National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

Issue 1 Misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8-9. The following statement is misleading: "Corresponding data for the licensed population were not provided by the manufacturer"	Please replace with "Corresponding data for the licensed population were not provided by the manufacturer as this was not readily available, however, Bayer offered to generate the data if the ERG confirmed they needed this data. Bayer did not believe that those data should differ among the licensed population."	The text is currently misleading. No impact on the appraisal other than clarity of Bayer's response.	Not a factual error; however, the text has been amended for clarity. "Corresponding data for the licensed population were not provided by the manufacturer at the initial request. The manufacturer offered to generate the data if the ERG confirmed they needed these data; however, given the timescales of the STA process, the ERG did not pursue these data."

Issue 2 Incorrect statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10,11-12,22, Incorrect statement about the acquisition cost of Xarelto	Please replace "…a yet to be confirmed acquisition cost of £58.80 per pack of 56 2.5mg rivaroxaban tablets" with "…a confirmed acquisition cost of £58.80 per pack of 56, 2.5mg rivaroxaban tablets". Please also amend all similar references on the pages identified in the first column.	The acquisition cost was confirmed by Bayer in response to the ERG questions. No impact on the appraisal other than clarity of Bayer's response.	We are happy with the original wording as the acquisition cost of rivaroxaban was not explicitly confirmed in the manufacturer's response, only the confirmation that there was a typographical error. For clarity, the manufacturer's response (further clarification question 23rd July 2014) stated that 'Bayer apologises that this error occurred in Table 63. We can confirm that rivaroxaban will be available for this indication as 2.5 mg film-coated tablets, provided as a pack of 56. The recommended dose is 2.5 mg twice daily which equates to a price of £2.10 per day. This equates to a pack price (56 tablets) of £58.80'.

Issue 3 Misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36. The following statement is misleading: "Corresponding data for the licensed population were not provided by the manufacturer, despite an	Please replace with "Corresponding data for the licensed population were not provided by the manufacturer as this was not readily available, however, Bayer offered to generate the data if the ERG confirmed they needed this data. Bayer did not believe that those data should differ among the	The text is currently misleading. No impact on the appraisal other than clarity of Bayer's response.	Not a factual error; however, the text has been amended for clarity. "Corresponding data for the

ERG request”	licensed population.”		licensed population were not provided by the manufacturer at the initial request. The manufacturer offered to generate the data if the ERG confirmed they needed these data (manufacturer’s response to clarification question A21); however, given the timescales of the STA process, the ERG did not pursue these data.”

Issue 4 Misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36. The following statement is misleading: “Of the subjects who withdrew consent, most were in the rivaroxaban treatment groups compared with the placebo group”	Please remove this statement.	This statement is misleading. The figures are as follows: **Stratum 1** Rivaroxaban 2.5mg 10% Rivaroxaban 5mg 9.4% Placebo 11.3% **Stratum 2** Rivaroxaban 2.5mg 8.6% Rivaroxaban 5mg 8.5% Placebo 7.6% No impact on the appraisal other than clarity of the data.	Not a factual error; however, the text has been amended for clarity. “A greater percentage of the subjects who withdrew consent, were in the rivaroxaban treatment groups (889/10,350 [8.6%; p70, MS]) than in the placebo group (405/5176 [7.8%], p70, MS).”

Issue 5 Misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 38, 47. Text implies that Bayer have not been transparent in how the data were presented.	Please replace "Where applicable, data have been re-tabulated in a consistent and more transparent format by the ERG", with "Where applicable, data have been re-tabulated by the ERG to provide further clarity".	The current wording implies that Bayer have not been transparent in the presentation of data. The pivotal study was complex, with two strata and two doses tested (as well as the combined dose arms); Bayer presented in the submission the data pertinent to the decision problem and in line with the marketing authorisation. No impact on the appraisal other than clarity around the data submitted by Bayer.	For clarity, the following amendment has been made: "Where applicable, data have been re-tabulated by the ERG to provide further clarity."

Issue 6 Update and correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 38. Text regarding Bayer response to ERG question A17. This data is now available.	Please amend the text as follows: "Unfortunately, secondary endpoint data for the licensed population were not available at the deadline for Bayer's response to the ERG questions. This data has subsequently been supplied by Bayer."	To reflect the extent of the data that Bayer has provided to the ERG. No impact on the appraisal.	We are happy with the original wording as the ERG have not been supplied any new data since the manufacturers clarification response on 31st July 2014.

Issue 7 Incorrect p value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42. P value reported is incorrect. Paragraph 3.	Please amend the text as follows: "[redacted]."	No impact on the appraisal other than clarity of the data.	Typographical error corrected to [redacted]

Issue 8 Incorrect statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50. Incorrect statement	The following statement (and	To reflect the extent of the	Not a factual error; however, the text has been amended for clarity. [redacted]"

nt about fatal intracranial bleeding	page reference) is incorrect – please amend: “Although the MS provided no data on fatal intracranial bleeding, data from the total population (p115, MS) sugg	data that Bayer has provided to the ERG. No impact on the appraisal.	Please note that the ICH data on p93 are not marked as CiC, whereas the same data are marked as CiC on p115, hence the CiC source on p115 has been referenced.

	est …..". Data on fatal ICH is presented in tables 22 and 23 of the MS. In addition, page 115 should be replaced with p93.		

Issue 9 Misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50. Text implies that Bayer have not been transparent in how the data	Please remove the statement "In the MS (p116-122), the reporting of treatment-emergent adverse events data was not well reported or transparent for the licensed (post-hoc analysis) and total population of	The current wording implies that Bayer have not been transparent in the presentation of data. The pivotal study was complex, with two	We are happy with the original wording. In the ERGs opinion, treatment-emergent adverse events data were not well

were presented.	the ATLAS ACS 2-TIMI 51 trial".	strata and two doses tested (as well as the combined dose arms); Bayer presented in the submission the data pertinent to the decision problem and in line with the marketing authorisation. No impact on the appraisal other than clarity around the data submitted by Bayer.	reported or transparent in the MS.

Issue 10 Misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60, section 5.2.1, incorrect reference to errors in the model.	Please replace the following "Several errors were identified with the initial model; some of these errors were fixed through the manufacturer's response to clarification questions. The errors which were fixed include:" with "In response to clarification questions, the manufacturer provided a version of the model with additional analyses/functionality, as follows:"	It is misleading to state that the changes made in response to clarification questions were as the result of errors in the initial model. No impact on the appraisal other than clarity around the data submitted by Bayer.	Not a factual error; however, the text has been amended for clarity. "Several errors and limitations were identified with the initial model. In response to the clarification questions, the manufacturer provided a version of the model with additional analyses/functionality, as follows:"

Issue 11 Inaccurate text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61. Section 5.2.2. text needs rewording for accuracy.	The text should be amended as follows: "The population modelled was the patient subgroup from the ATLAS ACS-2 TIMI 51 trial who were biomarker positive and had not experienced a previous stroke/TIA"	The current text is inaccurate and misleading. No impact on the appraisal other than clarity of the data.	The text has been amended for clarity. "The population modelled was

			the patient subgroup from the ATLAS ACS 2-TIMI 51 trial who were biomarker positive and had not experienced a previous stroke/TIA.”

Issue 12 Text lacks clarity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63. Section 5.2.4. Text needs rewording for clarity.	The following text should be amended: “The long term ACS events had two subsequent tunnel states to allow for the patients utility to improve over time, and for the cost of treatment and the relative risk of suffering from a subsequent event to fall over time”. Please replace with “The long term ACS events had two subsequent tunnel states to allow for the patients utility to improve over time, and for the cost of treatment of the event and the relative risk of suffering from a subsequent event to fall over time”	The current text lacks clarity. No impact on the appraisal other than clarity of the data.	Not a factual error; however, the text has been amended for clarity. “The long term ACS events had two subsequent tunnel states to allow for the patients utility to improve over time, and for the cost of treatment of the event and the relative risk of suffering from a subsequent event to fall over time.”

Issue 13 Misleading text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63. Section 5.2.4. Text needs rewording for clarity.	The following text is misleading and should be amended. “Secondly, for the patients who suffer from multiple events in separate time cycles any improvement over time that they may have experienced is ignored. Finally, for those patients who transition into the multiple event states from the single event states, the first event is not tracked.” Please take account of the following when rewording this text: Improvements between event 1 and event 2	The current text is misleading and could benefit from further explanation and reference to our acknowledged simplifying assumption.	Not a factual error; however, the text has been amended for clarity. “Secondly, for the patients who suffer from multiple events in separate time cycles any improvement over time that they

	are recorded each cycle and contribute to the end QALYs. We do acknowledge that a simplifying assumption was made that utility after 2 events would be the same for all patients, regardless of their history / timing of events, but we disagree that all improvements were ignored.		may have experienced becomes irrelevant."

Issue 14 Error in formula

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69. Additional bracket in the formula (highlighted in yellow)	And the probability that a MI is non-fatal should read: $$P_{MI}^{S}(t) = 1 - [Exp\left(Ln\left(1 - \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{MI}^{D}}\right) * \left(1 + r_{MI}^{change}\right)^{t}\right)) * P_{MI}(t)]$$	For accuracy. No impact on the appraisal.	Typographical error corrected

Issue 15 Lack of clarity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 71. Text could benefit from further clarity.	The following text "no treatment effect or cost was applied to those patients who discontinued rivaroxaban treatment" should be amended for clarity as follows: "no treatment effect or cost associated with rivaroxaban was assumed from the point of discontinuation. Patients still incurred the cost and transitions associated with aspirin for the remainder of the model, and incurred costs and benefits associated with rivaroxaban up until the point of discontinuation"	No impact on the appraisal other than clarity.	The text has been amended for clarity "No treatment effect or cost associated with rivaroxaban was assumed from the point of discontinuation. Patients still incurred the cost and transitions associated with aspirin for the remainder of the model, and incurred costs and benefits associated with rivaroxaban up until the point of discontinuation."

Issue 16 Incorrect referencing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 71. Incorrect reference in clarification questions.	Question B9 is referred to at the foot of page 71. Bayer believes this to be B7. Please amend.	The current reference is inaccurate. No impact on the appraisal other than clarity.	Typographical error corrected to "B7"

Issue 17 Incorrect reference in title of two tables

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82. Incorrect reference to MS	The title of the table 26 refers to "(Greenhalgh *et al.*53 and p56, Table 16, MS)". We believe the reference to the manufacturer's submission should be table 56, page 267. Please amend. Similarly, Table 27 also refers to "p273-4, Table 57, MS". We believe the reference to the manufacturer's submission should be table 56, page 267. Please amend.	The current referencing is inaccurate. No impact on the appraisal.	Typographical error corrected to "Table 26: Summary of quality of life values for cost-effectiveness analysis used in the manufacturer's base case (Greenhalgh et al.[53] and p269, Table 57, MS)" "Table 27: The utilities of the transient states (p268, Table 56 and p273, Table 57, MS)"

Issue 18 Incorrect number in table

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82. Incorrect number in table	The standard error for non-fatal MI in Table 26 should be 0.010, not 0.10. Please amend.	The current number is inaccurate. No impact on the appraisal.	Typographical error corrected to "0.010"

Issue 19 Incorrect figure in a table

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96. Incorrect figure in Table 32.	The cost assigned to rivaroxaban in the row “None” is incorrect. It is currently reported as £14,802.17 and should be £14,767.63. Please amend.	The currently reported number is incorrect. No impact on the appraisal other than clarity.	Typographical error corrected to “£14,767.63”

Issue 20 Potentially incorrect figure in a table

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106. Potential error in Table 37.	Should the highlighted figure be 1.0?	The currently reported number appears to be incorrect. No impact on the appraisal.	Typographical error corrected to “1.0”

Relative risks for subsequent events	After HS		
	1st 6 months	2nd 6 months	Post 12 months (later)
MI	1.0	1.0	1.0
IS	1.0	1.0	1.5
HS/ICH	4.9	2.1	1.5
Fatal MI	1.0	1.0	1.0
Fatal IS	1.0	1.0	1.0
Fatal HS/ICH	4.9	2.1	1.5
OCD	1.0	1.0	1.0