National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation [ID500]

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from **BMJ Group** to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, **1st November 2012** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

29th October 2009

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2 (page 13) "The subgroups of the cTTR analyses were defined differently in each of the included trials."	"The subgroups of the cTTR analyses were **reported** differently in each of the included trials **as the quartile limits stemmed from the distribution of patients observed**".	The quartiles are entirely dependent on the distribution of patients in the trial.	No change required. The ERG acknowledges the manufacturers comment that the quartile limits were dependent on the distribution of patients within the respective trials. However, the ERG does not consider the current text to be factually incorrect.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 13-14 "Subgroup analyses suggested that European patients may have derived slightly less benefit from apixaban for both the efficacy and safety outcomes when compared with the whole trial population. However, the results of the subgroup analyses by cTTR suggested that the safety and efficacy of apixaban compared with warfarin were	Please add the following text to the relevant paragraph "**It is important to note that the study was not powered to detect differences in efficacy and safety in different subgroups"**	On page 60 (paragraph 2) the ERG acknowledges that ARISTOTLE lacked power to detect differences in efficacy and safety in the different geographical subgroups. Therefore to retain this balance this sentence should be added to the text on pages 13 to 14	No change required. The ERG describes the limitations of the geographical region subgroup analyses with regards to lack of power on page 11 where the results for the Western Europe subgroup are first presented within the executive summary.

independent of the level of warfarin control i.e. %TTR. With respect to subgroup analyses by $CHADS_2$ score categories, [redacted]. However, the lack of detailed individual $CHADS_2$ score data, particularly for the higher $CHADS_2$ scores (i.e. 3, 4, 5 and 6) limits the ability of the ERG to comment on any potential variation in apixaban treatment effect for these subgroups"			

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 25 the ERG state	Please amend to "Therefore, apixaban will	BMS-Pfizer believe that savings	No change required.

"Therefore, apixaban will not require the NHS resource associated with warfarin INR monitoring and testing. However, the ERG considers it important to highlight that the use of apixaban instead of warfarin is unlikely to result in the redeployment of resources that are currently used to support warfarin monitoring. This is because warfarin is used for additional clinical indications (e.g. anticoagulation in heart valve replacement patients) to those for which apixaban is currently licensed or expected to be used in."	not require NHS resource associated with warfarin INR monitoring and testing. However, the ERG considers it important to highlight that the use of apixaban instead of warfarin is ~~un~~likely to result in **a reduction of the variable costs of clinics** ~~the redeployment of resources that are~~ currently used to support warfarin monitoring. **These clinics will still remain** ~~is~~ because warfarin is used for additional clinical indications (e.g. anticoagulation in heart valve replacement patients) to those for which apixaban is currently licensed or expected to be used in"	in variable costs are likely as the number of patients using warfarin is reduced. Indeed in the cost-effectiveness analysis and budget impact model fixed costs of warfarin monitoring in primary and secondary care were excluded.	The text referred to by the manufacturer represents the ERG's opinion. The manufacturer's proposed change is to reflect the manufacturer's opinion. The ERG does not consider this to be factual error.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In table 4 on page 27 (row, 3 , column 3) "As per the final scope plus aspirin for people for whom warfarin is suitable"	This should be" **warfarin unsuitable**"	Aspirin is not recommended for warfarin suitable patients	The ERG notes that the text in the table the manufacturer is referring to was copied from the table on page 32 of the manufacturer's submission (MS) and that the text highlighted by the manufacturer is also incorrect in the MS. The

			ERG has amended the text in table 4 of the ERG report to reflect the manufacturer's comment.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63 and 80 [redacted].	Add "However, the study was not powered to detect differences in efficacy and safety in the different geographical subgroups" to these statements	On page 60 (paragraph 2) the ERG acknowledges that ARISTOTLE lacked power to detect differences in efficacy and safety in the different geographical subgroups. Therefore to retain this balance this sentence should be added to the text on page 63 and 80.	No change required. The ERG does not consider this to be a factual error as the text referred to by the manufacturer on pages 63 and 80 of the ERG report are summary sections. The ERG have stated within the main description and critique sections of the ERG report that ARISTOTLE was not statistically powered to draw conclusions for any of the subgroup analyses reported.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P.65, second paragraph. 'The ERG notes that within the MS, the manufacturer did not report the DIC or residual deviance values for either the fixed or random effects models. However, upon request, the manufacturer supplied the residual deviance values for NMA 1 during the clarification stage. Although the ERG notes that values were not supplied for all of the outcomes reported in the base case. For the outcomes where the residual deviance was supplied, the ERG agrees with the manufacturer's assessment that both the fixed and random effects models fit the data well. However, it is unclear why the residual deviance for some of the outcomes was not provided by the manufacturer.'	'The ERG notes that within the MS, the manufacturer did not report the DIC or residual deviance values for either the fixed or random effects models. However, upon request, the manufacturer supplied the residual deviance values for NMA 1 during the clarification stage. ~~Although the ERG notes that values were not supplied for all of the outcomes reported in the base case.~~ **Based on these**, ~~For the outcomes where the residual deviance was supplied~~, the ERG agrees with the manufacturer's assessment that both the fixed and random effects models fit the data well. ~~However, it is unclear why the residual deviance for some of the outcomes was not provided by the manufacturer.~~'	ALL model residual deviances were provided. The tables in which these were presented could have been clearer as it appears as though, for example, base case residual deviance (RD) values were not supplied for any of the bleeding outcomes or for disabling, non-disabling, or fatal stroke. The reason for this is that the base-case for the bleeding outcomes used the RD values from the NMA analysis incorporating the ROCKET-AF OT population data (reported in the 3rd column of the table), as the OT safety analysis was the base-case analysis for all safety data, and in fact ITT safety data was not reported for ROCKET-AF. Similarly we could not find ITT data from ROCKET-AF for disabling, non-disabling, and fatal stroke so for the base case for these outcomes, we had to resort to using the OT population data reported in the	The ERG agrees that the current text is inaccurate and has amended the text on page 65 of the ERG report to reflect the information provided by the manufacturer.

		ROCKET-AF publication, and again the base case RD values were reported in the third column of the table submitted to the ERG. We apologize for the confusion caused by the way in which the data were presented, although we did set out clearly in the original submission report (section 6.7.4 and Table 110 [in Appendix 14, section 10.14]) exactly which population data from each of the trials went into the base case NMA for every outcome. Therefore in the interests of accuracy, please could you delete the indicated text in the specified paragraph?	

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P.66, 1st paragraph, sentences 2-5.The manufacturer considered that as a result of the small number of included studies, a random effects model would produce poor estimates of the variation in between-study treatment effects. The manufacturer also	Add: The manufacturer **cites text from the Cochrane Systematic Review Handbook (section 9.5.4) which notes** ~~considered~~ that as a result of the small number of included studies, a random effects model would produce poor estimates of the variation in between-study treatment effects. The manufacturer also cites text from the Cochrane Systematic Review	The ERG appear to have rejected the rationale for choosing fixed effects because calculations investigating heterogeneity should not be based on a small number of studies as stated in the Cochrane Review Handbook and instead argue that choice of	No change required. The ERG does not consider this to be a factual error. The ERG considers that the relevant model should be selected based on goodness of fit. The ERG acknowledges that where fixed and random effects

cites text from the Cochrane Systematic Review Handbook[41] that recommends that at least 10 studies are used in the calculations to investigate heterogeneity. The ERG notes that while a random effects model incorporates heterogeneity it does not investigate heterogeneity. Consequently, the ERG does not consider the number of studies in the network to be sufficient reason to choose a fixed effects model over a random effects model. Rather, the ERG considers that the best fitting model should be chosen.	Handbook[41] that recommends that at least 10 studies are used in the calculations to investigate heterogeneity. The ERG notes that while a random effects model incorporates heterogeneity it does not investigate heterogeneity. Consequently, the ERG does not consider the number of studies in the network to be sufficient reason to choose a fixed effects model over a random effects model. Rather, the ERG considers that the best fitting model should be chosen. **However, in a scenario where the goodness of fit is similar for both models, the ERG acknowledges that application of the random effects model to the current 3-trial network could produce a poor estimate of the between-study variance and may consequently introduce uncertainty into the results.**	model should be based solely on model fit. However, the ERG omit to mention that the manufacturer cited section 9.5.4 of the Cochrane Review Handbook in support of the assertion that where there are too few studies the random effects model will produce poor estimates of the variation in between-study treatment effects, rather than just 'considered' this to be case based on their own judgment. The implication of the random effects model producing a poor estimate in the between-study variance, is that this is likely to introduce bias into the credibility interval estimates within the NMA. While the manufacturer acknowledges that model fit is a key consideration of model choice, this only applies when the fit is importantly different between models. In the current scenario the model fit was similar between models, and hence choice of model came down to other considerations. In this case the key consideration is the unreliability of the random	are equally good fitting models, it is not unreasonable to select the fixed effects model. This selection process may or may not be affected by the number of trials available for analysis.

		effects model in estimating between-study variance where there are only small numbers of studies available for the analysis. The ERG needs to acknowledge the relevance of this consideration in the current analysis scenario.	

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P.66 'The between study heterogeneity generated using the random effects model reflects the prior value inputted into the model as there are insufficient trial data to further inform this estimate.'	The between study heterogeneity generated using the random effects model reflects the prior value inputted into the model ~~as~~ **and** there are insufficient trial data to further inform this estimate.	Section 4.4.4, p.70, first paragraph, last 3 sentences is much clearer on this issue. Tau in the random effects model is defined as tau = $1/sd^2$ and this is the between-trial precision or 1/between-trial variance. With so few trials, there is not enough data to inform this parameter, resulting in grossly overinflated values.	No change required. The ERG agrees with the manufacturer's comment. However, in the context of the current text in the ERG report the ERG does not consider the current text to be factually incorrect.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.5.1 (page 80) [redacted]	Please add the following text to the end of the relevant paragraph "**However, the interaction p value was not statistically significant suggesting that the benefit of apixaban was consistent across subgroup**s"	While numerically, there seems to be a greater reduction in the number of events in the patients at high risk, the p-value for interaction across these groups was not significant. A more detailed pre specified analysis was recently published (Lopes et al Lancet October 2012) and concluded that Apixaban significantly reduced stroke or systemic embolism with no evidence of a differential effect by risk of stroke.	No change required. The ERG does not consider this to be a factual error. The text referred to by the manufacturer is in a summary section of the ERG report and represents the ERG's opinion. In addition, in section 4.3.4 of the ERG report where the ARISTOTLE subgroup analysis results are presented, the ERG has reported the subgroup interaction p value.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 56 on page 120	The parameters for apixaban and warfarin need to be redacted as they are commercial in confidence. The references for apixaban and warfarin are incorrect and should be **AVERROES Case Study Report**.	Commercial in confidence data and incorrect referencing	The parameters have been marked as commercial in confidence and the reference corrected

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 139 “The results of these analyses are presented in Appendix 9.7”	Amend to “**Appendix 9.6”**	Incorrect referencing	The reference has been amended to Appendix 9.7.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 145 “The increase in the number of mild strokes is in turn driven by the distribution of recurrent stroke severity; assumed to be equivalent to that observed in ARISTOTLE for patients treated with apixaban for both scenario analyses is (i.e. [redacted] of recurrent strokes will be mild)”	Delete **“(i.e. [redacted] of recurrent strokes will be mild)**”	This is commercial in confidence data that is being approximated	The proportion of recurrent strokes that are mild has been marked as commercial in confidence

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 149 paragraph 3	A key finding from the trial has been omitted. Add the following text “**The rates of death from any cause were 3.52% and**	A key finding from the trial has been omitted	No change required. The text referred to by the

	3.94%, respectively for warfarin and apixaban (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P = 0.047)"		manufacturer relates to the conclusions of the ERG report. The ERG has summarised the primary safety and efficacy outcomes along with treatment discontinuation and adverse effect data. The ERG does not state that all statistically significant findings are summarised in their conclusion and thus the ERG does not consider this to be a factual error.

Issue 14

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Bullet point 2 on page 151 "rivaroxaban and dabigatran blend were extendedly dominated (i.e. resulted in a lower incremental cost-effectiveness ratio (ICER) versus warfarin despite having	Revise the text in the following way "rivaroxaban and dabigatran blend were extendedly dominated (i.e. resulted in a lower incremental cost-effectiveness ratio (ICER) versus warfarin despite having higher total **QALYs**) by apixaban"	Incorrect definition of extended dominance	Agreed, the sentence has been amended. In addition a similar sentence on p122 has been amended.

higher total costs) by apixaban”			