

NATIONAL PBM COMMUNICATION · July 28, 2011

Dronedaronone (Multaq®) and Increased Risk of Death and Serious Cardiovascular Events in Patients with Permanent Atrial Fibrillation

- On July 7, 2011, the manufacturer of dronedarone announced the discontinuation of their Phase IIIb study PALLAS (Permanent Atrial fibrillation outcome Study using Dronedaronone on top of standard therapy), designed to evaluate the efficacy of dronedarone in patients \geq 65 years of age with permanent atrial fibrillation (defined as atrial fibrillation/atrial flutter for 6 months prior to randomization without plans to restore sinus rhythm), due to a significant increase in cardiovascular (CV) events in the dronedarone treatment group compared to placebo. The two co-primary endpoints of the trial were: major CV events (stroke, systemic arterial embolism, myocardial infarction [MI] or CV death); unplanned CV hospitalization or death from any cause.
- Results from the preliminary analysis of the PALLAS trial were reported in the July 21, 2011 FDA Drug Safety Communication. Compared to placebo (N=1577), treatment with dronedarone (N=1572):
 - increased the risk for CV death, MI, stroke, systemic embolism: 32 (2%) vs. 14 (0.9%); HR 2.3; P=0.009;
 - increased the risk for death, unplanned CV hospitalization: 118 (7.5%) vs. 81 (5.1%); HR 1.5; P=0.006;
 - increased the risk for stroke: 17 (1.1%) vs. 7 (0.4%); HR 2.4; P=0.047;
 - increased the risk for heart failure hospitalization: 34 (2.2%) vs. 15 (1%); HR 2.3; P=0.008.

Although not statistically significant, there was more than a doubling of the risk for death with dronedarone compared to placebo: 16 (1%) vs. 7 (0.4%), respectively; HR 2.3; P=0.065. There was no significant difference in rate of MI between treatment groups.

- Dronedaronone (Multaq) is approved to reduce the risk of CV hospitalization in patients with paroxysmal or persistent atrial fibrillation or atrial flutter, with a recent history of atrial fibrillation/atrial flutter and associated CV risk factors (age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter \geq 50 mm or left ventricular ejection fraction <40%) who are in sinus rhythm or who will be cardioverted.
- VA National Dronedaronone Criteria for Use are available at: [Dronedaronone, Criteria for Use](#).
- **FDA recommends that dronedaronone not be prescribed in patients with permanent atrial fibrillation.**
 - FDA is evaluating the preliminary data from the PALLAS trial to determine whether the data relates to patients receiving dronedaronone for the current FDA indication for use in paroxysmal or persistent atrial fibrillation.
 - FDA recommends that patients should not discontinue dronedaronone without talking with their healthcare provider, and that patients should discuss whether dronedaronone should be continued for the management of paroxysmal or persistent atrial fibrillation (VA Patient Letter available at [Dronedaronone, Patient Letter](#); may be modified as appropriate per VA facility).
- As there is the potential for overlap in treating patients with dronedaronone for the FDA indication of persistent atrial fibrillation (i.e., recurring episodes lasting more than 7 days) and permanent atrial fibrillation (i.e., an ongoing long-term episode where cardioversion has failed or has not been attempted), providers should confirm (e.g., either by chart review or at the patient's next clinic visit), that their patient on dronedaronone has not progressed to permanent atrial fibrillation. If so, and there are no plans to restore sinus rhythm, dronedaronone should be discontinued.
- For previous National PBM Communication on adverse cardiac events associated with dronedaronone use, see: http://www.pbm.va.gov/vamedsafe/DRONEDARONE_ISMP%20SAFETY%20ALERT_NATIONAL%20PBM%20COMMUNICATION_111510_FINAL.PDF.
- Providers should continue to report any adverse reactions with the use of dronedaronone by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA 0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

REFERENCES

1. FDA Drug Safety Communication: Multaq (dronedaronone) and increased risk of death and serious cardiovascular events. <http://www.fda.gov/Drugs/DrugSafety/ucm264059.htm#sa>. (Accessed July 21, 2011)
2. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). <http://circ.ahajournals.org/content/114/7/e257.full>.

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., cardiologists, primary care providers 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).