NATIONAL PBM BULLETIN

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VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), VISN PHARMACIST EXECUTIVES (VPE), AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

Simvastatin: Updated Restrictions, Contraindications and Dose Limitations

I. ISSUE

On June 8th, 2011, the FDA announced new recommendations concerning the maximum dose of simvastatin (80 mg) because of an increased risk of muscle damage compared to lower simvastatin doses or other statins. In addition, the FDA is requiring changes to the simvastatin label adding new contraindications and more aggressive dose limitations for simvastatin when used with certain medications.[1]

II. BACKGROUND

In March 2010, the FDA announced an ongoing safety review of high-dose simvastatin (80 mg/day) and the potential for an increased risk of muscle injury compared to lower doses of simvastatin or potentially other statins.[2] In their announcement, the FDA indicated that the ongoing safety review was prompted by data from a large clinical trial, "Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine" (SEARCH)[3], and data from other sources.

In their March 2010 announcement, the FDA recommended that healthcare professionals:

- Understand that rhabdomyolysis is a rare event and has been reported with all statins
- Be aware of the potential increased risk for muscle injury with the 80 mg dose of simvastatin compared to lower doses or potentially other statins
- Adhere to recommended simvastatin dose limits when combined with drugs that may increase the risk for muscle injury when used in combination with simvastatin.

In the SEARCH Trial, 12,064 patients with a history of myocardial infarction were randomized to simvastatin 20 mg or 80 mg daily (with or without vitamin B12 or folate) and followed for a mean of 6.7 years. In this study, there were 53 patients (1%) on 80 mg and 2 patients (0.03%) on 20 mg with a diagnosis of myopathy; and 7 patients (0.1%) on 80 mg and none on the 20 mg dose who experienced rhabdomyolysis. Of the 53 patients with myopathy, eight were receiving amiodarone, subsequently leading to a labeling change limiting the dose of simvastatin in patients receiving concomitant amiodarone, to 20 mg daily. There was also a doubling of the risk for myopathy in patients taking calcium channel blockers, particularly diltiazem.[1]

In June 2011 announcement, the FDA summarizes the findings of their ongoing safety review of high dose simvastatin and conclude that based upon their analysis of data from SEARCH, FDA's adverse event reporting system (AERS) and other clinical trial data, 80 mg of simvastatin is associated with higher rates of myopathy and rhabdomyolysis compared to lower simvastatin doses or other statins.[1] They also refer to a "genetic variant" that was present in approximately 60% of patients with myopathy (SEARCH trial) which may alter the coding of the transporter responsible for uptake of simvastatin by the liver resulting in increased exposure to simvastatin, thus more adverse events.

As a result of their findings from the ongoing safety review, the FDA recommends:

- Simvastatin 80 mg be reserved for patients who have been taking this dose for 12 months or greater with no evidence of muscle injury. In the SEARCH trial, the risk of myopathy or rhabdomyolysis with the 80 mg dose was highest within the first 12 months (4-5 fold higher).
- Simvastatin 80 mg should not be started in new patients, including patients currently taking lower doses of simvastatin.
- Required change in current simvastatin product labeling (including labeling of combination products containing simvastatin [Vytorin, Simcor]) regarding concomitant use of drugs known to inhibit the metabolism of simvastatin.

- New contraindications against certain combinations with simvastatin: itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol.
- More aggressive simvastatin dose limitation:
  - Do not exceed 10 mg: Amiodarone, verapamil, diltiazem
  - Do not exceed 20 mg: Amlodipine (new), ranolazine (new)

III. PROVIDER RECOMMENDATIONS

- Reinforce to patients the importance of notifying their healthcare provider if they notice any unexplained muscle pain, tenderness or weakness while receiving statin therapy, especially after initiation of statins or change in statin therapy (e.g., escalation of dose or switch to another statin).
- Be aware that certain factors may increase an individual's susceptibility to statin-associated muscle toxicity including hypothyroidism, renal or liver impairment, frailty, advanced age, drug-drug interactions, female gender, etc.[4] Consider use of lower statin doses in these patients.
- Ensure patients are adherent to statin therapy prior to increasing statin doses or switching statin therapy.
- Simvastatin 80 mg daily:
  - Review patients on doses of 80 mg daily.
    - Patients taking simvastatin 80 mg daily for ≥12 months without muscle complaints, may continue their current simvastatin dose.
    - Patients receiving 80 mg of simvastatin for less than 12 months, consider reducing their dose to 40 mg daily and repeating a lipid panel in 6 weeks. Emphasize the importance of compliance with diet, exercise and statin treatment.
- Concomitant drugs known to inhibit metabolism of simvastatin:
  - New contraindications
    - Gemfibrozil-The PBM-MAP-VPEs discourage the use of any statin-fibrate combination because of the known risks and yet to be proven incremental benefit of these combinations beyond statin therapy alone.[5-6] Consider discontinuing gemfibrozil and continue simvastatin without a fibrate. If triglyceride (TG) lowering is needed, recommend intensive therapeutic lifestyle changes. In patients with very high TG levels (e.g., >500 mg/dL) or a history of TG induced pancreatitis, consider fish oils. If further LDL-C lowering is needed in a setting where triglycerides are elevated and the simvastatin dose is maximized, consider replacing gemfibrozil with niacin.
    - Strong CYP 3A4 inhibitors-
      - Long-term therapy [≥30 days] (e.g., azole antifungals, HIV protease inhibitors, nefazodone, cyclosporine, etc.)-Consider switching to an alternative statin while adhering to recommended dose limits for the selected statin.
      - Short-term therapy [<30 days] (e.g., macrolide therapy)-Consider withholding simvastatin until therapy with antibiotics is complete.
  - More aggressive dose limits
    - Adhere to manufacturer dose limits when prescribing statins in patients receiving drugs known to increase the risk for statin-associated muscle toxicity. *(e.g., simva-as listed above, cyclosporine-rosuvastatin 5 mg or atorvastatin 10 mg, gemfibrozil-rosuvastatin 10 mg, lopinavir/ritonavir, atazanavir/ritonavir-rosuvastatin 10 mg, various CYP 3A4 inhibitors-caution when using >20 mg of atorvastatin)*

IV. REFERENCES

1. http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm
2. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm
3. Intensive Lowering of LDL Cholesterol with 80 mg Versus 20 mg Simvastatin Daily in 12,064 Survivors of Myocardial Infarction: A Double-Blind Randomized Trial. Lancet 2010, 376:1658-1669.
4. Pasternak RC, Grundy SM, Smith SC, et al. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. J Am Coll Cardiol 2002;40:567-572.
5. http://www.pbm.va.gov/vamedsafe/High%20Dose%20Statins%20and%20Fibrates_National%20PBM%20Bulletin_111009_FINAL.PDF
6. ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. New Engl J Med 2010;362:1563-1574.

ACTIONS:

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS) and Chief Nurse Executives.*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers who prescribe this agent (e.g.,* ***primary care providers,*** *including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*