

Dronedarone Criteria for Use January 2012

VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE INCLUSION AND EXCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL LEVEL ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

EXCLUSION CRITERIA (if ONE is checked, patient is not eligible)

- Symptomatic heart failure (HF) with recent decompensation requiring hospitalization or New York Heart Association (NYHA) Class IV HF (Boxed Warning)
- Permanent atrial fibrillation (AF) (patients in whom normal sinus rhythm will not or cannot be restored) (Boxed Warning)
- Second or third degree atrioventricular block, or sick sinus syndrome (except in conjunction with a pacemaker)
- Significant bradycardia (e.g., < 50 bpm)
- Receiving concomitant strong CYP 3A inhibitor (e.g., ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazadone, and ritonavir)
- Uncorrected hypokalemia or hypomagnesemia
- QTc Bazett \geq 500 ms with appropriate correction for prolongation of QRS interval in patients with intraventricular conduction delay and ventricular pacing
- Receiving concomitant medications that may prolong the QT interval and increase the risk of torsade de pointes (e.g., phenothiazine antipsychotics, tricyclic antidepressants, certain oral macrolide antibiotics, Class I and III antiarrhythmic agents)
- Liver toxicity related to the previous use of amiodarone
- Severe hepatic impairment (i.e., Child-Pugh Grade C or baseline liver function tests [LFTs] > 2 X upper limit normal^a)
- Pregnancy (i.e., known pregnancy or positive pregnancy test; Category X)
- Nursing mothers^b

INCLUSION CRITERIA (must fulfill ALL the following to be eligible)

- Initial prescription restricted to VA Cardiology or local designee (monitoring must be documented by a VA provider)
- Symptomatic recurrent paroxysmal or persistent AF documented by electrocardiogram (ECG) within the past 6 months, with a second ECG in sinus rhythm or pending cardioversion
- Intolerance (e.g., unmanageable significant adverse event), contraindication to, or ineffective therapy with at least one other antiarrhythmic agent used for the rhythm management of AF (refer to pharmacologic management considerations for AF in the table below)

Considerations for Pharmacologic Maintenance of Sinus Rhythm in Patients with Recurrent Paroxysmal or Persistent AF^{1,2}				
	No or minimal structural heart disease	Hypertensive heart disease with substantial LVH	CAD	HF⁵
First line therapy³	Flecainide Propafenone Sotalol	Amiodarone	Dofetilide Sotalol	Amiodarone Dofetilide
Second line therapy	Amiodarone Dofetilide Dronedarone ⁴	Dronedarone ⁴	Amiodarone Dronedarone ⁴	

¹Adapted from ACC/AHA/ESC 2006 guidelines for the management of patients with AF. Circulation 2006;114:e257-e354; recommendations from 2011 ACC/AHA/HRS focused updated on the management of patients with AF (Circulation published online December 20, 2010 DOI: 10.1161/CIR.0b013e3181fa3c4) also taken into consideration

²Recommendations are not intended for switching patients who are stable on current therapy

³One or more of the agents listed should be considered prior to considering second line therapy; treatment selections listed alphabetically, not in order of preference

⁴Dronedarone is Nonformulary in the VA; medications on the VA National Formulary should be considered prior to treatment with Nonformulary agents. Dronedarone may be considered prior to amiodarone in a younger (e.g., < 60 years of age) patient on a case by case basis, subject to local adjudication

⁵Dronedarone is contraindicated in patients with symptomatic HF with recent decompensation requiring hospitalization or NYHA Class IV HF (Boxed Warning); the safety of dronedarone in patients with AF and left ventricular ejection fraction (LVEF) \leq 35% is unknown: inclusion criteria for ANDROMEDA (NEJM 2008) approximated LVEF \leq 35%, and found an increase in mortality with dronedarone vs. placebo; only ~ 12% patients included in ATHENA (NEJM 2009) had LVEF < 45% with subgroup evaluation in patients with LVEF < 35% (~4% of patients enrolled) that did not find a difference between dronedarone and placebo in the primary endpoint of first hospitalization due to CV events or death; in patients with permanent AF in PALLAS (NEJM 2011), increased rates of HF were reported in patients with a history of HF or left ventricular dysfunction, as well as patients without symptomatic HF and normal left ventricular function. As the LVEF may fluctuate in patients with AF (i.e., LVEF may fall into the range that puts a patient at high risk), this should be taken into account when considering treatment with dronedarone

For women of childbearing potential,

- Pregnancy must be excluded prior to receiving dronedarone and patient provided contraceptive counseling on potential risk vs. benefit of taking

dronedaronone if patient were to become pregnant

- Use of an effective method of contraception during dronedaronone therapy

DOSING RECOMMENDATIONS

- The recommended dose of dronedaronone is 400 mg administered twice daily with the morning and evening meals

MONITORING

- Adequate symptom control (e.g., frequency or duration of palpitations/irregular heartbeat, time to recurrence)
- Signs or symptoms of new or worsening HF; risk for serious adverse events unclear in patients who may experience transient decreases in ejection fraction
- Cardiac rhythm (by ECG) at least once every 3 months for evaluation of permanent AF; if the patient is in AF, either discontinue dronedaronone or, if clinically indicated, the patient should be cardioverted
- ECG for QT prolongation (dronedaronone should not be used if QTc Bazett \geq 500 ms)
- ECG for normal sinus rhythm; dronedaronone should not be used for treatment of long standing (> 6 months duration) atrial fibrillation without proven successful cardioversion; if patient remains in atrial fibrillation while on dronedaronone, they should be referred back to and/or provider should consult with Cardiologist
- Heart rate for bradycardia (it is recommended that dronedaronone be discontinued if significant bradycardia; e.g., < 50 bpm)
- Serum electrolytes for hypokalemia or hypomagnesemia, if receiving potassium depleting diuretics
- Serum creatinine for potential increase of 0.1 mg/dl (reported to plateau 7days after initiation; without an effect on GFR)
- Baseline liver function tests with periodic follow-up, especially during the first 6 months of treatment. If liver injury is suspected, dronedaronone should be discontinued with follow-up of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and serum bilirubin; if liver injury is confirmed, the patient should be appropriately managed and evaluated to determine the cause. Dronedaronone should not be reinitiated if another cause for the liver injury is not identified
- Dronedaronone should be used with caution in patients with moderate hepatic impairment (i.e., Child-Pugh Class B) due to an increase in dronedaronone exposure, with wide variability in drug exposure that may increase the risk for adverse events. These patients should be monitored closely for an increase in baseline values of liver enzymes (AST and/or ALT) of more than 0.5 X upper limit normal and to a value > 2 X upper limit normal^{a,c}
- Signs or symptoms related to hepatotoxicity (e.g., anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching); if these occur while taking dronedaronone, patients should be informed to contact a healthcare provider immediately
- Drug Interactions
 - *Warfarin*: monitor INR after initiation of dronedaronone in patients currently being treated with warfarin. Compared to placebo in the ATHENA trial, more patients treated with dronedaronone had an increase in their INR (\geq 5), which usually occurred within 1 week after the start of therapy in patients receiving oral anticoagulants. There was no increase in the risk of bleeding reported in the dronedaronone treatment group. In addition, there have been VA ADERS and postmarketing reports of a probable drug interaction with elevated INRs and bleeding
 - *CYP 3A inhibitors or inducers*: in addition to being contraindicated in patients receiving concomitant strong CYP 3A inhibitors (refer to exclusion criteria), it is recommended that dronedaronone not be administered with moderate CYP 3A inhibitors (e.g., diltiazem, verapamil, grapefruit juice) or CYP 3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort)
 - *Substrates of CYP 3A, 2D6, or P-glycoprotein (P-gP)*: dronedaronone may inhibit P-gP, and is also a moderate inhibitor of CYP 3A and CYP 2D6 and can therefore interact with substrates of these enzyme systems including some statins (it is recommended that the labeling recommendations be followed according to the respective statin for use with CYP 3A and P-gP inhibitors), sirolimus, tacrolimus and other medications metabolized by CYP 3A; beta-blockers, tricyclic antidepressants, SSRIs metabolized by CYP 2D6. Prior to initiating dronedaronone in patients treated with digoxin (P-gP substrate), reconsider use of digoxin. If dronedaronone is to be used in combination with digoxin, it is recommended that the dose of digoxin be halved; monitor digoxin levels closely and evaluate for toxicity. Use of dronedaronone with dabigatran (P-gP substrate) increases dabigatran exposure; caution is advised as concomitant therapy may increase the risk of bleeding. Based on pharmacokinetic estimates, a reduced dose of dabigatran (75 mg twice daily) is suggested by the manufacturer of dabigatran in patients with moderate kidney impairment (CrCl 30 to 50 ml/min) AND on concomitant dronedaronone; however, in the absence of clinical data evaluating the safety and efficacy of a reduced dose of dabigatran in these patients, VA PBM recommends generally avoiding the interaction by use of alternative treatment strategies (e.g., use of an alternative to dronedaronone, or dabigatran). Use of dronedaronone and dabigatran in patients with severe kidney impairment is not recommended

ISSUES FOR CONSIDERATION

- **FDA Approved Indication:** Dronedaronone is an antiarrhythmic agent approved by the FDA to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation
- The product information for dronedaronone recommends that patients be on appropriate antithrombotic therapy prior to and throughout therapy with dronedaronone. This recommendation is based on results from the PALLAS trial in patients with permanent AF (not recommended use for dronedaronone) where there was an increase in the risk for stroke in patients in the dronedaronone treatment group compared to placebo; most of these patients receiving dronedaronone did not have an INR within the therapeutic range of 2.0 to 3.0
- Consider discontinuation of dronedaronone if the patient does not experience adequate symptom control (e.g., no or inadequate change in frequency or duration of palpitations/irregular heartbeat; no or inadequate increase in time to recurrence AF/AFL). Dronedaronone should be discontinued in patients who develop permanent AF, unless cardioversion is planned. If cardioversion fails or is not planned, then dronedaronone should be discontinued
- **VA MEDSAFE:** Due to potential safety concerns for new onset or worsening HF in certain patient populations, unknown long-term pulmonary toxicity, post-marketing reports of acute hepatic failure requiring transplantation, and an increased risk of death in patients with severe HF or permanent AF, VA MedSAFE has implemented an ongoing analysis of patients treated with dronedaronone to monitor for these safety signals

^a Dronedaronone has not been studied in patients with baseline LFTs > 2 X upper limit normal

^b It is unknown if dronedaronone is excreted in human milk; due to the number of medications that are excreted in human milk and the potential for serious adverse reactions that may occur if a nursing infant is exposed to the drug, the risk vs. benefit of whether the mother should discontinue nursing or to begin dronedaronone should be discussed

^c e.g., patient with baseline ALT 30 IU/L that increases to 85 IU/L with treatment, would be considered to have a hepatic related adverse event potentially related to dronedaronone due to an increase from baseline of > 0.5 X upper limit normal AND a level of > 2 X upper limit normal