NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Dronedarone for the treatment of atrial fibrillation

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD) issued March 2010

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Sanofi-Aventis	Upon reading the second Appraisal Consultation Document (ACD2) received last month, sanofi-aventis would like to thank the Appraisal Committee for reconsidering the evidence and for fully considering the views expressed by ourselves, the clinical specialists and patient experts. We do not believe there are any major factual errors within the new document although we would like to provide some recommendations for minor changes/corrections. These are provided within the appendix to this letter. We look forward to this preliminary recommendation progressing to full guidance over the coming months.	Comment noted.
Sanofi-Aventis	Pg 3, section 1.1 We welcome the revised recommendation for dronedarone.	Comment noted.
Sanofi-Aventis	Pg 4, section 2.1 As previously requested we would ask the Committee to reflect in their description of dronedarone the wording that dronedarone offers benefits from reduced hospitalisation. The following wording might be considered helpful: "Dronedarone has a marketing authorisation…… to lower ventricular rate. Within section 5.1 of the SPC reference is also made to the reduction in the risk of AF hospitalisation."	Comment noted. This section of the FAD reflects the indication listed in the marketing authorisation not what is written elsewhere in the SPC.
Sanofi-Aventis	Pg 5, section 3.1 We recommend that Section 3.1 includes clarification around what the Committee mean by 'standard beta-blocker'. Sotalol, for example, might be considered a beta-blocker however it is generally used in AF as a Class III antiarrhythmic agent; therefore, we consider that it will be helpful to exclude it from the definition of standard beta-blocker. The following wording might be considered helpful: "According to 'The management of atrial fibrillation' (NICE clinical guideline 36), beta-blockers (excluding sotalol) in addition to anticoagulation should be the initial treatment option for people with…"	Comment noted. This section of the FAD reflects what is written in the NICE clinical guideline on atrial fibrillation (CG36).
Sanofi-Aventis	Pg 6, section 3.2 The main clinical evidence is based on four placebo-controlled randomised clinical trials, rather than the three stated in this paragraph. EURIDIS and ADONIS, whilst published in a joint manuscript, are in fact two individual clinical trials. They are also considered as separate trials later on in the ACD (see page 11 section 3.9). We therefore request that the opening sentence is corrected to read "…based on four randomised controlled trials…" Within the description of ATHENA we would also recommend that for consistency with descriptions of the other trials, the percentage of patients in ATHENA who, at baseline,	Comments noted. The FAD has been amended accordingly (see section 3.2).

Consultee	Comment	Response
	received beta-blockers and anticoagulation (70.6% and 60.2% respectively) should be reported.	
Sanofi-Aventis	Pg 8, section 3.5 For completeness, we recommend that all of the pre-specified secondary analyses of ATHENA should be presented. Consequently, we advise that the one missing analysis, comparing the time to first hospitalisation due to cardiovascular events is reported. The following wording might be considered helpful: "The hazard ratio for the time to first hospitalisation due to cardiovascular events was 0.74 (95% CI 0.67 – 0.82; p < 0.001)."	Comments noted. This section of the FAD summarises the key clinical evidence and is not intended to include a comprehensive list of all results of clinical trials.
Sanofi-Aventis	Pg 9, section 3.7 Please note that there is a factual error. The percentages for the primary composite outcome in DIONYSOS are 75.5% for dronedarone and 58.8% for amiodarone. The hazard ratio stated is correct.	Comment noted. The FAD has been amended accordingly (see section 3.7).
Sanofi-Aventis	Pg 10, section 3.8 Please note that where you have reported the results of DIONYSOS as academic in confidence they are now available in the public domain.	Comment noted. The FAD has been amended accordingly (see section 3.8).
Sanofi-Aventis	Pg 12, section 3.10 For clarity we would suggest the addition of a footnote into the following sentence: "When dronedarone was evaluated as part of initial treatment for people with a CHADS2 score of 4 or more (in addition to standard baseline therapy) the comparator was standard baseline therapy alone (including beta blockers* and anticoagulation)." *excluding sotalol	Comment noted. This section of the FAD reflects what is written in the NICE clinical guideline on atrial fibrillation (CG36).
Sanofi-Aventis	Pg 15, section 3.16 Please note that the DIONYSOS study had a minimum follow-up of 6 months and median treatment duration of 7 months. While it is reasonable to describe this study as short-term, the reference to "6 months" needs further clarification. The following wording might be considered helpful: "It also noted that the DIONYSOS trial was short-term (median treatment duration 7 months).	Comment noted. The FAD has been amended accordingly (see section 3.16).
Sanofi-Aventis	Pg 23, section 4.5 Please note that the only trials that investigated ventricular rate within the licensed population of non-permanent AF patients were the EURIDIS and ADONIS trials. The following wording might be considered helpful: "It noted that the licensed indication for dronedarone was to prevent recurrence of atrial fibrillation or to lower ventricular rate but that the only studies that assessed ventricular rate in the licensed population were the EURIDIS and ADONIS trials." In addition, sanofi-aventis believe that the unique combination of rhythm and rate	Comment noted. The FAD has been amended accordingly (see section 4.7). Comment noted. The statement about the

Consultee	Comment	Response
	properties of dronedarone are an integral part of its mode of action which ultimately manifests in the reduction in CV hospitalisation and death, compared to placebo, as noted in the ATHENA trial. Given that these outcomes are incorporated within the economic model it follows that the potential results of the rate control properties are also implicitly captured within the economic model. We recognise that the committee considered this, however we suggest a modest change is appropriate to the text. The following wording might be considered helpful: "The Committee was also aware that ventricular rate was not explicitly included in the manufacturer's economic model."	manufacturer's model is factually correct as is stands therefore no change has been made to the FAD (see section 4.7).
Sanofi-Aventis	Pg 26, section 4.11 The ANDROMEDA trial was an investigation of dronedarone in patients who were hospitalized with new or worsening heart failure (New York Heart Association [NYHA] functional class III or IV). Atrial fibrillation was not an inclusion criterion. Coincidentally some patients in this trial did have AF as would be expected given the nature of their condition; consequently, a correction should be made in this paragraph. The following deletion might be considered helpful: It was aware of the ANDROMEDA trial in which dronedarone was associated with an increased risk of mortality in people with severe congestive heart failure. and noted that this trial did not include people with atrial fibrillation.	Comment noted. The FAD has been amended accordingly (see section 4.13).
Sanofi-Aventis	Pg 29, section 4.15 For consistency with language elsewhere within the document, we suggest that the phrase "second-line antiarrhythmic" be changed slightly. The following change might be considered helpful: "It noted the ICERs from this analysis were below £15,000 per QALY gained for the analyses of dronedarone as a second-line treatment alternative to sotalol, class1c drugs and amiodarone."	Comment noted. The FAD has been amended accordingly (see section 4.17).
Sanofi-Aventis	Pg 31, section 4.19 For consistency of language we would suggest that the last sentence of this paragraph be changed slightly to add a footnote around the beta-blockers as per comment 3.10: "The Committee concluded that dronedarone could not be recommended as a first-line treatment for atrial fibrillation (in addition to standard baseline therapy usually including beta-blockers*)" * excluding sotalol	Comment noted. This section of the FAD reflects what is written in the NICE clinical guideline on atrial fibrillation (CG36). The guideline used the exact wording 'standard beta-blocker' and does not specify 'excluding sotalol'.
Sanofi-Aventis	Pg 31, section 4.20 For consistency of language we would suggest the following changes:	Comments noted. The FAD has been amended accordingly (see section 4.21).

Consultee	Comment	Response
	"The Committee considered that these cost-effectiveness estimates were largely based on data from the ATHENA trial, which included people who had a higher risk of a major cardiovascular event, and it was uncertain whether these data were applicable to people in England and Wales with atrial fibrillation who would receive a second-line treatment. Please note that in the sentence just after the above 'trial' is spelt incorrectly.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Atrial Fibrillation Association	*Has all of the relevant evidence been taken into account?* Yes, in my opinion the committee did review all of the available evidence and were able to hear informed opinion from and ask questions of the invited 'expert' panel. I am delighted that in light of this the committee has been able to reach the decision to recommend approval of dronedarone for use in suitable AF patients. *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* I believe so. *Are the provisional recommendations sound and a suitable basis for guidance to the NHS?* I believe that in recommending approval of dronedarone in certain categories of AF patients NICE will enable arrhythmia physicians to offer a new option where none is currently available and offer patients respite from symptomatic AF and a return to a much improved quality of life. *Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?* None to my knowledge. I would like to thank Professor Clark and all members of Committee D for their care in reviewing the evidence, listening to invited 'expert' panel and in ensuring the high number of responses received following the first ACD for dronedarone were considered.	Comments noted, no changes to the FAD required.

Comments received from commentators

Commentator	Comment	Response
Medicines and Healthcare products Regulatory Agency	In section 1.1, the appraisal committee recommends that dronedarone as an option for the second-line treatment of patients who (amongst other possible factors) have left ventricular ejection fraction less than 40%; this probably reflects the population in one of the pivotal trials. However, the summary of product characteristics, in section 4.4 (Special warnings and precautions for use) states: Because of limited experience in stable patients with recent (1 to 3 months) NYHA class III heart failure or with Left Ventricular Ejection Fraction (LVEF) <35%, the use of MULTAQ is not recommended. The appraisal consultation document acknowledges this point in section 4.11 You may wish to consider how the statement from section 4.4 of the summary of product characteristics impinges on the committee's recommendations.	Comment noted. The FAD has been amended – see sections 1.1, 2.2 and 4.22. The Committee was mindful that there might be some overlap between people with cardiovascular risk factors, and those in whom dronedarone was is contraindicated (with unstable NYHA class III or IV heart failure) or not recommended (with left ventricular ejection fraction less than 35%). Therefore the Committee considered it important to emphasise in its recommendations that dronedarone should not be used in people with unstable NYHA class III or IV heart failure and to refer to the SPC caution in the SPC about the use of dronedarone in people with left ventricular ejection fraction less than 35%.
Arrhythmia Alliance	*Has all of the relevant evidence been taken into account?* In the second meeting the committee were able to hear informed opinion from the full panel of experts and ask questions. It is opinion that they were able to consider all of the evidence and be informed of its relevance in the management of Atrial Fibrillation (AF). I am delighted as a result they were able to review and change the earlier decision and so recommend dronedarone for inclusion in the management of symptomatic AF. *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* I understand it to be. *Are the provisional recommendations sound and a suitable basis for guidance to the NHS?* Based on the information available and the informed guidance from the expert panel I believe the provisional recommendations are a suitable basis for guidance to the NHS. *Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination againstany group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?* None to my knowledge.	Comments noted, no changes to the FAD required.

Commentator	Comment	Response
	On behalf of all ofour members and the significant minority group of AF patients who will benefit from this positive recommendations, I would very much like to thank Professor Clark and all members of Committee D for their positive review.	
GUCH Patients Association	It appears that the various arguments have been put and some cases have sensibly been highlighted for when Dronedarone could be used. However, whilst the issue over the long term toxicity effect of alternate drugs in those with congenital heart disease was highlighted, there does not appear to be the appropriate inclusion in the categories for the use of the drug in these cases. This point was also raised at the meeting at the House of Commons where various parties met to discuss the NICE consultation. "4.3 The Committee also heard from patient experts that younger people who cannot take class 1c drugs or sotalol in particular might benefit from an antiarrhythmic drug that is more tolerable than amiodarone because of the longer length of time that they are likely to need treatment." The point is obviously not just "younger" patients as such but those who start on them when younger and need to be on them for most of their lives, therefore increasing the toxicity issues which are not so apparent in other patients. This indeed could be argued as discriminating against those who are young heart patients. I would therefore suggest that to the exemptions where use is permitted that the following line be added: - Those with congenital heart disease where it is considered the use of an alternative drug may not be as appropriate I hope that this is accepted.	Comment noted. The Appraisal Committee was not presented with any evidence on the use of dronedarone in patients with congenital heart disease and it could not make any recommendations specifically in this group.
Royal College of Nursing	*Has the relevant evidence has been taken into account?* The evidence considered seems comprehensive. *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?* This seems appropriate. *Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?* Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add.	Comments noted, no changes to the FAD required.

Commentator	Comment	Response
	The RCN would welcome guidance to the NHS on the use of this health technology. *Are there any equality related issues that need special consideration that are not covered in the ACD?* None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	
The Stroke Association	The Stroke Association welcomes the opportunity to comment on the new NICE appraisal consultation document: Dronedarone for the treatment of non-permanent atrial fibrillation (AF). We welcome the revised treatment recommendations in the document as this represents a step forward for the treatment of a subgroup of AF patients who are currently difficult to treat, as we understand that this new drug may both reduce the symptoms of AF and improve outcomes in respect of reduced death from stroke. We believe the adoption of these revised guidelines will expand the limited number of treatment options currently available to AF patients and could bring significant quality of life improvements for those patients who find existing anti-arrhythmic drugs ineffective or cannot tolerate the drug they are prescribed.	Comments noted, no changes to the FAD required.

Comments received from members of the public

Role*	Section	Comment	Response
Patient	1	For a drug that it is reported costs Â£2 per day and has significantly less side effects than ameoderone I am shocked at the limitations placed on this drug. Â You appear to be penalising young relatively healthy people who have atrial fibrilation and sentencing them to coninue to use a toxic substance to continue a normal life.	Comment noted. The Appraisal Committee considered that using dronedarone as a second-line alternative to amiodarone, class 1c drugs, or sotalol for the treatment of atrial fibrillation could be considered a cost-effective use of NHS resources in people who have the same characteristics as the population in the ATHENA trial (that is, they have at least one additional cardiovascular risk factor; see FAD section 4.22).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
Patient	2	The possible side effects of this drug seem to me, a long term user of ameoderone, quite trivial in comparison to liver kidney thiroid and eysite issues I am having tests for every few months.	Comment noted. The Appraisal Committee's considerations about the relative adverse effects of dronedarone and amiodarone can be found in section 4.14 of the FAD.
Patient	7	Whilst 2013 does seem a long way off I realise that it does sometimes take considerable time to obtain statistically significant amounts of data. Â With regard to the consultees how is this list put together? Â Does it include people from all demographics especially relatively young people who hope to be on the drug for 30 years plus?	Comment noted. The process for identifying stakeholders is explained in the section 2.2 of the Single Technology Appraisal Process guide (www.nice.org.uk/media/913/06/Guide_to_the_STA-proof_6-26-10-09.pdf).
Physician / academic	1	You have correctly identified the criteria used for enrolling patients in the pivotal ATHENA trial, but have not provided guidance for subsets of patients in which its use could be considered. For example, for patients with no or only minimal heart disease, including those with hypertension but no LV hypertrophy, the ACC/AHA guideline recommends flecainide, propafenone, and sotalol as first-line agents "based on their proven safety and efficacy in this population." For patients with coronary disease but no heart failure, dofetilide and sotalol are the recommended first-line agents, but "dronedarone might be a reasonable alternative to these drugs or to amiodarone. If you look at the guideline algorithm, the majority of the use of dronedarone is confined to a third-line choice, and in some instances a second-line choice. What about patients on dronedarone who go on to develop worsening CHF (greater than NYHA Class III)? Of course consideration of the individual patient preferences is important in clinical decision making.	Comment noted. The purpose of a single technology appraisal is to appraise a single product, device or other technology, with a single indication. NICE has produced a clinical guideline on atrial fibrillation (CG36) which outlines the pathway of care for different subsets of patients with this condition. The guideline will be considered for review in June 2011.
Physician / academic	2	Generally, this is faithful to the evidence and label	Comment noted, no changes to the FAD required.
Physician / academic	3	Dronedarone is modestly effective as an antiarrhythmic compared to placebo, it is half as effective as amiodarone and was not been proven to be better tolerated compared to 400 mg amiodarone in the DIONYSOS trial. A lower dose of amiodarone (200 mg daily) has a well-established safety track record, and it would be even more difficult to demonstrate superior safety of dronedarone compared with 200 mg amiodarone. Thus, given its modest antiarrhythmic efficacy, reduced efficacy compared with amiodarone, lack of a safety or cost advantage over amiodarone Â it is hard to envision an expensive and ineffective agent (dronedarone) as a first-line therapy in management of patients with AF.	Comment noted. The guidance recommends dronedarone as an option for the second line treatment of atrial fibrillation (see FAD section 1.1).

Role*	Section	Comment	Response
Physician / academic	4	The quality of the data underlying the pivotal trial ATHENA are suspect and do not stand up to scrutiny. First, the patient population enrolled was carefully selected to be low-risk (after the excess mortality observed in ANDROMEDA which enrolled a higher risk population). Second, the trial protocol was amended a few times and the actual enrollment exceeded the previously planned enrollment by approximately 300 patients (which ended up driving the difference in CV mortality towards significance). Third, the endpoints were not adjudicated by an events committee (it is puzzling to know why it wasnt given that the previous trial ANDROMEDA had utilized an events committee to adjudicate endpoints). Fourth, the primary composite endpoint was driven by CV hospitalization, an arguably soft endpoint. Fifth, the information regarding the reasons for CV hospitalizations was not captured. Sixth, reduced CV hospitalizations did not translate into improved symptom or QOL status. Finally, the patient population enrolled in ATHENA does not truly represent the population encountered in routine clinical practice, thereby challenging the relevance of the findings to guide clinical practice.	Comment noted. The Committee considered the patient population in the ATHENA trial and the relevance of the data from this trial to the population of people with atrial fibrillation in the UK (see FAD sections 4.16 and 4.22).
Physician / academic	5	Appropriate. Bottom line, dronedarone has very modest efficacy as an antiarrhythmic agent, and based on the current evidence, I agree with the original NICE recommendations that its use for the treatment of nonpermanent atrial fibrillation or atrial flutter can only be supported as a second- or third-line agent after guideline-recommended first-line agents have failed. Please refer to the following MS for details: Singh D, Cingolani E, Diamond GA, Kaul S. Dronedarone for atrial fibrillation. Have we expanded the antiarrhythmic armamentarium? J Am Coll Cardiol 2010 55:1569-1576.	Comment noted, no changes to the FAD required.
Physician / academic	6	To further understand how dronedarone will fare against amiodarone in the wider population with heart disease, more studies with longer follow-up are needed. At the very least, these studies need to demonstrate superior tolerability of dronedarone without unacceptable loss of efficacy in the maintenance of sinus rhythm and quality of life, or without an increase in morbidity or mortality compared with low-dose amiodarone.	Comment noted, no changes to the FAD required.
Physician / academic	7	Seems appropriate.	Comment noted, no changes to the FAD required.