National Drug Monograph
Dronedarone (Multaq®)
January 2010

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

The purpose of VA National PBM-MAP/VPE drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

Indications: Dronedarone (Multaq®) is an antiarrhythmic agent approved by the FDA to reduce the risk of cardiovascular (CV) hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated CV risk factors (i.e., age > 70 years, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter $\geq$ 50mm or left ventricular ejection fraction < 40%), who are in sinus rhythm or who will be cardioverted.
Efficacy: The effect of dronedarone on hospitalization for CV events or death in 4628 patients with AF was compared to placebo in a pivotal clinical trial (ATHENA) with mean follow-up of 21months. Treatment with dronedarone reduced the primary endpoint of composite first hospitalization for CV events or death compared to placebo (HR 0.76; 95% CI 0.69 to 0.84; P < 0.001). There was no significant difference in the secondary endpoint of all-cause mortality. According to combined data of 1237 patients with a history of AF, treatment with dronedarone increased the median time to first recurrence AF/AFL by 63 days, and reduced the rate of AF recurrence rate by 25% at 12 months compared to placebo. A reduction in the time to AF recurrence was also demonstrated in patients with persistent AF. According to unpublished data (DIONYSIS), the composite AF recurrence or premature drug discontinuation due to intolerance or inefficacy at 12 months occurred in 75.1% of patients treated with dronedarone and 58.8% of patients on amiodarone (HR 1.589; 95% CI 1.275 to 1.98; P<0.0001), with AF recurrence occurring in 42% of patients treated with amiodarone compared to 63.5% on dronedarone.
Safety: The most frequently occurring adverse events reported with dronedarone include diarrhea, nausea, abdominal pain, vomiting, and asthenia. Discontinuations due to adverse events were reported in 11.8% of patients treated with dronedarone compared to 7.7% of patients on placebo. In the pivotal clinical trial with dronedarone, there was no statistically significant difference in serious adverse events (e.g., cardiac, respiratory, gastrointestinal, endocrine, neurologic, skin-related, or increase sCr) with dronedarone compared to placebo. There was one reported case of torsades de pointes in a patient receiving dronedarone. Treatment with dronedarone was prematurely discontinued in one clinical trial in patients with moderate to severe HF and severe left ventricular systolic dysfunction, due to a doubling in the risk of all-cause mortality in patients treated with dronedarone compared to placebo. Dronedarone therefore includes a boxed warning that it is contraindicated in patients with New York Heart Association (NYHA) Class IV heart failure (HF) or NYHA Class II-III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic. Other contraindications include second or third degree atrioventricular block or sick sinus syndrome (except in conjunction with a pacemaker), bradycardia, concomitant strong CYP 3A inhibitors, concomitant use of medications or herbal products that prolong the QT interval and might increase the risk of torsades de pointes, hypokalemia or hypomagnesemia, QT prolongation, severe hepatic impairment, pregnancy, and nursing mothers.
Dose: The recommended dose for dronedarone is one 400 mg tablet twice daily with the morning and evening meals. Treatment with class I or III antiarrhythmic agents or medications that are strong CYP 3A inhibitors must be discontinued before treatment with dronedarone is initiated.
Conclusions: In the pivotal trial (ATHENA), treatment with dronedarone reduced first hospitalization for CV events or death compared to placebo in patients with paroxysmal or persistent AF/AFL. Patients with severe decompensated HF were not included in this trial as there was an increase in mortality with dronedarone compared to placebo in patients with moderate to severe HF and recent decompensation in a trial of patients without AF/AFL. Therefore, dronedarone is contraindicated in patients with NYHA class IV HF or NYHA class II-III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic. When compared to placebo, dronedarone reduced the time to recurrence of AF; results from one unpublished clinical head to head trial of dronedarone versus amiodarone showed that dronedarone was not as effective as amiodarone. Dronedarone is a derivative of amiodarone, exhibiting similar pharmacologic effects, and was designed to reduce the potential thyroid and pulmonary adverse effects with amiodarone. In the pivotal trial, there was no significant difference in the reporting of pulmonary or thyroid effects compared to placebo; although, the authors note that the trial may not have been long enough to conclude that dronedarone has a safer side effect profile (especially pulmonary) compared to amiodarone. Published head to head trials are needed to determine the efficacy and safety of dronedarone in comparison to other available antiarrhythmic agents used in the management of patients with AF/AFL.

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Introduction[1-11]

Dronedarone (Multaq®, Sanofi Aventis) is an antiarrhythmic agent approved by the FDA July 1, 2009 to reduce the risk of cardiovascular (CV) hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated CV risk factors (i.e., age > 70 years, hypertension [HTN], diabetes [DM], prior cerebrovascular accident [CVA], left atrial diameter ≥ 50mm or left ventricular ejection fraction [LVEF] < 40%), who are in sinus rhythm or who will be cardioverted.[1,2]

Atrial fibrillation can be managed by rate or rhythm control. Rate control of atrial fibrillation is often used in patients who are older and have minimal or no symptoms related to AF.[3] In general, trials comparing rhythm to rate control did not find a difference in total or CV death, or thromboembolic events,[3-9] with conflicting results on symptom improvement and quality of life;[10,11] although, there was an increase in hospitalizations[4,7] and medication related adverse events[8] in the rhythm control group. Patients with highly symptomatic paroxysmal or persistent AF may be considered for cardioversion and maintenance of sinus rhythm (i.e., rhythm control). The 2006 ACC/AHA/ESC (American College of Cardiology/American Heart Association/European Society of Cardiology) guideline recommendations for maintenance of sinus rhythm include stratification by concomitant cardiac conditions.[3]

<table>
<tr><th colspan="7">Recommendations for Maintenance of Sinus Rhythm in Patients with Recurrent Paroxysmal or Persistent AF</th></tr>
<tr><th colspan="2">No or minimal heart disease</th><th colspan="3">HTN</th><th colspan="2">CAD</th><th>HF</th></tr>
<tr><td colspan="2" rowspan="2">Flecainide
Propafenone
Sotalol</td><td colspan="3">Substantial LVH</td><td colspan="2" rowspan="2">Dofetilide
Sotalol</td><td rowspan="2">Amiodarone
Dofetilide</td></tr>
<tr><td colspan="2"><u>No</u>
Flecainide
Propafenone
Sotalol</td><td><u>Yes</u>
Amiodarone</td></tr>
<tr><td>Amiodarone
Dofetilide</td><td>Catheter ablation</td><td>Amiodarone
Dofetilide</td><td>Catheter ablation</td><td>Catheter ablation</td><td>Amiodarone</td><td>Catheter ablation</td><td>Catheter ablation</td></tr>
</table>

Dronedarone is similar in mechanism of action to amiodarone, with the potential for less severe adverse effects, and was studied to determine the long-term outcome of this medication in treating patients with AF.[1,2]

Pharmacology/Pharmacokinetics/Pharmacodynamics[1-2]

Dronedarone is a benzofuran derivative of amiodarone. The development of dronedarone was accomplished by altering the chemical structure of amiodarone, removing the iodine groups and adding a methane sulfonyl group (to reduce lipophilicity and tissue accumulation of the drug), to minimize the potential for adverse effects; specifically, those related to thyroid dysfunction and pulmonary disease.[2]

Like amiodarone, dronedarone acts primarily at the potassium ion channels and is therefore considered a Type III antiarrhythmic agent according to the Vaughan Williams classification. One of the main effects of dronedarone is to prolong the cardiac action potential in both the atria and ventricles. Similar to amiodarone, dronedarone also has properties belonging to the Vaughan Williams Types I-IV. Dronedarone may also exhibit some rate control properties as a result of prolongation of the AV node refractory period; however, the effect on rate is not as pronounced as with amiodarone.[2]

Vaughan Williams Classification of Antiarrhythmic Agents[3]		
Type	**Medications**	**General Actions**
Ia	Disopyramide Procainamide Quinidine	Lengthens action potential Decreases conduction velocity
Ib	Lidocaine Mexiletine	Shortens action potential
Ic	Flecainide Propafenone[a]	No effect on action potential Decreases conduction velocity
II	Beta-blockers	Decreases AV node conduction
III	Amiodarone[a,b] Dofetilide Dronedarone[a,b] Ibutilide Sotalol[a]	Prolongs action potential and refractory period Normal conduction velocity
IV	Diltiazem Verapamil	Shortens action potential Decreases AV node conduction

[a]Also exhibits beta-blocker properties
[b]Exhibits activity in Types I-IV

Dronedarone is extensively metabolized, primarily by CYP 3A. It undergoes first pass metabolism, with an absolute bioavailability (without food) of 4%; 15% when administered with a high fat meal. In the fed state, peak plasma concentrations are achieved within 3 to 6 hours; with steady state at 4 to 8 days after chronic administration. The elimination half-life of dronedarone is 13 to 19 hours.[1,2] In comparison, the terminal elimination half-life after chronic dosing of amiodarone is 40 to 55 days (major metabolite 57 to 61 days).[12] When studied in patients with moderate hepatic impairment, the mean dronedarone exposure increased 1.3 times compared to patients with normal hepatic function; the pharmacokinetics of dronedarone were not evaluated in patients with severe hepatic dysfunction and is contraindicated in this patient population.

FDA Approved Indication(s) and Off-Label Uses[1,2]

Dronedarone is approved by the FDA to reduce the risk of CV hospitalization in patients with paroxysmal or persistent AF/AFL, with a recent episode of AF/AFL and associated CV risk factors (i.e., age > 70 years, HTN, DM, prior CVA, left atrial diameter $\geq$ 50mm or LVEF < 40%), who are in sinus rhythm or who will be cardioverted.[1] The efficacy and safety of dronedarone in patients with ventricular arrhythmias has not been studied.

Current VA National Formulary Alternatives[3,4]

Other oral Type III antiarrhythmic agents used for maintenance of sinus rhythm in AF/AFL and listed on the VA National Formulary include amiodarone and sotalol. Dofetilide is a Type III antiarrhythmic agent available on a non-formulary basis. Flecainide and propafenone (immediate release) are Type Ic antiarrhythmic agents listed on the VANF that are also used for preventing the recurrence of AF/AFL.

Dosage and Administration[1,2]

The only recommended dose of dronedarone is 400 mg administered twice daily. Higher doses were not found to be more effective and were not as well-tolerated. Dronedarone tablets should be administered with the morning and evening meals. No dosage adjustment is necessary in patients with kidney impairment; dronedarone is contraindicated in patients with severe hepatic impairment. There are no requirements for inpatient initiation of therapy. Treatment with class I or III antiarrhythmic agents or medications that are strong CYP 3A inhibitors must be discontinued before treatment with dronedarone is initiated.

Efficacy Measures (Pivotal Clinical Trial)[13]

Primary Endpoints
- First hospitalization due to CV events or death

Secondary Endpoints
- All-cause mortality
- Death from CV causes
- Hospitalization due to CV events

Clinical Trial Data

A literature search was performed on PubMed/Medline using the search term dronedarone through 9 Oct 2009. The search was limited to clinical trials performed in adult humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All controlled trials published in peer-reviewed journals evaluating treatment with dronedarone in other than healthy subjects were included.

CV Events in Atrial Fibrillation

ATHENA[13]

The effect of dronedarone 400 mg twice daily on hospitalization for CV events or death in 4628 patients with AF were compared to placebo in ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter). The mean follow-up was 21months. Treatment with dronedarone reduced the primary endpoint of composite first hospitalization for CV events or death compared to the placebo group (HR 0.76; 95% CI 0.69 to 0.84; P < 0.001) which was driven by the secondary endpoint of CV hospitalizations. There was no significant difference in the secondary endpoint of all-cause mortality. Results of the clinical trial outcomes are provided in the table below; refer to Appendix A for additional trial details and results.[13]
Trial summary: Treatment with dronedarone reduced first hospitalization for CV events or death by 24% compared to placebo in patients with paroxysmal or persistent AF/AFL.

Outcomes	Dronedarone (n=2301)	Placebo (n=2327)	HR (95% CI)	P value	NNT
Composite first hospitalization for CV event or death*	734 (31.9%)	917 (39.4%)	0.76 (CI 0.69-0.84)	<0.001	13
All-cause mortality	116 (5.0)%	139 (6.0%)	0.84 (CI 0.66-1.08)	0.18	
First hospitalization due to CV event	675 (29.3)%	859 (36.9%)	0.74 (CI 0.67-0.82)	<0.001	

* Primary endpoint

Maintenance of Sinus Rhythm

EURIDIS and ADONIS[14]

The efficacy of dronedarone 400 mg twice daily on the primary endpoint of time to first recurrence of AF/AFL was compared to placebo in two randomized, multicenter trials of patients with a history of AF (at least one episode of AF within the past 3 months and in sinus rhythm for at least 1 hour prior to randomization). Patients with NYHA Class III or IV HF were excluded from the trial. Mean LVEF at baseline was 59%. The results of the two trials (ADONIS: 625 patients enrolled in the U.S., Canada, Australia, South Africa, and Australia; EURIDIS: 612 patients enrolled in 12 countries in Europe) are presented separately and combined in the table below. In ADONIS, the median time to first recurrence of AF/AFL was 158 days with dronedarone compared to 59 days in the placebo group; for EURIDIS, the results were 96 days with dronedarone and 41 days in patients receiving placebo. When

results of the trials were combined, the median time to AF recurrence was 116 days with dronedarone and 53 days in patients on placebo. The secondary endpoint of ventricular rate at first recurrence of AF was 103 with dronedarone compared to 117 on placebo (P<0.001). According to an evaluation of another secondary endpoint, the rates of symptomatic recurrence AF occurred in 38% of patients on dronedarone and 46% on placebo (P<0.001). The only reported adverse event that occurred more frequently in the dronedarone group was an increase in sCr (2.4% of patients vs. 0.2% on placebo; P=0.004). One patient receiving dronedarone was reported to have interstitial lung disease, and another with pulmonary fibrosis that was also found at baseline.[14]
Trial summary: Treatment with dronedarone increased median time to first recurrence AF/AFL by 63 days compared to placebo; the rate of AF recurrence at 12 months was reduced by 25% with dronedarone compared to placebo.

ADONIS				
Outcomes	**Dronedarone (n=417)**	**Placebo (n=208)**	**HR (95% CI)**	**P value**
Recurrence AF (median days)	158	59		
Recurrence AF at 12 months (% patients)	61.1%	72.8%	0.73 (0.59-0.89)	0.002
EURIDIS				
Outcomes	**Dronedarone (n=411)**	**Placebo (n=201)**	**HR (95% CI)**	**P value**
Recurrence AF (median days)	96	41		
Recurrence AF at 12 months (% patients)	67.1%	77.5%	0.78 (0.64-0.96)	0.01
Combined Trials				
Outcomes	**Dronedarone (n=828)**	**Placebo (n=409)**	**HR (95% CI)**	**P value**
Recurrence AF (median days)	116	53		
Recurrence AF at 12 months (% patients)	64.1%	75.2%	0.75 (0.65-0.87)	<0.001

Outcomes in HF

ANDROMEDA[15]
The effect of dronedarone 400 mg twice daily on the primary endpoint of all-cause mortality or hospitalization for worsening HF was to be evaluated in a randomized, double-blind, placebo-controlled, multicenter trial conducted in Europe. Patients hospitalized with new or worsening HF (with NYHA Class III or IV HF or paroxysmal nocturnal dyspnea within the last month), were included in the trial. Entry criteria also included a LVEF equivalent to no more than 35%. Approximately 40% of patients had a history of AF; 56% were in NYHA Class III HF and approximately 40% in Class II HF. The trial was planned to include at least 12 months of treatment for each patient, and was to be conducted over a period of 2 years. The trial was discontinued prematurely after 627 patients were enrolled and after a median follow-up of 2 months due to an increase in mortality in the treatment group: 25 deaths (8.1%) in patients treated with dronedarone compared to 12 deaths (3.8%) in patients on placebo (HR 2.13; 95% CI 1.07 to 4.25; P=0.03). It was reported that the increased mortality was primarily due to an increase in death due to worsening HF (10 deaths with dronedarone compared to 2 deaths on placebo). There was no difference in the primary endpoint reported at study termination (refer to the table below). According to subgroup analysis, the risk of death was greater in patients with a lower LVEF (approximately < 35%) compared to a higher LVEF. The only reported serious adverse event that occurred significantly more frequently in the dronedarone group was an increase in sCr (2.6% of patients vs. 0% on placebo; P=0.01).[15]
Trial summary: The risk of all-cause mortality was doubled in patients with moderate to severe HF and reduced LVEF who were treated with dronedarone compared to placebo.

Outcomes	Dronedarone (n=310)	Placebo (n=317)	HR (95% CI)	P value
Composite all-cause mortality and hospitalization for worsening HF*	53 (17.1%)	40 (12.6%)	1.38 (0.92-2.09)	0.12
All-cause mortality	25 (8.1%)	12 (3.8%)	2.13 (1.07-4.25)	0.03

* Primary endpoint

Additional Trials

DAFNE[16]

Patients with persistent AF scheduled for cardioversion (n=270; 199 analyzed) were randomized to treatment with dronedarone 400 mg twice daily, 600 mg twice daily, 800 mg twice daily, or placebo. The primary efficacy endpoint of median time to AF relapse during the 6 month evaluation period was 60 days with dronedarone 400 mg twice daily vs. 5.3 days with placebo (RRR 55%; 95% CI 72 to 28%; P=0.001). A significant benefit was not found at the higher doses of dronedarone; although, there was an increase in the discontinuation rate due to adverse events with 800 mg twice daily (22.6%) and 600 mg twice daily (7.6%) compared to the 400 mg twice daily treatment group (3.9%) or placebo (0%). The most frequent reason for drug discontinuation was due to diarrhea, nausea, or vomiting.[16]

ERATO[17]

The effect of dronedarone 400 mg twice daily on the primary endpoint of change in mean ventricular rate from baseline to day 14 compared to placebo was evaluated in 174 patients with symptomatic permanent AF. Treatment was continued for 6 months to evaluate tolerability. Mean 24-hour ventricular rate was reduced by 11 beats per minute (bpm) compared to an increase of 0.7 bpm with placebo (P<0.0001). Although the effect of dronedarone on resting heart rate appeared to achieve clinical significance, the reduction in exercise heart rate (dronedarone 27.4 bpm vs. placebo 2.9 bpm; P<0.0001) did not improve to clinically recommended levels.[3] Results from the per protocol analysis showed that dronedarone reduced mean ventricular rate by 12.3 bpm (from 88.8 to 76.5 bpm) compared to a reduction of 0.4 bpm with placebo (from 92.3 to 91.1 bpm). There was no significant difference in mean increase in maximal exercise duration (P=0.514). There was an increase in treatment emergent adverse events (TEAEs) with dronedarone compared to placebo (77% vs. 60%) and a slight increase in serious TEAEs with dronedarone (17%) vs. placebo (14%). The rates of any infection (31% vs. 25%), gastrointestinal disorder (20% vs. 14%), respiratory-related (19% vs. 7%), or nervous system disorder (17% vs. 12%), were all increased with dronedarone compared to placebo. There was one report of sudden death in a patient treated with dronedarone (reported to have a history of congenital heart disease and a family history of sudden death and Steinert's disease (myotonic dystrophy). It was reported that this patient's ECG abnormalities were not detected upon enrollment which would have resulted in exclusion from the study. There was a 41.4% increase in digoxin levels that was reported not to result in a significant difference in levels outside the therapeutic range compared to placebo.[17]

Unpublished Data

DIONYSIS[2,18]

A randomized, double-blind, multicenter trial in patients with documented AF > 72 hours and who were candidates for cardioversion was conducted to determine the efficacy of dronedarone (400 mg twice daily) compared to amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter). At 12 months, the primary endpoint of composite AF recurrence or premature drug discontinuation due to intolerance or inefficacy occurred in 75.1% of patients treated with dronedarone and 58.8% of patients on amiodarone (HR 1.589; 95% CI 1.275 to 1.98; P<0.0001). For the individual components of the primary endpoint, AF recurrence with amiodarone was 42% vs. 63.5% with dronedarone; drug discontinuations due to intolerance were 10.4% with dronedarone compared with 13.3% of patients on amiodarone. The difference in the main safety endpoint of thyroid, hepatic, pulmonary, neurologic, dermatologic, ocular, gastrointestinal, or study drug discontinuation was reported to be reduced by 20% with dronedarone compared to amiodarone; however, this was not statistically significant. Treatment emergent adverse events were reported in 60.6% of patients on dronedarone compared to 67.5% on amiodarone. There were two (0.8%) treatment emergent deaths reported with dronedarone compared to five (2.0%) with amiodarone; further

details were not provided. Serious TEAEs occurred in 13.7% of patients on dronedarone compared with 14.5% of patients receiving amiodarone.[2]

Meta-Analysis

An indirect meta-analysis was conducted comparing the efficacy and safety of dronedarone and amiodarone, including data from four published placebo-controlled trials, and one unpublished head to head comparison. Results showed that amiodarone was significantly more effective at reducing the recurrence of AF compared to placebo. Despite a higher percent recurrence of AF with dronedarone, the odds ratio showed a nonsignificant decrease with dronedarone treatment compared to placebo. Results of the indirect comparison meta-analysis between amiodarone and dronedarone showed there was a significant decrease in AF recurrence with amiodarone compared to dronedarone. There was a nonsignificant increase in mortality with amiodarone compared to placebo and a nonsignificant decrease with dronedarone vs. placebo, with a nonsignificant increase in mortality when amiodarone was indirectly compared with dronedarone. A significant increase in adverse events resulting in discontinuation was found with both amiodarone and dronedarone compared to placebo, with a significant increase in discontinuations due to adverse events according to the indirect comparison of amiodarone and dronedarone (results presented in the table below).[19]

Treatment Effect	Amiodarone	Placebo	OR (95% CI)*	Dronedarone	Placebo	OR (95% CI)*	Amiodarone vs. Dronedarone OR (95% CI)
AF Recurrence	199/419 (47.5%)	216/245 (88.2%)	0.12 (0.08-0.19)	683/904 (75.6%)	353/475 (74.3%)	0.79 (0.33-1.87)	0.16 (0.06-0.42)* 0.49 (0.37-0.63)[#]
Mortality	13/419 (3.1%)	3/245 (1.2%)	1.88 (0.54-6.56)	124/3205 (3.9%)	142/2802 (5.1%)	0.85 (0.66-1.11)	2.20 (0.61-7.88)* 1.61 (0.97-2.68)[#]
DC due to AE	27/161 (16.8%)	1/113 (0.9%)	11.04 (1.89-64.5)	293/2377 (12.3%)	187/2393 (7.8%)	1.166 (1.36-2.02)	6.65 (1.13-39.3)* 1.81 (1.33-2.46)[#]

* Indirect meta-analysis; [#] Normal logistic model
AE=adverse events; AF=atrial fibrillation; DC=discontinuations; OR=odds ratio

Adverse Events[1,2,12,20-25]

The most common adverse events reported with dronedarone include diarrhea, nausea, abdominal pain, vomiting, and asthenia.[1,2]

The manufacturer reports that the safety of dronedarone is based on accumulated data from 5 placebo-controlled trials with 3282 patients treated with dronedarone 400 mg twice daily compared to 2875 who received placebo; with a mean exposure of 12 months, and a maximum follow-up of 30 months.[1,2] Studies of longer duration are needed to adequately assess the long-term safety of dronedarone, especially for the potential development of pulmonary toxicity as has been seen with amiodarone.

Adverse drug reactions reported in more patients with AF/AFL receiving treatment with dronedarone than placebo are included in the table below.[1,2]

Adverse Drug Reaction	Dronedarone 400 mg twice daily (n=3282)	Placebo (n=2875)
Diarrhea	9%	6%
Nausea	5%	3%
Abdominal pain	4%	3%
Vomiting	2%	1%
Dyspepsia	2%	1%
Asthenia	7%	5%
Bradycardia	3%	1%
Rash, pruritus, eczema, dermatitis, allergic dermatitis	5%	3%
Photosensitivity	< 1%	NR
Dysgeusia	< 1%	NR
DC due to AE	11.8%	7.7%

[a]Adverse drug reactions reported more commonly with dronedarone than placebo
AE=adverse event; DC=discontinued; NR=not reported

The following adverse events are included for amiodarone, dofetilide, flecainide, propafenone, and sotalol as a comparison.[12,20-25]

The most frequently reported adverse effects with amiodarone are gastrointestinal, dermatologic, or neurologic symptoms.[12,20,21] Adverse events reported for amiodarone are compiled in the following table: 1) per reports in patients receiving lower dose (mean 152 mg to 330 mg daily);[20] 2) according to two reviews and one review of 217 patients treated for refractory arrhythmia;[21] and 3) in 241 patients with ventricular arrhythmias treated for a mean of 441.3 days.[12] Cardiovascular side effects with amiodarone include new or worsened arrhythmias (reported in 2-5%), congestive HF, and bradycardia.[12,20,21]

Adverse Event	1)Amiodarone (n=738)	2)Amiodarone	3)Amiodarone (n=241)
Hepatic	1.2%	15-30%	4-9%
Gastrointestinal	4.2%	30%	10-33% (Nausea/Vomiting) 4-9% (Constipation/Anorexia) 1-3% (Abdominal Pain)
Pulmonary	1.9%	2.0%	4-9%
Thyroid	3.7%	4-22% (hypothyroid) 2-12% (hyperthyroid)	1-3%
Neurologic	4.6%%	3-30%	1-9%
Dermatologic	2.3%	< 10% (blue discoloration) 25-75% (photosensitivity)	4-9%
Ocular	1.5%	< 1-5%	4-9%
Bradycardia/CV	3.3%	5%	1-3%
DC due to AE	22.9%	< 20%	7-18%

AE=adverse events; DC=discontinued; N=nausea; NR=not reported

The most frequently reported adverse effects with dofetilide are headache, chest pain, and dizziness.[22] The most frequently reported adverse effects with sotalol are gastrointestinal, cardiovascular, or related to the central nervous system.[23] Adverse effects in > 2% of patients with supraventricular arrhythmias treated with dofetilide and ≥ 2% of patients with AF/AFL treated with sotalol (160 to 240 mg daily), and reported more frequently than placebo are included in the table below.[22,23] Cardiovascular side effects with dofetilide include new or worsened arrhythmias (2.6 to 14.5%), AV block, bundle branch block, heart block, bradycardia, cardiac arrest, sudden death, angina, hypertension, and syncope.[22] Cardiovascular side effects with sotalol include new or worsened arrhythmias (4.3 to 9.8%), ECG abnormalities, cardiac death, new or worsened congestive HF, bradycardia, angina, hypertension, syncope, and hypotension.[23]

Adverse Event	Dofetilide (n=1346)	Sotalol (n-153)
Headache	11%	3.3%
Chest pain	10%	4.6%
Dizziness	8%	16.3%
Respiratory tract infection	7%	2.6%
Dyspnea	6%	9.2%
Nausea	5%	7.8% (N/V)
Flu syndrome	4%	2.0%
Insomnia	4%	2.6%
Accidental injury	3%	NR
Back pain	3%	NR
Procedure	3%	NR
Diarrhea	3%	5.2%
Rash	3%	NR
Abdominal pain	3%	3.9%
Fatigue	NR	19.6%
Weakness	NR	5.2%
Hyperhidrosis	> 2%*	5.2%
Cough	≤ 2%	3.3%
Vision disturbance	NR	2.6%
Musculoskeletal pain	NR	2.6%
Dyspepsia	NR	2.0%
Decreased appetite	NR	2.0%
Cold sensation	NR	2.0%
DC due to AE	8.7%	17%

*Not more frequently than placebo
AE=adverse events; DC=discontinued; N=nausea; NR=not reported; V=vomiting

The most frequently reported adverse effects with flecainide or propafenone are gastrointestinal, cardiovascular, or related to the central nervous system.[24,25] Adverse events for flecainide reported in patients treated for ventricular arrhythmia at a dose of 200 mg daily and for propafenone in patients with supraventricular arrhythmias are included in the table below.[24,25] Cardiovascular side effects with flecainide include new or worsened arrhythmias (1 to 7%), cardiac arrest (unable to resuscitate ventricular tachycardia or fibrillation), new or worsened congestive HF, 2nd or 3rd degree AV block, bradycardia, sinus pause or arrest, tachycardia, angina, hypertension, and hypotension.[24] Cardiovascular side effects associated with propafenone include new or worsened arrhythmias (1 to 5%), cardiac arrest, 1st degree AV block, intraventricular conduction delay, congestive HF, bradycardia, bundle branch block, atrial flutter, AV dissociation, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia, and prolongation of the PR and QRS intervals.[25]

Adverse Event	Flecainide (n=426)	Propafenone (n=480)
Dizziness	11.0%	9%
Dyspnea	5.2%	2%
Headache	4.5%	6%
Nausea	4.9%	11% (N/V)
Fatigue	4.5%	6%
Palpitation	3.5%	2%
Chest pain	3.1%	NR
Visual disturbances	5.4%	3% (blurred vision)
Unusual taste	NR	14%
Constipation	2.8%	8%
DC due to AE	5 to 15%	20%

AE=adverse events; DC=discontinued N=nausea; NR=not reported; V=vomiting

Deaths and Other Serious Adverse Events (Sentinel Events)[1,2,13,15,17]

In the pivotal trial with dronedarone (ATHENA), there was no statistically significant difference in serious adverse events (e.g., cardiac, respiratory, gastrointestinal, endocrine, neurologic, skin-related, or increase sCr) with dronedarone compared to placebo. There was one reported case of torsades de pointes in a patient receiving dronedarone.[13]

The ANDROMEDA study, a trial of 627 patients with symptomatic moderate to severe HF and severe left ventricular systolic dysfunction, was discontinued prematurely (mean 62.1 days) due to an increase in all-cause mortality: 25 of 310 (8.1%) patients treated with dronedarone 400 mg twice daily compared to 12 of 317 (3.8%) patients on placebo (HR 2.13; 95% CI 1.07 to 4.25; P=0.03). Of the patients who died, death due to worsening HF was reported in 40.0% of patients in the dronedarone group compared to 16.7% on placebo. The primary endpoint of all-cause mortality or hospitalization for worsening HF occurred in 17.1% of patients treated with dronedarone vs. 12.6% on placebo (HR 1.38; 95% CI 0.92 to 2.09; P=0.12).[2,15] Refer to additional data below reported for this trial.[2,15]

Endpoint	Dronedarone (n=310)	Placebo (n=317)	P Value
All-cause mortality and hospitalization for worsening HF	17.1%	12.6%	0.12
All-cause mortality	8.1%	3.8%	0.03
Death due to worsening HF	40.0%	16.7%	NR
Hospitalization for CV causes	22.9%	15.8%	0.02
Hospitalization for worsening HF	49.3%	60.0%	NS
Occurrence of AF/AFL	21.4%	24.8%	NS
Death from arrhythmia/sudden death	3.2%	1.9%	NS
TEAEs	74.2%	69.7%	NS
Serious TEAEs	42.3%	38.2%	NS

NR=not reported; NS=reported as not statistically significant; TEAEs=treatment emergent adverse events

In a placebo-controlled trial of 174 patients with permanent AF (ERATO), the incidence of safety events with dronedarone 400 mg twice daily (n=85) compared to placebo (n=89), respectively, were reported as follows: treatment emergent adverse events (TEAEs) 77% vs. 60%; serious TEAEs 17% vs. 14%; deaths 1.2% (n=1) vs. 0.0%.[2,17] None of these safety comparisons were reported as being statistically significant.[2,17] One potential

treatment related death was reported in a pilot study evaluating dronedarone at doses of 600 mg, 800 mg, or 1000 mg twice daily compared to placebo in 73 patients with internal cardiac defibrillators (ICD) with coronary artery disease (CAD) or dilated cardiomyopathy (DCM) and LVEF < 40%.[2] One death was reported during treatment with dronedarone (400mg once daily, 800 mg once daily, or 600 mg twice daily) in a study of 124 patients with LVEF ≤ 30% with NYHA class I and II HF (ACT2401); an additional two deaths were reported 12 days and 26 days after treatment with dronedarone was discontinued. No deaths were reported in patients who received placebo.[2] The DIONYSOS trial comparing treatment with dronedarone 400 mg twice daily (n=249) vs. amiodarone 600 mg for 28 days then 200 mg daily (n=255) reported death in 0.8% (n=2) of patients in the dronedarone treatment group compared to 2.0% (n=5) of patients receiving amiodarone. Serious TEAEs were reported in 13.7% of patients on dronedarone vs. 14.5% on amiodarone. Additional safety comparisons are reported in the efficacy section of the DIONYSOS trial.[2]

Contraindications[1,2]

Dronedarone is contraindicated in patients with the following:

- NYHA Class IV HF or NYHA Class II-III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic
- Second or third degree AV block or sick sinus syndrome (except in conjunction with a pacemaker)
- Bradycardia (< 50 bpm)
- Receiving concomitant strong CYP 3A inhibitor (e.g., ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazadone, and ritonavir)
- 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)
- Hypokalemia or hypomagnesemia (e.g., as can occur with potassium-depleting diuretics)
- QTc Bazett interval ≥ 500 ms or PR interval > 280 ms
- Severe hepatic impairment
- Pregnancy (Category X); contraindicated in females who are pregnant or who may become pregnant
- Nursing mothers (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 discontinue dronedarone should be discussed)

Warnings and Precautions[1,2]

Boxed Warning

Dronedarone is contraindicated in patients with NYHA Class IV HF or NYHA Class II-III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic. In a placebo-controlled trial in patients with severe HF requiring recent hospitalization or referral to a specialized HF clinic for worsening symptoms (ANDROMEDA study), patients on dronedarone had a more than two-fold increase in mortality.

New or Worsening HF: Patients should consult with their provider if they develop new or worsening HF symptoms (e.g., weight gain, dependent edema, increased shortness of breath). If HF develops, temporary or permanent discontinuation of dronedarone should be considered.

Hypokalemia/Hypomagnesemia: Potassium-depleting diuretics may cause hypokalemia or hypomagnesemia. These laboratory abnormalities should be corrected prior to instituting dronedarone, and maintained within normal limits throughout therapy.

QT Prolongation: The QTc interval may be prolonged with administration of dronedarone, with an average of 10 ms (although this has been greater in some patients). Dronedarone should be discontinued if the QTc Bazett interval is ≥ 500 ms; the drug is contraindicated in these patients and if the PR interval is > 280 ms.

Increased Serum Creatinine: An increase in serum creatinine of approximately 0.1 mg/dl occurs after treatment with dronedarone is initiated and is associated with inhibition of creatinine tubular secretion and does not affect glomerular filtration rate. This effect is reversible upon discontinuation.

Women of Child-bearing Potential: Dronedarone has been associated with fetal abnormalities in animals at comparable doses administered in humans. Dronedarone is contraindicated in women who are pregnant or who may become pregnant. Patients who are of child-bearing potential should be counseled on appropriate methods of contraception.

Overdosage: The patient's cardiac rhythm and blood pressure should be monitored if there is an overdose of dronedarone, and the patient provided supportive treatment based on symptoms.

Risk Evaluation and Mitigation Strategy (REMS)

As part of the mPACT MULTAQ® (Partnership for Appropriate Care and Treatment™) REMS program, a medication guide should be provided to each patient every time a prescription for dronedarone is filled (i.e., with every new prescription and refill). A health care professional information sheet is also available.

Look-alike/Sound-alike Error Risk Potential

As part of a JCAHO standard, look-alike/sound-alike (LASA) names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug name(s) may cause LASA confusion:

Drug name (generic) may be confused with: dronabinol
Drug name (trade) may be confused with: none identified

Drug Interactions[1,2]

Dronedarone is primarily metabolized by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6, and has the potential to inhibit P-glycoprotein transport; therefore, the following potential drug interactions should be noted.

Medications that prolong the QT interval: Medications that prolong the QT interval (certain phenothiazines, tricyclic antidepressants, certain macrolide antibiotics, and class I and III antiarrhythmic agents) are contraindicated in patients treated with dronedarone due to the increased risk for torsades de pointes.

Potent inhibitors of CYP 3A: Administration of potent inhibitors of CYP 3A including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and nefazodone with dronedarone are contraindicated. Concomitant administration of ketoconazole with dronedarone resulted in an increase in dronedarone exposure (17-fold) and increase in Cmax (9-fold).

Inducers of CYP 3A: Administration of CYP 3A inducers including rifampin, phenobarbital, carbamazepine, phenytoin, and St. John's wort with dronedarone should be avoided. Concomitant administration of rifampin with dronedarone resulted in an 80% decrease in dronedarone exposure.

Grapefruit juice: Consumption of grapefruit juice (moderate CYP 3A inhibitor) should be avoided in patients taking dronedarone; concomitant administration resulted in a 3-fold increase in dronedarone exposure and a 2.5-fold increase in Cmax.

Statins: Administration of dronedarone increased simvastatin exposure 4-fold; it is recommended that the labeling recommendations be followed according to the respective statin for use with CYP 3A and P-glycoprotein inhibitors.

Calcium channel blockers: Administration of verapamil and diltiazem (moderate CYP 3A inhibitors) resulted in a 1.4 to 1.7-fold increase in dronedarone exposure, and a 1.4 to 1.5-fold increase in exposure of the calcium channel blocker (verapamil, diltiazem, nifedipine). The cardiac depressant effect of verapamil and diltiazem may also potentiate that of dronedarone; initiate with low doses and increase after tolerability evaluated by ECG.

Beta-blockers and CYP 2D6 substrates: Administration of beta-blockers in conjunction with dronedarone increases the incidence of bradycardia; initiate beta-blockers at low doses and increase after tolerability evaluated by ECG. Dronedarone increased the propranolol exposure by 1.3-fold and metoprolol by 1.6-fold. The exposure of other CYP 2D6 substrates including other beta-blockers, tricyclic antidepressants, and SSRIs may be increased with concomitant administration of dronedarone.

CYP 2C9 substrates: Although there was no clinically significant increase in INR in healthy individuals administered dronedarone 600 mg twice daily (S-warfarin exposure was increased 1.2-fold with no change in R-warfarin) in conjunction with warfarin, additional monitoring and/or dose adjustments of warfarin may be warranted in patients receiving dronedarone given VA ADERS reports of a probable drug interaction with elevated INRs and bleeding. There was no increase in the risk for bleeding with dronedarone compared to placebo in clinical trials of patients with AF/AFL treated with warfarin.

CYP 3A substrates with a narrow therapeutic range: The plasma concentrations of sirolimus, tacrolimus, and other CYP 3A substrates with a narrow therapeutic range can be increased with concomitant administration of dronedarone; plasma concentrations should be monitored with doses adjusted accordingly.

Digoxin: Administration of digoxin can enhance the cardiac effects (e.g., decreased AV node conduction) of dronedarone. In addition, concomitant administration increased the digoxin exposure by 2.5-fold, and increased digoxin levels. Gastrointestinal complaints were also increased. The manufacturer of dronedarone recommends that the need for digoxin therapy be reconsidered if initiating dronedarone, and if continued, to decrease the dose of digoxin by half and monitor digoxin levels.

Acquisition Cost and Price Comparison

Drug/Regimen[a]	Price[b]/Dose	Price/Patient/Month	Annual Price/Patient
Dronedarone 400 mg tablet twice daily	$2.6122	$156.73	$1880.78
Amiodarone 200 mg tablet once daily	$0.1444	$4.33	$51.98
Dofetilide250 mcg capsule twice daily	$1.6125	$96.75	$1161.00
Flecainide 100 mg tablet twice daily	$0.1274	$7.64	$91.73
Propafenone150 mg tablet three times daily	$0.0683	$6.15	$73.76
Sotalol 80 mg tablet twice daily	$0.0654	$3.92	$47.09

[a] Usual dose for long-term prophylaxis (estimates for maintenance dose based on VA utilization and/or recommended daily dose)
[b] Prices per Low2000 as of 09242009; check VA pricing sources for updated information

Utilization of Antiarrhythmic Agents in the VA

Refer to Appendix B for outpatient utilization of oral antiarrhythmic agents in VA (FY2007 through FY2009). Note: utilization includes all indications.

Cost-Effectiveness Analysis[2]

There are currently no published pharmacoeconomic evaluations with dronedarone compared to treatment with other antiarrhythmic drug therapies.

Conclusions

In patients with either recurrent paroxysmal or persistent AF, where long-term antiarrhythmic therapy is felt to be indicated, treatment is often based on patient comorbidities. It is recommended that flecainide, propafenone, or sotalol (VANF) be used in patients with minimal or no structural heart disease or who have hypertension but without

significant left ventricular hypertrophy (LVH); dofetilide or sotalol may be considered for patients with coronary artery disease; amiodarone or dofetilide in patients with HF; and amiodarone in patients with hypertension and significant LVH.

Dronedarone is a derivative of amiodarone, exhibiting similar pharmacologic effects, and was designed to reduce the potential thyroid and pulmonary adverse effects with amiodarone. In the pivotal trial, there was no significant difference in the reporting of pulmonary or thyroid effects compared to placebo; although, the authors note that the trial may not have been long enough to conclude that dronedarone has a safer side effect profile (especially pulmonary) compared to amiodarone. The potential reduction in these adverse effects needs to be confirmed in published long-term, head to head comparison trials with amiodarone.

In the pivotal ATHENA trial, treatment with dronedarone reduced the combined endpoint of first hospitalization for CV events or death compared to placebo in patients with paroxysmal or persistent AF/AFL, with the benefit being primarily driven by a reduction in first hospitalizations for AF. Patients with severe decompensated HF were not included in this trial as there was an increase in mortality with dronedarone vs. placebo in patients with moderate to severe HF and recent decompensation in a trial of patients without AF/AFL. Therefore, dronedarone is contraindicated in patients with NYHA class IV HF or NYHA class II-III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic. When compared to placebo, dronedarone reduced the time to recurrence of AF; although, results from one unpublished clinical trial showed that dronedarone is not as effective as amiodarone. Published head to head trials are needed to determine the efficacy and safety of dronedarone in comparison to other available antiarrhythmic agents used in the management of patients with AF/AFL.

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Appendix A: Pivotal Clinical Trial

Trial	Inclusion/Exclusion	Endpoints/Treatment	Results/Study Assessment	AEs/Conclusions
ATHENA (2009)[13] MC, R, DB, PC n=4628 Mean follow-up: 21±5 months U.S., Australia, Asia, Canada, Central America, Europe, New Zealand, South Africa, South America Supported by a grant from Sanofi-Aventis	**Inclusion Criteria** Paroxysmal or persistent AF/AFL with at least one of the following: 70 yrs (changed to > 70 yrs with at least one of the following RF or > 75 yrs); HTN (on tx w/at least 2 drugs); DM; previous stroke, TIA, or systemic embolism; LAD ≥ 50 mm; LVEF ≤ 40% **Exclusion Criteria** Permanent AF/AFL; decompensated HF w/in past 4 wks; NYHA class IV CHF; planned major surgery; acute myocarditis; bradycardia (heart rate < 50 bpm or PR interval > 0.28 sec); previous significant sinus node disease w/o pacemaker; serious illness limiting life expectancy; pregnancy or child-bearing potential w/o adequate birth control, or breast-feeding; baseline GFR < 10 ml/min; potassium < 3.5 mmol/l; other class I or III antiarrhythmic agents	**Endpoints** **Primary:** First hospitalization for CV event or death **Secondary:** All-cause death CV death First hospitalization for CV event **Treatment** Dronedarone400 mg twice daily vs. Placebo **Concomitant medications at baseline** beta-blockers: 70.6% CCBs: 13.8% digoxin: 13.6% ACEI or ARB: 69.5% vitamin K antagonist: 60.2% aspirin: 44.0%	**Baseline** Mean age 71.6yrs; 53.1% male; 25% AF/AFL at baseline; 59.6% structural heart disease; 86.3% HTN; NYHA: 17.1% class II, 4.4% class III; LVEF: 11.9% < 45%, 6.0% < 35% **Endpoint** / **Dronedarone (n=2301)** / **Placebo (n=2327)** / **HR (95% CI)** / **P** / **ARR** / **NNT** **Primary** 1st hosp CV event or death: 734 (31.9%) / 917 (39.4%) / 0.76 (0.69-0.84) / <0.001 / 7.5% / 13 **Secondary** All-cause death: 116 (5.0%) / 139 (6.0%) / 0.84 (0.66-1.08) / 0.18 1st hosp for CV event: 675 (29.3%) / 859 (36.9%) / 0.74 (0.67-0.82) / <0.001 **First hospitalization due to AF** Dronedarone: 335 (14.6%) Placebo: 510 (21.9%) HR 0.63 95% CI 0.55 to 0.72; P<0.001 **CV death*** Dronedarone: 63 (2.7%) Placebo: 90 (3.9%) HR 0.71 95% CI 0.51 to 0.98; P=0.03 **Study Assessment** • Intention-to-treat analysis • Randomized by AF/AFL at baseline • Data collection, management, and statistical analysis conducted by sponsor • Inclusion criteria modified during trial to increase enrollment of patients at higher risk due to lower than expected mortality • High discontinuation rate • Primary endpoint largely driven by reduction in first hospitalizations for AF • *Secondary endpoint of CV death should only have been compared if the first secondary endpoint of all-cause mortality had been found to be significant	**DC study drug** **Reason for DC** / **Dronedarone** / **Placebo** AE: 12.7% / 8.1% Pt request: 7.5% / 7.5% Other: 9.4% / 14.4% Total DC: 696 (30.2%) / 716 (30.8%) **Adverse Events** **TEAE*** / **Dronedarone** / **Placebo** Any cardiac: 11.3% / 9.6% Bradycardia: 3.5% / 1.2% QT prolongation: 1.7% / 0.6% GI: 26.2% / 22.0% Diarrhea: 9.7% / 6.2% Nausea: 5.3% / 3.1% Skin-related: 10.3% / 7.6% Rash: 3.4% / 2.0% ↑ sCr: 4.7% / 1.3% Any TEAE: 1649 (72.0%) / 716 (30.8%) *Statistically significant increases in TEAE with dronedarone vs. placebo No significant difference in reported respiratory, endocrine, neurologic, or serious AEs **Study Conclusions** Treatment with dronedarone significantly reduced first hospitalization for CV events or death compared to placebo. There was no difference in all-cause mortality.

ACEI=angiotensin-converting enzyme inhibitor; AE=adverse event; AF=atrial fibrillation; AFL=atrial flutter; ARB=angiotensin II receptor blocker; bpm=beats per minute; CCBs=calcium channel blockers; CHF=congestive heart failure; CV=cardiovascular; DB=double-blind; DC=discontinuation; DM=diabetes mellitus; GFR=glomerular filtration rate; HF=heart failure; HR=hazard ratio; HTN=hypertension; hx=history; LAD=left atrial diameter; LVEF=left ventricular ejection fraction; MC=multicenter; n=number of patients; NR=not reported; NYHA=New York Heart Association; PC=placebo-controlled; pt=patient; R=randomized; RF=risk factors; sec=seconds; sCr=serum creatinine; sx=symptoms; TEAE: treatment-emergent adverse events; TIA=transient ischemic attack; tx=treatment; wks=weeks; yrs=years

Appendix B: VA Outpatient Utilization of Oral Antiarrhythmic Agents (FY2007 through FY2009)

FY2007 FY2008 FY2009

VA Product	Day30Rxs	Dose/Day	Total Rxs	Uniques	Day30Rxs	Dose/Day	Total Rxs	Uniques	Day30Rxs	Dose/Day	Total Rxs	Uniques
SOTALOL HCL 120MG TAB	27,214	234.65	11,586	3,129	27,832	234.7	11,901	3,167	28,484	234.07	12,258	3,296
SOTALOL HCL 160MG TAB	26,202	251.11	11,023	2,952	25,973	252.77	10,819	2,861	25,050	252.08	10,255	2,776
SOTALOL HCL 240MG TAB	11,441	261.38	4,991	1,313	10,976	261.53	4,646	1,236	10,322	262.97	4,484	1,204
SOTALOL HCL 80MG TAB	113,851	148.83	49,300	12,711	105,654	148.01	45,450	11,866	95,487	147.51	40,916	10,944
AMIODARONE HCL (CORDARONE) 200MG TAB	9,152	218.92	4,488	1,379	5,078	218.43	2,750	814	3,180	213.07	1,875	476
AMIODARONE HCL (GENEVA) 200MG TAB	38	200	13	10								
AMIODARONE HCL 200MG TAB	15,337	210.89	8,281	2,390	15,990	211.64	8,268	2,272	14,023	212.55	6,627	2,104
AMIODARONE HCL (SANDOZ) 200MG TAB	8,199	226.14	3,379	1,294	5,533	220.29	2,262	767	5,876	223.18	2,569	1,001
AMIODARONE HCL 100MG TAB	83	148.95	49	30	15	100	5	2				
AMIODARONE HCL (PACERONE) 300MG TAB												
AMIODARONE HCL (PACERONE) 200MG TAB	316,558	216.07	141,099	41,356	301,911	215.31	133,343	38,988	280,904	214.9	124,901	36,888
AMIODARONE HCL (PACERONE) 100MG TAB	1,722	112.82	673	264	1,489	111.67	593	240	1,661	120.06	669	293
AMIODARONE HCL (EON) 200MG TAB	1,102	220.9	539	395								
DOFETILIDE 500MCG CAP	2,111	1	1,250	258	2,994	1	1,782	360	4,445	1	2,730	550
DOFETILIDE 125MCG CAP	1,339	0.34	924	171	1,822	0.33	1,265	282	2,340	0.34	1,573	304
DOFETILIDE 250MCG CAP	3,279	0.53	2,037	417	4,283	0.54	2,659	570	5,213	0.53	3,226	673
FLECAINIDE ACETATE 100MG TAB	23,035	191.97	11,513	2,506	22,917	191.78	11,326	2,540	22,522	191.75	11,269	2,596
FLECAINIDE ACETATE 150MG TAB	2,751	271.04	1,291	321	2,855	268.45	1,407	329	2,848	265.43	1,415	340
FLECAINIDE ACETATE 50MG TAB	4,450	126.2	2,393	569	4,570	123.47	2,460	589	4,838	125.78	2,652	648
PROPAFENONE HCL 150MG TAB	27,321	449.98	13,351	3,117	25,083	449.97	12,351	2,889	22,897	448.17	11,341	2,667
PROPAFENONE HCL 225MG TAB	10,776	589.66	5,190	1,243	10,179	587.64	4,928	1,182	10,055	584.12	4,925	1,155
PROPAFENONE HCL 300MG TAB	2,580	773.89	1,225	310	2,591	779.62	1,205	304	2,343	764.56	1,164	293
PROPAFENONE HCL 325MG CAP,SA	531	649.07	291	79	788	649.65	414	107	981	646	488	131
PROPAFENONE HCL 225MG CAP,SA	528	494.36	309	84	808	466.17	471	118	1,161	476.86	616	161
PROPAFENONE HCL 425MG CAP,SA	148	840.26	98	20	267	819.95	165	34	222	826.33	138	29
DRONEDARONE 400MG TAB									41	800	35	25