

**DEPARTMENT OF VETERANS AFFAIRS VETERAN HEALTH ADMINISTRATION (VHA)  
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM) & MEDICAL ADVISORY PANEL (MAP)  
VA CENTER FOR MEDICATION SAFETY (VAMedSAFE)**

**NATIONAL PBM COMMUNICATION · March 11, 2011**

### **Long-Term Proton Pump Inhibitor (PPI) Use and Risk of Hypomagnesemia**

- The Food and Drug Administration (FDA) has warned that prescription proton pump inhibitors (PPI) may cause hypomagnesemia if taken for prolonged periods of time (e.g., more than one year). This information will be added to the WARNINGS AND PRECAUTIONS sections for all prescription PPIs.
- FDA reviewed 38 reports from the Adverse Event Reporting System (AERS) and 23 cases from the medical literature (8 cases overlapped), but the available data are insufficient to quantify an incidence rate for hypomagnesemia with PPI therapy.
  - Onset of hypomagnesemia occurred after at least 3 months to more than a year of therapy.
  - Serious adverse events included tetany, seizures, tremors, carpo-pedal spasm, atrial fibrillation, supraventricular tachycardia, abnormal QT interval, and concomitant hypocalcemia in light of normal parathyroid hormone levels.
  - About 25% of these cases required discontinuation of PPI treatment in addition to magnesium supplementation.
    - Median time for the magnesium to normalize was one week after PPI discontinuation.
    - Median time to develop hypomagnesemia again after rechallenge with PPI was two weeks.
    - Most patients did not continue on PPIs after treatment of hypomagnesemia.
- The mechanism for hypomagnesemia with long term PPI use remains unclear, but could be related to altered intestinal absorption of magnesium.
- Treatment of hypomagnesemia may necessitate magnesium supplementation as well as discontinuation of the PPI.
- Little risk of hypomagnesemia exists when over-the-counter (OTC) PPIs are used due to lower dose and shorter course of treatment than prescription PPIs. However, unapproved use of OTC PPIs for longer than directed in OTC labelling can increase the risk of hypomagnesemia, especially when the patient has additional risk factors, which include:
  - Concomitant use of magnesium-depleting agents, such as chronic diuretic therapy, aminoglycosides, amphotericin B, foscarnet, pentamidine, cis-platinum, and cyclosporine;
  - Acute and chronic alcoholism;
  - Malnutrition and/or dietary magnesium deficiency;
  - Disturbances in the intestinal tract or kidney.
- FDA recommends that healthcare professionals:
  - *Consider obtaining serum magnesium levels prior to initiation of prescription PPI treatment and checking levels periodically thereafter for patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics).*
  - *Hypomagnesemia occurs with both loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) and thiazide diuretics (chlorothiazide, hydrochlorothiazide, indapamide, and metolazone). These agents can cause hypomagnesemia when used as a single agent or when combined with other anti-hypertensives (e.g., beta-blockers, angiotensin receptor blockers and/or ACE inhibitors).*
  - *Advise patients to seek immediate care from a healthcare professional if they experience arrhythmias, tetany, tremors, or seizures while taking PPIs. These may be signs of hypomagnesemia.*
  - *Consider PPIs as a possible cause of hypomagnesemia, particularly in patients who are clinically symptomatic.*
  - *Recognize that patients who develop hypomagnesemia may require PPI discontinuation in addition to magnesium replacement.*
  - *Be aware that consumers either on their own, or based on a healthcare professional's recommendation, may take OTC PPIs for periods of time that exceed the directions on the OTC label. This is considered an off-label (unapproved) use. Healthcare professionals should communicate the risk of hypomagnesemia to patients if they are recommending prolonged use of an OTC PPI.*
- Providers should consider whether patients require PPIs for prolonged periods and/or whether patients can utilize alternate therapies such as H2Blockers.
- Providers should continue to report any adverse events with PPIs by entering the information into CPRS' Allergies/Adverse Reactions field and/or via local reporting mechanisms. Facilities should continue to report adverse events into VA ADERS and to the FDA (as appropriate).

#### **REFERENCES**

FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs). <http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm>.  
(Accessed March 3, 2011)

#### **ACTIONS**

- **Facility Director (or physician designee):** Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe these medications (e.g., **primary care providers as well as medical, surgical and rehabilitation specialists, and gastroenterologists**, 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).