sanofi aventis
Because health matters

Dr Carole Longson
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22nd April 2010

Dear Dr Longson,

Re: NICE Technology appraisal of dronedarone for atrial fibrillation (AF) March 2010

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.

Yours sincerely

[redacted]

Inc.

Appendix 1: Tabulated comments on the ACD document (March 2010)

APPENDIX

Location within ACD	Comment
Pg 3, section 1.1	We welcome the revised recommendation for dronedarone.
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."
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…"
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, received beta-blockers and anticoagulation (70.6% and 60.2% respectively) should be reported.
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; $p < 0.001$)."

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.
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.
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
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).
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 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."

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~~.
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."
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
Pg 31, section 4.20	For consistency of language we would suggest the following changes: "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.