PUBLIC SUMMARY DOCUMENT
Product: Dronedarone hydrochloride, tablet, 400 mg, Multaq®
Sponsor: Sanofi-Aventis Australia Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission sought an Authority Required (Streamlined) listing for the treatment of paroxysmal or persistent atrial fibrillation or flutter in addition to standard therapy in patients with at least one additional cardiovascular risk factor.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Dronedarone was TGA registered on 2 August 2010 to reduce the risk of cardiovascular hospitalisation in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or who will be cardioverted, on top of standard therapy.

4. Listing Requested and PBAC's View

Authority Required (Streamlined)

Treatment of patients with paroxysmal or persistent atrial fibrillation or flutter and at least one additional cardiovascular risk factor (e.g. hypertension, diabetes mellitus or previous stroke or transient ischaemic attack), in addition to standard care. Treatment should only be initiated in consultation with a specialist.

CAUTION:

Dronedarone is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II-III heart failure with a recent decompensation requiring hospitalisation.

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Paroxysmal atrial fibrillation or flutter is a condition consisting of intermittent and recurrent irregular heart beats that resolve spontaneously. Persistent atrial fibrillation or flutter involves a continued irregular heart beat – cardioversion is required to return to sinus rhythm.

The submission proposed that the place in therapy of dronedarone is as add-on therapy to standard therapy (anti-coagulation plus a rate controller) and as an alternative antiarrythmic agent to amiodarone or sotalol.

For PBAC's view, see Recommendations and Reasons.

6. Comparator

The submission nominated placebo on top of standard therapy, amiodarone and sotalol as the comparators.

The Committee considered that amiodarone is the most appropriate main comparator, with sotatol and flecainide appropriate secondary comparators.

7. Clinical Trials

The basis of the submission was:

- Five direct randomised comparative trials comparing dronedarone and placebo (DAFNE, EURIDIS/ADONIS, ERATO, ATHENA);
- One direct randomised trial comparing dronedarone and amiodarone (DIONYSIS);
- Four direct randomised trials comparing amiodarone and placebo (Channer 2004, Galperin 2001, Kochiadakis 2000, Singh 2005 (SAFE-T));
- Ten direct randomised trials comparing sotalol and placebo (Bellandi 2001, Benditt 1999, Brodsky 1994, Fetsch 2004 (PAFAC), Kochiadakis 2000, Kochiadakis 2004 Lombardi 2006 (A-COMET II), Patten 2004 (SOPAT), Singh 1991, Singh 2005 (SAFE-T)); and
- Three meta-analyses (Hohnloser 2009, Lafuente-Lafuente 2007 and Piccini 2009).
- A mixed treatment comparison (MTC) reported by Freemantle et al and a MTC more relevant to the Australian setting, including studies of dronedarone, amiodarone and sotalol only (ie studies assessing flecainide and propafenone were excluded) referred to as the "Australian MTC".

Publication details of the trials presented in the submission are in the following table.

Trials and associated reports presented in the submission

Trial ID/First author	Protocol title/ Publication title	Publication citation
Dronedarone versus placebo		
ATHENA Hohnoser SH, et al.	Effect of dronedarone on cardiovascular events in atrial fibrillation.	*N Engl J Med* 2009; 360(7):668-678.
Connolly SJ	Analysis of stroke 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.	*Circulation* 2009; 120(13):1174-1180.
Hohnloser SH, et al.	Rationale and design of 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.	*J Cardiovasc Electrophysiol* 2008; 19(1):69-73.
DAFNE Touboul P, et al.	Dronedarone for prevention of atrial fibrillation: a dose-ranging study.	*Eur Heart J* 2003; 24(16):1481-1487.
EURIDIS/ ADONIS Singh BN, et al.	Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter.	*N Engl J Med* 2007; 357(10):987-999

Trial ID/First author	Protocol title/ Publication title	Publication citation
ERATO Davy JM	Dronedarone for the control of ventricular rate in permanent atrial fibrillation: The Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) study.	*Am Heart J* 2008; 156(3): 527.e1-527.e9.
Dronedarone versus amiodarone		
DIONYSOS Le-Heuzey J, et al.	A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of Dronedarone versus Amiodarone in patients with persistent atrial fibrillation: The DIONYSOS study.	*J Cardiovasc Electrophysiol* 2010;21(6):597-605
Amiodarone versus placebo		
Channer KS, et al.	A randomized placebo-controlled trial of pre-treatment and short- or long-term maintenance therapy with amiodarone supporting DC cardioversion for persistent atrial fibrillation.	*Eur Heart J* 2004; 25(2):144-150.
Galperin J, et al.	Efficacy of amiodarone for the termination of chronic atrial fibrillation and maintenance of normal sinus rhythm: a prospective, multicenter, randomized, controlled, double blind trial.	*J Cardiovasc Pharmacol Therapeutics* 2001; 6(4):341-350.
Kochiadakis GE, et al.	Low dose amiodarone and sotalol in the treatment of recurrent, symptomatic atrial fibrillation: a comparative, placebo controlled study.	*Heart* 2000; 84(3):251-257.
Singh BN, et al. (SAFE-T)	Amiodarone versus sotalol for atrial fibrillation.	*N Engl J Med* 2005; 352(18):1861-1872+1937.
Sotalol versus placebo		
Bellandi F	Long-term efficacy and safety of propafenone and sotalol for the maintenance of sinus rhythm after conversion of recurrent symptomatic atrial fibrillation.	*Am J Cardiol* 2001; 88(6):640-645.
Benditt D, et al.	Maintenance of sinus rhythm with oral d,l-sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. d,l-Sotalol Atrial Fibrillation/Flutter Study Group.	*Am J Cardiol* 1999; 84(3):270-277.
Brodsky M	Comparative effects of the combination of digoxin and dl-sotalol therapy versus digoxin monotherapy for control of ventricular response in chronic atrial fibrillation.	*Am Heart J* 1994; 127(3):572-577.
Fetsch T, et al. (PAFAC)	Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial.	*Eur Heart J* 2004; 25(16):1385-1394.
Kochiadakis GE, et al.	Low dose amiodarone and sotalol in the treatment of recurrent, symptomatic atrial fibrillation: a comparative, placebo controlled study.	*Heart* 2000; 84(3):251-257.
Kochiadakis GE	Sotalol versus propafenone for long-term maintenance of normal sinus rhythm in patients with recurrent symptomatic atrial fibrillation.	*Am J Cardiol* 2004; 94(12):1563-1566.
Lombardi F, et al. (A-COMET-II)	Azimilide vs. placebo and sotalol for persistent atrial fibrillation: the A-COMET-II (Azimilide-CardiOversion MaintEnance Trial-II) trial.	*Eur Heart J* 2006; 27(18):2224-2231.

Trial ID/First author	Protocol title/ Publication title	Publication citation
Patten M (SOPAT)	Suppression of paroxysmal atrial tachyarrhythmias - Results of the SOPAT trial.	*Eur Heart J* 2004; 25(16):1395-1404.
Singh S, et al.	Efficacy and safety of sotalol in digitalized patients with chronic atrial fibrillation.	*Am J Cardiol* 1991; 68 (Nov.1)
Singh BN, et al. (SAFE-T)	Amiodarone versus sotalol for atrial fibrillation.	*N Engl J Med* 2005; 352(18):1861-1872+1937.
Meta-analyses		
Hohnloser	Effect of dronedarone on cardiovascular outcomes: a meta-analysis of 5 randomized controlled trials in 6157 patients with atrial fibrillation/flutter	Presented at American College of Cardiology 58th Annual Scientific Session 2009
Lafuente – Lafuente C, et al.	Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation.	*Cochrane Database of Systematic Reviews* 2007; (4):CD005049
Piccini JP	Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation.	*J Am Coll Cardiol* 2009; 54(12):1089-1095.

8. Results of Trials

Results for the primary outcome of the ATHENA trial which was a composite endpoint of time from randomisation to first cardiovascular hospitalisation or death from any cause, as assessed by the Investigator, are presented in the table below.

Results of the comparison of dronedarone and placebo for the primary outcome of the ATHENA trial

Outcome	Dronedarone N=2,301 n (%)	Placebo N=2,327 n (%)	HR (95% CI)
First CV hospitalisation or death from any cause[a]	734 (31.9)	917 (39.4)	**0.76 (0.69, 0.84)**
First hospitalisation due to CV event	675 (29.3)	859 (36.9)	**0.74 (0.67, 0.82)**
First hospitalisation			
For AF	335 (14.6)	510 (21.9)	**0.63 (0.55, 0.72)**
For CHF	112 (4.9)	132 (5.7)	0.86 (0.67, 1.10)
For ACS	62 (2.7)	89 (3.8)	**0.70 (0.51, 0.97)**
For syncope	27 (1.2)	32 (1.4)	0.85 (0.51, 1.42)
For ventricular arrhythmia or non-fatal cardiac arrest	13 (0.6)	12 (0.5)	1.09 (0.50, 2.39)
Death from any cause	116 (5.0)	139 (6.0)	0.84 (0.66, 1.08)
From non CV causes	53 (2.3)	49 (2.1)	1.10 (0.74, 1.62)
From CV causes	63 (2.7)	90 (3.8)	**0.71 (0.51, 0.98)**
From non-arrhythmic cardiac causes	17 (0.7)	18 (0.8)	0.95 (0.49, 1.85)
From cardiac arrhythmia	26 (1.1)	48 (2.1)	**0.55 (0.34, 0.88)**
From non-cardiac CV causes[b]	20 (0.9)	24 (1.0)	0.84 (0.47, 1.52)
Any hospitalisation due to any CV event or death from any cause	1,253 (54.4)	1,668 (71.7)	**0.76 (0.68, 0.84)**

[a] primary outcome [b] includes stroke

HR = hazard ratio, CV = cardiovascular, AF = atrial fibrillation, CHF = congestive heart failure, ACS = acute coronary syndrome, AE = adverse event, ECV = electrical cardioversion

Bold typography indicates statistically significant differences

The results showed that patients treated with dronedarone were statistically significantly less likely to be hospitalised or die from any cause than placebo treated patients (31.9% vs. 39.4%; HR 0.76 [95% CI: 0.69, 0.84]).

The overall mortality reported in the dronedarone, amiodarone and sotalol placebo controlled trials are shown in the table below:

Overall mortality reported in the dronedarone, amiodarone and sotalol placebo controlled trials

Trial	Dron n/N (%)	Placebo n/N (%)	Treatment[a] n/N (%)	OR (95% CI)[b]	Peto OR (95% CI)[b]
Dronedarone versus amiodarone					
DIONYSOS	2/249 (0.8)	-	5/255 (2.0)	0.40 (0.04, 2.54)	0.43 (0.10, 1.91)
Dronedarone versus placebo					
ATHENA	116/2301 (5.0)	139/2327 (6.0)	-	0.84 (0.64, 1.09)	0.84 (0.65, 1.08)
DAFNE	0/54 (0.0)	0/48 (0.0)	-	NE	NE
EURIDIS/ADONIS	8/828 (1.0)	3/409 (0.7)		1.32 (0.31, 7.77)	1.30 (0.37, 4.60)
ERATO	1/85 (1.2)	0/89 (0.0)		3.18 (0.03, ∞)	7.75 (0.15, 390.73)
Meta-analysis (random effects)				0.86 (0.67, 1.10)[e]	0.86 (0.67, 1.10)
Amiodarone versus placebo					
Channer 2004	-	0/38 (0.0)[#]	0/123 (0.0)[#]	NE	NE
Galperin 2001	-	0/47 (0.0)	0/48 (0.0)	NE	NE
Kochiadakis 2000	-	0/60 (0.0)	0/65 (0.0)	NE	NE
Singh 2005	-	3/137 (2.2)	13/267 (4.9)	2.29 (0.61, 12.70)	2.02 (0.70, 5.80)
Meta-analysis (random effects)				2.29 (0.64, 8.16)[e]	2.02 (0.70, 5.80)
Indirect estimate of effect (dronedarone vs amiodarone)[c]				0.38 (0.10, 1.37)	0.43 (0.14, 1.26)
Sotalol versus placebo					
Bellandi 2001	-	0/92 (0.0)[#]	0/106 (0.0)[#]	NE	NE
Benditt 1999	-	0/69 (0.0)	0/184 (0.0)	NE	NE
Brodsky 1994	-	0/21 (0.0)	0/39 (0.0)	NE	NE
Fetsch 2004[f]	-	0/88 (0.0)	6/383 (1.6)	3.05 (0.27, ∞)	3.47 (0.44, 27.30)
Kochiadakis 2000	-	0/60 (0.0)	0/61 (0.0)	NE	NE
Kochiadakis 2004	-	0/83 (0.0)	0/85 (0.0)	NE	NE
Lombardi 2006	-	0/224 (0.0)	4/223 (1.8)	9.21 (0.67, ∞)	7.52 (1.05, 53.77)
Patten 2004	-	0/251 (0.0)	2/264 (1.0)	4.79 (0.18, ∞)	7.06 (0.44, 113.29)
Singh 1991	-	0/10 (0.0)	0/24 (0.0)	NE	NE
Singh 2005	-	3/137 (2.2)	15/261 (5.7)	2.72 (0.75, 14.90)	2.27 (0.84, 6.14)
Meta-analysis (random effects)				**3.40 (1.24, 9.35)[e]**	**3.19 (1.46, 6.98)**
Indirect estimate of effect (dronedarone vs sotalol)[c]				**0.25 (0.09, 0.72)**	**0.27 (0.12, 0.61)**

[a] amiodarone or sotalol
[b] dronedarone or treatment (amiodarone or sotalol versus placebo), calculated during the evaluation using StatsDirect
[c] dronedarone versus treatment (amiodarone or sotalol), calculated during the evaluation
[d] primary outcome
[e] random effects
[f] Table 3, p1390 Fetsch 2004
[#] not reported, assumed to be 0
Bolded typography indicates statistically significant differences

No statistically significant differences between dronedarone or amiodarone versus placebo were observed for overall mortality. There was no clear trend for mortality when comparing dronedarone to placebo, however there was a trend toward increased mortality for amiodarone. Sotalol demonstrated a statistically significant increase in the risk of mortality compared with placebo.

Mortality results from the Freemantle MTC and Australian MTC are shown in the table below.

Comparison of MTC (Freemantle and Australian) results with the relevant direct and indirect comparisons for mortality

Comparison	Dronedarone	Amiodarone	Sotalol	Amiodarone	Sotalol
	versus placebo			versus dronedarone	
Direct (Peto OR, 95% CI)	0.86 (0.67, 1.10)	2.02 (0.70, 5.80)	**3.19 (1.46, 6.98)**	2.32 (0.52, 10.32)	NA
Standard indirect (Peto OR, 95% CI)	NA	NA	NA	2.35 (0.79, 6.96)	**3.71 (1.63, 8.43)**
Freemantle MTC	0.86 (0.61, 1.22)	2.17 (0.63, 7.51)	**3.44 (1.02, 11.59)**	2.52 (0.72, 8.90)	**3.99 (1.16, 13.82)**
Freemantle MTC using data derived during the evaluation	0.86 (0.68, 1.10)	**2.11 (1.01, 4.40)**	**3.11 (1.56, 6.21)**	1.75 (0.61, 5.07)	2.44 (0.83, 7.20)
Australian MTC	0.87 (0.69, 1.09)	**2.92 (1.17, 7.31)**	**4.67 (1.89, 11.57)**	**3.37 (1.34, 8.52)**	**5.39 (2.15, 13.52)**
Australian MTC using data derived during the evaluation	0.86 (0.67, 1.10)	**2.49 (1.03, 6.01)**	**3.80 (1.59, 9.07)**	1.83 (0.56, 6.04)	2.60 (0.76, 8.99)
Australian MTC including ERATO and Fetsch 2004	0.87 (0.68, 1.11)	**2.63 (1.11, 6.22)**	**3.98 (1.72, 9.21)**	1.76 (0.58, 5.37)	2.44 (0.77, 7.70)

NA = not applicable; NR = not reported
Bold typography indicates statistically significant differences

The MTC was an attempt to obtain a more precise estimate (i.e. narrower Confidence Intervals) of differences in mortality (by combining trials against different comparators).

The Freemantle MTC results mirrored those derived from the direct and "standard" indirect comparisons of dronedarone, amiodarone and sotalol versus placebo and those derived from the comparisons of amiodarone and sotalol versus dronedarone, although the point estimates for mortality were slightly increased.

The results of the Australian MTC which indicated a statistically significant increase in mortality for patients treated with amiodarone compared with placebo and dronedarone, were not supported by the results obtained from direct comparisons of these respective treatments. As for the Freemantle MTC, the point estimates were also increased.

The PBAC noted that dronedarone is less effective than amiodarone in terms of AF recurrence, as shown in the results from the DIONYSOS trial comparing dronedarone and amiodarone where a statistically significantly greater proportion of patients treated with dronedarone experienced AF recurrence (63.5% vs. 42%; OR 2.4 [95% CI: 1.65, 3.49]), and in a mixed treatment comparison of amiodarone versus dronedarone.

There were no differences in the incidence of treatment-emergent adverse events, serious adverse events, deaths and discontinuations due to adverse events, between dronedarone and placebo treated patients as well as dronedarone and amiodarone treated patients.

9. Clinical Claim

The submission claimed that dronedarone is superior in terms of comparative effectiveness over placebo, amiodarone and sotalol and with an acceptable safety and tolerability profile.

The PBAC did not accept this claim. *See Recommendation and Reasons.*

10. Economic Analysis

Three modelled economic evaluations were presented in the submission comparing:

- Dronedarone versus placebo
- Dronedarone versus amiodarone
- Dronedarone versus sotalol

The types of economic evaluations presented were cost-effectiveness and cost-utility analyses. Each modelled economic evaluation used a decision analysis incorporating a Markov process.

The time horizon in the modelled economic evaluations was 10 years for the base case analyses. The models used a cycle length of 1 year duration. A 5% discount rate was applied in all models to costs and outcomes.

In all three modelled economic evaluations, it was the probability of having an event that was the main driver in the model, and the relative difference in the probabilities of these events between the two arms (i.e. treatment effect [RR]) that was the underlying basis of the entire economic evaluation.

The 1-year event rates from the Geelong AF study (nominated in the submission as most representative of the requested PBS population, were applied in the economic evaluations.

For all three economic evaluations, the incremental cost per extra quality adjusted life year (QALY) gained was less than $15,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The financial costs per year to the PBS were estimated in the submission to be in the range of $60 – $100 million in Year 5 of listing. The submission estimated net Medicare Benefits Scheme (MBS) savings per year of between $30 - $60 million in Year 5 due to a reduction in hospitalisations.

12. Recommendation and Reasons

The PBAC agreed with the hearing presenter, that the appropriate clinical place of dronedarone in the management of atrial fibrillation or flutter is in the second line setting after anticoagulant/rate control therapy, and as an alternative to flecainide, propafenone (not available in Australia) or sotalol. If dronedarone were to be made available through the PBS, amiodarone would most likely be reserved for third-line use in patients in whom these second line medicines are ineffective or not tolerated. The only exception to this is patients with NYHA Class III or IV heart failure or unstable NYHA Class II heart failure, in whom amiodarone remains the most appropriate second line treatment. The Committee therefore considered that amiodarone is the most appropriate main

comparator, with sotatol and flecainide appropriate secondary comparators. The Committee further noted that flecainide is not commonly used in Australia.

The Committee noted that the restriction proposed by the sponsor, which is consistent with the inclusion criteria for the ATHENA trial of dronedarone versus placebo, had been extensively commented on in the evaluation. The PBAC considered that the sponsor's proposed requirement for an additional cardiovascular risk factor to AF would not be consistent with the treatment guidelines presented in the hearing, and could not be effectively administered by Medicare Australia. Although the PBAC noted that the cost-effectiveness claim of the submission relied, at least in part, upon the identification of a narrower PBS population than that which would be eligible under a PBS restriction similar to that for amiodarone, the Committee nonetheless agreed that a restriction such as "*prevention of recurrence of atrial fibrillation or flutter"* is to be preferred from a clinical/treatment guidelines perspective and that any future submission to the PBAC for dronedarone should be based upon such a restriction.

The PBAC noted that the submission's clinical and economic claim for dronedarone was not based upon its effectiveness as an anti-arrhythmic agent per se. Indeed, the only head-to-head comparison of dronedarone and amiodarone, DIONYSOS, showed dronedarone to be statistically significantly worse than amiodarone in terms of the primary composite outcome of AF recurrence or premature discontinuation due to adverse events. The submission rather made the claim that decreased mortality is associated with dronedarone treatment of AF, whereas increased mortality is associated with amiodarone and sotalol treatment. The difference in mortality between these treatments was the basis for the submission's claim of superior comparative effectiveness over amiodarone and sotalol, and underpinned the economic analyses presented.

The Committee then noted that in the ATHENA trial of dronedarone versus placebo, dronedarone was found to reduce the rate of the primary end point of cardiovascular hospitalisation and any cause mortality by 24% (31.9% vs. 39.4%; HR: 0.76; 95% CI: 0.69 to 0.84), primarily driven by the reduction in cardiovascular hospitalisations. Death from any cause was not statistically significantly reduced (5.0% vs. 6.0 %; HR: 0.84; 95% CI 0.66 to 1.08). Death from cardiovascular causes was reduced by 29% (2.7% vs. 3.8%; HR: 0.71; 95% CI: 0.51 to 0.98).

However the PBAC considered that the statistical significance of the result for cardiovascular mortality from ATHENA needed to be interpreted with caution. This was because the statistical plan for the ATHENA trial applied a hierarchical procedure to the secondary endpoints to protect the global type I error of 5%. The primary secondary endpoint in ATHENA was death from any cause. If the difference in this endpoint was statistically significant, then first cardiovascular hospitalisation endpoint data and, subsequently, the cardiovascular death endpoint data were to be analysed. Each analysis was only to be performed if the prior analysis gave a statistically significant result. As no statistically significant difference was found for the endpoint death from any cause, the statistical analyses of the cardiovascular hospitalisation and cardiovascular death outcomes data should not have been performed.

Other clinical studies of dronedarone have yielded inconsistent results with respect to mortality. The DIONYSOS head-to-head comparison of dronedarone and amiodarone demonstrated no statistical differences in mortality, however there was a trend toward

decreased mortality in patients treated with dronedarone compared with amiodarone. On the other hand, the ANDROMEDA trial raised the possibility that dronedarone treatment might be associated with an increased risk of cardiovascular mortality in some patients Although ANDROMEDA was performed in a different population (a subpopulation of patients with severe left ventricular dysfunction who had recently been hospitalised for decompensated heart failure who did not necessarily have AF/AFL) from the intended PBS population, the PBAC considered that the clinical factors associated with an increased risk of cardiovascular mortality for dronedarone have not yet been satisfactorily determined, and therefore this risk cannot be adequately excluded, even with the note proposed for inclusion in the restriction.

The PBAC also had concerns about the relative paucity of clinical mortality data from randomised clinical trials of amiodarone. Additionally, the increased mortality observed for the amiodarone and sotalol versus placebo comparisons were driven by the trial reported by Singh et al (2005) (SAFE-T), particularly for amiodarone. Interpreting the data from SAFE-T is made more difficult as this study was conducted in patients with persistent AF, a subgroup of the total AF population which probably has a worse prognosis than other AF subgroups and as the patients in SAFE-T received higher doses of amiodarone than used in Australian clinical practice. Most importantly, after adjustment for the duration of follow-up (344.08 patient-years in the amiodarone group, 297.93 in the sotalol group, and 105.72 in the placebo group), the mortality ratios were 1.3 in the amiodarone group as compared with the placebo group (P=0.19) and 1.8 in the sotalol group as compared with the placebo group (P=0.11) [Singh, B. NEJM 352:1861;2005]. Thus, the Committee considered it likely that the submission overstated the harm associated with amiodarone.

The Committee had a number of concerns with the Australian MTC presented in the submission and which is used to derive the mortality difference included in the modelled economic evaluations of dronedarone versus amiodarone and versus sotalol. Firstly, the results of the Australian MTC indicated a statistically significant increase in mortality for patients treated with amiodarone compared with placebo and with dronedarone that is not supported by the results obtained from direct comparisons of these respective treatments, or from conventional indirect comparisons performed during the evaluation using placebo as a common reference. Secondly, as with the Freemantle MTC, the point estimates for mortality are increased. Thirdly, the Australian MTC inappropriately excluded studies assessing flecainide and propafenone, as the strength of an MTC is argued to come from including all available studies across the widest possible network.

The PBAC thus considered that the submission's assertion that dronedarone treatment will be associated with 3.37 times less mortality than amiodarone treatment, as derived from the Australian MTC, was implausibly large.

Other issues with the economic models presented included that in the model, dronedarone both extends life and improves quality of life. However, no quality of life benefit was seen in the only dronedarone study which showed an improvement in the composite end point of cardiovascular morbidity and mortality, ATHENA. The trial population of the Geelong AF study may not have been representative of the population for whom dronedarone listing was sought and thus the baseline risk derived from this study may not have been reliable. The extrapolation and the method of extrapolation of the baseline event risks from the Geelong AF study to 10 years in the modelled economic evaluation

may not be appropriate. The simpler decision analytic model used to compare dronedarone to amiodarone/sotalol favoured dronedarone compared to the more complex model used for the dronedarone versus placebo comparison.

The PBAC also noted the estimated cost to the PBS was both high and uncertain.

Overall, the PBAC rejected the submission because of uncertainty about the extent of clinical benefit in terms of improved survival over the main comparator, amiodarone, and because of the resultant uncertainty in the economic analysis.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The Sponsor is currently working towards addressing the issues raised by the PBAC in order to achieve a positive PBAC recommendation for dronedarone. The Sponsor is committed to achieving a PBS listing for dronedarone, due to what the sponsor believes to be a high unmet clinical need in the treatment of patients with atrial fibrillation in Australia.