16th September 2009

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Dear Phil,

Re: Single Technology Appraisal – Dronedarone for atrial fibrillation and atrial flutter

The Evidence Review Group (NHS Centre for Reviews & Dissemination and Centre for Health Economics – York) and the technical team at NICE have now had an opportunity to take a look at submission received on the 26th August 2009 by Sanofi-Aventis. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports. As there will not be any consultation on the evidence report prior to the Appraisal Committee meeting you may want to respond to the points raised and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by **17:00, 30th September 2009**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Where whole documents or further details have been requested, such as the full report of cost-effectiveness studies as offered on page 65 of the submission, please provide these straight away if possible.

If you have any further queries on the technical issues raised in this letter then please contact Sally Gallaugher – Technical Lead (sally.gallaugher@nice.org.uk). Any procedural questions should be addressed to Philip Higham – Project Manager (philip.higham@nice.org.uk) in the first instance.

Yours sincerely

Helen Chung
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. The proposed treatment algorithms on p71 and p72 indicate that patients can be 're-treated' with dronedarone after treatment failure. Please clarify whether this is the correct interpretation and if so explain the rationale for assuming this.

A2. Please provide any information available on how any beneficial effect of dronedarone on mortality and reducing the risk of stroke is mediated. For example, is this assumed to be via antiarrhythmic effects alone, or via another mechanism, such as rate control?

ATHENA trial

A3. Please provide the full clinical study report for the ATHENA trial.

A4. On p36 and p37 of the submission, the composite endpoint of the number of hospitalisations due to any cardiovascular event or death from any cause is reported. Table 6.5 provides figures for first hospitalisation only. Please provide the number of hospitalisations (at any stage) due to any cardiovascular event.

A5. On p39 of the submission, with regard to study discontinuation and adverse events, it states that the imbalance in the "other reasons" category was mainly due to the more frequent investigator initiation of study disallowed anti-arrhythmic medication or recurrent atrial fibrillation in the placebo group. This indicates that episodes of atrial fibrillation were recorded as part of the ATHENA trial. However, rate of recurrence of AF is not mentioned as an outcome measure in the submission nor in the article by Hohnloser et al., 2009. Please clarify whether data on AF episodes were measured in the ATHENA trial and also whether data on rate control data were measured?

A6. On p42 of the submission, a post hoc analysis of subgroups categorised by risk of stroke of CHADS2 score ≥ 4 is described. Please provide:

i. A rationale for this post-hoc analysis

ii. Full details of the post hoc analysis

iii. Details of any other studies of anti-arrhythmic drugs that have used CHADS2 in their analysis

ADONIS and EURIDIS trials

A7. Please provide a breakdown of the number of patients with atrial flutter in each study arm for ADONIS and EURIDIS separately and combined.

A8. Please provide full details of the treatment-emergent adverse events in the ADONIS and EURIDIS trials.

Meta-analysis and mixed treatment comparison (MTC)

A9. Please provide full details of the MTC, including the code and raw data for the analysis. (The document provided does not contain sufficient details of the MTC).

A10. There seem to be inconsistencies in the inclusion/exclusion criteria applied between the meta-analyses and the MTC. Please provide clarification on whether additional inclusion/exclusion criteria were applied to the meta-analysis of non-active control and head-to-head data presented in Tables 6.9 - 6.13 over and above the inclusion criteria reported in Table 6.8, page 51.

A11. Please provide additional justification for restricting trials in the MTC to those with at least 100 subjects per randomised group and at least 1 event in either group. Also, provide the rationale for separate criteria for the outcome of stroke, i.e. at least 50 subjects per randomised group (page 57).

A12. Please explain the issue of not achieving convergence in the MTC analysis. Please report whether all outcomes were affected by this issue.

A13. Please clarify whether the MTC results are based on a fixed or random effects analysis.

A14. Please provide additional justification for assuming no treatment effect in the absence of results for the MTC, e.g. Class 1c for all cause mortality and stroke.

A15. Tables 6.9, 6.10, 6.11, 6.12, and 6.13 (p52-57) are difficult to interpret as they do not contain information with respect to the number of trials or the number of patients in each treatment comparison. Even though this information may be included elsewhere in the submission or appendices please redraft these tables and include:

i. The number of trials in each treatment comparison

ii. The number of patients in each treatment comparison

iii. Please provide the MTC results for each AAD vs. control, i.e. consistent with the data reported in Table 7.5, page 92 and subsequently used in the model.

A16. Although the raw data for the direct comparisons are included in the Abacus report, it is not clear which data are included in the indirect meta-analysis comparisons. Please provide these details (or state where they are in the report).

Section B: Clarification on cost-effectiveness data

B1. Please provide the full report of cost-effectiveness studies as offered on p65 of the submission.

Risk of mortality

B2. Please provide additional explanation of the approach used for estimating time to mortality (p91). Please clarify whether this approach was applied to the entire model period or just to the period beyond the follow-up of the ATHENA trial?

B3. Please provide the coefficients for the equations estimating time to mortality. Please clarify whether alternative curve fits were examined based on Akaike's Information Criterion and Bayesian Information Criterion goodness of fit criterion for time to mortality.

B4. On p90, all cause mortality is adjusted for CHADS2 score. Please clarify whether this risk of mortality includes mortality from stroke. Please also clarify whether the inclusion of an additional mortality effect through adding stroke to the model constitutes double counting. Is the treatment effect applied to both mortality and stroke?

B5. Please provide 95% confidence intervals for the relative risk of mortality reported in table 7.4 (p90).

B6. Please explain why alternative curve fits were not explored for the outcomes ACS and AF recurrence (Appendix 14).

Quality of life

B7. Please provide additional clarification on the derivation of the health state and event utility weights presented in table 7.7 (p96). Are these values derived from published studies or new analyses?

Costs

B8. Please provide additional information on the resource use and unit cost assumptions associated with adverse events, and the sources of this information (table 7.16, p104).

B9. Please indicate how the costs presented in table 7.17 (p104) relate to those in table 7.16.

Results

B10. Please explain the reasons for different costs and QALYs gained for treatment with dronedarone between positions 2 and 3 in table 7.18 (p108), i.e. only the comparator drug has changed between position 2 and position 3.

B11. Please clarify why the absolute QALYs gained in table 7.20 (patients with paroxysmal AF with left ventricular dysfunction; p109) are higher than the absolute QALYs gained in table 7.18, where patients have no structural heart disease. Please also clarify this point for tables 7.21 and 7.22 (p110-111).

B12. Please provide the results of the analysis where the model has been validated against the ATHENA trial as offered in the submission (p115).

Section C: Textual clarifications and additional points

Discrepancies

C1. The baseline CHADS2 score distributions presented in table 7.3 (p90) do not correspond with the values presented in appendix 12. Please clarify which values are correct.

C2. The treatment effects reported in appendix 12 do not correspond with the values presented in the main report. Please clarify which values are correct.

C3. The treatment effect on AF recurrence for class 1c reported in table 7.5 (p92) does not match the value used in the model. Please clarify which value is correct.

C4. The standard deviation for AF symptoms presented in table 7.7 (p96) does not match the value used in the model. Please clarify which value is correct.

C5. The initialisation cost for dronedarone presented in table 7.12 (p101) does not match the value used in the model. Please clarify which value is correct.

C6. The cost of regular monitoring for amiodarone presented in table 7.14 (p102) does not match the value used in the model. Please clarify which value is correct.

Simul8 code

C7. In the a_NextEvent code, the code beginning if lbl_TimeofACS has the + and - transposed compared with the other lines. Please clarify whether this is an error and provide the correct code and revised results accordingly.

C8. In the a_OneOffCosts code, please clarify whether the discounting is done correctly. The number of 'monitorings' is calculated, based on 2 per year, and this is discounted at the rate when the transition / initiation occurred. Therefore at start up, all 6 monitorings would be assumed to happen in Yr 1. Please clarify whether this is an error and provide the correct code and revised results accordingly.

C9. The number of patients per run, selected from the Model Controls input sheet in Excel, is divided by 10 (see 'Selecte4d Values' B8 in the Excel sheet). Please can you clarify why the number of patients per run is divided by 10.

C10. The second choice of survival curves does not seem to work, i.e. changing cell J43 from the Model Controls input sheet in Excel from 1st to 2nd reproduces the same model results. Please provide a corrected version of the model.

C11. Errors reported by Simul8. There are 5 times where Simul 8 reports that the router label was greater than the number of routes. Normally, the label takes a number 1 to x, and then sends the entity down the appropriate route from 1 to x. Where this is a mismatch, i.e. router =8 and there were only 5 routes, Simul8 defaults to the greatest number route (i.e. 5). Please clarify whether this is an error and provide the correct code and revised results accordingly.

Search clarifications following initial submission

C12. Appendix 2: Search strategy for section 6, clinical effectiveness; The search description states that Medline, EMBASE and the Cochrane Library were accessed in March 2009. However the search strategies listed in the Appendix show searches carried out in May 2009. Please confirm the date each database was searched.

C13. Appendix 4: Search strategy for meta-analysis and MTC; The search description states that the Cochrane Library, OVID EMBASE and OVID Medline were searched. However only one search strategy is listed in the Appendix and it is not marked which database this search strategy was used for.

i. Please confirm the date each database was searched.

ii. Please provide the search strategy used for each database.

iii. The search strategy listed in the Appendix contains lines (45,46,51,52,53,54,55,56) that are not incorporated into the final combined results. Please confirm that the strategy shown is complete and that these lines were purposely excluded.

C14. Appendix 10: Search strategy for health economic evaluations of dronedarone; The search description states that the Cochrane Library, Medline (PubMed) and EMBASE were searched. Please confirm the following:

i. The date each database was searched.

ii. That the first strategy listed in the Appendix is the EMBASE strategy.

iii. Which host (eg OVID) was used to search EMBASE.

From: Philip Higham
Sent: 06 October 2009 10:43
To: 'Phil.Booth@sanofi-aventis.com'; 'Ann-Marie.CRAIG@sanofi-aventis.com';
'Audrey.Lugris@sanofi-aventis.com'
Cc: Sally Gallaugher; Helen Chung; Meindert Boysen
Subject: AF - dronedarone clarification - subsequent issues
Attachments: Updated_Appendix12_commented.doc; Sanofi Aventis Updated Model
V2.0.zip

Importance: High

Dear Phil / Ann-Marie,

I am sending this e-mail on behalf of Meindert Boysen.

The ERG has contacted us with the following:
“We can't replicate the revised cost-effectiveness results reported in the Addendum: Results word
file. As in the initial submission, there still appears inconsistency between some of the input values
reported in the report, the revised appendix and the revised model.”

Attached are 2 files sent from the ERG:

(i) a word file which lists the discrepancies in the inputs reported in the revised appendix, revised
model and report. The values in red correspond to the values used in the model.

(ii) the latest version of the revised model submitted - to check this is the same version used to
generate the results section.

ERGs have limited time to perform the critical appraisal and their valuable time shouldn't be spent on
quality assuring the model; that's what we would have expected the model developer(s) to have
done.

We expect the corrected model to be returned to us by tomorrow (Wednesday) morning at the latest.

Yours sincerely,
Meindert Boysen
Programme Director Technology Appraisals