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National Institute for Health and Clinical Excellence

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Dear [redacted]

Re: Single Technology Appraisal – Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation

The Evidence Review Group The Centre for Reviews and Dissemination, University of York and the technical team at NICE have now had an opportunity to take a look at submission received on the 5th October 2010 by Boehringer-Ingelheim. 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.

We request you to provide a written response to this letter to the Institute by **17:00, Thursday 11th November 2010**. 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 turquoise, 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.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Helen Tucker– Technical Lead (Helen.Tucker@nice.org.uk) Any procedural

questions should be addressed to Marcia Miller for this appraisal Marcia.Miller@nice.org.uk in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

The Re-LY trial data

A1. **Priority Question:** From Table 34, page 88 of the manufacturer submission, it is clear that there is a substantial increase in the rate of bleeding at 65 years. Please provide:

- Justification for swapping from DE150 mg to DE110 mg at 80 years of age rather at a younger age.
- Evidence for the dose reduction at aged 80yrs.
- The method for deriving the overall effect for the sequence population.

A2. **Priority Question:** There was a protocol amendment where investigators were cautioned against the use of quinidine (and other P-glycoprotein inhibitors) due to an increased rate of bleeding with dabigatran.

- Please comment on what the impact of being unable to utilise P-glycoprotein inhibitors would be on the use of dabigatran for, and the management of, atrial fibrillation in clinical practice.
- Please comment on any bias this change in recommendation may have on the trial results.

A3. The RE-LY trial provides data for the risk of events while on warfarin or dabigatran. Please comment on the generalisability of the RE-LY trial to the UK population, including:

- How similar are the event rates from the RE-LY trial to those in the UK atrial fibrillation patient population and
- How similar are the characteristics of the patients in the RE-LY trial to the atrial fibrillation patients of the UK

A4. According to the clinical trial report (CTR), there were 846 patients with important protocol violations (that is they did not meet the entry requirements): 282 in the dabigatran 110mg group, 304 in the dabigatran 150mg group, and

260 in the warfarin group. According to Table 27 (page 71) in the manufacturers submission, the difference in the numbers of patients in the randomised/ITT population and the per protocol population were: 1194 in the dabigatran 110mg group, 1279 in the dabigatran 150mg group, and 910 in the warfarin group. Please explain these differences and the nature of the protocol violations.

A5. Please justify the protocol amendment for measuring quality of life in the RE-LY trial (measurements up to 12 months rather than up to 36 months).

A6. Please comment on why some analyses in the CTR report statistically significant p-values when the CI for the HR includes 1, and why there is such a large increase in the p-value in associated analyses for very small differences in the HR and CI. For example, composite of stroke, systemic embolism, PE, MI, death and major bleed:

DE 150 vs. warfarin: HR 0.91 (95% CI 0.82, 1.00), p=0.0393

DE 110 vs. warfarin: HR 0.93 (95% CI 0.84, 1.02), p=0.1050

The Mixed Treatment Comparison

A7. **Priority Question:** Please provide a justification for choosing the MTC (SAS) for the base-case instead of the results from the MTC (WinBUGs).

A8. **Priority Question:** Please provide a comparison of the different hazard ratios from the MTC (SAS), MTC (WinBUGs) analyses and the direct pairwise results and justify any discrepancies between them. A template is provided below to assist in reporting these results (See Appendix A).

A9. **Priority Question:** Please provide the WinBUGs code used for the MTC (WinBUGs).

A10. **Priority Question:** Please provide the statistics on model fit.

A11. **Priority Question:** Please provide testing for inconsistency (that is, variation in treatment effects between pair wise contrasts; frequentist pairwise analyses for the head to head trials in the network analyses).

A12. **Priority Question:** Please explain how the SAS code is dealing with the correlation within the multi-arm trials.

A13. **Priority Question**: Covariates were individually explored for four outcomes; please explain why these variables were explored in these four outcomes only, and not the other seven clinical outcomes presented in the MTC

A14. **Priority Question**: Trials with zero event arms were excluded from the MTC, please justify the exclusion of these trials.

Section B: Clarification on cost-effectiveness data

Treatment sequence

For questions B1-B4: Currently the economic model allows the evaluation of a restricted number of treatment sequences. Therefore please provide the information

requested in order to allow the assessment of all treatment sequences which could be considered appropriate to UK clinical practice.

B1. **Priority Question:** The ERG wish to evaluate the potential cost-effectiveness of dabigatran (110mg and 150mg) used as either a first line treatment or as a second line treatment option following warfarin. Please provide a revised model with the ability to choose any of the included treatments as either a first line or a second line treatment option.

B2. **Priority Question:** Please provide the base-case cost-effectiveness results comparing dabigatran 110mg and 150mg when used as either a first line treatment or as a second-line treatment following warfarin. Please present these results for both the single and sequential dose models.

B3. **Priority Question:** Please consider incorporating a third line of treatment in the model, which will allow the user to choose any sequence of treatment and provide a revised model with this additional functionality

B4. **Priority Question:** Please analyse and provide the base-case cost-effectiveness results of the comparison between these two specific treatment sequences: Dabigatran → Warfarin → Aspirin → No treatment in comparison with Warfarin → Aspirin → No treatment. Please present these results for both the single and sequential dose models for dabigatran 110mg and 150mg.

Pairwise comparisons

B5. **Priority Question** Please provide the results of the cost-effectiveness analysis using simultaneous comparisons between dabigatran (150mg and 110mg) and all comparators, namely:

- Fully incremental comparison of the ICERs
- Cost-effectiveness acceptability curves
- Probability of cost-effectiveness at willingness-to-pay thresholds of £20,000 and £30,000 per QALY.
- For all patients and separately for patients aged <80 and 80+.

Treatment adherence and discontinuation

B6. **Priority Question:** Page 166 of the manufacturer's submission states "To represent this discontinuation rate for first-line treatment, Kaplan-Meier curves from the RE-LY trial were fitted to Weibull distributions for DBG and WFN (Table 82)". Please provide the original Kaplan-Meier curves for treatment discontinuation.

B7. **Priority Question:** Please also provide the Kaplan-Meier probabilities of discontinuation at 30 days, 90 days, 1 year and 2 years.

B8. **Priority Question:** Please provide additional justification for using a Weibull distribution for treatment discontinuation of first-line treatments rather than alternative distributions. Provide the results of fitting the Kaplan-Meier curves for treatment discontinuation to different distributions including, log logistic, log

normal, Gompertz and exponential. Results should include the goodness of fit statistics and parametric estimates.

B9. **Priority Question:** Please also present additional sensitivity analysis for the the cost-effectiveness results using alternative survival distributions as well as using the Kaplan-Meier curves followed by constant discontinuation after 2 years. Please present the results of these sensitivity analyses for both the single and sequential dose models

B10. **Priority Question:** Discontinuation from aspirin is currently estimated by applying the absolute discontinuation rates from the Mant et al (2007) paper. Please present an additional sensitivity analysis using the relative effect of discontinuation for aspirin compared to warfarin from the same paper (2007) applied to the RE-LY data (warfarin) to obtain a new estimate for aspirin discontinuation rates. Present the results of these sensitivity analyses for both the single and sequential dose models.

B11. **Priority Question:** The adherence curves used in the sequence models do not appear to match those presented in the report (figure 20 and figure 21, page 168). Please justify this discrepancy and discuss any implications this may have for the cost-effectiveness results.

B12. **Priority Question:** Please clarify the meaning and model implications to the expression "permanent discontinuation" used in table 69, page 154 of the manufacturer's submission to refer to the effect on treatment status from haemorrhagic stroke and intracranial haemorrhage events. Please also provide a sensitivity analysis in which the discontinuation due to events is varied between 0% and 100%.

Model Structure

B13. Please comment further on the justification of modelling acute myocardial infarction as an acute event with only one-off costs and disutility, and with no consequences beyond 3-months. Please discuss any potential biases with the current approach.

B14. Please provide additional justification for the exclusion of pulmonary embolism from the economic model. Please discuss any potential biases with the current approach.

B15. Please provide additional justification for switching stroke status to a 'yes' following a transient ischaemic attack.

B16. Please comment on why all non- intracranial haemorrhage events incur only a one-off cost and disutility.

B17. Please justify why only one event can occur in each 3-month cycle in the model

B18. Page 244 of the manufacturer's submission. When real-world warfarin INR distribution is changed to trial-like warfarin INR distribution, as expected the ICER is equal to the ICER in the base-case. However, changing the proportion of individuals on target range to 100% provides different ICERs for trial-like and real-world WFN: trial-like – ICER=£49,301/QALY; real-world=£60,259/QALY. Please justify the reasons behind these results, including:

- How the different warfarin scenarios impact the economic model?
- Does the choice of scenario have an influence on any inputs besides the proportion of individuals in each INR range?

Model programming

B19. When the cost and utilities values are reset using the VBA button 'Reset Model Inputs' the parameter inputs no longer match those included in the base case analysis. Please confirm that the model is using the preferred base case parameter inputs and correct the stored inputs on each sheet if necessary.

Section C: Textual clarifications and additional points

C1. Please explain the following discrepancies between the CTR and the main submission (see below table):

- The incidence of MI and PE.
- The HR and CIs:

Outcome	110 vs. WFN HR (95% CI)		150 vs. WFN HR (95% CI)	
	CTR	Submission	CTR	Submission
Composite Stroke/SE	0.91 (0.75, 1.12)	0.90 (0.74, 1.10)	0.66 (0.53, 0.82)	0.65 (0.52, 0.81)
Ischaemic stroke	1.14 (0.91, 1.44)	1.13 (0.89, 1.42)	0.76 (0.58, 0.98)	0.75 (0.58, 0.97)
MI	1.35 (0.98, 1.87)	1.29 (0.96, 1.75)	1.38 (1.00, 1.91)	1.27 (0.94, 1.71)

Appendix A

Table template for reporting results of MTC analyses and direct pairwise results

(i) MTC (SAS) analyses compared to direct pairwise results

	DBG 150mg	**DBG 110mg**	**WFN**	**ASA**	**A+C**
DBG 150mg	*	**RR (95% CI)**	**RR (95% CI)**	NA	NA
DBG 110mg	RR (95% CI)	*	**RR (95% CI)**	NA	NA
WFN	RR (95% CI)	RR (95% CI)	*	**RR (95% CI)**	**RR (95% CI)**
ASA	RR (95% CI)	RR (95% CI)	RR (95% CI)	*	**RR (95% CI)**
A+C	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	*

Figures in upper part of matrix (in bold) are the direct pairwise results and figures in lower part of the matrix are the MTC results for all possible pairwise comparisons. NA = not applicable

(ii) MTC (WinBUGs) analyses compared to direct pairwise results

	DBG 150mg	**DBG 110mg**	**WFN**	**ASA**	**A+C**
DBG 150mg	*	**RR (95% CI)**	**RR (95% CI)**	NA	NA
DBG 110mg	RR (95% CI)	*	**RR (95% CI)**	NA	NA
WFN	RR (95% CI)	RR (95% CI)	*	**RR (95% CI)**	**RR (95% CI)**
ASA	RR (95% CI)	RR (95% CI)	RR (95% CI)	*	**RR (95% CI)**
A+C	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	*

Kind Regards

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