NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Dronedarone for the treatment of atrial fibrillation and atrial flutter

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to….

- provide clarification on the positioning of dronedarone in the care pathway
- provide information on the mechanism of action of dronedarone
- provide further information on the methods for identifying and selecting relevant studies
- provide additional clinical trial data, including number of hospitalisations due to any cardiovascular event, recurrence of atrial fibrillation (AF), and rate control outcomes for the ATHENA trial
- explain the rationale for the post-hoc analysis of subgroups by risk of stroke in the ATHENA trial and provide further details of the analysis
- provide additional clinical trial data for ADONIS and EURIDIS trials, including the number of patients with atrial flutter (AFL) and full details of treatment-emergent adverse events
- explain why no treatment effect was assumed in the absence of results in the mixed treatment comparison (MTC)
- provide additional details of the MTC, including search strategy used, the code and raw data used, whether the results are based on a fixed or random effects analysis, the number of trials and patients in each comparison, and results for each comparator compared with a control
- explain the methods used to estimate time to mortality and provide coefficients for the equations used

- explain whether alternative curves fits were examined for time to mortality, acute coronary syndrome and AF recurrence
- clarify how health states and event utility weights were derived
- provide additional information on the resource use and unit cost assumptions associated with adverse events
- explain why there are different costs and quality-adjusted life years (QALYs) gained for treatment with dronedarone between positions 2 and 3 in the care pathway
- clarify the reasons for the different cost-effectiveness estimates for dronedarone at different positions in the care pathway and for the different QALYs gained with or without structural heart disease
- provide clarification of the computer coding used in the economic analysis.

Indicative licensed indication

In September 2009, dronedarone (Multaq, Sanofi-Aventis) received a positive Committee for Medicinal Products for Human Use (CHMP) opinion for use in adult clinically stable patients with history of, or current, non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate. The draft summary of product characteristics (SPC) provided by the manufacturer states that the use of dronedarone [redacted] is contraindicated. The draft SPC [redacted] is not recommended.

Key issues for consideration

Clinical effectiveness

- Does the Committee consider that the population of the ATHENA trial is representative of people with AF who would be eligible for dronedarone in routine clinical practice?
- Does the Committee consider the use of $CHADS_2$[1] for predicting stroke and all-cause mortality valid?
- Does the Committee consider the post-hoc analysis of all-cause mortality for the $CHADS_2$ subgroups appropriate?
- Does the Committee consider that the evidence from the MTC comparing dronedarone with other anti-arrhythmic drugs (AADs) is robust?
- What is the Committee's view of the adverse events associated with the use of dronedarone compared with other AADs?
- Does the Committee consider that the use of dronedarone as a first-line treatment in addition to standard baseline therapy fits with its marketing authorisation?
- What is the Committee's opinion of the lack of data on ventricular rate control despite this being specified in the marketing authorisation (although this outcome was not specified in the scope)?

Cost effectiveness

- What is the Committee's view about the additional benefits of dronedarone in the economic model being attributed to a reduction in all-cause mortality and stroke despite the modelled assumption that dronedarone is less effective than other AADs for AF recurrence?
- Does the Committee consider the use of ATHENA trial data to inform the baseline event rates applied in the economic model appropriate?

[1] $CHADS_2$ is a clinical prediction score for estimating the risk of stroke in patients with AF. Scores are based on one point for recent congestive heart failure, hypertension, age 75 years or older, or diabetes mellitus, and two points for a history of stroke or transient ischaemic attack. A higher score corresponds to a greater risk of stroke.

- What is the Committee's opinion of the use of post-hoc analyses from the ATHENA trial to inform the cost-effectiveness analysis of dronedarone as an addition to standard baseline therapy?
- What is the Committee's opinion of the use of the results of the MTC to inform the event rates in the economic model (particularly in regard to all-cause mortality)?
- Does the Committee consider that an assumption of no mortality benefit for class 1c agents (as used in the economic analyses) is appropriate?
- Does the Committee consider estimation of adverse event rates and their associated costs appropriate?
- Does the Committee consider that the utilities used in the model are appropriate?
- What is the Committee's opinion of the differential costs attributed to dronedarone in the economic model (specifically, initiation and monitoring costs)?
- What is the Committee's view about the lack of specific consideration of dronedarone for people with AFL in the manufacturer's submission?
- Does the Committee consider that the treatment pathways evaluated by the manufacturer represent the full range of relevant strategies or sequences for dronedarone?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Stable adult people with either a recent history of, or current non-permanent AF. Not including people with NYHA class IV heart failure and people with NYHA class III heart failure with recent haemodynamic instability.
Intervention	Dronedarone at a dose of 400 mg twice daily indefinitely.
Comparators	In people with multiple cardiovascular risk factors (corresponding to a $CHADS_2$ score of at least 4), dronedarone is given on top of baseline therapy, therefore the comparator is: • standard baseline therapy with or without beta blockers. In all other eligible people, dronedarone is considered as an alternative to first-line anti-arrhythmic agents, therefore the comparators are: • class 1c agents • sotalol • amiodarone.
Outcomes	The primary endpoint in two clinical trials (EURODIS/ADONIS) was time to recurrence of AF or AFL. The primary endpoint in another trial (ATHENA) was first hospitalisation due to a cardiovascular event or death from any cause. Secondary outcomes included all-cause mortality, cardiovascular mortality, stroke, cardiac events, and adverse events of treatment. Quality of life was not assessed in the dronedarone clinical trials. It was based on the AFTER cohort of the Euro Heart Survey on AF using the EQ-5D questionnaire.
Economic evaluation	The economic evaluation performed was a cost–utility analysis, based on an individual patient lifetime discrete event simulation methodology. Patients are individually simulated and their progression through the disease model recorded, taking account of the events that they incur and the associated costs and quality of life detriments. The model included four health states: normal sinus rhythm, permanent AF with uncontrolled symptoms, permanent AF with controlled symptoms, and death. The model was developed over a lifetime time horizon (25 years). This required extrapolation of outcomes in the ATHENA trial, which was the longest available study (follow-up: 21 months). Costs are estimated from the perspective of the NHS.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG noted that the population addressed in the manufacturer's submission differed from that in the scope because it was restricted to the anticipated licence, and therefore excluded people with NYHA class IV heart failure and also NYHA class III heart failure with recent haemodynamic instability. The ERG noted that this exclusion reflects concerns over the use of dronedarone in such patients given the results of the terminated ANDROMEDA trial. In this trial, dronedarone was found to be associated with increased early mortality related to worsening heart failure in people who were hospitalised with symptomatic heart failure or severe left ventricular systolic dysfunction (hazard ratio [HR] 2.13; 95% confidence interval [CI] 1.07 to 4.25).

The ERG also stated that the population for first-line use of dronedarone was further restricted to people with multiple cardiovascular risk factors (specifically, those with a $CHADS_2$ score of 4 or higher).

The ERG noted that although the scope specified the analysis of subgroups according to type of arrhythmia (AF or AFL), these subgroups were not considered separately in the manufacturer's submission.

1.2.2 Comparators

The ERG commented that in the final NICE scope, comparators were divided into first- and second-line therapy; however, in the manufacturer's decision problem the wording was altered so that the comparison of dronedarone as a second-line therapy versus other AADs was changed to "as an alternative 1st line to current anti-arrhythmic agents when it is considered appropriate to introduce an AAD" (although the interpretation appears the same).

The ERG commented that it is not clear from the manufacturer's submission why dronedarone should be introduced to elderly people with moderate- to

high-risk AF at an earlier stage than current AADs. It noted that the submission did not consider the cost effectiveness of dronedarone at different time points within the treatment pathway (for example, as a second-line treatment after failure of an alternative first-line AAD). The ERG noted that the draft SPC states that dronedarone is used to lower ventricular rate. The ERG commented that if dronedarone is administered primarily for rate control, then comparators should include purely rate-limiting drugs.

1.2.3 Outcomes

The ERG thought that the outcomes in the manufacturer's decision problem reflected those in the NICE scope. However, it noted that time to recurrence of AF or AFL was not considered in the broader evidence synthesis even though this outcome is reported in some of the randomised controlled trials (RCTs). Furthermore, the ERG pointed out that although the indicative license for dronedarone specifies that it is used to lower ventricular rate, rate control was not included as an outcome in the scope or the manufacturer's decision problem.

1.2.4 Timeframe

The ERG noted that although the manufacturer's submission states that dronedarone should be given indefinitely, most of the RCTs had only short-term follow-up (less than 21 months) and therefore long-term evidence is lacking.

1.2.5 Subgroups

The ERG stated that the manufacturer's submission defines subgroups using the $CHADS_2$ score, which is a clinical prediction score for estimating the risk of stroke in patients with AF. The ERG considered the validity of the $CHADS_2$ score for predicting cardiovascular disease risk in general and for predicting all-cause mortality was uncertain and that it has a poor ability to separate

people with AF into risk categories that correspond to different rates of thromboembolism. Therefore, the use of $CHADS_2$ score to define patient groups at risk of cardiovascular disease in general (rather than only stroke) and to stratify treatment effectiveness for all-cause mortality may not be clinically meaningful.

1.3 Statements from professional/patient groups and nominated experts

Clinical experts stated that the treatment of AF, specifically the choice of rhythm or rate control, is largely driven by symptoms. They commented that amiodarone is the most effective rhythm control agent but that it is associated with serious potential side effects and is therefore kept for situations in which other AADs are contraindicated. Other AADs include class 1c agents, which are preferred in younger people with structurally normal hearts, and sotalol, which is also used for people with structurally normal hearts or coronary heart disease. The experts stated that second-line treatment of AF includes atrioventricular node ablation and pacemaker implantation. The clinical experts indicated that there is considerable variation in practice between centres, particularly in the perseverance of rate control and use of catheter ablation.

The clinical experts stated that dronedarone is likely to be used in secondary and tertiary care settings and specialist community clinics until it becomes an established treatment. They commented that if dronedarone is prescribed in secondary care and specialist centres, it is unlikely that further training would be required. The use of dronedarone might also have an impact on the number of patients choosing a rhythm control strategy to treat AF, and an increase in the number of cardioversions performed might be observed.

Experts commented that the ATHENA trial showed a statistically significant reduction in cardiovascular deaths with dronedarone and that this was mainly due to a reduction in arrhythmic deaths, but they pointed out that the absolute

number of deaths was small. The experts noted that the results of the post-hoc analysis of the ATHENA trial had not been published in peer-reviewed journals. Clinical experts stated that the serious adverse events associated with amiodarone, thyroid dysfunction and pulmonary fibrosis were no more common with dronedarone than placebo; however, the longest follow-up for dronedarone is 21 months and this may not be sufficient to observe these events, particularly pulmonary fibrosis.

Clinical experts suggested the following issues should be taken into account in appraising dronedarone: long-term safety, efficacy in the maintenance of sinus rhythm, efficacy in regard to hospital admissions, and association with increased mortality in people with heart failure and severely reduced systolic function.

Patient experts commented that AF and AFL can be debilitating conditions and currently the choice of treatments is limited. The experts stated that the main advantage of dronedarone is that it appears to improve symptoms with fewer side effects than current treatment options and therefore could be available to more people, particularly those who have adverse reactions to other AADs. They commented that this would result in fewer visits to hospital, the ability to continue work and maintain their usual lifestyle and therefore improved quality of life. The patient experts also commented that dronedarone may not be suitable for all people with AF or AFL, particularly those with significant heart failure. They stated that all AADs appear to have a limited duration of effect, eventually becoming less effective at reducing symptoms, and that dronedarone offers another treatment option to extend the duration that symptoms are improved.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The evidence of clinical effectiveness in the manufacturer's submission comes from several dronedarone trials, meta-analyses of comparator studies and an MTC.

2.1.1 Dronedarone trials

The main evidence of dronedarone for persistent or paroxysmal AF and AFL comes from four phase III RCTs: EURIDIS, ADONIS (which includes European and non-European trials of the same design, the results of which were combined and reported together), ATHENA and DIONYSOS. DIONYSOS was the only RCT that compared dronedarone with an active comparator (amiodarone).

Summary details of the four studies are presented in table 1.

Table 1. Summary of dronedarone trials

	EURIDIS/ADONIS	ATHENA	DIONYSOS
Design and duration	Phase III double-blind RCT 12 months	Phase III double-blind RCT Multi-centre 12 months	Phase III double-blind RCT Multi-centre 6 months
Participants	People with ≥ 1 AF episode within previous 3 months and in normal sinus rhythm for ≥ 1 hour before randomisation Exclusions: NYHA class III or IV	People aged ≥ 70 years with AF or < 70 years plus ≥ 1 of: hypertension, diabetes, prior cerebrovascular accident, left atrium diameter ≥ 50 mm or LVEF < 0.40 Exclusions: NYHA class IV	People with AF for > 72 hours, cardioversion and anti-arrhythmic medication indicated, receiving anti-coagulant
Intervention	Dronedarone 400 mg twice daily (n = 828)	Dronedarone 400 mg twice daily (n = 2301)	Dronedarone 400 mg twice daily (n = 249)
Comparator	Placebo (n = 409)	Placebo (n = 2327)	Amiodarone 600 mg once daily for 28 days then 200 mg daily (n = 255)
Primary outcome	Time to first AF or AFL recurrence	First hospitalisation due to CV event or all-cause death	AF recurrence or premature study drug discontinuation for intolerance or lack of efficacy

AF, atrial fibrillation; AFL, atrial flutter; CV, cardiovascular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

EURIDIS/ADONIS trials

The EURIDIS/ADONIS trials included a total of 1237 people with a mean age of 63 years, of whom 69% were male. Eleven percent of people had AFL, 41% had structural heart disease and 17% had congestive heart failure. The

median times to AF recurrence were 116 days in the dronedarone group and 53 days in the placebo group. At 12 months, 64% and 75% of each group, respectively, had recurrence of AF or AFL (HR 0.75; 95% CI 0.65 to 0.87; $p < 0.001$). In the dronedarone group, the mean ventricular rate during the first adjudicated AF or AFL recurrence was 103 beats per minute compared with 117 beats per minute in the placebo group ($p < 0.001$).

The rates of death and most treatment-emergent adverse events were similar between the study groups (numbers not reported), although there was a lower incidence of hyperthyroidism in the dronedarone group compared with the placebo group (8.4% and 14.1% in each group, respectively; $p = 0.002$) and a higher incidence of serum creatinine elevation (2.4% and 0.2% in each group, respectively; $p = 0.004$). The manufacturer states that there was a slightly higher rate of serious treatment-emergent adverse events in the placebo group and a slightly lower rate of treatment discontinuations in the dronedarone group (numbers not reported).

ATHENA trial

The ATHENA trial included 4628 people with paroxysmal and persistent AF who had additional risk factors for death. At the start of the trial, people were eligible if they were aged 70 years or older, or if they were younger than 70 years of age and had at least one additional risk factor for cardiovascular death (such as hypertension or diabetes). Owing to a lower than expected mortality rate, the eligibility criteria were changed during the trial so that people younger than 70 years of age were no longer eligible and people aged between 70 and 75 years had to have at least one additional risk factor. The mean age of people in the ATHENA trial was 72 years and 53% were male. In the dronedarone group, 31.9% had a primary composite outcome of first hospitalisation due to a cardiovascular event (29.3%) or death before hospitalisation (2.6%). In the placebo group, 39.4% had a first hospitalisation due to a cardiovascular event (36.9%) or death (2.5%; HR for composite outcome 0.76; 95% CI 0.69 to 0.84; $p < 0.001$). There was no statistically

significant difference in death from any cause (at any stage) in the dronedarone (5.0%) and the placebo groups (6.0%; p = 0.18). However, there were fewer cardiovascular deaths (at any stage) in the dronedarone group than the placebo group (HR 0.71; 95% CI 0.51 to 0.98; p = 0.03).

Two post-hoc analyses were conducted using data from the ATHENA trial. The first analysis was an assessment of the effect of dronedarone on stroke, which was not an *a priori* specified outcome. The results showed that over a mean follow-up of 21 months, dronedarone was associated with a reduction in adjusted risk of stroke compared with placebo (HR 0.66; 95% CI 0.46 to 0.96; p = 0.027). The second analysis was a subgroup analysis of people in the ATHENA trial categorised by risk of stroke (according to $CHADS_2$ score). The results showed that the risk of all-cause mortality [redacted] The study drug was prematurely discontinued in 30.2% of people receiving dronedarone compared with 30.8% of those receiving placebo. Of these discontinuations, 12.7% in the dronedarone group and 8.1% in the placebo group were due to an adverse event (p < 0.001). People in the dronedarone group had statistically significantly higher incidences of bradycardia, QT-interval prolongation, diarrhoea, nausea, rash and serum creatinine elevation than those in the placebo group.

DIONYSOS trial

The DIONYSOS trial compared dronedarone with amiodarone in 504 people with persistent AF who were eligible for electrical cardioversion. People in the trial had a mean age of 64 years and two-thirds were male. The primary composite endpoint of recurrence of AF or premature study discontinuation due to intolerance or lack of efficacy occurred in 73.9% of the dronedarone group and 55.3% of the amiodarone group (HR 1.59; p < 0.0001). This difference was primarily due to recurrence of AF, which occurred in [redacted] and [redacted] of the dronedarone and amiodarone groups, respectively. The number of

people who prematurely discontinued the study drug at any time during the trial was [redacted] in the dronedarone group and [redacted] in the amiodarone group (no statistical comparison provided). Of the dronedarone discontinuations, [redacted] were due to lack of efficacy (including discontinuations due to AF recurrence) and [redacted] were due to adverse events or intolerance. Whereas of the discontinuations in the amiodarone group, [redacted] were due to lack of efficacy and [redacted] were due to AF recurrence.

The incidence of treatment-emergent adverse events was [redacted] in the dronedarone group compared with [redacted] in the amiodarone group, and the incidence of serious adverse events was [redacted] and [redacted] in each group, respectively (no statistical comparison provided). During the treatment period (median duration 7 months), there were two deaths in the dronedarone group and five in the amiodarone group. People in the dronedarone group had [redacted]

2.1.2 Meta-analyses and mixed treatment comparison

The manufacturer conducted three analyses to compare the effectiveness of dronedarone to other anti-arrhythmic treatment options for AF. These were:

- a direct meta-analysis using pooled study data when head-to-head trials were available
- an indirect meta-analysis of pooled study data from placebo-controlled trials (using the placebo as the common comparator)
- an MTC combining evidence from the indirect meta-analysis with evidence from head-to-head trials.

The analyses were conducted for five outcomes: AF recurrence, all-cause mortality, treatment discontinuation, treatment discontinuation due to adverse

events, and stroke. For details of the methodology of these analyses see pages 39 to 43 of the ERG report.

The indirect meta-analysis indicated that

The MTC showed that dronedarone is associated with a lower risk of all-cause mortality than amiodarone (OR 3.19; 95% CI 1.16 to 8.76; p = 0.032). The results of the direct and indirect meta-analyses also supported this finding, however the estimates did not reach statistical significance. Dronedarone also had a lower risk of mortality than sotalol in the MTC (OR 5.05; 95% CI 1.84 to 13.87; p = 0.009). There was no statistically significant difference in all-cause mortality between dronedarone and control and not enough evidence to compare dronedarone and class 1c agents.

There were limited data on stroke available; however, the MTC showed that

Regarding treatment discontinuations

For serious adverse events, the meta-analyses and MTC indicated that

[redacted] The full results of these analyses can be found on pages 51 to 61 of the manufacturer's submission.

In addition to the meta-analyses and MTC results for safety, the manufacturer submitted results of a pooled analysis of five placebo-controlled dronedarone trials (ATHENA, EURIDIS and ADONIS plus two additional trials which did not meet inclusion criteria for the main clinical-effectiveness review: ERATO and DAFNE). The analysis included a total of 6285 people with a mean exposure across studies of 12 months. The main adverse events associated with dronedarone were diarrhoea, nausea or vomiting, serum creatinine elevation, rash and cardiac effects (bradycardia and QT prolongation). The incidence of serious adverse events was similar in the dronedarone and placebo groups (18.0% and 19.7%, respectively) and these were mainly related to infections and infestations, gastrointestinal disorders, and cardiac disorders. There were more premature discontinuations in the dronedarone group than the placebo group (11.8% and 7.7%, respectively) and the most common reason for discontinuation with dronedarone was diarrhoea.

2.2 Evidence Review Group comments

Overall, the ERG thought that the search strategies used to identify clinical-effectiveness studies were appropriate. The ERG's independent search did not find any additional studies of dronedarone that met the inclusion criteria. However, the ERG pointed out that although the protocol of the systematic review stated that quality assessment of RCTs was done, no details of this assessment was provided in the manufacturer's submission or supporting documents.

The ERG commented that the ADONIS/EURIDIS RCTs were good-quality trials that demonstrated that dronedarone is more effective than placebo for reducing AF recurrence and for reducing ventricular rate during AF recurrence in people with persistent and paroxysmal AF.

The ERG commented that the ATHENA trial showed dronedarone was associated with a statistically significant reduction in the primary composite endpoint of time to first cardiovascular hospitalisation or death from any cause in patients with AF when compared with placebo. However, it noted that this result was mainly driven by a reduction in time to first cardiovascular hospitalisation due to a significant reduction in hospitalisation for AF. The ERG noted that the people in the ATHENA trial were older and had a higher risk of stroke than people in the other trials and also that the results of this trial may not be generalisable to a lower risk and younger population.

The ERG commented on the post-hoc analysis of ATHENA trial results by $CHADS_2$ score. It noted that $CHADS_2$ is a clinical prediction score for estimating the risk of stroke in people with AF and that its validity for stratifying treatment effectiveness by risk of cardiovascular disease more generally and by all-cause mortality is not known. The ERG further noted that this appears to be the first instance of the $CHADS_2$ score being used to stratify treatment effectiveness for all-cause mortality in an AAD study (upon request by the ERG, the manufacturer searched for studies in which AF patients had been stratified according to $CHADS_2$ score and could not find any).

With regard to the evidence syntheses conducted by the manufacturer in general, the ERG noted a number of limitations. The inclusion and exclusion criteria used to identify studies for the direct meta-analysis, the indirect meta-analysis, and the MTC were different, leading to a different set of studies being used for each type of analysis and for each outcome analysed. Of particular concern to the ERG was the limited number of studies included in the MTC. The ERG noted that there was no investigation of statistical or clinical heterogeneity among trials in the meta-analyses and therefore the

validity of pooling the results in the different analyses is uncertain. It also noted that the populations in the trials appeared to be inconsistent, with some analyses including people with permanent AF (and others only including people with paroxysmal AF).

The ERG also outlined a number of issues with the meta-analyses and MTC of each outcome (the full critique is provided on pages 46 to 62 of the ERG report).

Overall, the ERG stated that it was unable to fully appraise the MTC results because a full copy of the programme code and dataset was not supplied. However, it concluded that the methods used for the MTC are likely to be reliable but the results from the evidence synthesis in general should be treated with caution owing to the reasons outlined above.

The ERG's conclusions about clinical effectiveness and safety based on the meta-analyses and MTC are summarised below for each outcome.

- AF recurrence: despite a number of limitations with the analyses, the results indicated that all AADs decreased AF recurrence but dronedarone had the smallest effect.
- All-cause mortality: the analyses inconsistently used continuity corrected data[2]. The ERG's recalculation of the indirect comparison and the MTC for all-cause mortality found contrasting results with those reported in the manufacturer's submission. Specifically, it found that there was no statistically significant difference in all-cause mortality between dronedarone, amiodarone and class 1c agents and that sotalol had the highest risk of mortality compared with control.
- Stroke: the evidence for the effect of dronedarone on the risk of stroke is highly uncertain because only a small number of studies reported this

[2] A correction used when the distribution of a continuous random variable is used to approximate that of a discrete random variable (for example, when a normal distribution is used to approximate a binomial distribution).

outcome and the MTC results showed no significant difference was reported between dronedarone and amiodarone or sotalol.

- Treatment discontinuations: it is uncertain whether dronedarone is associated with a lower rate of discontinuations than other AADs because the results from the direct analysis and MTC were not significant, with confidence intervals crossing the null effect value (one).
- Treatment discontinuations due to adverse events: the results of direct analysis, indirect analysis and the head-to-head MTC showed that dronedarone is associated with less risk of serious adverse events compared with other AADs. However, data from the EURIDIS/ADONIS trials were excluded from the analyses and therefore these results are unreliable.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The model used in the manufacturer's cost-effectiveness analysis was a discrete event simulation which predicts a person's course when treated with dronedarone compared with the predicted courses with alternative treatment pathways. The model was developed using two types of software. The main structure of the model, consisting of the discrete event simulation, was developed using SIMUL8 software. An Excel file was also submitted to allow input values to be changed.

The manufacturer evaluated the cost effectiveness of dronedarone in two positions in the care pathway.

- For patients with multiple cardiovascular risk factors (corresponding to a $CHADS_2$ score of 4 or higher) on top of standard baseline therapy (including anti-coagulation and beta blockers in accordance with NICE

Clinical Guideline 36 [CG36] on AF and referred to within CG36 as first-line treatment).

- For patients when it is deemed appropriate to introduce an AAD, as a first-line alternative to current AADs (referred to within CG36 as second-line treatment).

The model compared dronedarone against a number of comparators depending on the position in the care pathway, the type of AF, and the baseline risk factors in line with CG36. The comparisons are outlined in table 2.

Table 2. Cost-effectiveness comparisons in the manufacturer's submission

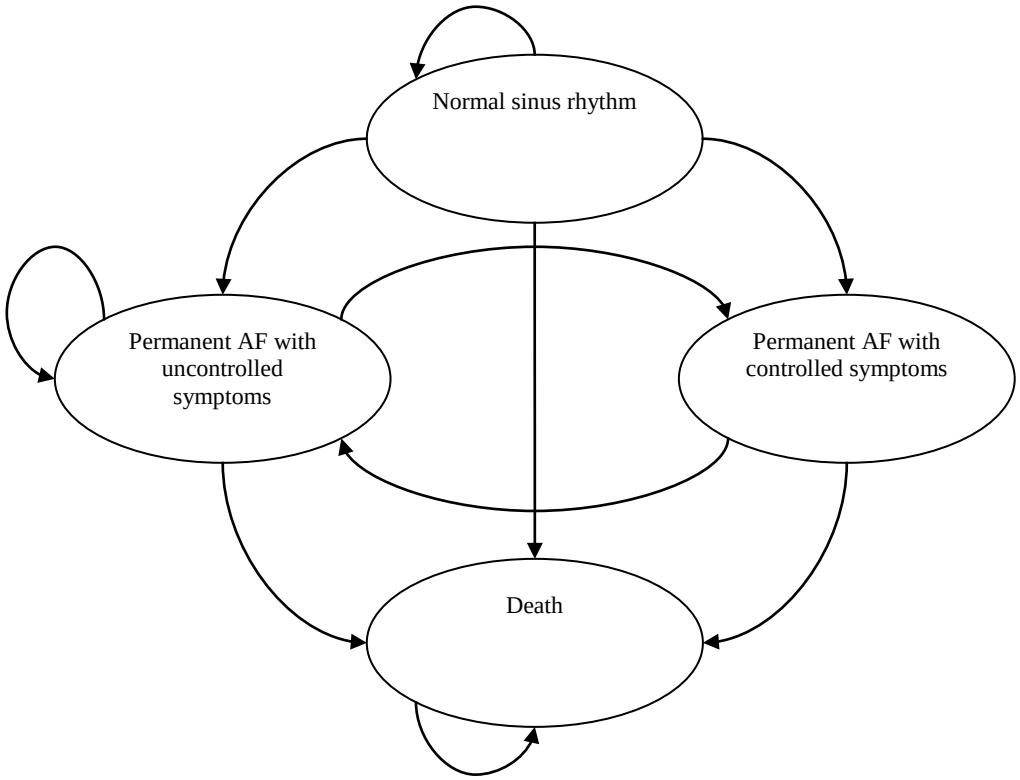
	Dronedarone in addition to standard baseline therapy*	**Dronedarone as an alternative first AAD**
Paroxysmal AF with no structural heart disease	Standard baseline therapy alone	Sotalol Class 1c agents
Paroxysmal AF with coronary heart disease	Standard baseline therapy alone	Sotalol
Paroxysmal AF with left ventricular dysfunction	Standard baseline therapy alone	Amiodarone
Persistent AF with no structural heart disease	Standard baseline therapy alone	Sotalol Class 1c agents
Persistent AF with structural heart disease	Standard baseline therapy alone	Amiodarone

* For people with $CHADS_2$ score ≥ 4.
AAD, anti-arrhythmic drug; AF, atrial fibrillation.

The model included four health states: normal sinus rhythm, permanent AF with uncontrolled symptoms, permanent AF with controlled symptoms, and death. From the normal sinus rhythm state, people could move to any of the other states. From the two permanent AF health states (with uncontrolled and controlled symptoms), people could move between these states or die. Transition between health states was determined by the following events: AF recurrence, acute coronary syndrome, stroke, congestive heart failure,

treatment discontinuation, change in AF symptoms (for the permanent AF states), or death.

Figure 1. Schematic representation of the modelled health states



3.1.1 Clinical evidence

The baseline risk of events (AF recurrence, acute coronary syndrome, stroke, congestive heart failure, and treatment discontinuation) was taken from the ATHENA trial (median follow-up: 21 months) and extrapolated to a lifetime time horizon. The baseline risk of events was adjusted for each treatment arm using odds ratios from the MTC. Owing to the low number of deaths in the ATHENA trial, all-cause mortality was estimated using age-specific UK life tables (from the Government Actuary's Department) and adjusted for $CHADS_2$ score (see page 90 of manufacturer's submission for further details). The risk of death following stroke and congestive heart failure events was estimated

using published sources (owing to the low number of strokes in the ATHENA trial).

The model included adverse events associated with each treatment; these were taken from a variety of sources (owing to lack of evidence from the meta-analysis or MTC). Adverse event rates came from the pooled analysis of clinical trials for dronedarone, from the DIONYSOS trial for amiodarone, and from the SPCs for sotalol and class 1c agents (owing to lack of data). For adverse events rates of each AAD, see page 94 of the manufacturer's submission.

3.1.2 Utilities

Health-related quality of life was not measured in the dronedarone trials therefore utilities for the health states have been taken from the AFTER cohort of the European Heart Survey on AF (which included data on survival status and EQ-5D-assessed quality of life for a total of 3045 people with AF). Regression approaches were used to derive the coefficients used in the model (see page 96 of the manufacturer's submission). The disutilities associated with adverse events were derived from a study undertaken by the manufacturer (n = 127) using a time trade-off approach (owing to absence of suitable published evidence).

3.1.3 Costs

Drug costs for comparators were taken from the 'British national formulary' (BNF). At the time of submission, the final acquisition price for dronedarone had not yet been confirmed. The manufacturer stated that the price was anticipated to be between £2.20 and £2.50 per day. Therefore a unit cost of £2.30 per day was used in the base case, and unit costs of £2.20 and £2.50 were explored in a sensitivity analysis. (The cost has now been confirmed as £2.25 per day). Drug administration costs were sourced from NHS Reference Costs 2007/08. For dronedarone, these consisted only of one specialist

outpatient cost for treatment initiation and a general practitioner visit for a day seven creatinine test (£202). For comparators it was assumed that hospitalisation is required for treatment initiation (£249), and 6-monthly general practitioner visits and tests are required for monitoring (£58 to £76 depending on the treatment).

Costs for most of the health events (for example, AF recurrence and acute coronary syndrome) were taken from the published literature. Most events were assumed to incur a one-off cost; however, for stroke and congestive heart failure, ongoing daily costs were assumed.

Costs for adverse events came from NHS Reference Costs 2006/07. A proportion of adverse events were assumed to require hospitalisation (based on expert clinical opinion) and the rest were assumed to require an outpatient consultant visit. For short-term adverse events, a one-off cost at treatment initiation was incurred and for adverse events with lifetime effects, a 6-monthly GP visit was assumed to be required.

Resource use data were sourced from clinical opinion and published literature (rather than from the ATHENA trial which is where the risk of events came from).

3.1.4 Results

Cost-effectiveness estimates were provided for the five patient groups described in table 2. The manufacturer provided an updated model and revised base-case results in response to a number of issues identified by the ERG (the changes involved correction of a minor coding error within the model and use of a new random number seed in the model to allow replication of the results). The most recently revised base-case results are presented in table 3 and used throughout the remainder of this briefing.

Table 3. Base-case results

	Dronedarone vs standard baseline therapy	Dronedarone vs solatol	Dronedarone vs class 1c agents	Dronedarone vs amiodarone
Paroxysmal AF with no structural heart disease				
Incremental costs	£3446	£4091	£2081	-
Incremental QALYs	0.44	2.07	0.10	
Cost per QALY gained	£7885	£1980	£21,026	
Paroxysmal AF with coronary heart disease				
Incremental costs	£3412	£4482	-	-
Incremental QALYs	0.42	2.00		
Cost per QALY gained	£8142	£2246		
Paroxysmal and left ventricular dysfunction				
Incremental costs	£3424	-	-	£3633
Incremental QALYs	0.44			1.33
Cost per QALY gained	£7865			£2724
Persistent and no structural heart disease				
Incremental costs	£3167	£4324	£2169	-
Incremental QALYs	0.45	2.08	0.10	
Cost per QALY gained	£7007	£2082	£21,770	
Persistent with structural heart disease				
Incremental costs	£3020	-	-	£4078
Incremental QALYs	0.42			1.28
Cost per QALY gained	£7163			£3185

AF, atrial fibrillation; QALY, quality-adjusted life year.

Probabilistic sensitivity analyses were conducted for all twelve clinical scenarios indicated in table 3 (these analyses were only conducted for the original, not the revised, base-case results). The results of this analysis suggested that the likelihood of the incremental cost-effectiveness ratio (ICER) being greater than £20,000 ranged from 50% (for paroxysmal AF with no structural heart disease compared with class 1c agents) to 96% (for

paroxysmal AF with no structural heart disease compared with sotalol). The likelihood of the ICER being less than £30,000 ranged from 82% to 98% for the same two clinical scenarios described above. The manufacturer completed a number of one-way sensitivity analyses (these analyses were only conducted for the original, not the revised, base-case results; see appendix 20 of the manufacturer's submission). The scenarios that had the greatest effect on the ICER were those using a 1-year time horizon (rather than lifetime) and using the lower 95% CI of mortality benefit for comparators and the upper 95% CI for dronedarone (that is, assuming minimum mortality benefit from dronedarone).

3.2 Evidence Review Group comments

The ERG considered that the manufacturer's economic evaluation met all the requirements of the NICE reference case, had an appropriate structure for the decision problem, and was overall, of high quality. The ERG could not perform a comprehensive validation of the SIMUL8 model owing to delays in receiving an updated model following identification of several coding errors and the complexities of the coding. It commented that a number of coding errors were addressed in a revised model submitted by the manufacturer. However, it noted that the manufacturer was not able to provide revised sensitivity and probabilistic analyses because of lack of time.

The ERG made several comments about the economic evaluation of dronedarone compared with standard baseline therapy (as a first-line treatment in people with multiple cardiovascular risk factors). It was uncertain whether the use of dronedarone as a first-line treatment alongside standard therapy is in accordance with its indicative licence, which does not indicate the use of dronedarone for preventing mortality or other cardiovascular disease events. The ERG noted that the manufacturer claimed the appropriateness of dronedarone in this group of people was based on a subgroup analysis of ATHENA trial results by $CHADS_2$ score. The ERG commented that although

the results show mortality benefits of dronedarone for the people with higher risk of stroke ($CHADS_2$ score of 4 or higher), this was a post-hoc analysis and the trial was not set up to address this question. It stated that in the trial, dronedarone was only compared with placebo, therefore it is not known whether another anti-arrhythmic agent could have achieved the same or greater benefits. The ERG also noted that it is unclear how the pharmacological mechanism of dronedarone is different from that of any other AAD.

The ERG noted that the manufacturer used step-wise comparisons to evaluate the cost effectiveness of dronedarone, which do not address the full decision problem when there are two or more comparators (for example, the treatment for people with paroxysmal or persistent AF with no structural heart disease whose AF has not been controlled with standard therapy is either sotalol or class 1c agents). The ERG also pointed out that it is possible that dronedarone is more cost effective when used at later points in the treatment pathway but the economic evaluation does not consider alternative sequences of treatments (for example, as a second-line AAD alternative to amiodarone in people with paroxysmal AF and coronary artery disease in whom a first-line AAD fails).

The ERG was concerned about the use of the control arm of the ATHENA trial as a key source of data for baseline events rates. It considered that the people in the ATHENA trial represented a moderate- to high-risk population that may not be generalisable to typical people with AF in the NHS.

As stated earlier, the ERG was concerned about the different inclusion and exclusion criteria used to identify studies for the meta-analyses and MTC (see page 12). The ERG considered that the exclusion of available evidence from the MTC raised uncertainty about the appropriateness of using the treatment effects estimated from the MTC in the economic model. It noted that there were some inconsistencies in the direction of effects reported in the direct and indirect analyses and the MTC. The ERG commented that even though the

meta-analyses and MTC included a synthesis of data on adverse events, this information was not used in the economic model. The ERG also commented that there was inconsistency in the methods and sources used for estimating dronedarone event rates and those used for comparators.

The ERG commented that in general, the manufacturer's approach to estimating resource use and costing is appropriate. However, it considered that the assumptions around initiation and monitoring costs were not sufficiently justified (for example, it is not clear why dronedarone can be initiated in an outpatient setting whereas other AADs require hospitalisation). The ERG also commented that the costing of adverse events was based on expert opinion and is subject to uncertainty.

The ERG was concerned about the assumption that class 1c agents have a similar effect on mortality as dronedarone and no effect on stroke (owing to lack of effectiveness evidence, no studies of class 1c agents met the inclusion criteria of the MTC for these two outcomes). Following a request for clarification, the manufacturer updated the model so that there was no mortality benefit for dronedarone compared with class 1c agents but maintained the treatment effect for dronedarone for the outcome of stroke. The ERG commented that an absence of evidence does not imply a lack of treatment effect and the assumption that class 1c agents have no mortality benefit suggests a potential positive bias in favour of dronedarone. The ERG also noted that the direct analysis suggested a positive effect of class 1c agents on all-cause mortality relative to standard therapy (OR 0.68) and the indirect analysis suggested a positive effect relative to dronedarone (OR 0.80).

The ERG commented on a number of issues with the derivation of utilities from the AFTER cohort (see page 90 of the ERG report). The ERG's main concern was that the regression model used in the manufacturer's economic model differed from the one reported in the AFTER study in that it did not allow for differences according to the type of AF. This meant that QALYs were

driven entirely by the incidence of events and there was no underlying difference between different subgroups. The ERG also pointed out that utilities in the economic model appeared to be higher than EQ-5D norms for the UK population and therefore the overall estimates of QALYs associated with the different treatments are likely to be optimistic.

The ERG stated that the results of the univariate sensitivity analyses showed that the base-case results were relatively robust to the majority of the inputs considered. However, it noted that while the majority of the sensitivity analyses had a minor impact on the ICERs, it is unclear what impact these may have in combination. The ERG thought that the robustness of the cost-effectiveness results could have been reinforced by using multivariate sensitivity analyses.

3.2.1 Additional work undertaken by the ERG

The ERG made two revisions to the model. The first was to correct an inconsistency in adverse event costs between the Excel and SIMUL8 files of the model (for revised adverse event costs, see page 101 of the ERG report). The second was to correct an inconsistency between cells in the Excel file in relation to the length of time that mortality benefits were applied in the model. The ERG noted that in the manufacturer's base case, mortality benefits are assumed to be incurred over a lifetime; however, owing to a coding error, the benefits are only applied for 2 years. The ERG's revisions resulted in considerably lower ICERs for the comparison of dronedarone with sotalol and amiodarone than those of the manufacturer's base case (ICERs ranged from £1895 to £4014 in the ERG's analysis applying a lifetime mortality benefit compared with £1980 to £8142 in the base case). The results for dronedarone compared with class 1c agents were unaffected because both drugs are assumed to have the same mortality benefit as standard care.

The ERG also conducted exploratory analyses to identify the main drivers of the cost-effectiveness results (see pages 103 to 106 of the ERG report). Based on these analyses, the ERG made the following conclusions.

- Dronedarone is not cost effective relative to comparators if it is assumed that the only effect of treatment is a reduction in AF recurrence (ICERs ranged from £1,355,984 to £70,323,846 when only a treatment effect on AF recurrence is assumed).
- The main driver of cost effectiveness of dronedarone compared with standard therapy, sotalol or amiodarone is mortality benefit (ICERs ranged from £1815 to £4566 when a treatment effect on both AF recurrence and mortality is assumed).
- Treatment effect on stroke and adverse events had a limited impact on cost effectiveness for the comparisons of dronedarone with standard therapy, sotalol or amiodarone (ICERs ranged from £1688 to £3964 when a treatment effect on AF recurrence, mortality and stroke is assumed).
- The main driver of cost effectiveness of dronedarone compared with class 1c agents is the combined benefits of reductions in stroke and adverse events. When stroke benefits (but not adverse events) were included in the model, the ICERs were approximately £45,000 per QALY gained; however, in the base case (which included treatment effect on both stroke and adverse events), the ICERs were approximately £20,000 per QALY gained.

The ERG also performed analyses exploring the impact on the cost-effectiveness results of key assumptions about treatment estimates. Each analysis and the impact on the base-case ICERs are summarised below (full results are on pages 107 to 113 of the ERG report).

- When assuming there is no difference in dronedarone mortality benefit across subgroups by $CHADS_2$ score, the ICERs increased by approximately 200% but were still well below £20,000 per QALY (ranging from £7,589 to £9,147).

- When assuming sotalol and amiodarone have no effect on mortality relative to standard therapy but keeping the mortality benefit of dronedarone (rather than assuming a negative effect on mortality with sotalol and amiodarone), the ICERs increased by approximately 400% but were still below £20,000 per QALY (ranging from £7,242 to £8,839).
- When assuming sotalol and amiodarone have the same effect on mortality as dronedarone, the ICERs increased to between £55,063 and £119,704.
- When assuming class 1c agents have the same effect on mortality as dronedarone, there were marginal changes to the ICERs (ICERs not reported).
- When assuming class 1c agents have greater mortality benefits than dronedarone (using an odds ratio of 0.68 taken from the direct meta-analysis), dronedarone was dominated by class 1c agents (that is, class 1c agents had higher effectiveness and lower costs than dronedarone).
- When assuming class 1c agents have the same effect on stroke as dronedarone, the ICERs doubled and were above £30,000 per QALY (£36,975 for paroxysmal AF and £38,584 for persistent AF).

In addition to the above analyses, the ERG re-calculated the MTC of all-cause mortality using a wider range of studies than that used in the manufacturer's MTC (that is, including studies reporting 12-month mortality data and studies with zero events by using continuity correction). The resulting odds ratios were lower than those in the manufacturer's MTC for all comparisons. When using these estimates in the economic model, all ICERs increased relative to the base case, although they were still well below £20,000 per QALY.

The ERG also explored the uncertainty around treatment initiation and monitoring costs and utility weights used in the model (see pages 111 to 113 of the ERG report). The impact on the ICERs for all analyses and comparisons was marginal.

3.3 Further considerations following premeeting briefing teleconference

3.3.1 Equality and diversity

No equality and diversity issue were identified during scoping or in the manufacturer's submission.

4 Authors

Sally Gallaugher and Bhash Naidoo, with input from the Lead Team (Simon Dixon, Stephen Saltissi and Paddy Storrie).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Reviews and Dissemination and the Centre for Health Economics, University of York:

- McKenna C, Maund E, Sarowar M, et al. Dronedarone for atrial fibrillation and atrial flutter. A Single Technology Appraisal. Centre for Reviews and Dissemination and Centre for Health Economics, October 2009.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Sanofi-Aventis

II Professional/specialist, patient/carer and other groups:

- Arrhythmia Alliance
- Atrial Fibrillation Association
- Primary Care Cardiovascular Society
- Society for cardiothoracic surgery of Great Britain & Ireland