**National Institute for Health and Clinical Excellence**

# Dronedarone for the treatment of atrial fibrillation and atrial flutter

**Comment 1: the draft remit**

| Section | Consultees | Comments | Action |
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| Appropriateness | Sanofi-aventis | Sanofi-aventis believe that an appraisal of dronedarone for the reduction of cardiovascular (CV) hospitalisation or mortality in patients with a history of, or current, atrial fibrillation (AF) and atrial flutter (AFL) is appropriate. Dronedarone has been subject to an extensive clinical trial programme which has consistently demonstrated the efficacy and safety of the product in the AF/AFL population (total number of patients = 6285)<br>It is the first anti-arrhythmic product that has demonstrated a significant improvement in reducing the risk of CV hospitalisation and mortality in patients with a history of or current AF/AFL. | Comment noted |

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| Wording | Sanofi-aventis | The pharmacological management of AF/AFL has been constrained by the lack of newer, more effective technologies in recent years. Those agents that are commonly used have supporting data that has typically measured markers of disease such as time to AF recurrence from sinus rhythm, but have never demonstrated a direct benefit on key clinical outcomes such as mortality and morbidity. For the first time in the arena of this significant disease a new anti-arrhythmic drug is able to offer evidence of reduction of cardiovascular hospitalisation and mortality. The landmark ATHENA trial, presented at the Heart Rhythm Symposium in May 2008 (www.hrsonline.org), showed that moderate to high CV risk patients with AF and AFL could significantly reduce their risk of CV hospitalisation and mortality with the use of dronedarone in addition to standard baseline therapy compared to baseline therapy alone.<br>The wording of the remit does not adequately reflect the cost burden felt by the NHS as a result of AF and AFL. AF/AFL consumes around 1% of all health care expenditures and indirectly contributes to an additional 2% of the health care costs in the UK (Stewart S et al, 2004). Stroke, a major outcome of AF, is estimated to cost between £2,680 and £4,102 per acute admission (HRG Data - National Tariff 2008/2009). 20 to 30% of all acute stroke patients are found to be in AF, this has been the attributed cause of stroke in one-quarter of patients over 80 years of age. (Glader EL et al, 2004. Wolf PA et al, 1987)<br>Costs as a result of hospitalisation (due to cardiac causes) observed in trials involving dronedarone range from £661 (syncope - E31/32) to £4,787 (acute MI - E11/12) with admissions due to arrhythmia or conduction disorder estimated to cost between £898 (<70 or w/o cc - E30) and £1,767 (>69 or w cc - E29)(HRG Data, National Tariff 2008/2009). By demonstrating a reduction in cardiovascular hospitalisation it is expected that dronedarone could be shown to lead to a reduction in cost burden on the NHS due to these causes. | Comment noted. The background is not an exhaustive summary of the disease. The scope does not take account of the resource consumption or saving associated with a technology though these are important considerations in the economic analysis |
| Timing Issues | Sanofi-aventis | The landmark ATHENA study (presented at Heart Rhythym Symposium, May 2008. Slide set available at http://www.theheart.org/article/867591.do ) showed that dronedarone significantly reduces the risk of CV hospitalisation or mortality in patients with AF/AFL. Dronedarone is the first AAD to have demonstrated such an impact on key clinical endpoints and offers the potential to address an urgent unmet medical need in the provision of treatment within the NHS. To ensure that patients can benefit from this significant advance in treatment we would welcome the opportunity to work with NICE to ensure guidance is available soon after launch. | Comment noted |

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| Additional comments on the draft remit | | None received | |

**Comment 2: the draft scope**

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| Background information | Sanofi-aventis | The cumulative data from 44 studies in a systematic review of AF (Lafuente-Lafuente et al, 2006) showed that several drugs are effective at preventing recurrences of atrial fibrillation (including flecainide, sotalol and amiodarone) but all of them increased adverse effects and in some studies a trend to increased mortality was observed. The review accepts as a limitation that studies do not typically look at outcomes associated with AF (e.g. stroke) and concludes that it is unclear if the long-term benefits obtained with antiarrhythmic drugs outweigh their risks. It is clear that outcome data and safety profiles are important factors when considering efficacy of anti-arrhythmic drugs. | Comment noted. |
| The technology/ intervention | Sanofi-aventis | Sanofi-aventis believe the description to be accurate. | Comment noted |
| Population | Sanofi-aventis | Sanofi-aventis believe that the appropriate population for dronedarone will be moderate to high CV risk patients with paroxysmal or persistent AF or AFL on top of standard baseline therapy including beta-blockers. This assertion is based on the ATHENA population who were observed to experience the beneficial effects of dronedarone.<br>The expected population will exclude patients with NYHA Class IV heart failure as these patients were excluded from the ATHENA study. | The population has been amended in the scope to take account of the expected clinical use of dronedarone in keeping with the trial population. The population is not limited to moderate and high cardiovascular risk as clinical experts at the workshop believed it would be considered even in people with low risk.<br>Exclusions from the population would depend on the marketing authorisation of the drug |

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| Comparators | Sanofi-aventis | Dronedarone is the only AAD that has demonstrated a reduction in cardiovascular hospitalisation and mortality within a clinical trial setting while used as an adjunctive therapy to standard baseline therapy (ATHENA). Based on the results of this study it is felt that an appropriate comparator would be standard baseline therapy for paroxysmal and persistent AF and AFL including Beta-Blockers (BBs). | Comparators have been amended in the scope to consider standard baseline care and beta blockers at first line and other anti-arrhythmic drugs at second line according to their indications |
| Outcomes | Sanofi-aventis | The appraisal should focus on outcomes that are of most relevance to patients, clinicians and decision makers. In this respect we believe that the primary outcomes should seek to address benefits in mortality and cardiovascular hospitalisation.<br>Outcomes to be measured should include:<br>-CV hospitalisation or mortality<br>-Adverse event profile<br>-Health related quality of life (QoL) | It was decided at the workshop that mortality should include all cause mortality in the scope. The avoidance of hospitalisation will be considered in the economic analysis |
| Economic analysis | | No comments received | |
| Equality | Sanofi-aventis | Sanofi-aventis is not aware of any factors relating to the development or use of dronedarone that would lead to discrimination. | Comment noted |
| Other considerations | Sanofi-aventis | The results of the landmark ATHENA study have only recently been made public and a full publication is anticipated later this year. This study is significant and has implications for the framework of the scope. We would welcome the opportunity to explore the key issues with NICE and other stakeholders during the scoping workshop. | Comment noted |

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| Questions for consultation | Sanofi-aventis | • *Would an improved side-effect profile lead to dronedarone replacing other AADs used earlier in the treatment pathway?*<br>Sanofi-aventis believe that the positive outcome data seen in ATHENA should represent the main factor when considering the position that dronedarone should adopt in the Atrial Fibrillation / Atrial Flutter management guidelines.<br>• *Are the comparators for AF the same as for flutter?*<br>Patients included in ATHENA, EURIDIS and ADONIS had either AF or AFL so comparators could be considered to be the same. The scope of the CG36 guidelines includes "Atrial flutter that is indistinguishable from AF in terms of aim of treatment." That appears to be the same for the trials as mentioned.<br>• *Should non-pharmacological interventions be included as comparators, if so which interventions should be included?*<br>Current non-pharmacological therapies are carried out in relatively limited numbers in the UK and are largely performed on patients who have AF that is resistant to pharmacological treatment. This also reflects the NICE recommendations as found in CG36 section 12.3.3 R66. As this group of patients are typically identified much later in the AF management guidelines than the proposed position of dronedarone we believe that a comparison with non-pharmacological therapies would not be appropriate. We are also not aware of any definitive data demonstrating reduction in morbidity and mortality for non-pharmacological treatments compared to standard medical management of AF/AFL.<br>• *Which process would be the most suitable for appraising this technology?*<br>Sanofi-aventis agree that the STA process is the most suitable. | Noted<br><br>Ablation would be considered early on in the management of AFL and where this is not appropriate it will be managed along the lines of AF.<br><br>Ablation is not a comparator in the scope as it would be considered before dronedarone and not instead of it.<br><br>Noted. |
| Additional comments on the draft scope. | | None received | |

**Comment 4: Regulatory issues**

| Section | Consultees | Comments | Action |
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| Remit | | No comments received | |
| Current or proposed marketing authorisation | Sanofi-aventis | CiC removed | |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

Action Heart
British Society for Heart Failure
Department of Health
National Public Health Service for Wales
Royal College of Nursing
RICE – The Research Institute for the Care of Older People (formerly the Research Institute for the Care of the Elderly)
Welsh Assembly Government