NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome [ID532]

Dear [redacted]

The Evidence Review Group, School of Health & Related Research Sheffield (ScHARR), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 23rd June 2014 by Bayer. 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 **5pm** on 30th July 2014. 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 [redacted]. Any procedural questions should be addressed [redacted] in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Section A: Clarification on effectiveness data

General

A1. Our clinicians indicate that maintaining patients on rivaroxaban beyond 12 months may be unlikely because, for example, the risk of an infarction is highest in the 12 months following an infarction. Please clarify how patients will be selected for treatment beyond 12 months?

A2. Please clarify when rivaroxaban should be started for maintenance therapy e.g. within 7 days after hospital admission for ACS

A3. The submission (p8) states that 'a PASS [post authorisation study] was considered conditional to the MA [marketing authorisation]'. Please could you provide further details of this study including any results that may be available.

A4. The submission (p131) states that 'The most recent 2012 ESC guidelines for patients with STEMI recommend low dose rivaroxaban…' Please provide further details including class of recommendation, definition and suggested wording of recommendation proposed by the guideline.

Literature searching

A5. Please clarify why line '#6' of the EMBASE and MEDLINE search strategies excludes 'Phase 1 Clinical Trial'/de. (p B361, Section 10.2 Appendix 2)

A6. Please provide justification (including limitations) for restricting searches to English language studies only

A7. Please clarify if any searching was undertaken for non-RCT evidence (p B366, Section 10.6, Appendix 6) as the submission states (p104) that 'there are no relevant non-RCTs included in this submission.'

Systematic review process

A8. Please confirm if study selection, data extraction and quality assesment was undertaken independently by a minimum of two reviewers. If not, why?

A9. Please provide a detailed breakdown of all excluded full text studies (i.e. full reason for exclusion and reference) for the rivaroxaban systematic review.

A10. Please present evidence to support the view that the treatment effect is constant over the lifetime of the patients and thus that proportional hazards is an appropriate assumption.

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Quality assessment, data synthesis, analysis

A11. Please clarify to what extent the mITT analysis could influence the results compared with an ITT analysis. It is noted that an FDA briefing document for the Cardiovascular and Renal Drugs Advisory Committee for rivaroxaban suggests that three deaths in the intervention group were uncounted for in the ATLAS ACS 2 TIMI 51 trial because they occurred after withdrawal of consent.

A12. Please clarify the criteria for choosing the selected sites at which data for quality of life and medical resource utilsation were collected (p60). In addition, please clarify the EQ-5D measure used in the trial, for example was it EQ-5D-VAS or EQ-5D-VAS and EQ-5D-3L?

A13. Please provide evidence to support the assumption that withdrawal rate is independent of treatment (i.e. no informative censoring)

A14. Please provide references for the following statement (p B-363, Section 10.3, Appendix 3) 'Although discontinuation rates were slightly higher than some similarly designed studies…'

A15. Please provide supporting evidence to confirm that appropriate methods were used to account for missing data (p72, Table 13 and B364). In addition, comment on the impact of the missing data on the overall interpretability of the ATLAS ACS 2 TIMI 51 trial.

A16. Please provide further details on the rates of PCI and CABG (separately) by dose and study group for the total and licensed population

A17. The submission states that '…rates presented in the study publication are Kaplan Meier estimates whereas the data presented in the submission are crudes rates' (p78, Section 6.5.3). Please provide rationale and limitation of this approach. For completeness, please provide event rates as Kaplan Meier estimates for ALL primary and secondary endpoints for the total and licensed populations by dose, each strata and analysis type (e.g. mITT and ITT)

A18. Please see tables 14 and 15 (pg79 and p88). Rivaroxaban 2.5mg BID significantly reduces the rate of CV death and death from any cause, whereas this was not seen with rivaroxaban 5mg BID. Please clarify why, as this does not appear intuitive.

In addition, a reduction in MI is observed with rivaroxaban 5mg BID but not rivaroxaban 2.5mg BID. Please clarify why.

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A19. Please provide tabulated results (including explanations, where appropriate) on whether the efficacy of rivaroxaban in the total and licensed population (by dose and each strata) varied by age, sex and geographical region.

A20. The NICE decision problem states that 'if evidence allows the following subgroups will be considered: people with NSTEMI; people with STEMI; people with diabetes mellitus; people who received prior primary PCI; and people who did not receive prior primary PCI in the acute phase of management. As evidence is available, please could you provide ALL primary and secondary endpoint data, (incuding safety data) for the total and licensed populations by dose and each strata

A21. Please provide a full tabulated breakdown of the following by study group, dose, and strata for the total and licensed population (including p value):

- Protocol deviations
- Discontinuation of treatment, with reason
- Discontinuation from study, with reason
- Unknown vital status.

A22. For completeness, please provide tabulated safety data for treatment related adverse events using the GUSTO bleeding event classification scale and the International Society on Thrombosis and Haemostasis (ISTH) event classification scale for the total and licensed populations by dose and each strata.

A23. Please provide full tabulated details on compliance/adherence with study treatment (by dose) for each drug in the intervention arm (rivavaroxaban, thienopyrimidine and aspirin separately and combined) and in the control group (thienopyrimidine and aspirin separately and combined).

A24. For completeness, please confirm that an indirect comparison, to supplement the direct evidence, could not be generated due to there only being one trial using rivaroxaban plus clopidogrel and aspirin in patients with ACS.

Section B: Clarification on cost-effectiveness data

Probabilistic data issues

B1. **Priority Question:** For the majority of parameters within the PSA, it has been assumed that the range is +/- 25% of the deterministic value. Please clarify why this method was used rather than using published standard errors, (for example those presented in Bagust el al (Table 16, p56) or calculating standard errors from trial data, or from NHS reference cost data).

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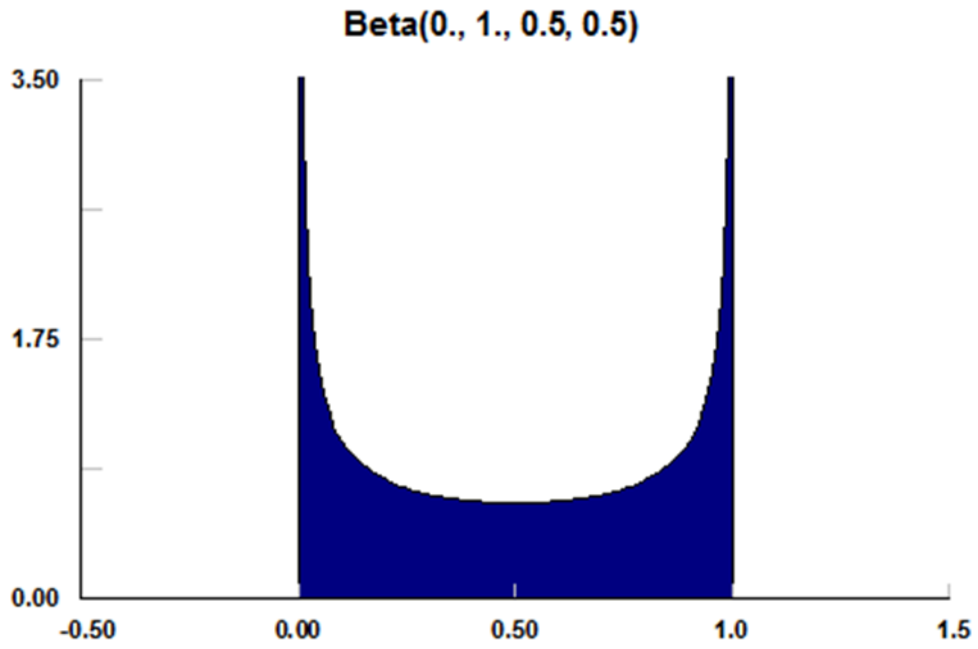
B2. **Priority Question:** Further to B1 the method of sampling from the +/- 25% range appears to be non-standard and apparently uses a Beta distribution with an alpha of 0.5 and beta of 0.5.

The probability density function of a Beta distribution with alpha=0.5 and beta=0.5 is presented in the diagram below which shows that this favours values towards the ends of the distribution.

Please clarify why this distribution was used for most of the parameters in the PSA.



B3. **Priority Question:** please clarify why there is no correlation assumed between the shape and scale parameters in the PSA of each of the Weibull distributions used in the observation period of the model.

Time issues

B4. **Priority Question:** please clarify why 48 weeks is often considered to represent one year in both the model and in the submission? This causes a problem when transition probabilities are using different assumed cycle lengths than costs and utilities.

B5. It is stated that the probability of transitioning from the 'no event' health state to the 'two MI' health state is calculated by multiplying the transition probabilities in the first four weeks in the first model cycle (manufacturer's submission, page 202). The first

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model cycle is stated as being 12 weeks; please clarify why this approach was appropriate.

B6. Please clarify that the cycle lengths of the initial two cycles are 4 weeks and 8 weeks rather than 12 weeks as reported in the MS.

Model data issues

B7. **Priority Question:** please clarify why the base case was considered to be appropriate when Table 70 (manufacturer's submission, page 325) shows that the model consistently over predicts event rates when compared to the observed trial data.

B8. **Priority Question:** please clarify why the relative risk reduction (RRR) of the combined endpoint of the ATLAS 2 trial is used as the RRR of rivaroxaban for MI death, MIs, ISs and HS/ICHs, not the relative risk reduction from each of the individual endpoints.

B9. **Priority Question:** please clarify which calibration methods have been used in the model and the parameters which are calibrated by each calibration method.

B10. Please clarify how the numbers in Table 44 (manufacturer's submission, page 207) are calculated and the assumptions made in calculating these values.

B11. Further to question B10, please clarify why, in Table 44, some events have a higher relative risk after 12 months of rivaroxaban treatment than during the 12 months of rivaroxaban treatment. For example, after MI or IS, the risk for HS/ICH over the 1st and 2nd 6 months is 1.0, but increases to 1.5 during the 'post 12 months' period.

B12. Please clarify why the calibration method(s) used to calculate the values in Table 47 (manufacturer's submission, page 210) was not amended to limit the possibility of producing results that may not have face validity. For example for patients who experience a myocardial infarction (MI) in the model, the proportion of MIs that result in a fatality declines as age increases. There is a similar concern with how ischaemic and haemorrhagic stroke fatality rates are modelled over time.

B13. In the deterministic sensitivity analysis presented in Table 77 the lower and upper values of the ICER from changing each parameter is presented. Please clarify the upper and lower value each parameter was set at to produce the upper and lower bound of those ICERs. It is noted that some ICERs appear to be the same number for both upper and lower values.

B14. It is unclear how the deterministic sensitivity analysis on the efficacy parameters has been conducted as the description is inadequate. Please clarify how the deterministic

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sensitivity analyses on the efficacy parameters were conducted by providing full step by step details of the method used to calculate these values. Please also provide the regression output with a description of each variable used in the regression.

B15. Please clarify why a deterministic sensitivity analysis on the relative risk reduction of rivaroxaban was not conducted.

If the deterministic sensitivity analysis on the efficacy parameters was designed to replace this sensitivity analysis, please clarify why using the regression methods was superior to conducting a deterministic sensitivity analysis on the relative risk reduction of rivaroxaban.

B16. Figure 28 (manufacturer's submission, page 217) presents a relative difference in risk across age groups for men and women. Please clarify what the baseline risk is in this figure.

B17. Please clarify why the incidence of first AMIs for men and women is negative for some age groups in Figure 26 (manufacturer's submission, page 216).

Please also clarify how the method used is deemed appropriate for the age groups considered in the model despite the lack of face validity at younger ages

B18. Please clarify why the Weibull distributions used when interpolating the data were not extrapolated to provide the probability that an event will occur in the future time periods.

B19. Please clarify what checks were conducted to see if the last cycle values from the interpolated data were not outliers.

B20. Please clarify why men and women have not been modelled separately in the cost effectiveness model.

B21. Please clarify why it is not possible to transition from the clean health state to the multiple event health states in the extrapolation period (beyond the second year) of the model.

Utility issues

B22. **Priority Question:** please clarify why utility decrements due to ageing have not been applied in the model.

B23. For the utility scores from the trial presented in Table 53 (manufacturers submission page 243), please clarify the numbers of patients used in the calculation of each utility value and standard errors associated with each utility value.

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B24. Please clarify why it was appropriate to model the utility of the post-stroke health states as improving by 33% over one year (manufacturer's submission, table 56, page 267). The advice from your clinician expert stated that an improvement of approximately 10% was appropriate in Table 58 (manufacturer's submission, page 275).

Cost issues

B25. **Priority Question:** From reading the submission (page 316) and looking at the model, it is believed that the cost of treating a multiple event state is the sum of the two when two events occur. For example, if a patient suffers from a MI and an IS their cost of treatment will be the sum of the treatment costs of both events.

It is also believed that the follow up costs of both events are applied when two unlike events occur. This can lead to double counting of costs for patients suffering from multiple events if they enter these health states from the single event health states, as the cost of treating the first event has already been counted in the model.

Please clarify if this perceived error exists.

Other issues

B26. **Priority Question:** Please clarify exactly how the non-parametric transition probabilities sensitivity analysis was conducted (Table 79, p 338). The response should provide sufficient detail so that the ERG can replicate the analysis.

B27. **Priority Question:** on page 450 of the manufacturer's submission, the formula for the change in the proportion of MI deaths over time is stated to be:

$$P_{MI}^{D}(t) = \exp\left(\ln(1 - \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{MI}^{D}}) . \frac{1}{(1 + r_{MI}^{change})^{t}} \right) P_{MI}(t)$$

Please clarify why the pmid1 function used to calculate the clean to MI death transition uses the following formula, assuming the cells have been correctly specified.

$$P_{MI}^{D}(t) = Exp\left(Ln\left(1 - \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{MI}^{D}} \right) * \left(1 + r_{MI}^{change}\right)^{t} \right) * P_{MI}(t)$$

B28. Please clarify why a scenario analysis limiting the treatment duration of rivaroxaban to one year only in the model, was not presented.

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B29. Please clarify why it is stated that the Kaplan Meier curves presented in Figures 20 to 23 (manufacturer's submission, page 192) do not make clinical sense.

B30. Please clarify the rationale for applying country specific exclusion criteria to the clinical-effectiveness, utility and resource use systematic reviews prior to extracting the data?

B31. Please clarify why 46 studies were identified by the cost-effectiveness systematic review but only 38 quality assessments presented in Appendix 11.

B32. Please clarify the source of Table 47 (manufacturer's submission, page 210). The column title for the percentages is '% Increase with age from literature' but the source is stated to be calibration.

B33. Are there data to support an assumption that efficacy and adverse events, particularly bleeding risk would be the same for elderly patients (over 70 years) and those with multiple complex morbidities compared with a younger population (under 65 years)? If there are no data, please clarify the approach taken when modelling the risk of bleeding.