

Dronedarone Criteria for Use August 2016

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 <https://vawww.cmopnational.va.gov/cmop/PBM/default.asp> 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, 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 or lung 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)
- Hypersensitivity to dronedarone or any inactive ingredients
- 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 Rhythm Control in Patients with Paroxysmal or Persistent Atrial Fibrillation^a

<u>No Structural Heart Disease</u>	<u>Coronary Artery Disease</u>	<u>Heart Failure^g</u>
Amiodarone^b Dofetilide^{c,d} Flecainide^{c,e} Propafenone^{c,e} Sotalol^{c,d} <i>Dronedarone^f</i>	Amiodarone^b Dofetilide^{c,d} Sotalol^{c,d} <i>Dronedarone^f</i>	Amiodarone^b Dofetilide^{c,d}

VA National Formulary agents (bolded) listed in alphabetical order (not by treatment preference), non-formulary agent (italicized) listed last.

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

^a Adapted, in part, from 2014 AHA/ACC/HRS Guideline for the management of patients with Atrial Fibrillation (JACC 2014)

^b Consider risk vs. benefit; individualize therapy

^c Not recommended in patients with severe left ventricular hypertrophy (wall thickness > 1.5 cm)

^d Use with caution in patients at risk for torsades de pointes

^e Should be combined with atrioventricular nodal blocking agents

^f Dronedarone is Nonformulary in 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

^g Dronedarone 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

May 2010; March 2011; August 2011; October 2011; January 2012; October 2012; Update August 2016

Updated versions may be found at www.pbm.va.gov or <https://vawww.cmopnational.va.gov/cmop/PBM/default.asp>

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 dronedarone if patient were to become pregnant
- Use of an effective method of contraception during dronedarone therapy

DOSING RECOMMENDATIONS

- The recommended dose of dronedarone 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 dronedarone or, if clinically indicated, the patient should be cardioverted
- ECG for QT prolongation (dronedarone should not be used if QTc Bazett \geq 500 ms)
- ECG for normal sinus rhythm; dronedarone 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 dronedarone, they should be referred back to and/or provider should consult with Cardiology
- Heart rate for bradycardia (it is recommended that dronedarone be discontinued if significant bradycardia; e.g., < 50 bpm)
- Serum electrolytes for hypokalemia or hypomagnesemia, if receiving potassium depleting diuretics; maintain potassium and magnesium levels within normal range
- Serum creatinine for potential increase (approximately 0.1 mg/dl, reported to plateau 7 days after initiation; without an effect on GFR); post-marketing reports of larger increases in serum creatinine, some with increases in blood urea nitrogen, have also been reported, and were reported to be reversible upon discontinuation in most cases. Marked increases in serum creatinine, pre-renal azotemia and acute renal failure have also been reported (seen in patients with heart failure or hypovolemia)
- Baseline liver function tests with periodic follow-up, especially during the first 6 months of treatment. If liver injury is suspected, dronedarone 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. Dronedarone should not be reinitiated if another cause for the liver injury is not identified
- Dronedarone should be used with caution in patients with moderate hepatic impairment (i.e., Child-Pugh Class B) due to an increase in dronedarone 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 dronedarone, patients should be informed to contact a healthcare provider immediately
- Pulmonary toxicity with reports of interstitial lung disease including pneumonitis and pulmonary fibrosis has been reported during post-marketing surveillance. Patients with onset of dyspnea or non-productive cough should be evaluated for potential pulmonary toxicity; if confirmed, dronedarone should be discontinued
- Drug Interactions
 - *Warfarin*: monitor INR after initiation of dronedarone in patients currently being treated with warfarin. Compared to placebo in the ATHENA trial, more patients treated with dronedarone 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 dronedarone treatment group. In addition, there have been VA ADERS and post-marketing 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 dronedarone not be administered with grapefruit juice (moderate CYP 3A inhibitor) or CYP 3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort). Use of dronedarone with diltiazem or verapamil (moderate CYP 3A inhibitors) may enhance the drug's effects on cardiac conduction and increase drug levels; it is recommended to use the lowest doses of diltiazem or verapamil and increase only after ECG confirmation that the patient is tolerating the combination of either of these agents with dronedarone
 - *Substrates of CYP 3A, 2D6, or P-glycoprotein (P-gP)*: dronedarone 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 (due to increased exposure of simvastatin with dronedarone, avoid doses greater than 10 mg simvastatin; 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 (may also increase risk for bradycardia due to pharmacodynamics interaction; initiate low dose beta-blocker and increase only after ECG confirmation that the patient is tolerating the combination), tricyclic antidepressants, SSRIs metabolized by CYP 2D6. Prior to initiating dronedarone in patients treated with digoxin (P-gP substrate), the manufacturer recommends to consider discontinuing digoxin. If dronedarone 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. In addition, it was noted that in two clinical trials (ANDROMEDA in patients with recently decompensated HF; PALLAS in patients with permanent AF), patients receiving baseline digoxin therapy experienced a higher rate of death due to arrhythmias in the dronedarone treatment groups compared to placebo; without a difference in deaths due to arrhythmias between treatment groups in those patients not on digoxin. Use of dronedarone 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 dronedarone; 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 dronedarone, or dabigatran). Use of dronedarone and dabigatran in patients with severe kidney impairment is not recommended

ISSUES FOR CONSIDERATION

- **FDA Approved Indication:** Dronedarone 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

May 2010; March 2011; August 2011; October 2011; January 2012; October 2012; Update August 2016

Updated versions may be found at www.pbm.va.gov or <https://vaww.cmopnational.va.gov/cmop/PBM/default.asp>

- The product information for dronedarone recommends that patients be on appropriate antithrombotic therapy prior to and throughout therapy with dronedarone. This recommendation is based on results from the PALLAS trial in patients with permanent AF (not recommended use for dronedarone) where there was an increase in the risk for stroke in patients in the dronedarone treatment group compared to placebo; most of these patients receiving dronedarone did not have an INR within the therapeutic range of 2.0 to 3.0
- Consider discontinuation of dronedarone 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). Dronedarone should be discontinued in patients who develop permanent AF, unless cardioversion is planned. If cardioversion fails or is not planned, then dronedarone should be discontinued

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

^b It is unknown if dronedarone 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 dronedarone 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 dronedarone due to an increase from baseline of > 0.5 X upper limit normal AND a level of > 2 X upper limit normal