

NATIONAL PBM COMMUNICATION · January 27, 2011

Dronedaronone (Multaq®) and Liver Injury

- In January 2011, FDA received case reports of liver injury and failure in patients treated with dronedarone. (For previous National PBM Communication on adverse cardiac events associated with dronedarone use, see: http://www.pbm.va.gov/vamedsafe/DRONEDARONE_ISMP%20SAFETY%20ALERT_NATIONAL%20PBM%20COMMUNICATION_111510_FINAL.PDF).
- Two post-marketing reports of acute hepatic failure requiring transplantation have been documented:
 - Both patients were female.
 - Both patients were approximately 70 years of age.
 - Acute hepatic failure occurred between 4-6 months after starting dronedarone in patients whose hepatic serum enzymes were previously within normal limits.
 - Symptoms included: jaundice, coagulopathy, transaminitis and hyperbilirubinemia, which progressed to hepatic encephalopathy in case 1; weakness, abdominal pain, coagulopathy, transaminitis and hyperbilirubinemia in case 2.
 - No alternative etiology of liver failure appeared in their transplant work-ups.
 - Both explanted livers revealed extensive hepatocellular necrosis.
- Dronedaronone (Multaq®) is approved to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent history of AF/AFL and associated cardiovascular risk factors (age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥ 50 mm or left ventricular ejection fraction <40%) who are in sinus rhythm or who will be cardioverted.
- The Warnings and Precautions and Adverse Reactions sections of the product labeling for dronedaronone are currently being revised to include information on the risk for potential liver injury.
- VA National Dronedaronone Criteria for Use (pending addition of updated safety information) are available at: [VA National Dronedaronone Criteria for Use](#).
- The PBM-MAP recommends that providers discuss the following with patients on dronedaronone (during a clinic visit, or at the time of initial prescribing, or upon renewal):
 - Educate patients on the signs and symptoms of hepatic injury or toxicity such as, anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching.
 - Advise patients to contact a healthcare professional immediately if they experience the above signs and symptoms of hepatic injury or toxicity while taking dronedaronone.
- In addition, FDA recommends healthcare practitioners to:
 - *Consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment. However, it is not known whether routine periodic monitoring of serum liver enzymes (ALT, AST, and alkaline phosphatase) and bilirubin in patients taking dronedaronone will prevent the development of severe liver injury.*
 - *If hepatic injury is suspected, dronedaronone should be promptly discontinued and testing of serum liver enzymes and bilirubin should be performed. If hepatic injury is found, appropriate treatment should be initiated.*
 - *Dronedaronone should not be restarted in patients who experience hepatic injury without another explanation for the observed liver injury.*
- Providers should continue to report any adverse events with dronedaronone 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

1. FDA Drug Safety Communication: Severe liver injury associated with the use of dronedaronone (marketed as Multaq). <http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm>. (Accessed January 21, 2011)
2. National PBM Communication: ISMP Medication Safety Alert: Dronedaronone (Multaq®) Adverse Event Signal. http://www.pbm.va.gov/vamedsafe/DRONEDARONE_ISMP%20SAFETY%20ALERT_NATIONAL%20PBM%20COMMUNICATION_111510_FINAL.PDF. (Accessed January 21, 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, cardiologists, and clinic staff, 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).