

FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury

Safety Announcement

[3-19-2010] Based on review of data from a large clinical trial and data from other sources, the U.S. Food and Drug Administration (FDA) is informing the public about an increased risk of muscle injury in patients taking the highest approved dose of the cholesterol-lowering medication, Zocor* (simvastatin) 80 mg, compared to patients taking lower doses of simvastatin and possibly other drugs in the "statin" class.

The clinical trial data being reviewed is from the **Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)** trial. The agency is also reviewing data from other clinical trials, observational studies, adverse event reports, and data on prescription use of simvastatin to better understand the relationship between high-dose simvastatin use and muscle injury (see Data Summary below).

The muscle injury, also called myopathy, is a known side effect with all statin medications. Patients with myopathy generally have muscle pain, tenderness or weakness, and an elevation of a muscle enzyme in the blood (creatine kinase). The higher the dose of statin used, the greater the risk of developing myopathy. The risk of myopathy is also increased when simvastatin, especially at the higher doses, is used with certain drugs (see Simvastatin Dose Limitations below).

The most serious form of myopathy is called rhabdomyolysis. It occurs when a protein (myoglobin) is released as muscle fibers break down. Myoglobin can damage the kidneys. Patients with rhabdomyolysis may have dark or red urine and fatigue, in addition to their muscle symptoms. Damage to the kidneys from rhabdomyolysis can be so severe that patients may develop kidney failure, which can be fatal.

Known risk factors for developing rhabdomyolysis include age (> 65 years), low thyroid hormone levels (hypothyroidism), and poor kidney function. Myopathy and rhabdomyolysis are listed as possible side effects in the simvastatin and other statin drug labels.

Healthcare professionals should:

- Understand that rhabdomyolysis is a rare adverse event reported with all statins.
- Be aware of the potential increased risk of muscle injury with the 80 mg dose of simvastatin compared to lower doses of simvastatin and possibly other statin drugs.
- Follow the recommendations in the simvastatin label regarding drugs that may increase the risk for muscle injury when used with simvastatin (see Simvastatin Dose Limitations below).

Patients should:

- Not stop taking simvastatin unless told to by their healthcare professional.

- Talk to their healthcare professional about any questions they have about the use of simvastatin.
- Call their healthcare professional if they experience any of the following: muscle pain, tenderness or weakness, urine that is dark or red-colored, or unexplained tiredness.

This communication is in keeping with FDA's commitment to inform the public about its ongoing safety review of drugs. The agency will update the public as soon as this review is complete.

**Simvastatin is sold as a single-ingredient generic medication and as the brand-name, Zocor. It is also sold in combination with ezetimibe as Vytorin; and niacin as Simcor.*

Additional Information for Patients

Patients currently using 80 mg simvastatin should:

- Know that rhabdomyolysis is a rare side effect reported with all statin medications.
- Not stop taking simvastatin unless told to by their healthcare professional.
- Review their medical history and current medications with their healthcare professional to determine if they should continue using simvastatin.
- Talk to their healthcare professional about any questions or concerns they have about simvastatin.
- Call their healthcare professional if they have muscle pain, tenderness or weakness, dark or red colored urine, or unexplained tiredness.
- Report any side effects with simvastatin to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals should:

- Understand that rhabdomyolysis is a rare adverse event reported with all statins.
- Be aware of the potential increased risk of muscle injury with the 80 mg dose of simvastatin compared to lower doses of simvastatin and possibly other statin drugs.
- Review patients' medical history and medications to determine if simvastatin is clinically appropriate.
- Discuss with patients the benefits and risks, including the risk of myopathy and rhabdomyolysis, of simvastatin therapy.
- Be aware of potential drug-drug interactions with simvastatin.
- Report any adverse events associated with the use of simvastatin to FDA's MedWatch program using the information in the "Contact Us" box at the bottom of the page.

Data Summary

FDA's review of the SEARCH trial is part of the agency's continuing effort to evaluate the risk of muscle injury with simvastatin; this review includes evaluating data from clinical trials, observational studies, and adverse event reports, as well as data on prescription use of simvastatin.

The SEARCH trial evaluated over 6.7 years the number of major cardiovascular events (heart attack, revascularization, and cardiovascular death) in 6031 patients taking 80 mg of simvastatin compared to 6033 patients taking 20 mg of simvastatin. All patients in the study had previously had a heart attack.

Preliminary SEARCH trial results revealed that more patients in the simvastatin 80 mg group developed myopathy compared to patients in the simvastatin 20 mg group (52 [0.9%] cases compared to 1 case [0.02%]). Further, FDA's preliminary analyses of the primary data suggest that 11 (0.2%) of the patients in the simvastatin 80 mg group developed rhabdomyolysis compared to no patients in the simvastatin 20 mg group.

In 2008, the agency alerted the public about an increased risk of developing rhabdomyolysis when doses greater than 20 mg of simvastatin are given with amiodarone. The agency also included information about this drug interaction in its Summer 2008 issue of the [FDA Drug Safety Newsletter](#)¹ and in its November 2008 [Patient Safety News broadcast](#)².

In March 2010, FDA approved a labeling revision for simvastatin based on interim results from an ongoing clinical trial – the Heart Protection Study 2 (HPS2). The revised label states that patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products. Further, the revised label recommends caution when such patients are treated with simvastatin 40 mg or less in combination with cholesterol-modifying doses of niacin-containing products. The interim HPS2 results showed that the incidence of myopathy was higher in patients of Chinese descent (0.43%) compared with patients not of Chinese descent (0.03%) taking 40 mg simvastatin plus cholesterol-modifying doses (≥ 1 g/day) of a niacin-containing product. It is not known if the increased risk for myopathy observed in these patients applies to other patients of Asian descent.

Moreover, FDA has requested that the sponsor of simvastatin change the product labeling to instruct healthcare professionals to avoid prescribing simvastatin doses greater than 40 mg daily when patients are taking the medication diltiazem, due to an increased risk for myopathy.

A 2010 review of prescription drug use data conducted by FDA found that, despite dose limitations and drug-drug interaction precautions included in the simvastatin drug label, patients are continuing to be prescribed higher doses of simvastatin with other medications that are known to increase the risk for rhabdomyolysis (see Simvastatin Dose Limitations below).

It is important for healthcare professionals to consider the potential risks and known benefits of simvastatin compared to other cholesterol-lowering therapies when deciding to use simvastatin. Healthcare professionals should also carefully review patients' medications for potential drug-drug interactions before prescribing or dispensing simvastatin.

This communication is in keeping with FDA's commitment to inform the public about its ongoing safety review of drugs. The agency will update the public as soon as this review is complete.

Simvastatin Dose Limitations

These limitations apply to ALL patients taking simvastatin.

Do not use simvastatin with these medications:

- Itraconazole
- Ketoconazole
- Erythromycin
- Clarithromycin
- Telithromycin
- HIV protease inhibitors
- Nefazodone

Do not use more than 10mg of simvastatin with these medications:

- Gemfibrozil
- Cyclosporine
- Danazol

Do not use more than 20mg of simvastatin with these medications:

- Amiodarone
- Verapamil

Do not use more than 40mg of simvastatin with this medication:

- Diltiazem