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VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM),
MEDICAL ADVISORY PANEL (MAP), & CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

SAFETY OF HIGH DOSE STATIN-FIBRATE COMBINATIONS

I. ISSUE

High dose HMG CoA Reductase Inhibitors (statins) combined with fibric acid derivatives have unclear benefit on clinical outcomes and may cause harm through increased risk of muscle toxicity and rhabdomyolysis.

II. BACKGROUND

The clinical benefit of statin-fibrate combinations is not clear.¹ However, the risk for muscle toxicity with combination therapy is greater than that for either statins or fibrates alone.² The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study is investigating the effect of the statin-fibrate combination versus a statin alone on cardiovascular outcomes. Results from ACCORD are expected in 2010.³ Until then, the combination should be used with caution, and clinicians should consider that certain factors can also increase an individual's risk for muscle toxicity with the combination including further drug-drug interactions (see below under 3d, for examples), advanced age, impaired renal function, female gender, alcoholism and hypothyroidism. In general, high dose statins and fibrates should be avoided. Due to limited literature and adverse event reporting, whether certain high-potency statins are safer when combined with a fibrate is unclear.¹ Moreover, there is as yet little clinical evidence that one fibrate is safer than another when used with statins.⁴

III. PROVIDER RECOMMENDATIONS¹

1. Avoid routine use of statin-fibrate combinations because there is no evidence for additional cardiovascular event reduction with statin-fibrate combinations over statins alone; but there is evidence for an added risk of serious adverse events (e.g. rhabdomyolysis or severe myalgia).
2. For patients already on a statin-fibrate combination:
 - a. If LDL-C lowering is paramount, discontinue the fibrate and use a statin as the primary agent, add other agents as necessary (e.g., niacin, bile acid sequestrants) to reach goal.
 - b. If triglyceride lowering is the primary objective (e.g., with TG >500 mg/dL), discontinue the statin and continue the fibrate.
 - c. If LDL-C lowering and triglycerides require reduction, discontinue the fibrate, titrate the statin as necessary (for LDL-C lowering) and utilize niacin or fish oils, if at all possible.
 - d. Consider that there is little clinical evidence that one fibrate is safer than another when used in combination with a statin.
3. If combination therapy with a statin-fibrate is considered clinically necessary and benefits are deemed to outweigh the risks, then:
 - a. Use the lowest effective statin dose, regardless of the statin or fibrate used.
 - b. Adhere to statin dose limits in the product labeling (i.e., simvastatin 10 mg, lovastatin 20 mg or rosuvastatin 10 mg daily) in combination with gemfibrozil. Atorvastatin does not list a maximum dose but the lowest effective dose of this agent should be used when combined with a fibrate.
 - c. Only consider the combination if patients have normal renal (eGFR >60 ml/min), liver and thyroid function.
 - d. Use added caution in patients receiving other drugs known to inhibit statin metabolism (For example, serum concentrations of simvastatin, lovastatin and atorvastatin are increased in the presence of macrolides, azole antifungals, protease inhibitors, cyclosporine, amiodarone, verapamil, diltiazem, etc.).
 - e. Discuss the risks and benefits of combination therapy with patients and document the discussion in the patient's medical record.
 - f. Warn the patient to report any new muscle pain, tenderness or weakness to their providers immediately.
4. When a statin-fibrate combination is used, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III⁵ and the VA/DoD Dyslipidemia Guideline recommend a baseline creatine kinase (CK) level prior to initiating combination therapy. Measurement of CK is repeated if the patient reports muscle symptoms resembling myopathy. Both groups also recommend discontinuing combination therapy (both statin and fibrate) if CK is greater than 10 times the upper limit of normal with muscle symptoms (tenderness, pain or weakness). Once symptoms resolve completely and CK has normalized, either drug can be restarted at a lower dose.

IV. REFERENCES

1. *STATIN-FIBRATE REPORT: Focus on Safety*. Washington, DC: Pharmacy Benefits Management Services and the Medical Advisory Panel, Veterans Health Administration, Department of Veterans Affairs. September 2004.
<http://vawww.national.cmop.va.gov/PBM/Clinical%20Guidance/Clinical%20Recommendations/statin-fibrate%20safety%20report-Final.doc> (Accessed 9-30-09)
2. Shepherd J. Fibrates and Statins in the Treatment of Hyperlipidemia: An Appraisal of Their Safety and Efficacy. *Eur Heart J* 1995; 16:5-13.
3. <http://clinicaltrials.gov/ct2/show/NCT00000620> (Accessed 9-30-09)
4. Jacobson TA. Myopathy with statin-fibrate combination therapy: clinical considerations. *Nat Rev Endocrinol*. 2009 Sep; 5 (9):507-18.
5. <http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf> (Accessed 9-30-09)

ACTIONS:

- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe/use/handle this agent (e.g., **primary care providers cardiologists, lipidologists, and endocrinologists**, 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).