# Appropriate Statin Therapy

Inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, commonly called statins, block conversion of HMG-CoA to mevalonate, an early rate-limiting step in the biosynthesis of cholesterol. The statins effectively decrease LDL- and VLDL-cholesterol and triglyceride levels and increase HDL-cholesterol levels. Clinical trials have demonstrated that statin use decreases cardiovascular morbidity and mortality.[1] Despite positive effects, the statins have the potential to cause increased liver enzyme levels, myopathy, and rhabdomyolysis. Although the exact mechanism for statin-induced myopathy is unknown, factors such as absorption, hepatic uptake, solubility, protein binding, drug elimination, and drug interactions are known to play a role.[2,3]

**Illinois Medicaid Drug Utilization Review.** The Food and Drug Administration (FDA) issued warnings about appropriate simvastatin use in 2011 based on an increased potential for muscle damage in the first year of therapy in patients taking 80-mg doses of simvastatin as evidenced by the SEARCH Trial and post-marketing surveillance.[4,5,6] Simvastatin 80 mg became non-preferred for Illinois Medicaid clients on May 23, 2013. Between May and December 2013 at least 331 prior authorization requests were received for simvastatin 80 mg. The Medication Review and Academic Detailing staff identified 537 additional patients receiving simvastatin 80 mg for less than one year. Provider education resulted in medication changes. Provider outreach revealed lack of awareness of SEARCH Trial results, FDA warnings, preferred statin alternatives to simvastatin, statin potencies for conversion to a new statin, and patient noncompliance with medication fills. The Illinois Drug Utilization Review Board recommended provider education regarding these issues on January 15, 2014. Information provided below will help providers better manage patients receiving statin therapy.

**The SEARCH Trial.** The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH trial) compared intensive lowering of LDL-cholesterol with simvastatin 20 mg and 80 mg in 12,064 adult survivors of myocardial infarction. Supplementation with oral vitamin B12 and folic acid was also evaluated. Over an average follow-up of 6.7 years, the double-blind randomized study demonstrated minor differences in LDL-cholesterol lowering and increased incidence of myopathy and rhabdomyolysis in patients receiving simvastatin 80 mg compared to patients receiving simvastatin 20 mg. Simvastatin 80 mg achieved a 13.5 mg/dL greater decrease in LDL-cholesterol and a non-significant reduction in risk of experiencing a major vascular event (risk ratio 0.94, 95% confidence interval 0.88-1.01, p = 0.10). This 6% proportional risk reduction of major vascular events associated with a 13.5 mg/dL decrease in LDL-cholesterol was comparable to reductions achieved in other clinical trials. Comparable rates of hemorrhagic strokes and deaths due to vascular or non-vascular causes were demonstrated between dosage strengths. No significant differences were noted in elevations of liver enzymes between treatment groups. More patients taking simvastatin 80 mg demonstrated increased levels of creatine phosphokinase (145 cases vs 43 cases with 20 mg), myopathy (53 cases vs 2 cases with 20 mg), and rhabdomyolysis (7 cases vs no cases with 20 mg). Increased cases of myopathy were observed in the first year after randomization. The risk of myopathy was increased in patients who were older, female, or had a genetic variant in the transporter for hepatic simvastatin uptake. The risk for myopathy almost doubled if patients were taking a calcium channel blocker.[4]

**FDA warnings**. The FDA noted that approximately 2.1 million patients in the United States were prescribed simvastatin 80 mg in 2010. In 2011 the FDA issued several drug safety communications regarding simvastatin therapy that resulted in the following recommendations for prescribers[5,6]:

- Do not start simvastatin 80 mg because of an increased risk of myopathy.
- The maximum safe dose of simvastatin is 40 mg.
- Risk for simvastatin-induced myopathy at doses of 80 mg is greatest in the first year of therapy.
- Simvastatin 80 mg may be continued only if simvastatin has been taken for longer than 12 months and the patient has not experienced myopathy throughout therapy.

- Simvastatin is contraindicated for use concomitantly with azole antifungals, erythromycin antibacterials, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol. Patients who require a medication that interacts with simvastatin should be switched to an alternate statin that has less potential for the drug interaction.
- Limit simvastatin to a maximum dose of 10 mg if taken with verapamil or diltiazem.
- Limit simvastatin to a maximum dose of 20 mg if taken with amiodarone, amlodipine, or ranolazine.
- If LDL-cholesterol goal is not achieved with simvastatin 40 mg, switch to a statin that has greater LDL-cholesterol lowering capability.

The FDA is monitoring for adverse effects on an ongoing basis. Side effects due to simvastatin-containing medications should be reported to the FDA MedWatch program.[7]

**Managing simvastatin therapy.** Simvastatin doses should be titrated appropriately to a maximum of 40 mg. If LDL-cholesterol goals cannot be achieved with simvastatin 20-40 mg, the patient should be switched to a more potent statin, rather than increasing the simvastatin dose to 80 mg. *Table 1* lists statins that are on the Illinois Medicaid Preferred Drug List (PDL).[8] Medications on the PDL should be used first. If not adequate and other agents must be used, prior authorization will be required for non-preferred statins. *Table 2* provides comparable statin potencies to aid in appropriate titration or conversion to other statin therapy. [1,5]

**Table 1. Statins on the Illinois Medicaid Preferred Drug List** [8]

| Preferred statins | Non-preferred statins |
|---|---|
| Generic versions of<br>• Atorvastatin<br>• Fluvastatin<br>• Lovastatin<br>• Pravastatin<br>• Simvastatin | • Brand versions of atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin<br>• Brand combination products containing atorvastatin, lovastatin, simvastatin<br>• Pitavastatin (Livalo)<br>• Rosuvastatin (Crestor)<br>• Simvastatin 80 mg |

**Table 2. Comparable Statin Potencies**[1,5*]

| Statin | Dose | LDL-lowering | Dose | LDL-lowering | Dose | LDL-lowering | Dose | LDL-lowering |
|---|---|---|---|---|---|---|---|---|
| Atorvastatin (Lipitor) | - | | 10 mg | | 20 mg | | 40 mg | |
| Fluvastatin (Lescol) | 40 mg | | 80 mg | | - | | - | |
| Lovastatin (Mevacor) | 20 mg | | 40 or 80 mg | | 80 mg | | - | |
| Pitavastatin (Livalo) | 1 mg | 30% | 2 mg | 38% | 4 mg | | - | |
| Pravastatin (Pravachol) | 20 mg | | 40 mg | | 80 mg | 41% | - | 47% |
| Rosuvastatin (Crestor) | - | | - | | 5 mg | | 10 mg | |
| **Simvastatin (Zocor)** | **10 mg** | | **20 mg** | | **40 mg** | | **80 mg** | |
| Simvastatin + ezetimibe (Vytorin)† | - | | - | | 10/10 | | 10/20 | |

* LDL-cholesterol lowering of 55% can be achieved with atorvastatin 80 mg, rosuvastatin 20 mg or Vytorin 10/40 mg and LDL-cholesterol lowering of 63% can be achieved with rosuvastatin 40 mg or Vytorin 10/80 mg. † The combination product Vytorin has not demonstrated additional benefit over simvastatin alone for cardiovascular morbidity and mortality.

**Drug interactions.** Hepatic metabolism of the statins increases risk of drug interactions with other medications that share the same hepatic metabolic pathways. For simvastatin these are primarily the cytochrome-p450-3A4 isoenzyme and glucuronidation. Concomitant therapy may increase statin levels, potentially augmenting adverse reactions, such as increased levels of creatine phosphokinase. This can result in myopathy and potentially fatal rhabdomyolysis. [2,3,9,10]

**Concomitant therapy with gemfibrozil.** Gemfibrozil is a fibric acid derivative that primarily decreases triglycerides and increases HDL-cholesterol. Concurrent use of simvastatin with gemfibrozil, a strong hepatic CYP3A4 isoenzyme inhibitor, is contraindicated due to increased risk of myopathy and rhabdomyolysis with each drug individually. This adverse effect is exacerbated if the medications are combined because gemfibrozil inhibits statin glucuronidation and shares the same metabolic pathways.[2] The FDA and the product package inserts note that combination gemfibrozil and simvastatin therapy is contraindicated.[5,11,12] Currently, HFS has an edit is in place to prevent concomitant use of simvastatin and gemfibrozil.[13] Caution is also advised when patients take lipid-lowering doses of niacin (≥ 1 gram/day) along with high-dose simvastatin.[1] Patients that require additional therapy for hypertriglyceridemia may use the fibrate fenofibrate instead of gemfibrozil because it uses different metabolic pathways.[2] Alternatively, a different statin, such as fluvastatin, can be used instead of simvastatin because it has been studied in patients with statin-induced myopathy.[3,10] In general, all statin package inserts recommend avoidance of combination therapy with gemfibrozil.[11,14-19,] The rosuvastatin package insert recommends a maximum rosuvastatin dose of 10 mg if administered with gemfibrozil.[14]

**Concomitant therapy with calcium channel blockers (CCBs).** All CCBs and statins undergo hepatic metabolism as noted in *Table 3.*[11,14-22] Concomitant simvastatin therapy with CCBs can increase total or maximum levels of certain statins or provide an enhanced hypotensive effect due to CCBs if they are both substrates of the same enzyme, inhibit the same enzyme, or are metabolized by the same enzyme.

**Table 3. Cytochrome P-450 isoenzymes, Calcium Channel Blockers, and Statins**[11,14-22]

| Cytochrome P-450 isoenzyme | Drug or Enzyme Action | CCB | Statin |
|---|---|---|---|
| **1A2** | 1A2 Metabolizes drug | Verapamil | - |
| **2C8** | 2C8 Metabolizes drug | Verapamil | Fluvastatin<br>Lovastatin<br>Pitavastatin<br>Simvastatin |
| **2C9** | Substrate | - | Fluvastatin<br>Pitavastatin<br>Rosuvastatin |
| | Inhibitor | Nifedipine (reversible) | Fluvastatin<br>Pravastatin (modest) |
| | 2C9 Metabolizes drug | Verapamil | Fluvastatin<br>Pitavastatin<br>Rosuvastatin |
| **2C18** | 2C18 Metabolizes drug | Verapamil | - |
| **2C19** | 2C19 Metabolizes drug | - | Rosuvastatin |
| **2D6** | Inhibitor | Nifedipine (reversible) | Pravastatin (modest) |
| **3A4** | Substrate | Diltiazem<br>Felodipine<br>Verapamil | Atorvastatin<br>Lovastatin<br>Simvastatin |
| | Inhibitor | Diltiazem (potent)<br>Nicardipine (potent)<br>Nifedipine (reversible)<br>Verapamil | Pravastatin (modest) |
| | 3A4 Metabolizes drug | Felodipine<br>Verapamil | Atorvastatin<br>Fluvastatin<br>Lovastatin<br>Simvastatin |

Although concomitant statin and CCB therapy results in a drug interaction and pharmacokinetic changes, concurrent use is not contraindicated. Agents in both classes that do not share the same metabolic pathways can be used. Dosage adjustments are recommended in select situations of concomitant statin and CCB therapy as indicated in *Table 4.*[5,6] Patients who have been tolerating simvastatin 80 mg and require therapy with an interacting medication, should be switched to a different statin that has less potential for the drug-drug interaction. Occasionally patients require diltiazem or verapamil therapy in addition to a dihydropyridine CCB. The potential for interactions increases further, thus these patients should be monitored for hypotension, for example amlodipine co-administered with diltiazem and simvastatin.

**Table 4. Recommendations for Dosing Statins and Calcium Channel Blockers Concurrently**[5,6,11,15,20-22]

| Statin | Calcium Channel Blocker | Dosing Adjustment for Concurrent Therapy |
|---|---|---|
| Lovastatin (Mevacor) | Diltiazem | Maximum dose: Lovastatin 20 mg |
| | Verapamil | Maximum dose: Lovastatin 20 mg (Verapamil PI: 40 mg) |
| Simvastatin (Zocor) | Amlodipine | Maximum dose: Simvastatin 20 mg |
| | Diltiazem | Maximum dose: Simvastatin 10 mg per PI (FDA: 40 mg)<br>Maximum dose: Diltiazem 240 mg |
| | Verapamil | Maximum dose: Simvastatin 10 mg per PI (FDA: 20 mg) |

PI = package insert; FDA = Food and Drug Administration

The Illinois Drug Utilization Board encourages providers to be attentive in prescribing statin therapy appropriately. Additional educational materials for providers can found on the Drug Utilization Review Board Web page at http://www.hfs.illinois.gov/pharmacy/dur.html.

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