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

Pro-forma Response

ERG report

Rivaroxaban for the treatment of pulmonary embolism and the prevention of recurrent venous thromboembolism

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *Southampton Health Technology Assessments Centre (SHTAC)*to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, *15th February 2013* 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.

February 2013

Issue 1 Search strategies for economic model parameters were supplied

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P16. A statement is not correct: `Brief details of these searches are given (e.g. databases) but full search strategies are not supplied'.	Full search strategies were provided in an accompanying report (pages 202-240 of reference 115), with a summary in the MS.	Bayer conducted systematic searches as required by the Methods Guide, and supplied full description of this as part of the appraisal. It is misleading to suggest only `brief details' were given.	Brief details of the searches were given in the manufacturer's submission which is the main focus of our appraisal. The sentence in in the ERG report which follows acknowledges the accompanying report: "A reference is given for these searches to an unpublished systematic review conducted by IMS Health for Bayer (Reference 115 in the MS). The ERG has not appraised these searches". Not a factual inaccuracy.

Issue 2 Reason why EINSTEIN-Ext was not included in the clinical systematic review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Paragraph 2 of P18. This provides a critique of Bayer's rationale that the EINSTEIN-Ext was not included in the clinical systematic review. The paragraph includes `exclusion of this study contradicts the manufacturer's inclusion criteria' and that the non-availability of certain data `appears to be the justification of	An inclusion criterion of the clinical systematic review was `patients with symptomatic PE' and an exclusion criterion was `populations for which PE data cannot be separated'. The full inclusion/exclusion criteria are given in the MS (Table 6). As EINSTEIN-Ext was not only in patients with PE and data was not available specific to a population whose index event was PE, this trial did not meet the inclusion/exclusion criteria.	The text suggests poor methodological practice, which is unreasonable, and mis-states the reasoning for not considering further the EINSTEIN-Ext. We agree, of course, that the trial may be `relevant in part to the scope and decision problem', which is why this study specifically was referred to in the MS (page 49).	The ERG report acknowledges the manufacturer's stated reasons for excluding the study (notwithstanding the apparent divergence between the manufacturer's inclusion criteria and the scope/decision problem). The point about the contradiction with the inclusion criteria, specifically about the

their exclusion criteria'. Both phrases are incorrect, and their full context does not appear to clarify.			criteria allowing "any comparator" to be included, was made for context, hence why it is in parentheses. In short, the manufacturer could have made their justification for excluding this study more concise. Not a factual inaccuracy.

Issue 3 Hospitalisation input to the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P62. It is not true that the hospitalisation input (described in last para of P61 / first para of P62) is used only to model recurrent events.	This input is also used in quantifying the cost saving due to reduced length of stay and therefore for the index event.	The ERG's original description is not correct, and unreasonably suggests that the economic model may be mis-structured or inflexible.	The ERG report text does not state that the hospitalisation input is used only to model recurrent events. Not a factual inaccuracy.

Issue 4 Retaining confidentiality of certain important, unpublished trial data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P64. The mean length of LMWH treatment is confidential and unpublished, but can be back-calculated easily from information which is not marked-up as confidential in the last paragraph.	[redacted]	The cost is directly calculable from the unit cost (not confidential) and mean length of LMWH treatment (confidential).	The ERG agrees that this whole sentence should be marked as AIC, and has revised this page accordingly.

Issue 5 Costing of CTEPH

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P66. It is not true that 100% of CTEPH patients are assigned the cost of PEA surgery (£3522.38).	The cost of a PEA is applied to 68% of CTEPH patients only (see para 1 of P179 and table 47 on P180 of MS).	Incorrect description of an aspect of the economic model.	The ERG report does not state that 100% of patients are assigned the cost of PEA surgery. The ERG report uses text given on MS p185. The report notes that 68.4% of CTEPH patients require a PEA on p64 (second paragraph). Not a factual inaccuracy.

Issue 6 Modelling of incidence of PTS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P67. Bayer considers that the `second error' in para 3 is not in fact an error.	The model is structured such that a certain proportion of post DVT patients are assumed to have coincident PTS at any time. PTS is not modelled in a cumulative manner. The reasons for this are discussed in the final paragraph of P136 of the MS.	Incorrect description of an aspect of the economic model.	The ERG agrees that this may not necessarily be an error in the model and therefore this sentence has been removed from the report.

Issue 7 Uncertainty in relative adherence to treatment with VKA (INR monitoring) vs rivaroxaban

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P77. It is implied, as apparent fact, that the need for INR monitoring `encourage[s] patients to adhere to their treatment regime'. It is possible that this is	If the assertion is an opinion (as implied later on P85, `belief'), this should be clarified.	It should be clear what statements are fact, which are based on empirical evidence (and what this is), and which reflect opinions of	The text written in the ERG report expresses the view of the ERG's clinical expert. This is not a factual inaccuracy.

opinion rather than fact, and no supporting reference is provided.		advisors.	

Issue 8 Relative incidence of PTS with rivaroxaban vs enoxaparin/VKA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P59 states that `patients on rivaroxaban are more likely to experience PTS'.	Appropriate qualification, contextual explanation and referencing. Does this just relate to projections into certain model states?	This assertion may not be well-founded and is not referenced. PTS was observed in EINSTEIN-PE in [redacted] of 2412 rivaroxaban patients in comparison to [redacted] of 2405 enoxaparin/VKA patients. PTS was one of many adverse events measures in the study.	As noted by the manufacturer PTS was observed in more rivaroxaban patients than enoxaparin/VKA patients. This is not a factual inaccuracy.

Issue 9 Cost and requirement for rFVIIa treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P67 states that the `cost of treating a patient with rFVIIa is estimated as £19,303 for a patient weighing 70kg'. It is implied that this cost relates to patients relevant to the decision problem, whereas this is not the case.	In scenarios where this is relevant: recalculate a cost relevant to this patient group, use this as an input to the model, adapt the model to account of any differential effect to be expected in patients treated with rFVIIa vs PC vs other courses of action or interventions in response to bleeding, consider and report the CI used in any probabilistic analysis. Alternatively, such scenarios should be removed if they cannot be conducted reliably or reflecting appropriate uncertainty.	This input has an important effect on certain scenarios the ERG has evaluated, therefore it is important that the input is accurate and its provenance and uncertainty not misrepresented.	The ERG report states that 'the proportionate need for anticoagulant reversal drugs in clinical practice is uncertain'.(p82) The ERG analyses provide a range of scenarios rather than specifying the proportions of patients receiving rVIIa vs. PPC. Not a factual inaccuracy.