseline LDL-C levels of 74 mg per deciliter *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

SIMCOR should be taken as a single daily dose at bedtime, with a low fat snack. Patients not currently on niacin extended-release and patients currently on niacin products other than niacin extended-release should start SIMCOR at a single 500/20 mg tablet daily at bedtime. Patients already taking simvastatin 20 to 40 mg who need additional management of their lipid levels may be started on a SIMCOR dose of 500/40 mg once daily at bedtime *[see Warnings and Precautions (5.3)]*. The dose of niacin extended-release should not be increased by more than 500 mg daily every 4 weeks - see Table 1.

Table 1. Recommended niacin extended-release dosing

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

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

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

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

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

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

2.2 Coadministration with Other Drugs

Patients taking Amiodarone, Amlodipine or Ranolazine

- The dose of SIMCOR should not exceed 1000/20 mg/day *[see Warnings and Precautions (5.2), Drug Interactions (7.4), and Clinical Pharmacology (12.3)]*.

2.3 Chinese Patients Taking SIMCOR

Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products, caution should be used when prescribing SIMCOR in doses that exceed 1000/20 mg/day to Chinese patients. The cause of the increased risk of myopathy is not known. It is also unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients *[see Warnings and Precautions (5.2)]*.

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 (5.3)]*
- Patients with active peptic ulcer disease
- Patients with arterial bleeding
- Concomitant administration of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) *[see Warnings and Precautions (5.2)]*
- Concomitant administration of gemfibrozil, cyclosporine, or danazol *[see Warnings and Precautions (5.2)]*
- Concomitant administration of verapamil or diltiazem *[see Warnings and Precautions (5.2)]*
- Women who are pregnant or may become pregnant. SIMCOR may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy. There are no adequate and well-controlled studies of SIMCOR use during pregnancy; however in rare reports congenital anomalies were observed following intrauterine exposure to HMG-CoA reductase inhibitors. If SIMCOR is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use In Specific Populations (8.1)]*. In rat and rabbit animal reproduction studies, simvastatin revealed no evidence of teratogenicity. There are no animal reproductive studies conducted with niacin.
- Nursing mothers. SIMCOR contains simvastatin and nicotinic acid. Nicotinic acid is excreted into human milk and it is not known whether simvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because of the potential for serious adverse reactions in nursing infants, women who require SIMCOR treatment should not breastfeed their infants *[see Use In Specific Populations (8.3)]*.
- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including one of more of the following adverse reactions have been reported for simvastatin and/or niacin extended-release: anaphylaxis, angioedema, urticaria, fever, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and flushing *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

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

5.1 Mortality and Coronary Heart Disease Morbidity

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial was a randomized placebo-controlled trial of 3414 patients with stable, previously diagnosed cardiovascular disease. Mean baseline lipid levels were LDL-C 74 mg/dL, HDL-C 35 mg/dL, non-HDL-C 111 mg/dL and median triglyceride level of 163-177 mg/dL. Ninety-four percent of patients were on background statin therapy prior to entering the trial. All participants received simvastatin, 40 to 80 mg per day, plus ezetimibe 10 mg per day if needed, to maintain an LDL-C level of 40-80 mg/dL, and were randomized to receive niacin extended-release tablets 1500-2000 mg/day (n=1718) or matching placebo (niacin immediate-release tablets, 100-150 mg, n=1696).

On-treatment lipid changes at two years for LDL-C were -12.0% for the simvastatin plus niacin extended-release group and -5.5% for the simvastatin plus placebo group. HDL-C increased by 25.0% to 42 mg/dL in the simvastatin plus niacin extended-release group and by 9.8% to 38 mg/dL in the simvastatin plus placebo group (P<0.001). Triglyceride levels decreased by 28.6% in the simvastatin plus niacin extended-release group and by 8.1% in the simvastatin plus placebo group.

The primary outcome was an ITT composite of the first study occurrence of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome or symptom-driven coronary or cerebral revascularization procedures. The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. The primary outcome occurred in 282 patients in the simvastatin plus niacin extended-release group (16.4%) and in 274 patients in the simvastatin plus placebo group (16.2%) (HR 1.02 [95% CI, 0.87-1.21], P=0.79.

In an ITT analysis, there were 42 cases of first occurrence of ischemic stroke reported, 27 (1.6%) in the simvastatin plus niacin extended-release group and 15 (0.9%) in the simvastatin plus placebo group, a non-statistically significant result (HR 1.79, [95%CI = 0.95-3.36], p=0.071). The on-treatment ischemic stroke events were 19 for the simvastatin plus niacin extended-release group and 15 for the simvastatin plus placebo group *[see Adverse Reactions (6.1)]*.

5.2 Myopathy/Rhabdomyolysis

Simvastatin

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high

levels of HMG-CoA reductase inhibitory activity in plasma. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

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

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

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

All patients starting therapy with SIMCOR, or whose dose of SIMCOR is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing SIMCOR. SIMCOR therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with SIMCOR or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. SIMCOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. SIMCOR therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

Drug Interactions

The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which inhibit

this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily), and combination of these drugs with SIMCOR is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with SIMCOR must be suspended during the course of treatment *[see Contraindications (4) and Drug Interactions (7.1)]*. *In vitro* studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the SIMCOR dose may be needed to reduce the risk of myopathy/rhabdomyolysis if voriconazole must be used concomitantly with simvastatin *[see Drug Interactions (7.1)]*.

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

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

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

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

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

Cases of myopathy, including rhabdomyolysis, have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In an ongoing, double-blind, randomized cardiovascular outcomes trial, an independent safety monitoring committee identified that the incidence of myopathy is higher in Chinese compared with non-Chinese patients taking simvastatin 40 mg coadministered with lipid modifying doses of a niacin-containing product. Caution should be used when prescribing SIMCOR in doses that exceed 1000/20 mg/day to Chinese patients. It is unknown if the risk for myopathy with coadministration of simvastatin with lipid modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients *[see Dosage and Administration (2.3)]*.

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

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

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

SIMCOR

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

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

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

5.3 Liver Dysfunction

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

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

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

It is recommended that liver enzyme tests be obtained prior to initiating therapy with SIMCOR and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with SIMCOR, promptly interrupt therapy. If an alternate etiology is not found do not restart SIMCOR. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy *[see Warnings and Precautions (5.2)]*.

5.4 Laboratory Abnormalities

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

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

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

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

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

5.5 Endocrine Function

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

6 ADVERSE REACTIONS

Overview

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

6.1 Clinical Studies Experience

SIMCOR

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

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

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

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

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

Adverse Event	SIMCOR overall *	Simvastatin overall **
Total Number of Patients	N=403	N=238
Headache	18 (4.5%)	11 (4.6%)
Pruritus	13 (3.2%)	0 (0.0%)
Nausea	13 (3.2%)	10 (4.2%)
Back Pain	13 (3.2%)	5 (2.1%)
Diarrhea	12 (3.0%)	7 (2.9%)
* SIMCOR overall included all doses from 500/20 mg to 2000/40 mg		

** Simvastatin overall included 20 mg, 40 mg, and 80 mg doses

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH)

In AIM-HIGH involving 3414 patients (mean age of 64 years, 15% women, 92% Caucasians, 34% with diabetes mellitus) with stable, previously diagnosed cardiovascular disease, all patients received simvastatin, 40 to 80 mg per day, plus ezetimibe 10 mg per day if needed, to maintain an LDL-C level of 40-80 mg/dL, and were randomized to receive NIASPAN 1500-2000 mg/day (n=1718) or matching placebo (IR Niacin, 100-150 mg, n=1696). The incidence of the adverse reactions of "blood glucose increased" (6.4% vs. 4.5%) and "diabetes mellitus" (3.6% vs. 2.2%) was significantly higher in the simvastatin plus NIASPAN group as compared to the simvastatin plus placebo group. There were 5 cases of rhabdomyolysis reported, 4 (0.2%) in the simvastatin plus NIASPAN group and one (<0.1%) in the simvastatin plus placebo group *[see Warnings and Precautions (5.1)]*.

Simvastatin

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

Other Clinical Studies

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

Niacin Extended-Release

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

Clinical Laboratory Abnormalities:

SIMCOR

Chemistry

Elevations in serum transaminases *[see Warnings and Precautions (5.3)]*, 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 (5.4)]*.

6.2 Postmarketing Experience

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

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

Simvastatin

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

There have been rare reports of immune-mediated necrotizing myopathy with statin use *[see Warnings and Precautions (5.2)]*.

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

NIASPAN

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

7 DRUG INTERACTIONS

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

Simvastatin

7.1 Strong CYP3A4 Inhibitors, Cyclosporine, or Danazol

Strong CYP3A4 inhibitors: Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of CYP3A4. Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4.

Elevated plasma levels of HMG-CoA reductase inhibitory activity increases the risk of myopathy and rhabdomyolysis, particularly with higher doses of SIMCOR *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*. Concomitant use of drugs labeled as having a strong inhibitory effect on CYP3A4 is contraindicated *[see Contraindications (4)]*. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with SIMCOR must be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of simvastatin. It is recommended that dose adjustment of SIMCOR be considered during concomitant use of voriconazole and SIMCOR to reduce the risk of myopathy, including rhabdomyolysis *[see Warnings and Precautions (5.2)]*.

Cyclosporine or Danazol: The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol. Therefore, concomitant use of these drugs is contraindicated *[see Contraindications (4), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

7.2 Verapamil or Diltiazem

The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of verapamil or diltiazem with doses of simvastatin exceeding 10 mg. Because all doses of SIMCOR contain simvastatin in excess of 10 mg, concomitant use of these drugs is contraindicated *[see Contraindications (4), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

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

Gemfibrozil: Contraindicated with SIMCOR *[see Contraindications (4) and Warnings and Precautions (5.2)]*. Other fibrates: Combined use with SIMCOR should be avoided *[see Warnings and Precautions (5.2)]*.

7.4 Amlodipine or Ranolazine

The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of amlodipine or ranolazine *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2) and Table 5 in Clinical Pharmacology (12.3)]*.

7.5 Propranolol

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

7.6 Digoxin

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

7.7 Coumarin Anticoagulants

In normal volunteers and hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants since the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteers and patients, respectively. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting SIMCOR and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of SIMCOR is changed or discontinued, the same procedure should be repeated.

7.8 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing SIMCOR with colchicine *[see Warnings and Precautions (5.2)]*.

Niacin

7.9 Aspirin

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

7.10 Antihypertensive Therapy

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

7.11 Bile Acid Sequestrants

An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding

to cholestyramine. These results suggest that 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of SIMCOR.

7.12 Other

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

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

8.3 Nursing Mothers

It is not known whether simvastatin is excreted into human milk; however, a small amount of another drug in this class does pass into breast milk. Niacin is excreted into human milk but the actual infant dose or infant dose as a percent of the maternal dose is not known. Because of the potential for serious adverse reactions in nursing infants, nursing mothers who require SIMCOR treatment should not breastfeed their infants. A decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother *[see Contraindications (4)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Because advanced age (≥65 years) is a predisposing factor for myopathy, including rhabdomyolysis, SIMCOR should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥65 years of age had an increased risk of myopathy, including rhabdomyolysis, compared to patients <65 years of age *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

8.6 Gender

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

8.7 Renal Impairment

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

8.8 Hepatic Impairment

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for SIMCOR *[see Warnings and Precautions (5.3)]*.

10 OVERDOSAGE

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

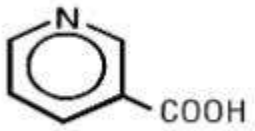
A few cases of overdosage with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

11 DESCRIPTION

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

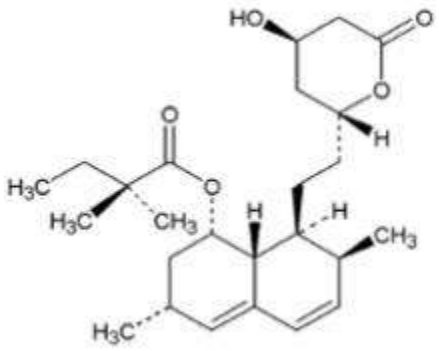
Niacin Extended-Release

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



Simvastatin

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3-7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*4S*),-8aβ]]. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in chloroform, methanol, and ethanol. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Simvastatin has the following structural formula:



SIMCOR is available for oral administration as tablets containing 500 mg of niacin extended-release (NIASPAN) and 20 mg simvastatin (SIMCOR 500/20 mg), 500 mg of niacin extended-

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Niacin

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

Simvastatin

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

12.2 Pharmacodynamics

A variety of clinical studies have demonstrated that elevated levels of Total-C, LDL-C, and Apo B promote human atherosclerosis. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C, and inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoprotein (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

SIMCOR

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

Niacin

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

Simvastatin

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

12.3 Pharmacokinetics

Absorption and Bioavailability

SIMCOR

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

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

Niacin

Due to extensive and saturable first-pass metabolism, niacin concentrations in the general circulation are dose dependent and highly variable. Peak steady-state niacin concentrations were

0.6, 4.9, and 15.5 mcg/mL after doses of 1000, 1500, and 2000 mg NIASPAN once daily (given as two 500 mg, two 750 mg, and two 1000 mg tablets, respectively). To reduce the risk of gastrointestinal upset, administration of niacin extended-release with a low-fat meal or snack is recommended.

Simvastatin

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

Metabolism

SIMCOR

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

Niacin

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

Simvastatin

Simvastatin is a substrate of CYP3A4. Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives.

Elimination

SIMCOR

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

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

Niacin

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

Simvastatin

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

Special Populations

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

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

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

Drug Interaction

Effect of other drugs on simvastatin:

Table 5
Effect of Coadministered Drugs or Grapefruit Juice on Simvastatin Systemic Exposure

Coadministered Drug or Grapefruit Juice	**Dosing of Coadministered Drug or Grapefruit Juice**	**Dosing of Simvastatin**	**Geometric Mean Ratio (Ratio* with / without coadministered drug) No Effect = 1.00**		
				AUC	C_{max}
Contraindicated with simvastatin *[see Contraindications (4) and Warnings and Precautions (5.2)]*					
Telithromycin[†]	200 mg QD for 4 days	80 mg	simvastatin	12	15

			acid‡ simvastatin	8.9	5.3
Nelfinavir†	1250 mg BID for 14 days	20 mg QD for 28 days	simvastatin acid‡ simvastatin	 6	 6.2
Itraconazole†	200 mg QD for 4 days	80 mg	simvastatin acid‡ simvastatin		13.1 13.1
Posaconazole	100 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid simvastatin	7.3 10.3	9.2 9.4
	200 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid simvastatin	8.5 10.6	9.5 11.4
Gemfibrozil	600 mg BID for 3 days	40 mg	simvastatin acid simvastatin	2.85 1.35	2.18 0.91
Avoid >1 quart of grapefruit juice with simvastatin *[see Warnings and Precautions (5.2)]*					
Grapefruit Juice§ (high dose)	200 mL of double-strength TID¶	60 mg single dose	simvastatin acid simvastatin	7 16	
Grapefruit Juice§ (low dose)	8 oz (about 237 mL) of single-strength#	20 mg single dose	simvastatin acid simvastatin	1.3 1.9	
Avoid taking with >10 mg simvastatin, based on clinical and/or post-marketing experience *[see Warnings and Precautions (5.2)]*					
Verapamil SR	240 mg QD Days 1-7 then 240 mg BID on Days 8-10	80 mg on Day 10	simvastatin acid simvastatin	2.3 2.5	2.4 2.1
Diltiazem	120 mg BID for 10 days	80 mg on Day 10	simvastatin acid simvastatin	2.69 3.10	2.69 2.88
Diltiazem	120 mg BID for 14 days	20 mg on Day 14	simvastatin	4.6	3.6
Avoid taking with >20 mg simvastatin, based on clinical and/or post-marketing experience *[see Warnings and Precautions (5.2)]*					
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	simvastatin acid simvastatin	1.75 1.76	1.72 1.79
Amlodipine	10 mg QD for 10 days	80 mg on Day 10	simvastatin acid simvastatin	1.58 1.77	1.56 1.47
Ranolazine SR	1000 mg BID for 7 days	80 mg on Day 1, and Day 6-9	simvastatin acid simvastatin	2.26 1.86	2.28 1.75

No dosing adjustments required for the following:					
Fenofibrate	160 mg QD for 14 days	80 mg QD on Days 8-14	simvastatin acid simvastatin	0.64 0.89	0.89 0.83
Niacin extended-release [Þ]	2 g single dose	20 mg single dose	simvastatin acid simvastatin	1.6 1.4	1.84 1.08
Propranolol	80 mg single dose	80 mg single dose	total inhibitor active inhibitor	0.79 0.79	↓ from 33.6 to 21.1 ng·eq/mL ↓ from 7.0 to 4.7 ng·eq/mL

[*] Results based on a chemical assay except results with propranolol as indicated.
[†] Results could be representative of the following CYP3A4 inhibitors: ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone.
[‡] Simvastatin acid refers to the β-hydroxyacid of simvastatin.
[§] The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.
[¶] Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose simvastatin and 30 and 90 minutes following single dose simvastatin on Day 3.
[#] Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and simvastatin was administered in the evening on Day 3.
[Þ] Because Chinese patients have an increased risk for myopathy with simvastatin coadministered with lipid-modifying doses (≥1 gram/day niacin) of niacin-containing products, and the risk is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products *[see Warnings and Precautions (5.2)]*.

Simvastatin effect on other drugs:

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

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

Niacin effect on other drugs:

Niacin did not affect fluvastatin pharmacokinetics.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Niacin

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

Simvastatin

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

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC). In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC). A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose. No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow. There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal

maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

13.2 Animal Toxicology and/or Pharmacology

SIMCOR

No animal toxicology or pharmacology studies were done with SIMCOR.

Niacin

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

Simvastatin

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day. A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

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

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

Reproductive Toxicology Studies

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

14 CLINICAL STUDIES

14.1 Modifications of Lipid Profiles

SIMCOR

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

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

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

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

Table 6. Non-HDL Treatment Response Following 24-Week Treatment Mean Percent Change from Simvastatin 20-mg Treated Baseline			
Group A			
	SIMCOR 2000/20	SIMCOR 1000/20	Simvastatin 20

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

[a] n=number of subjects with values in the analysis window at each timepoint
[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.
† significant vs. simvastatin 20 mg at the primary endpoint (Week 24), $p<0.05$

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

Group B

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

[a] n=number of subjects with values in the analysis window at each timepoint
[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.
[c] non-inferior to Simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for SIMCOR 2000/40 vs. Simvastatin 80 is (-7.7%, 4.5%)
[d] non-inferior to Simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for SIMCOR 1000/40 vs. SIMCOR 80 is (-6.6%, 5.3%)

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

		Treatment Group A				
TREATMENT	**N**	**LDL-C**	**Total-C**	**HDL-C**	**TG[a]**	**Apo B**

Baseline (mg/dL)*	266	120	207	43	209	102
Simvastatin 20 mg	102	-6.7%	-4.5%	7.8%	-15.3%	-5.6%
SIMCOR 1000/20	108	-11.9%	-8.8%	20.7%	-26.5%	-13.2%
SIMCOR 2000/20	56	-14.3%	-11.1%	29.0%	-38.0%	-18.5%

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

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

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

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

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 "a" logo and a code number specific to the tablet strength. Please see the table below:

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

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

17 PATIENT COUNSELING INFORMATION

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

Patients should be advised about substances they should not take concomitantly with simvastatin *[see Contraindications (4) and Warnings and Precautions (5.2)]*. Patients should also be advised to inform other healthcare professionals prescribing a new medication or increasing the dose of an existing medication that they are taking SIMCOR.

17.1 Muscle Pain

All patients starting therapy with SIMCOR should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing SIMCOR. The risk of myopathy, including rhabdomyolysis, occurring with the use of SIMCOR is increased when taking certain types of medication or consuming larger quantities of grapefruit juice. Patients should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes

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

17.3 Dosing Time

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

17.4 Tablet Integrity

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

17.5 Dosing Interruption

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

17.6 Flushing

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

17.7 Use of Aspirin

Taking aspirin approximately 30 minutes before dosing can minimize flushing.

17.8 Diet

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

17.9 Supplements

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

17.10 Dizziness

To notify their physician if symptoms of dizziness occur.

17.11 Diabetics

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

17.12 Pregnancy

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

17.13 Breastfeeding

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

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