NATIONAL PBM RESPONSE
to FDA Information for Healthcare Professionals Regarding
Simvastatin and Amiodarone Drug-Drug Interaction
August 18, 2008

On August 8, 2008, the FDA issued an "Information for Healthcare Professionals" sheet to remind clinicians of an increased risk of developing rhabdomyolysis in patients taking simvastatin at doses greater than 20 mg daily in combination with amiodarone.

In 2002, the manufacturer's product labeling for simvastatin was revised to include information regarding a dose-related increased risk for the development of rhabdomyolysis in patients receiving more than 20 mg per day of simvastatin in combination with amiodarone. In response, the VA Pharmacy Benefits Management Services sent an informational letter to its providers describing the interaction and provided recommendations/considerations for the management of those patients receiving the combination.[1]

Despite the label revision in 2002, the FDA has indicated that they continue to receive reports of rhabdomyolysis in patients receiving the combination, particularly in those patients taking more than 20 mg of simvastatin daily. The FDA is recommending that providers be aware of the increased risk of rhabdomyolysis when simvastatin and amiodarone are prescribed concurrently, and to avoid doses greater than 20 mg of simvastatin per day in patients taking amiodarone. (For more detailed information, refer to the FDA communication at the end of this e-mail).

VA MedSAFE has queried VA prescription databases to determine the numbers of patients that may be receiving this combination (simvastatin >20 mg per day plus amiodarone) in the VA system. A search of the VA's Adverse Event Reporting System (VA ADERS) over the past 17 months (March 2007 through August 2008) did not show any reported cases of rhabdomyolysis with this combination.

PBM and VAMedSAFE recommendations for patients receiving statins and amiodarone:
It is not clear what course of action is best in patients requiring long-term therapy with amiodarone in combination with simvastatin, without adverse effects. While the manufacturer recommends limiting doses of simvastatin to 20 mg daily, the benefit of lipid control may exceed the risk of adverse events. In new patients who require amiodarone, doses of simvastatin should be limited to 20 mg daily. The exact mechanism responsible for the interaction of simvastatin with amiodarone is not known but is likely to be related to amiodarone's inhibition of cytochrome P-450 3A4 (CYP 3A4). Lovastatin and atorvastatin are also metabolized via CYP 3A4 and limited data do support that the risk of rhabdomyolysis with these statins may also be increased in the presence of amiodarone.[2] Although rosuvastatin does not undergo CYP 3A4 metabolism, there is one reported case in which increased liver function tests were observed in an elderly individual taking both rosuvastatin and amiodarone.[2-3] Amiodarone does not appear to alter the pharmacokinetics of pravastatin[4] but data are insufficient to address the safety of fluvastatin in combination with amiodarone. As a result, it is prudent to use the lowest possible dose of any statin in patients also taking amiodarone and to warn patients to report unexplained muscle pain, tenderness or weakness to their providers immediately.

Please refer to the FDA Information for Healthcare Professionals for detailed information available at the following link: http://www.fda.gov/cder/drug/InfoSheets/HCP/simvastatin_amiodaroneHCP.htm.

REFERENCES
1. http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Clinical%20Recommendations/Simvastatin%20(Labeling%20Changes),%20Clinical%20Recommendations.pdf (accessed 8-11-08)
2. Micromedex Online (Drug Interaction Query)
3. http://www.ajhp.org/cgi/content/abstract/64/17/1818 (accessed 8-11-08)
4. Alsheikh-Ali AA, Karas RH. Adverse events with concomitant amiodarone and statin therapy. Prev Cardiol 2005;8:95-7