Recommendations for the Use of 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitors (statins) in Veteran Patients Receiving Medications with the Potential for Drug-Drug Interactions

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Dear Healthcare Provider,

Baycol (cerivastatin) was voluntarily withdrawn from the U.S. market because of a significantly higher number of cases of cerivastatin-associated rhabdomyolysis compared to the other available statins. Reports of fatal rhabdomyolysis with cerivastatin were more often associated with higher dosages, when prescribed in elderly patients, and when used in combination with gemfibrozil. Symptoms of rhabdomyolysis include muscle pain and weakness, malaise, fever, dark-colored urine, nausea and vomiting. Rhabdomyolysis is a syndrome that may be complicated by electrolyte imbalances, renal failure, metabolic acidosis and myocardial damage resulting from severe muscle damage and myoglobin release[1].

All of the available statins (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia, and myopathy to rhabdomyolysis[2]. Factors that may increase the risk for myopathy or rhabdomyolysis with statins are higher dosages, drug interactions, other myotoxic drugs and renal impairment[3,4,5,6].

Simvastatin, lovastatin, and atorvastatin are all metabolized via the cytochrome P450 3A4 (CYP 3A4) isoenzyme system. As a result, all three agents are susceptible to drug interactions when administered concomitantly with agents known to inhibit metabolism via CYP 3A4 resulting in increased statin concentrations and the possibility for adverse effects (Table 1). Table 1 does not include all drugs capable of inhibiting metabolism via the CYP 3A4 isoenzyme system. The significance of interactions with many drugs that inhibit CYP 3A4 is not known; examples include diltiazem, verapamil and fluoxetine. Thus, caution should be exercised when using these or other such drugs in combination with simvastatin, lovastatin, or atorvastatin. When doing so it is generally prudent to start the statin at a low dose and titrate upward, as needed to reach LDL-c goal, while observing for any adverse or untoward effect (e.g. myopathy or myalgias). Fluvastatin is primarily metabolized via CYP 2C9 and is vulnerable to interactions with drugs known to inhibit CYP 2C9 metabolism (Table 2). Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore not affected by drugs inhibiting metabolism via these pathways[2,7,8].

Table 1. Potent Inhibitors of CYP 3A4[2,7]

Clarithromycin*
Erythromycin*
Cyclosporine*
Protease inhibitors (indinivir, nelfinavir, ritonavir, saquinavir, amprenavir, lopinavir/ritonavir)
Delavirdine
Itraconazole*
Fluconazole
Ketoconazole
Nefazodone*
Grape fruit juice

*Published reports of rhabdomyolysis exist in patients receiving concomitant statin.

Table 2. Drugs Known to Inhibit Metabolism Via CYP 2C9[2,7]

Amiodarone	Fluvoxamine
Azole Antifungals	Metronidazole
Omeprazole	Cimetidine
Fluoxetine	TMP/SMX
Zafirlukast	

Myopathy and rhabdomyolysis have also been reported in patients receiving monotherapy with fibrates (gemfibrozil), especially in patients with impaired renal function[1,9] Although the mechanism of the interaction is not completely known, the combination of any statin with gemfibrozil and to a lesser extent niacin, can result in a higher risk for myopathy or rhabdomyolysis[9,10].

PBM-MAP Recommendations:

1. Patients receiving simvastatin, lovastatin, or atorvastatin who require short-term treatment with an antifungal agent (ketoconazole, itraconazole, fluconazole) or a macrolide (erythromycin, clarithromycin) should have their statin temporarily withheld or closely monitored during their course of therapy[11,12].

2. In those patients requiring long-term therapy with agents known to be potent inhibitors of CYP 3A4, consideration should be given to using pravastatin or limiting doses of simvastatin to 10 mg qd or lovastatin to 20 mg qd [11,12]. Although no specific guidance is provided by the manufacturers of atorvastatin, doses should be maintained well below the maximum recommended daily dose (e.g. 10 mg qd).

3. In general, the statin manufacturers recommend limiting the maximum daily dose of the statin, avoidance of the statin or close monitoring of therapy when combining a statin with gemfibrozil or niacin. If a provider considers the benefit of the combination of a statin with a fibrate or niacin to outweigh the risk, patients must be advised to promptly report any unexplained muscle pain, tenderness or weakness. The combination is not advised in patients receiving drugs known to inhibit CYP 3A4 or those patients with liver, muscle or renal impairment [8] as a result of an increased risk for adverse events.

   a. Manufacturer recommendations:

   - **Simvastatin or lovastatin**: Limit doses of simvastatin to 10 mg qd and lovastatin to 20 mg qd if combined with gemfibrozil or niacin [11,12].
   - **Atorvastatin:** Closely monitor patients on combined therapy with gemfibrozil or niacin [13].
   - **Fluvastatin or pravastatin:** Avoid the combination with gemfibrozil unless the benefit outweighs the risk of such therapy [14,15].

4. Statin therapy should be temporarily withheld in patients experiencing a serious acute condition that may predispose them to acute renal failure and rhabdomyolysis including severe infection, hypotension, major surgery or trauma, severe endocrine, metabolic or electrolyte disorder or uncontrolled epilepsy [14].

All patients receiving treatment with statins should be advised to report any unexplained muscle pain, tenderness or weakness. Patients experiencing any of these symptoms should be advised to discontinue their lipid therapy immediately and providers should obtain a CK level as soon as possible, if clinically indicated. Since there can be varying degrees of myotoxicity, (e.g. myalgia-normal or slightly elevated CK, myositis-with or without CK elevation, myopathy-elevated CK{>10 times ULN}, rhabdomyolysis-myoglobinemia and myoglobinuria with an elevated CK {>10 times ULN}) the CK may not always be elevated [4]. Therefore if the CK is normal, a second trial with a statin may be appropriate with especially close monitoring and reinforcement to the patient to discontinue their lipid therapy immediately and contact their provider if muscle pain and weakness recurs.

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