

SPINE SAFETY CAUTIONARY NOTICE:

Information for Healthcare Professionals: Simcor (niacin extended-release/simvastatin) tablets: Labeling Changes

According to MedWatch, FDA notified healthcare professionals of labeling changes for Simcor (niacin extended-release/simvastatin) tablets. The following has been added to the labeling:

CONTRAINDICATIONS

- Concomitant administration of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol
- Concomitant administration of amiodarone, verapamil, or diltiazem

WARNINGS AND PRECAUTIONS

Myopathy/Rhabdomyolysis

Simvastatin

- Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.
- In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with Zocor (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day; the incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) was approximately 0.4% in patients on 80 mg/day compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.
- All patients starting therapy with SIMCOR, or whose dose of SIMCOR is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report symptoms promptly. Simcor therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.
- Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring.

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

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, 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. 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
 - The combined use of Simcor with gemfibrozil, cyclosporine, or danazol is contraindicated. The combined use of Simcor with amiodarone, verapamil, or diltiazem is contraindicated, because dosages of simvastatin are not to exceed 10 mg when these drugs are co-administered and all doses of Simcor contain simvastatin in excess of 10 mg.
 - The combined use of Simcor with drugs that cause myopathy/rhabdomyolysis when given alone, such as fibrates, should be avoided.
 - Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing Simcor with colchicine.
 - The benefits of the combined use of SIMCOR with amlodipine or ranolazine should be carefully weighed against the potential risks of combination...
 - Cases of myopathy, including rhabdomyolysis, have been observed with simvastatin coadministered with lipid-modifying doses (³1 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...
 - Prescribing recommendations for interacting agents are summarized in Table 3...
- Liver Dysfunction
- Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy.

ADVERSE REACTIONS

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.

DRUG INTERACTIONS

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...
- Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism in vitro (human liver microsomes). Therefore, voriconazole is likely to increase the...
- 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.

Amiodarone, Verapamil, or Diltiazem

- The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of amiodarone, verapamil, or diltiazem with doses of simvastatin exceeding 10 mg. Because all doses of Simcor contain simvastatin in excess of 10 mg, concomitant use of these drugs is contraindicated.

Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

- Gemfibrozil: Contraindicated with Simcor.
- Other fibrates: Combined use with Simcor should be avoided.

Amlodipine or Ranolazine

- The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of amlodipine or Ranolazine.

Colchicine

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

USE IN SPECIFIC POPULATIONS

Geriatric Use

- 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.

The North American Spine Society is committed to quality patient care through promotion of patient safety and prevention of medical errors. NASS monitors a variety of government and other resources for patient safety related notices that may be useful to our members. Information from these notices is also archived on the NASS website at <http://www.spine.org/Pages/PracticePolicy/ClinicalCare/SpineSafetyAlerts/Default.aspx>. This information is provided as a service for information and education only.