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UPDATE: Dronedarone (MULTAQ) and Increased Risk of Death and Serious Cardiovascular Events in Patients with Permanent Atrial Fibrillation

- Dronedarone (MULTAQ) received approval from the Food and Drug Administration (FDA) in July 2009, and is currently indicated to reduce the risk of hospitalization for atrial fibrillation (AF) in patients in normal sinus rhythm with a history of paroxysmal or persistent AF.
- A completed review by the FDA finds that:
  - Dronedarone (MULTAQ) increases the risk of serious cardiovascular (CV) events, including death, when used by patients in permanent AF. New boxed warning as per product information appears below:

WARNING:
INCREASED RISK OF DEATH, STROKE AND HEART FAILURE IN PATIENTS WITH DECOMPENSATED HEART FAILURE OR PERMANENT ATRIAL FIBRILLATION

MULTAQ is contraindicated in patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure. MULTAQ doubles the risk of death in these patients (4, 5.1, 14.3).

MULTAQ is contraindicated in patients in atrial fibrillation (AF) who will not or cannot be cardioverted into normal sinus rhythm. In patients with permanent AF, MULTAQ doubles the risk of death, stroke, and hospitalization for heart failure. (4, 5.2,14.4)

  - Dronedarone provides a benefit for patients with non-permanent AF (i.e., paroxysmal AF: AF that terminates spontaneously within 7 days; or persistent AF: recurring episodes of AF lasting more than 7 days).
- The review evaluated data from two clinical trials:
  - The PALLAS trial (Permanent Atrial FibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy)
    - The manufacturer of dronedarone (MULTAQ) discontinued this Phase IIIb study in July 2011 due to a significant increase in CV events in the dronedarone treatment group compared to placebo:

	Multaq (dronedarone) N 1619 N	Placebo N 1617 N	Hazard Ratio (95 % Confidence Intervals)
Total Deaths	25	13	1.94 (0.99 to 3.79)
Death from arrhythmia or Sudden Death	13	4	3.26 (1.06 to 10.0)
Stroke	23	10	2.32 (1.11 to 4.88)
Hospitalization for Heart Failure	43	24	1.81 (1.10 to 2.99)

  - The ATHENA trial (which supported MULTAQ's approval for treatment of non-permanent AF)
    - FDA re-examined outcomes (arrhythmic death, stroke, and heart failure) in patients with the non-permanent AF indication for use.
    - Findings indicated a reduction in the risk of hospitalizations for patients with non-permanent AF taking dronedarone.

- Revised dronedarone (MULTAQ) product labeling includes the following warnings/recommendations:
  - ***Cardiovascular Death and Heart Failure in Permanent AF***
    MULTAQ doubles the risk of cardiovascular death (largely arrhythmic) and heart failure events in patients with permanent AF. Patients treated with dronedarone should undergo monitoring of cardiac rhythm no less often than every 3 months. Cardiovert patients who are in atrial fibrillation (if clinically indicated) or discontinue MULTAQ. MULTAQ offers no benefit in subjects in permanent AF.
  - ***Increased Risk of Stroke in Permanent AF***
    In a placebo-controlled study in patients with permanent atrial fibrillation, dronedarone was associated with an increased risk of stroke, particularly in the first two weeks of therapy. MULTAQ should only be initiated in patients in sinus rhythm who are receiving appropriate antithrombotic therapy.
  - ***New Onset or Worsening Heart Failure***
    New onset or worsening of heart failure has been reported during treatment with MULTAQ in the postmarketing setting. In a placebo controlled study in patients with permanent AF increased rates of heart failure were observed in patients with normal left ventricular function and no history of symptomatic heart failure, as well as those with a history of heart failure or left ventricular dysfunction. Advise patients to consult a physician if they develop signs or symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath. If heart failure develops or worsens and requires hospitalization, discontinue MULTAQ.
- VA National Dronedarone Criteria for Use are available at: Dronedarone, Criteria for Use (update in progress).
- Providers should continue to report any adverse reactions with the use of dronedarone 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: Review update of Multaq (dronedarone) and increased risk of death and serious cardiovascular events. **http://www.fda.gov/Drugs/DrugSafety/ucm283933.htm.** (Accessed December 19, 2011).
2. MULTAQ (dronedarone) [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; December 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.,* ***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).*