Information for Healthcare Professionals
Simvastatin (marketed as Zocor and generics), Ezetimibe/Simvastatin (marketed as Vytorin), Niacin extended-release /Simvastatin (marketed as Simcor),
used with Amiodarone (Cordarone, Pacerone)

FDA ALERT [08/08/2008]: The FDA is notifying the public of the risk of a rare condition of muscle injury called rhabdomyolysis, which can lead to kidney failure or death, when simvastatin is used with amiodarone. This risk is dose-related and increases when a dose of simvastatin greater than 20 mg per day is given with amiodarone. A revision of the simvastatin labeling in 2002 described an increased risk of rhabdomyolysis when amiodarone is taken with simvastatin doses greater than 20 mg daily. However, the FDA continues to receive reports of rhabdomyolysis in patients treated concurrently with amiodarone and simvastatin, particularly with simvastatin doses greater than 20 mg daily. Prescribers should be aware of the increased risk of rhabdomyolysis when simvastatin is prescribed with amiodarone, and they should avoid doses of simvastatin greater than 20 mg per day in patients taking amiodarone.

This information reflects FDA's current analysis of data available to FDA concerning these drugs. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of these drugs, please contact the FDA MedWatch program and complete a form on line at http://www.fda.gov/medwatch/report/hcp.htm or report by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.

Recommendations and Information for Healthcare Professionals to Consider When Prescribing Simvastatin to Patients Taking Amiodarone:

- Healthcare professionals, who prescribe simvastatin or simvastatin-containing medications (Simcor, Zocor, Vytorin), should be aware that patients taking amiodarone should not take more than 20 mg per day of simvastatin. Doses higher than 20 mg each day increase the risk of rhabdomyolysis, a rare condition of muscle injury.

- As with other statins, the risk of rhabdomyolysis is dose related. All patients, starting therapy with simvastatin or whose dose of simvastatin is being increased, should be advised of the risk of rhabdomyolysis and told to report promptly any unexplained muscle pain, tenderness or weakness.

- The risk of rhabdomyolysis is increased when higher doses of simvastatin are administered with amiodarone. The precise mechanism is unknown, but is related to the fact that amiodarone inhibits the cytochrome P450 3A4 (CYP3A4) enzyme. This is the same enzyme that metabolizes simvastatin. Prescribers should consider use of another statin for patients taking amiodarone, or initiating amiodarone therapy, who require simvastatin doses greater than 20 mg daily to meet their lipid goals.

- Rhabdomyolysis has been reported with all statins. Predisposing risk factors for rhabdomyolysis include advanced age (≥65 years), uncontrolled hypothyroidism, and renal impairment.

Information for Healthcare Professionals to Consider When Counseling Patients:

- Amiodarone is used to control a heart rhythm problem and simvastatin is used to lower cholesterol.

- Simvastatin interacts with amiodarone and can cause a rare muscle injury condition called rhabdomyolysis. This condition can lead to kidney failure and possibly death.

- If you are taking amiodarone and a cholesterol-lowering drug product containing simvastatin, you should not take more than 20 mg of simvastatin each day because your risk of developing rhabdomyolysis increases.

- If you are starting therapy with simvastatin, or your dose of simvastatin is being increased, contact your doctor immediately if you experience symptoms of unexplained muscle injury, such as muscle cramps, pain, tenderness, stiffness or spasm.

- Tell your doctor about all the medications you are taking.

Data Summary

Simvastatin is a member of the class of drugs known as HMG-CoA reductase inhibitors or "statins". Simvastatin has demonstrated benefit in lowering cholesterol and reducing some cardiac risks. Amiodarone is an antiarrhythmic drug approved only for controlling life-threatening recurrent ventricular arrhythmias.

The simvastatin prescribing information was updated in May 2002, to warn of an increased risk of rhabdomyolysis when amiodarone is used with simvastatin at doses greater than 20 mg daily. Despite the added warning to the prescribing information of simvastatin drug products, the FDA continues to receive serious reports of rhabdomyolysis when amiodarone is used with simvastatin, particularly with simvastatin doses greater than 20 mg daily.

Compared to other statins, the risk of rhabdomyolysis is more pronounced when simvastatin is administered with amiodarone. All statins carry a potential risk of rhabdomyolysis, whether or not they are administered with amiodarone.

The FDA does not have data on how varying the dose of amiodarone in patients taking simvastatin affects the risk of developing rhabdomyolysis.

The FDA and the manufacturer are revising the Cordarone (amiodarone) prescribing information to warn of an increased risk of rhabdomyolysis when amiodarone is taken with simvastatin doses exceeding 20 mg daily.

References

Schmidt, G. et al. (2007) Severe Rhabdomyolysis and Acute Renal Failure Secondary to Concomitant Use of Simvastatin, Amiodarone and Atazanavir. JABFN, 20(4):411-416.

Williams, D and Feely, J. (2002) Pharmacokinetic-Pharmacodynamic Drug Interactions with HMG-CoA Reductase Inhibitors. Clinical Pharmacokinetics, 41(5):343-370.

Beaird, S. (2000) HMG-CoA Reductase Inhibitors: Assessing Differences in Drug Interactions and Safety Profiles. J. Am. Pharm. Assoc., 40:637-644.

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Date created: August 8, 2008