



# Dronedaronone for the treatment of atrial fibrillation and atrial flutter

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## Abstract

This paper presents a summary of the evidence review group (ERG) report on the clinical effectiveness and cost-effectiveness of dronedaronone for the treatment of atrial fibrillation (AF) or atrial flutter based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The population considered in the submission were adult clinically stable patients with a recent history of or current non-permanent AF. Comparators were the current available anti-arrhythmic drugs: class Ic agents (flecainide and propafenone), sotalol and amiodarone. Outcomes were AF recurrence, all-cause mortality, stroke, treatment discontinuations (due to any cause or due to adverse events) and serious adverse events. The main evidence came from four phase III randomised controlled trials, direct and indirect meta-analyses from a systematic review, and a synthesis of the direct and indirect evidence using a mixed-treatment comparison. Overall, the results from the different synthesis approaches showed that the odds of AF recurrence appeared statistically significantly lower with dronedaronone and other anti-arrhythmic drugs than with non-active control, and that the odds of AF recurrence are statistically significantly higher for dronedaronone than for amiodarone. However, the results for outcomes of all-cause mortality, stroke and treatment discontinuations and serious adverse events were all uncertain. A discrete event simulation model was used to evaluate dronedaronone versus antiarrhythmic drugs

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum ([www.hta.ac.uk/correspond](http://www.hta.ac.uk/correspond)).

and standard therapy alone. The incremental cost-effectiveness ratio of dronedarone was relatively robust and less than £20,000 per quality-adjusted life-year. Exploratory work undertaken by the ERG identified that the main drivers of cost-effectiveness were the benefits assigned to dronedarone for all-cause mortality and stroke. Dronedarone is not cost-effective relative to its comparators when the only effect of treatment is a reduction in AF recurrences. In conclusion, uncertainties remain in the clinical effectiveness and cost-effectiveness of dronedarone. In particular, the clinical evidence for the major drivers of cost-effectiveness (all-cause mortality and stroke), and consequently the additional benefits attributed in the economic model to dronedarone compared to other anti-arrhythmic drugs are highly uncertain. The final guidance, issued by NICE on 25 August 2010, states that: Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation **only** in people: whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option, **and** who have at least one of the following cardiovascular risk factors: - hypertension requiring drugs of at least two different classes, diabetes mellitus, previous transient ischaemic attack, stroke or systemic embolism, left atrial diameter of 50 mm or greater, left ventricular ejection fraction less than 40% (noting that the summary of product characteristics [SPC] does not recommend dronedarone for people with left ventricular ejection fraction less than 35% because of limited experience of using it in this group) or age 70 years or older, **and** who do not have unstable New York Heart Association (NYHA) class III or IV heart failure. Furthermore, 'People who do not meet the criteria above who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop'.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA.<sup>2</sup>

## Description of the underlying health problem

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence that increases with age. Symptoms of AF include difficulty breathing, palpitations, chest pain, dizziness and loss of consciousness. AF is also associated with an increased risk of thrombus formation and consequently a fivefold increased risk of stroke compared to people without AF.<sup>3</sup> AF and its symptoms can be treated using pharmacological or electrophysiological/surgical interventions to either control ventricular rate, which does not eliminate AF but improves AF symptoms, or restore normal sinus rhythm. There are three different types of AF: paroxysmal, which spontaneously terminates within 7 days; persistent, which requires treatment (cardioversion) to terminate; and permanent, in which normal heart rhythm can not be restored by treatment.

## Scope of the evidence review group report

Dronedarone, Multaq® (Sanofi–Aventis), is an antiarrhythmic drug (AAD) that has properties belonging to all four Vaughan–Williams' classes of AAD. It is indicated in adult clinically stable patients with history of, or current, non-permanent AF to prevent recurrence of AF or to lower ventricular rate. The recommended dose is 400 mg twice daily, with patients expected to remain indefinitely on dronedarone unless there is lack of efficacy, or intolerability.

The manufacturer (Sanofi Aventis Ltd) presented a submission to NICE on the use of dronedarone, (within the context of its licensed indication) for

the treatment of AF and atrial flutter (AFL), both as a first-line adjunctive treatment to standard baseline therapy (with or without beta-blockers and anticoagulation therapy) and as a second-line treatment compared to other AADs: (i) class 1c agents (flecainide and propafenone); (ii) sotalol; and (iii) amiodarone.

Evidence for the efficacy and safety of dronedarone and other AADs came from randomised controlled trials (RCTs), meta-analysis (presenting direct and indirect comparisons) and a synthesis of the direct and indirect evidence using a mixed-treatment comparison (MTC). A total of 39 studies, including four studies of dronedarone [EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) ADONIS (American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm), ATHENA (A placebo-controlled, double-blind parallel arm Trial to assess the efficacy of dronedarone 400mg bid for the prevention of cardiovascular Hospitalisation or death from any cause in patiENts with Atrial fibrillation/atrial flutter) and DIONYSOS (Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation)] conducted by the manufacturer, were considered eligible for inclusion in the direct and indirect meta-analyses and the MTC; however, the studies included in the direct meta-analysis and the MTC were subject to different inclusion criteria. Outcomes of interest were: AF recurrence, all-cause mortality, stroke, treatment discontinuation (due to any cause or adverse events) and serious adverse events of treatment (SAEs).

The manufacturer's submission included a discrete event simulation model which was used to estimate the cost-effectiveness of dronedarone with other licensed AADs and standard therapy alone for AF. The comparison with standard therapy alone was restricted to high-risk elderly AF patients with a CHADS<sub>2</sub> score  $\geq 4$  (CHADS<sub>2</sub> is a stroke risk stratification scheme which is based on specific risk factors including congestive heart failure, hypertension, age > 75 years, diabetes mellitus, and prior stroke or transient ischaemic attack). This model was used to evaluate the cost-effectiveness of five main patient groups according to their clinical AF type and baseline risk factors in line with UK guidelines: (i) paroxysmal AF with no structural heart disease (SHD); (ii) paroxysmal AF with coronary heart disease; (iii) paroxysmal AF

with left ventricular dysfunction; (iv) persistent AF with no SHD; and (v) persistent AF with SHD.

## Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG critiqued the search strategy, study selection, validity assessment, outcome selection and the statistical methods used in the manufacturer's submission of clinical effectiveness. It also explored the inconsistency of inclusion and exclusion of studies and use of continuity corrected data both within and between different types of statistical analyses. In addition, the ERG also checked the validity of the MTC analysis by running it using WINBUGS software. The ERG critiqued the methods used in the manufacturer's economic evaluation. It corrected the cost-effectiveness results presented by the manufacturer, undertook additional exploratory work to identify the main drivers of cost-effectiveness and key assumptions for the different comparisons, and explored the robustness of the cost-effectiveness to specific assumptions and additional uncertainties identified by itself.

## Results

### Summary of submitted clinical evidence

The EURIDIS/ADONIS trials (see *Table 1* for study details) demonstrated that dronedarone was statistically significantly more effective than placebo for maintenance of sinus rhythm [hazard ratio (HR) 0.75; 95% confidence interval (CI) 0.65 to 0.87,  $p < 0.001$ ] and in reducing the ventricular rate during recurrence of AF/AFL [ $103.4 \pm 25.9$  beats per minute (b.p.m) vs  $117.1 \pm 30.4$  b.p.m,  $p < 0.001$ ].<sup>4</sup>

The ATHENA study (see *Table 1*), which recruited only moderate- to high-risk elderly AF patients, 75% of whom were in sinus rhythm, showed that dronedarone resulted in a significant reduction in the primary composite end point of time to first cardiovascular hospitalisation or death from any cause (HR 0.76; 95% CI 0.69 to 0.84,  $p < 0.001$ ). The primary end point appeared to be mainly

**TABLE 1** Summary of dronedarone trials included in the manufacturer's submission

	<b>ADONIS/EURIDIS<sup>a</sup></b>	<b>ATHENA</b>	<b>DIONYSOS</b>
<b>Population characteristics</b>			
<i>n</i>	1237	4628	504
Dose	400mg BD	400mg BD	400mg BD
Age range	Dronedarone: mean 63.5 (10.7) years Placebo: mean 62.2 (11.1) years	Mean: 71.6 (SD 9.0) years <65 years: 18.9% 65 to <75 years: 39.5% ≥75 years: 41.6%	Mean 64 years Range 28–90 years <65 years: 52% >75 years: 19%
Type of AF	Paroxysmal and persistent AF	Paroxysmal and persistent AF At least one risk factor for cardiovascular hospitalisation	Persistent (cardioversion indicated); (although excluded, some were classed as having paroxysmal or permanent AF)
Anticoagulation used?	Majority of patients were receiving anticoagulants	44% receiving aspirin	Yes
Hypertension	Dronedarone: 60% Placebo: 50.1%	86.3%	67%
SHD	Dronedarone: 42.4% Placebo: 39.7%	59.6%	28%
CHF	Dronedarone: 17.3% Placebo: 17.87%	21.2%	22% (not III or IV at time of randomisation)
Treatment duration	12 months	Minimum 12 months	>6 months
<b>Outcome measure</b>			
Primary outcome measure	Recurrence of AF (measured by transtelephonic ECG when symptomatic)	First hospitalisation due to CV events or death	AF recurrence or premature discontinuation due to intolerance or lack of efficacy (AF recurrence measured by unscheduled ECG)
Secondary outcomes	Symptoms related to AF Mean ventricular rate during first recurrence of AF	Death from any cause Death from CV causes First hospitalisation due to CV event	Occurrence of major safety end point Occurrence of drug specific AEs
Post hoc analyses		AF recurrence (measured by scheduled ECGs, hospitalisation for AF/AFL, electrical cardioversion) Stroke	
AEs, adverse events; AF, atrial fibrillation; AFL, atrial flutter; BD, twice a day ; CHF, congestive heart failure; CV, cardiovascular; ECGs, electrocardiograms; SHD, structural heart disease; SD, standard deviation.			
a These two trials have identical protocols and are often considered as a single trial.			

driven by a reduction in time to first cardiovascular hospitalisation due to a significant reduction in hospitalisation for AF (HR 0.63; 95% CI 0.55 to 0.72,  $p < 0.001$ ). There was no statistically significant difference in all-cause mortality between patients receiving dronedarone and those receiving placebo (HR 0.84; 95% CI 0.66 to 1.08,  $p = 0.18$ ). A post hoc analysis showed that there was a statistically significant reduction in the risk of

stroke in patients receiving dronedarone compared to those receiving placebo (HR 0.66; 95% CI 0.46 to 0.96,  $p = 0.027$ ).<sup>5</sup>

The DIONYSOS trial (see *Table 1*), which directly compared dronedarone with amiodarone, showed that the incidence of recurrence of AF or premature study drug discontinuation was statistically significantly greater for dronedarone

**TABLE 2** Incremental cost per QALY results for the base-case analysis, a sensitivity analysis exploring the assumption that sotalol and amiodarone have the same effect on mortality as dronedarone; and a sensitivity analysis exploring the assumption of a treatment effect on AF recurrence alone

<b>Summary of incremental cost per QALY results for each of the base case populations</b>					
	<b>Paroxysmal AF</b>			<b>Persistent AF</b>	
	<b>No SHD</b>	<b>CAD</b>	<b>LVD</b>	<b>No SHD</b>	<b>SHD</b>
Dronedarone vs standard therapy	£3620	£4014	£3577	£3358	£3520
Dronedarone vs sotalol	£1692	£1,988	NA	£1848	NA
Dronedarone vs class Ic	£18,206	NA	NA	£18,955	NA
Dronedarone vs amiodarone	NA	NA	£1895	NA	£2349
<b>Incremental cost per QALY results for each base case population when amiodarone and sotalol are assumed to have the same effect on mortality as dronedarone</b>					
	<b>Paroxysmal AF</b>			<b>Persistent AF</b>	
	<b>No SHD</b>	<b>CAD</b>	<b>LVD</b>	<b>No SHD</b>	<b>SHD</b>
Dronedarone vs sotalol	£119,704	£102,668	NA	£92,009	NA
Dronedarone vs amiodarone	NA	NA	£55,063	NA	£71,306
<b>ERG's incremental cost per QALY results for each of the base case populations when the model assumes a treatment effect on AF recurrences alone</b>					
	<b>Paroxysmal AF</b>			<b>Persistent AF</b>	
	<b>No SHD</b>	<b>CAD</b>	<b>LVD</b>	<b>No SHD</b>	<b>SHD</b>
Dronedarone vs standard therapy	£7,486,908	£70,323,846	£1,355,984	£1,630,715	£2,254,522
Dronedarone vs sotalol	£5,232,678	D	NA	D	NA
Dronedarone vs class Ic	D	NA	NA	D	NA
Dronedarone vs amiodarone	NA	NA	£5,694,862	NA	D

AF, atrial fibrillation; CAD, coronary artery disease; D, dominated; LVD, left ventricular dysfunction; NA, not applicable; SHD, structural heart disease.

than for amiodarone (73.9% vs 55.3%,  $p$ -value < 0.0001).

Overall, the results from the direct and indirect meta-analyses and the MTC showed that the odds of AF recurrence appeared statistically significantly lower with all AADs than with non-active control, but that the odds of AF recurrence are statistically significantly higher for dronedarone than for other AADs.

There were no statistically significant differences between AADs for all-cause mortality based on the head-to-head RCT (DIONYSOS) or the results from the indirect comparison. However, in the MTC, dronedarone was reported to have a statistically significant reduction in the odds of all-cause mortality compared to both sotalol and amiodarone.

For stroke, results from the MTC analysis only were reported in the manufacturer's submission. Dronedarone was associated with a statistically

significant reduction in stroke compared to control. No significant difference was reported between dronedarone and either amiodarone or sotalol based on the results from the MTC.

With regard to treatment discontinuations, the results reported from the direct and indirect meta-analyses were inconsistent with the MTC, suggesting considerable uncertainty. Results from the different synthesis approaches showed that compared with other AADs, dronedarone had the lowest odds of SAEs. However, the omission of data from the EURIDIS/ADONIS trial for this outcome means that the results are unreliable.

### Summary of submitted cost-effectiveness evidence

No previous published cost-effectiveness studies of dronedarone in patients with AF/AFL were identified by the manufacturer. The results from the manufacturer's submission demonstrated that dronedarone appeared highly cost-effective in each

of the populations compared to using standard baseline therapy alone as first-line treatment, or compared to sotalol or amiodarone as a first-line antiarrhythmic (*Table 2*). The results for dronedarone, relative to class Ic agents, showed that dronedarone was borderline in terms of cost-effectiveness, with an incremental cost-effectiveness ratio (ICER) just above £20,000 per quality-adjusted life-year (QALY) and a 50% probability of being cost-effective at this threshold. The findings were reported to be robust across a wide range of alternative assumptions. The results appeared most sensitive to assumptions regarding the benefits from AADs on mortality.

The main driver of cost-effectiveness for the comparisons of dronedarone versus standard therapy as first-line treatment, and sotalol or amiodarone as first line antiarrhythmics, is the additional mortality benefit attributed to dronedarone. If sotalol and amiodarone are assumed to have the same effect on mortality as dronedarone, dronedarone is no longer considered to be cost-effective (see *Table 2*). Stroke benefits and differences in treatment-related adverse events have only a very limited impact on cost-effectiveness for these comparisons. In contrast, the main drivers of cost-effectiveness for the comparison of dronedarone versus class Ic agents are a combination of the benefits assumed from stroke and a reduction in adverse events. The ERG noted that if only the potential benefits of AF recurrence are included in the model then dronedarone does not appear cost-effective for any of the populations considered (see *Table 2*).

### Commentary on the robustness of submitted evidence

#### Strengths

The manufacturer conducted a comprehensive systematic review that identified not only all relevant trials of dronedarone but also additional RCTs for other relevant comparator AADs, including class Ic agents, sotalol and amiodarone. A range of alternative synthesis approaches was employed by the manufacturer in order to assess the relative effectiveness of dronedarone compared to other AADs that are currently used in the NHS. The results of these separate comparisons were reported for each of the main clinical outcomes.

In general, the ERG considered the economic submission to be of high quality, meeting the requirements of the NICE reference case. The

economic model structure was considered appropriate for the decision problem, and the detailed sensitivity analyses were thorough and informative in exploring the robustness of the results.

#### Weaknesses

Potential weaknesses that the ERG identified in relation to the clinical effectiveness evidence were:

1. The inclusion/exclusion criteria applied to studies to be included in the direct and indirect analyses were not explicitly stated.
2. Different inclusion/exclusion criteria were applied to studies for the direct meta-analysis and the MTC, with a substantial reduction in the number of studies entering the MTC compared to the direct meta-analysis.
3. Issues of clinical and statistical heterogeneity between the different studies were insufficiently reported or were not explored.
4. Neither the exchangeability of the ATHENA study with lower risk and younger AF populations nor the generalisability of the ATHENA population to the overall AF population managed in the NHS were considered.

The ERG identified a number of potential weaknesses related to the economic submission and electronic model which were considered to impact on the validity of the cost-effectiveness results. These included:

1. The treatment pathways evaluated by the manufacturer may not represent the full range of relevant strategies or sequences.
2. The use of baseline data from the ATHENA trial may not be generalisable to the UK AF population.
3. The use of a restricted set of studies to inform the relative effectiveness estimates applied in the model.
4. The assumptions used for class Ic agents, that for all-cause mortality there is no difference between dronedarone and class Ic agents, whilst for stroke, class Ic agents have no effect compared to standard care alone.
5. The estimates of the mortality effects of amiodarone and dronedarone.
6. Uncertainty surrounding the health-related quality of life (HRQoL) data used in the model.
7. Uncertainty in relation to the acquisition costs, initiation and monitoring costs of dronedarone.

The ERG explored the robustness to a number of these uncertainties. The ICER of dronedarone remained relatively robust throughout (< £20,000 per QALY) except for the following assumptions: (i) amiodarone and sotalol have the same effect on all-cause mortality as dronedarone; and (ii) class 1c has the same effect on stroke as dronedarone. In these situations, the ICER of dronedarone was well above £30,000 per QALY (see *Table 2*).

Finally, the submission does not explicitly consider the potential clinical effectiveness or cost-effectiveness of dronedarone for patients with AFL.

### Areas of uncertainty

The relative effectiveness and cost-effectiveness of dronedarone versus other AADs remains subject to a number of areas of uncertainty in terms of informing current NHS practice. These uncertainties include: (i) the generalisability of evidence from the ATHENA study to inform the management of a lower risk and younger AF population; (ii) the relative efficacy of dronedarone compared to other AADs; (iii) the validity of pooling the individual studies in the different synthesis approaches given the lack of consideration of clinical and statistical heterogeneity across the different studies; (iv) the clinical evidence for the major drivers of cost-effectiveness (e.g. all-cause mortality and stroke) and consequently, the additional benefits attributed in the economic model to dronedarone compared to other AADs; (v) the clinical evidence for the efficacy of dronedarone and other AADs to lower ventricular rate as rate control was not included as an outcome measure in the submission; and (vi) the presence and potential magnitude of any quality of life benefits attributed to dronedarone as HRQoL have not been directly assessed in any of the existing dronedarone RCTs.

There remains a number of additional sources of uncertainty related to the cost-effectiveness of dronedarone that the ERG has been unable to adequately address. This includes establishing the most appropriate source of data to inform the baseline event rates applied in the model; the position for dronedarone in the pathway of treatment sequences; HRQoL benefits of dronedarone; and the maintenance of benefits over the longer term.

## Conclusions

The effectiveness of dronedarone as an adjunctive treatment to standard care is highly uncertain, the key issue being the generalisability of the ATHENA study which reflects a moderate- to high-risk elderly AF population relative to the general AF population.

In terms of the broader comparison of dronedarone with AADs, the ERG considers that the clinical evidence is highly uncertain for the key drivers of the cost-effectiveness of dronedarone: all-cause mortality and stroke. The uncertainty arises because the potential clinical and statistical heterogeneity of the included RCTs has not been adequately considered, and the exchangeability of the ATHENA study with the other studies is questionable. Also, the additional restrictions imposed on the inclusion of RCTs in the MTC are likely to increase the overall decision uncertainty compared to a fuller use of this evidence. Furthermore, the question of how the reduction in all-cause mortality or stroke is mediated, given that dronedarone is the least effective AAD in terms of AF recurrence, remains to be elucidated.

Key issues specifically relevant to the economic evaluation include: establishing the most appropriate source of data to inform the baseline event rates applied in the model; the potential cost-effectiveness of dronedarone in a range of alternative and feasible treatment sequences; the potential HRQoL benefits of dronedarone and the maintenance of benefits over the longer term; and the absence of a final confirmed acquisition price at the time of the submission of the ERG report. Finally, the lower initiation and monitoring costs assumed for dronedarone are uncertain, although these do not appear to have a significant impact on the final ICER results.

### Implications for research

Further and longer term trials or the implementation of registries would be helpful to further establish the efficacy and safety of dronedarone relative to other AAD treatments that are regularly used in this indication within UK clinical practice. This is of particular importance in regard to outcomes of all-cause mortality and stroke, as these appear to be the key drivers of the cost-effectiveness results. Given the lack of existing HRQoL data, future RCTs of dronedarone and other AADs should also consider using a relevant

HRQoL measure. Additional evidence related to the effectiveness of AADs for patients with AFL would also be valuable.

## Summary of NICE guidance issued as a result of the STA

The final guidance, issued by NICE on 25 August 2010, states that:

Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation only in people: whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option, and who have at least one of the following cardiovascular risk factors: - hypertension requiring drugs of at least two different classes, diabetes mellitus, previous transient ischaemic attack, stroke or systemic embolism, left atrial diameter of 50 mm or greater, left ventricular ejection fraction less than 40% (noting that the summary of product characteristics [SPC] does not recommend dronedarone for people with left ventricular ejection fraction less than 35% because of limited experience of using it in this group) or age 70 years or older, and who do not have unstable New York Heart Association (NYHA) class III or IV heart failure.

Furthermore, 'People who do not meet the criteria above who are currently receiving dronedarone

should have the option to continue treatment until they and their clinicians consider it appropriate to stop'.

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