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Subj: Simvastatin Labeling Changes
To: VISN Formulary Leaders

1. The Medical Advisory Panel has received several anecdotal reports that recent changes in the product labeling for simvastatin are being cited as a reason to switch patients to nonformulary statins. The PBM/MAP had previously developed recommendations for using statins in patients taking medications with the potential for drug-drug interactions when combined with statins. These recommendations are available on the PBM/MAP web site ¹.

The FDA has recently approved several labeling changes related to simvastatin's potential for drug-drug interactions. These changes were recommended to the FDA by the manufacturer as a result of data from clinical trials involving simvastatin. The following is a list of the changes:

- The first change relates to combining simvastatin with fibrates (e.g. gemfibrozil) or niacin:

The product labeling for simvastatin previously stated that if simvastatin is used in combination with fibrates or niacin, the dose of simvastatin should generally not exceed 10 mg daily. The new labeling states that the dose of simvastatin should not exceed 10 mg daily.

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 rhabdomyolysis². 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}.

Myopathy and rhabdomyolysis have also been reported in patients receiving monotherapy with fibrates (gemfibrozil), especially in patients with impaired renal function⁷. 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^{7,8}. However, the combination is considered by the National Cholesterol Education Panel (NCEP) Adult Treatment Panel III (ATP III) as an appropriate option for patients with some types of dyslipidemias¹⁷.

There are no good data to support greater safety with one particular statin when combined with a fibrate or niacin. In fact the American College of Cardiology, American Heart Association, and the National Heart, Lung, Blood Institute (ACC/AHA/NHLBI) released a clinical advisory of the use and safety of statins which states "that clinicians should consider the rates of severe myopathy as equivalent among all of the approved statins."¹⁶

The FDA has approved the following recommendations when combining fibrates and/or niacin with a statin:

- Atorvastatin: Combination of statins and fibrates should generally be avoided. However, if combined, the risks and benefits should be carefully weighed and close monitoring for signs and symptoms of muscle pain or weakness is recommended¹¹.
- Fluvastatin: Combination of statins and fibrates should generally be avoided¹³.
- Lovastatin: Combination of statins with fibrates or niacin should generally be avoided. However if combined, the dose of lovastatin should not exceed 20 mg daily¹⁰.
- Pravastatin: The combined use of fibrates with pravastatin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk¹².
- Simvastatin: Combination of statins with fibrates or niacin should generally be avoided.

However if combined, the dose of simvastatin should not exceed 10 mg daily⁹.

PBM/MAP recommendations when combining statins with gemfibrozil or niacin:

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, they may choose to initiate therapy. However, they must also advise patients to promptly report any unexplained muscle pain, tenderness or weakness. Appropriate chart documentation should reflect a providers assessment of risks and benefits plus all efforts to educate the patient regarding adverse effects. The combination, in general, is not advised in patients receiving drugs known to inhibit CYP 3A4 or those patients with liver, muscle or renal impairment¹⁵ as a result of an increased risk for adverse events.

- The second change provides daily dose limits for simvastatin in patients also receiving amiodarone or verapamil.

Amiodarone: The new labeling states: In patients receiving amiodarone in combination with simvastatin, the daily dose of simvastatin should be limited to 20 mg.

This change was sought in response to data from a large ongoing trial in patients randomized to simvastatin 20 mg or 80 mg daily. Upon examination of the data, a higher than expected incidence of myopathy (n=6 out of approximately 100) was observed in patients receiving simvastatin 80 mg daily in combination with amiodarone. No cases of myopathy were seen in those taking amiodarone with simvastatin 20 mg daily. There were no reports of rhabdomyolysis in any of these patients. Safety data were inadequate to address moderate doses of simvastatin (e.g. 40 mg daily) in combination with amiodarone. Although the exact mechanism of this interaction is not known (e.g. not known if CYP 3A4 mediated), daily doses of simvastatin should be limited to 20 mg in patients receiving amiodarone. Data are lacking to address the safety of the combination of atorvastatin, fluvastatin, lovastatin or pravastatin with amiodarone.

PBM/MAP 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 mechanism responsible for the interaction of simvastatin with amiodarone is not known (e.g. unknown if CYP 3A4 mediated). Data are lacking to address the safety of the combination of atorvastatin, fluvastatin, lovastatin, pravastatin or moderate doses of simvastatin with amiodarone.

Verapamil: The new labeling states: In patients receiving any dose of verapamil in combination with simvastatin, the daily dose of simvastatin should be limited to 20 mg.

This change in dosing was recommended when clinical trial data (n=approx. 25,000), involving simvastatin, were reviewed by the manufacturer. They observed a higher than expected number of patients receiving verapamil and simvastatin who developed myopathy (4/635 or 0.63%) compared to those on simvastatin without verapamil (13/21,224 or 0.061%). None of these patients developed rhabdomyolysis. The exact mechanism for the interaction is not entirely known, but can be partially explained by verapamil's ability to inhibit cytochrome P450 3A4

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). 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^{2,14,15}

Table 1. Potent Inhibitors of CYP 3A4^{2,14}

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 1 does not include all drugs capable of inhibiting metabolism via the CYP 3A4 isoenzyme system.

Table 2. Drugs Known to Inhibit Metabolism Via CYP 2C9^{2,14}

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

PBM/MAP recommendations for statins in combination with verapamil:

It is not clear what course of action is best in patients on long-term therapy with amiodarone and/or verapamil 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. If amiodarone or verapamil can safely be discontinued or changed to another agent without interactions to the statins, this is preferable. In new patients who require amiodarone and/or verapamil, doses of simvastatin should be limited to 20 mg daily. If the interaction between verapamil and simvastatin is partially explained by inhibition of statin metabolism, caution should also be exercised if considering atorvastatin or lovastatin because their metabolism is similar to simvastatin. Never the less, in patients who require statin therapy, it is prudent to avoid concomitant use of verapamil or limit the statin dose. Furthermore, since fluvastatin and pravastatin are not metabolized via CYP 3A4, they may offer safer alternative in patients receiving verapamil and requiring more than simvastatin 20 mg daily to meet their cholesterol goals.

Additional PBM/MAP recommendations for patients taking medications with the potential for drug-drug interactions with statins:

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^{9,10}.
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, as is generally recommended in patients on protease inhibitors, or, in other instances, to using fluvastatin or limiting doses of simvastatin to 10 mg qd or lovastatin to 20 mg qd^{9,10}. Although no specific guidance is provided by the manufacturers of atorvastatin, doses should be maintained well below the maximum recommended daily dose of 80 mg (e.g. 5 mg qd).
3. 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 epilepsy¹⁴.

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 elevated⁴. 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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