National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Atrial fibrillation (stroke prevention) – rivaroxaban

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from the *BMJ Technology Assessment Group* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, *31st October 2011,* 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.

October 2011

Issue 1 Population in ROCKET compared to the scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 – suggestion that the population in the pivotal study did not match the scope	The Evidence Review Group are correct that the ROCKET AF study recruited patients with $CHADS_2$ scores ≥2. At the time the study was designed, the inclusion/ exclusion criteria were set to recruit patients considered representative of the majority of subjects with non-valvular atrial fibrillation for whom oral anticoagulation was considered appropriate. The ERG state later in the report that there is agreement with the suggestion that relative treatment effect is likely to be consistent across patient populations at different risk. It is proposed that the wording on page 9 reflect this.	The CHMP have issued a positive opinion for rivaroxaban for the following indication: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with **one or more risk factors**, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. The CHMP have therefore considered the evidence from the ROCKET AF trial and other data submitted to conclude that the data from ROCKET AF can be extrapolated to a wider group of patients in terms of level of stroke risk. In addition, the ERG state later in the report that there is agreement with the suggestion that relative treatment effect is likely to be consistent across patient populations at different risk.	No change required. The text referred to by the manufacturer is an overview of the population covered within the manufacturer's submission, which the manufacturer highlights is correct. The manufacturer is requesting additional text to be added to justify the suitability of the population, however the ERG do not consider this to be a factual error.

Issue 2 Comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 – the ERG report states that a comparison against (1) dabigatran and (2) antiplatelet agents was not conducted in the population of patients unsuitable for warfarin (also addressed on page 13 and on several occasions throughout the report)	Rivaroxaban was compared to dabigatran using a cost minimisation approach which found rivaroxaban to be dominant. The ERG are correct that this comparison used studies for which patients were eligible and therefore suitable for warfarin – it would not have been ethical to conduct RCTs compared to warfarin under any other circumstance. Rivaroxaban was compared to aspirin, the most commonly used antiplatelet, in those patients who are considered unsuitable for warfarin. A warfarin unsuitable population does not necessarily indicate a low risk population. Clinical practice indicates that among patients at moderate to high risk of stroke who are eligible for warfarin treatment according to clinical guidelines, a substantial proportion are not receiving warfarin because they are not compliant or otherwise unsuited to warfarin because of lifestyle or personal characteristics. In such patients, the appropriate active comparator would still be warfarin in a RCT. The ERG are correct that we used the outputs of a NMA for this comparison to be made. However the ERG are incorrect in stating that the patients in the aspirin studies were all suitable for warfarin (please refer to Appendices	The limitation of the comparison vs dabigatran are recognised but the ERG are not correct to state that the comparison was not conducted. The ERG are incorrect in their suggestion that the comparison against antiplatelet agents was not conducted in a population of patients unsuitable for warfarin.	No change required. The ERG notes that all patients in ROCKET AF (the trial providing all the clinical data for rivaroxaban within the manufacturer's submission) were randomised to either rivaroxaban or warfarin and thus must have been eligible for treatment with warfarin. The ERG also note that in the trial used by the manufacturer to provide data on dabigatran (RE-LY), patients were also randomised to either dabigatran or warfarin and thus must have been eligible for treatment with warfarin. The ERG does not report that all of the patients in the aspirin studies were unsuitable for warfarin. However, the ERG do note that some of the trials used by the manufacturer to provide data for the network meta analysis comparison of rivaroxaban versus aspirin include patients who were randomised to aspirin or warfarin, and thus at least

	in the systematic review report provided). Taking all of this into account, the aspirin comparison presented in the original submission is an accurate representation of the scope agreed with NICE. The ERG should reconsider the wording here.		some of the patients in the aspirin studies were eligible for treatment with warfarin. The ERG thus does not believe that suitable data has been presented within the manufacturer's submission to enable a comparison between rivaroxaban and dabigatran or antiplatelet agents in a population of patients unsuitable for warfarin.

Issue 3 HRQoL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 – the ERG state that it is not clear whether HRQoL data were collected in the ROCKET AF study	As stated on page 51 of the submission, data on treatment satisfaction were collected as part of ROCKET AF. As stated on page 165 of the submission, no data suitable for HRQoL analysis was collected as part of ROCKET AF, so a systematic search of the literature was conducted for these inputs into the health economic model. This is reflected further on in the ERG report but could be mentioned here.	For clarity.	No change required. The ERG note that the manufacturer reported "no data suitable for HRQoL analysis was collected as part of ROCKET AF" in the economic part of their submission. However, the manufacturer does not report any HRQoL data within the clinical part of the manufacturer's submission (MS) although as the manufacturer highlights, it is stated in the MS that data on treatment satisfaction was collected.

			The ERG is unclear whether the treatment satisfaction data could have provided information on HRQoL in ROCKET AF.

Issue 4 Safety endpoint

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, paragraph 2 and page 132 – the ERG report incorrectly refers to adverse event rates	The ERG state that the overall adverse event rate was 20.7% vs 20.3%. These numbers actually relate to the proportion of patients in each arm experiencing the principal safety endpoint. This should be amended accordingly.	For clarity.	The ERG agrees that the current text is inaccurate. The sentence highlighted by the manufacturer has been amended to: "The overall safety profile of rivaroxaban and warfarin, from ROCKET AF, were similar (treatment-emergent adverse events: 81.44% vs 81.54%)."

Issue 5 **********

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
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Issue 6 **NMA**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, last	**********	The data do not	**********

paragraph – interpretation of ITT results	**********	support the difference suggested.	**********

Issue 7 *

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
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			**********

Issue 8 Recommended place of rivaroxaban

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22 of ERG report – ERG have expressed concern about the use of rivaroxaban in patients with a $CHADS_2$ score of ≥1	Whilst we agree with the ERG that the ROCKET AF study did not include patients with $CHADS_2$ scores <2, it is of note that the CHMP have issued a positive opinion for a broad licence based on the ROCKET AF data. In addition, the ERG state in the report that there is agreement with the suggestion that relative treatment effect is likely to be consistent across patient populations at different risk. It is suggested that the concern expressed by the ERG is balanced by these points.	For clarity in line with the proposed indication. Also to reflect the comment by the ERG that there is agreement with the suggestion that relative treatment effect is likely to be consistent across patient populations at different risk.	No change required. The text referred to by the manufacturer is an overview of the population covered within the manufacturer's submission, which the manufacturer highlights is correct. The manufacturer is requesting additional text to be added to justify the suitability of the population, however the ERG do not consider this to be a factual error.

Issue 9 Recommended place of rivaroxaban

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26 of ERG report –	The ERG report states"********** This is currently not in the public domain so should be marked as confidential.	The information is	The ERG has amended

information is confidential	.	confidential	the highlighting of confidential information in the ERG report to reflect this.

Issue 10 Adverse events compared in NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27 of ERG report – ERG have expressed concern about the NMA only reporting comparisons for bleeding adverse events	We are not clear why this is highlighted. Bleeding adverse events are the most important adverse events associated with anticoagulants. We feel that the ERG should reconsider this comment.	The current wording implies that important information has been omitted which is not the case.	No change required. The ERG notes that adverse effects of treatment including haemorrhage were listed as outcomes in the final scope issued by NICE. The ERG provides an account of the data presented in the manufacturer's submission compared to that requested by the final scope issued by NICE. The ERG does not attempt to draw any conclusions from the absence of other non-bleeding adverse effect data in the manufacturer's network meta-

			analysis.

Issue 11 Description of study follow-up

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28 of ERG report – ERG refer to an open-label extension study. This is not correct. This also applies on page 42	The ERG report states "At the end of study visit, patients were transitioned from study drug to an open-label VKA or other appropriate therapy (e.g., aspirin or no therapy) as determined by the investigator and followed up in an open-label extension study for approximately 30 days". This is not correct – the 30 days were not an open-label extension study but a post-treatment observation period. This should be amended.	For clarity.	The ERG agrees that the current text is inaccurate and has amended the text relating to follow-up highlighted by the manufacturer to "post-treatment observation period".

Issue 12 Statistical power

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28 of ERG report – ERG express concerns about power to demonstrate superiority	The ERG report states "the ERG has concerns regarding the power of the study to demonstrate superiority using the safety-on-treatment and ITT populations". We refer to	This comment warrants further substantiation in light of the pre-specified statistical analysis plan. Full details were provided in the	The ERG agrees that the current text is inaccurate and has deleted the text in the ERG report relating to the power of

	page 56-57 of the submission for information regarding the statistical analysis and suggest that the ERG reconsider this statement.	MS.	ROCKET AF to demonstrate superiority.

Issue 13 GCP violating site

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 of ERG report – incorrect information regarding the GCP violating site	The ERG report states "The ERG notes that there was one trial site (96 people) that was excluded from all the data analysis sets due to violations in Good Clinical Practice guidelines." It is correct that all of the efficacy analyses excluded this site, however all safety analyses included safety data from this site. This should be amended accordingly.	For clarity.	The ERG agree that the current text is inaccurate and the number of people reported in the ERG report is incorrect (should be 93 according to the manufacturer's submission). The ERG has amended the text to "The ERG notes that there was one trial site (93 people) that was excluded from all the efficacy data analysis sets due to violations in Good Clinical Practice guidelines." The ERG has also amended the related text and numbers in table 8 on page 43 of the ERG report.

Issue 14 Haemorrhagic stroke

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 39 of ERG report – clarity for ERG	The ERG report states “the ERG is unsure whether haemorrhagic strokes were also counted in the safety bleeding outcomes of ROCKET AF”. For clarity, ********** ********** ********** **********	For clarity.	No change required. The ERG would like to thank the manufacturer for providing clarification on this point. How

			ever, the manufacturer has provided additional information in the factual error check response. The existing text in the ERG report reflects the available information

			from the manufacturer's submission.

Issue 15 Follow up

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41 of ERG report – clarity for ERG	The ERG report states "Patients in both the rivaroxaban and warfarin groups were followed up at week 1, week 2, week 4 and then monthly up until the "End of Study visit" (within 30 days of the date of site notification [28th May 2010]; site notification took place once the pre-specified number of on-treatment primary clinical efficacy endpoint „events" had occurred)." There was further follow up - patients were seen at fixed intervals that were identical for rivaroxaban and warfarin groups: week 1, week 2 and week 4 and every month thereafter, the 'End of Study visit', and a 'follow-up' visit 30 days later at the end of the observation period. This should be amended accordingly.	For clarity.	No change required. The ERG describe the 30 day observation period later on in the section referred to by the manufacturer (section 4.2.6, page 42).

Issue 16 TTR achieved

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 and 55 of ERG report – inappropriate comparison to RE-LY	The ERG report makes reference to the difference in time in therapeutic range observed in ROCKET AF and that observed in RE-LY. As stated in the submission, as well as differing patient populations, there are a number of different methods for calculating TTR and these are likely to differ between trials, making between trial comparisons problematic. It would be helpful if the ERG make a comment to this effect.	For clarity.	No change required. The ERG notes the manufacturer's comments but does not feel that the current text in the ERG report is incorrect. In the ERG report the ERG only make brief comparison to the RE-LY trial being similar to the ROCKET AF trial. The ERG does not attempt to compare the two trial populations.

Issue 17 Follow-up assigned medication

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43 of ERG report – Table 8 – small rewording needed	The text at the bottom of table 8 states "*i.e., patients were off randomised treatment and taking an alternative anticoagulant". This should say alternative thromboprophylaxis as antiplatelets were given to some patients.	For accuracy.	The ERG agrees that the current text is inaccurate and has amended it to "i.e., patients were off randomised treatment and taking open-label vitamin K antagonist or other appropriate regimen as determined by the investigator"

Issue 18 Statistical analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 44 of ERG report – paragraph 2	The ERG report states "In ROCKET AF, the ERG notes that the manufacturer ********** assess for superiority in a list of primary and secondary outcomes should rivaroxaban be found to be non-inferior to warfarin in preventing stroke and systemic embolism (primary efficacy outcome) in the safety-on-treatment population." Safety-on-treatment population should be replaced with per protocol on treatment population.	For accuracy.	The ERG agree that the current text is inaccurate and has amended it to "In ROCKET AF, the ERG notes that the manufacturer ********** assess for superiority in a list of primary and secondary outcomes should rivaroxaban be found to be non-inferior to warfarin in preventing stroke and systemic embolism (primary efficacy outcome) in the per protocol population."

Issue 19 Discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46 of	The ERG report states ********** ********** **********	For accuracy.	The ERG agree that the current text is inaccurate

ERG report – incorrect p value cited	**********		and has amended ********** ********** ********** *

Issue 20 Transition to open-label treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48 of ERG report – ERG comment about transition	The ERG report states "The manufacturer also points out that the timing and type of event in the rivaroxaban arm suggest that the events were associated with suboptimal anticoagulation over the transition period from rivaroxaban to a VKA, and that this transition may be addressed more swiftly in true clinical practice. However, the ERG is unsure of the validity of this proposal and considers that, in clinical practice, it would be necessary for people discontinuing rivaroxaban and starting warfarin to go through a period of warfarin dose finding to reach a therapeutic INR." Bayer agree that in clinical practice if a patient discontinued rivaroxaban and were started on warfarin that dose finding and INR adjustment would be necessary. However, ********** ********** This would not be an issue in clinical practice. Indeed there will be specific recommendations in the SmPC about transitioning between treatments.	For accuracy.	No change required.*The ERG accurately reports the manufacturer's proposal for the transition period as

			reported in the manufacturer's submission. The ERG is unable to comment on how long the transition period from rivaroxaban to therapeutic warfarin dose would take in clinical practice in comparison to that reported in ROCKET AF or draw conclusions on the likely number of events that would occur during the transition

			period.

Issue 21 Supplementary TTR data supplied

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55 of ERG report – ERG incorrect labelling of data supplied	The ERG report states "The ERG thus requested some additional data from the manufacturer for the subgroups of patients with a TTR <60% and those with a TTR ≥60%. **********	For accuracy.	The ERG agrees that the current text is inaccurate and has amended ********** ******The ERG has also identified and corrected this error on pages 12, 56, 61 and 76.

Issue 22 Supplementary TTR data supplied

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58 of ERG report – Information needs to be marked as confidential	The ERG report states ********** ********** ********** ********** This information should be marked as AIC.	This is confidential information.	The ERG has amended the highlighting of confidential information in the ERG report to

			refl ect this.

Issue 23 Dabigatran in ERG NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 71 of ERG report – dabigatran 220mg per day was not included in the ERG NMA	The ERG report states that "trials selected to inform the ERG"s NMA were assessed for comparability based on patient population, severity of disease, and treatments received. In particular, to ensure a homogeneous set of trials for analysis, only comparable dosing strategies were included (i.e., rivaroxaban 20 mg/day, dabigatran etexilate 300 mg/day, aspirin 300 mg/day, and dose-adjusted warfarin aiming at a target INR range between 2 and 3). …….Dabigatran etexilate 220 mg/day was excluded from the NMA because the economic model supplied by the manufacturer cannot accommodate a treatment strategy of 300 mg/day stepping down to 220 mg/day once a patient has reached 80-years-old." It is not appropriate to exclude dabigatran 220mg/day from the NMA. This biases any comparison in favour of dabigatran due to the differential profile of efficacy and safety between the two dabigatran doses. Bayer provided an alternative model using the dabigatran dosing sequence as requested by the ERG.	Excluding dabigatran 220mg/day from the NMA biases any efficacy comparison in favour of dabigatran.	No change required. The manufacturer's model submitted as part of the clarification response was not functional; consequently analysis of rivaroxaban versus dabigatran 220mg/day as part of the sequential regimen was not feasible. The ERG's NMA has not been used to inform a comparison of rivaroxaban with dabigatran 220mg/day, as dabigatran 220mg/day is not a stand alone treatment. The ERG's NMA has been used to inform a comparison of rivaroxaban versus dabigatran 300mg/day, the exclusion of dabigatran 220mg/day from the ERG's NMA will not introduce bias into the comparison of rivaroxaban with dabigatran 300mg/day.

Issue 24 Dabigatran vs placebo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 85 - The figures for dabigatran vs placebo are incorrect	The ERG report uses the rivaroxaban RRs from the NMA, not the Dabigatran ones. The correct ones are in the NMA report. These should be amended.	For accuracy	No change required The ERG has reported the rivaroxaban RRs for dabigatran as these were the risks used in the manufacturer's model.

Issue 25 MI figure incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87-88 – Table 30, the figures for MI are incorrect	For the ITT comparison, the RR and 95% CI for MI should read 0.91 (0.72-1.16).	For accuracy	The ERG agrees that the current text is inaccurate. The current text has been amended to **********

Issue 26 Aspirin dose

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 94 of ERG report – Table 35 – incorrect daily dose of aspirin represented	The ERG have adapted table 50 from the MS, however the daily dose of aspirin in the MS was 150mg, not 75mg as suggested in the ERG table.	For accuracy.	No change required The text in ERG table 35 correctly reflects how aspirin was used in the economic model. That is a daily dose of 75mg is used at a daily cost of £0.02.

Issue 27 IC bleed re-initiation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96 of ERG report – Table 37 – incorrect box ticked	The high risk population would RE-initiate on anti-coagulation after an IC bleed, so it should not be ticked as initiation.	For accuracy.	No change required Conceptually, the ERG agrees that people post IC bleeding should incur re-initiation costs. However, in the model, patient in the post IC bleeding health state are assumed to incur initiation costs as described in table 37.

Issue 28 Risk of further events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 109 of ERG report – how 'suspended events' are managed	The ERG report states "However, the ERG notes that the manufacturer's model also suspends the risk of further events in the subsequent model cycle. The ERG considers that this additional suspension of risk is likely to bias the analysis against the more effective treatment as the overall event rate will be lower, and as such the potential to demonstrate clinical and economic benefit will also be lower." The risk of further events has been suspended after certain select clinical events in the model. However, costs and disutilities to account for the 'suspended' events are included in the pay-offs of all subsequent model cycles, so there is no bias against the more effective comparator. The ERG are asked to reconsider the wording here.	For clarity	No change required The risk of further events was suspended for all temporary and permanent model events. In that, following a permanent event a person can only transition to the post event health state or die. For temporary events a person can only transition to the initiation or stable AF health states or die. Consequently, patients are not exposed to the risk of further events at the time when in practice, events are more likely to occur. Thus in terms of effectiveness, the more effective treatments will be disadvantaged since the opportunity to prevent events is reduced. The costs and utilities referred to by the manufacturer are those associated with temporary events; patients are still exposed to temporary events once they have entered a post event health state. However, this is a different

			issue to the suspension of risk described by the ERG.

Issue 29 Rationale for different bleeding patterns

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 110 of ERG report – ERG states that no rationale was provided	The ERG report states "In the clarification response, the manufacturer provided no rationale for the difference between rivaroxaban and warfarin in gastrointestinal bleeding." This is inaccurate. Whilst it was stated that any rationale regarding GI bleeding events was speculation, a rationale was provided based on published literature. In addition, further confidential information was provided to support the response.	For accuracy.	The ERG agrees that the current text is inaccurate. The text has been updated to: In the clarification response, the manufacturer stated that any rationale for the difference between rivaroxaban and warfarin in gastrointestinal bleeding would be pure speculation.

Further erratum

The following errors were identified by the ERG after the report had been sent for consultation:

Section 1.5.1 page 15. The ERG conducted a scenario analysis that used lower monitoring costs for warfarin. The ICER was incorrectly entered as £55,106 per QALY gained. The ICER has been amended to £62,568 per QALY gained.

Section 4.5 page 70. The confidential information in the text was not highlighted appropriately and has been amended.