NHS
National Institute for
Health and Clinical Excellence

27 October 2008

[redacted]
Bayer Schering Pharma
Bayer House
Strawberry Hill, Newbury
Berkshire, [redacted]

NICE
MidCity Place
71 High Holborn
London
WC1V 6NA
Tel: 0845 003 7780

Dear [redacted],

Single Technology Appraisal - Rivaroxaban for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

The Evidence Review Group, (School of Health and Related Research, Sheffield) and the technical team at NICE have now had an opportunity to take a look at submission by Bayer Schering Pharma. 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 points in their reports. As there will not be any consultation on the evidence report prior to the Appraisal Committee meeting you may want to do this work and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by 17:00, Monday 10 November 2008. 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.

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.

If you have any further queries on the technical issues raised in this letter then please contact David Chandiwana or Helen Chung. Procedural questions should be addressed to Bijal Chandarana in the first instance.

Yours sincerely

Elisabeth George
Associate Director - Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A. Clarification on effectiveness data

A1 pages 8 and 82
The submission states that no comparison with fondaparinux has been presented on the grounds that it is not routinely used in clinical practice. Please provide further reasoning for this, because the relevant comparators in an appraisal may not be limited to routine practice only (see the Guide to the Methods of Technology Appraisal 2008, section 2.2.4). It may be useful to bear in mind the evidence, and considerations of the evidence, set out in NICE Clinical Guideline No.46, and NICE Technology Appraisal Guidance No.157.

A2 page 38:
Please specify which location the majority of the participants were drawn from, for RECORD 2 and 4 to be consistent with RECORD 1 and 3 as reported under the critical appraisal of the relevant RCTs section?

A3 page 44:
Please provide information on when the follow up periods were and which follow up periods are reported in the results of the relevant comparative clinical effectiveness RCTs section and in particular Table 8.

A4 page 58:
Please provide an explanation for the higher efficacy event rates for enoxaparin in the dabigatran/enoxaparin studies compared to the rivaroxaban/enoxaparin studies? The submission acknowledges that the enoxaparin efficacy event rates are higher as described above.

A5 page 58:
Please provide a reference for the statement 'where extended prophylaxis is now demonstrated to be more effective.'

A6 page 66:
Please provide a more descriptive explanation of the method of indirect comparison used to compare rivaroxaban with dabigatran and provide a critique of the pros and cons of this approach.

A7 page 20:
Please clarify the statement in section 5.1 that there are over 25,000 deaths due to VTE in England. Page 15 states that this figure includes all patients admitted for medical care of serious illness, not just those patients undergoing orthopaedic surgery

Section B. Clarification on cost-effectiveness data

Please note. The page numbers are not consecutive as the issues should be addressed in a cumulative manner.

B1 page 86:
Please explain why the key assumption: ‘All recurrent VTE events are DVTs’ is a ‘model simplifying assumption’

B2 page 94:
Please make clear where in the model (which cells) were used to adjust the utility for surgery in the first year.

B3 page 94:
Please provide the evidence that all utility estimates have been identified and selected systematically. The NICE reference case requires that ‘The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.’ Please note that a review of cost-effectiveness literature will fail to find some utility studies.

B4 page number not applicable:
Please explain the logic behind cell I147 on sheet ‘Long term complications’.

B5 page number not applicable:
Please explain the logic behind cell I148-I151 on sheet ‘Long term complications’.

B6 page number not applicable:
Please explain whether the following analysis does not constitute double counting? Cell J54 on the ‘Outputs sheet’ already contains the first 5 years of utility. In cell L31 lifetime and 0-5 years are added together.

B7 page number not applicable:
Please explain why in cell J151 on the ‘Long term complications’ sheet, the utility is divided by 2 whereas in cell K106 it is not.

B8 page 91:
Please note the following PTS costs discrepancies and adjust the cost of PTS in the model accordingly to reflect the proportion of severe and mild to moderate using the costs reported by Caprini et al or other relevant costs. The probability of developing PTS was taken from an Italian study, Prandoni et al. The study reported the cumulative incidence of severe PTS (23.5% of patients) and all PTS. The probabilities used in the model were taken from the ‘all PTS’ population and therefore includes a proportion of severe PTS. The cost of PTS is taken from an American study, MacDougall et al. and was estimated as £2865. However another American study by Caprini et al[1] reports that the cost of PTS is: mild to moderate $839 in the first year and $341 in subsequent years; severe PTS $3817 in the first year and $1677 in subsequent years. It would appear that the cost of PTS used in the model represents severe PTS whereas the probability of PTS is taken from a population with both mild to moderate and severe PTS. The opinion of the ERG is that the cost of PTS should reflect the severity of PTS.

B9 page 83:

Please provide a breakdown of the incremental costs and QALYs gained for every year of the lifetime scenario (base case) for both THR and TKR.

B10 page 96:
Please adjust the PTS utility to reflect the severity of the PTS population taken from Prandoni et al. The utility of PTS is taken from Lenert et al and represents severe PTS. Both costs and utilities should reflect the severity of PTS in the population. Lenert et al also report utilities for mild/moderate.
B11 page 91:
Please could you explain how the assumption that 'the occurrence of new PTS or recurrent VTE is assumed to last for the first 5 years post-surgery' was made given that the ERG are aware of a number of studies that report rates of PTS and recurrent VTE, for patients that had experienced a DVT, over a period of 13 years.

B12 page 100:
Please explain how the Hull et al study was identified and provide a justification for its use. This study was used to estimate the proportion of post-discharge events.

B13 page 100:
Please explain how the studies used to inform the false positive rate of suspected DVT were identified and provide a justification for their use.

B14 page 101
Please explain how the MacDougall et al study that was used to obtain the cost of treating PTS was identified and provide a justification for its use.

B15 page 86:
Please provide an updated model with results of the actual outcomes of the trials even if they were not statistically significant. In the base case analysis the following assumption was made 'If the results of the clinical trial or indirect comparison do not show any statistically significant difference between the two arms the model assumes parity between the two comparators'. Even if there is no statistically significant difference in an outcome in the trial, any difference could still make a difference to the cost-effectiveness results, especially if the outcome incurs high costs.

B16 page 86:
Please provide a list of all outcome event rates used in this sensitivity analysis and to provide an updated model with these rates in use. Please could you also repeat the PSA with trial data for all trial outcomes included in the model with the trial reported uncertainty? The submission states that the sensitivity analysis included a scenario where actual rates were used regardless of the trial findings and it is not clear which outcomes this applied to.

B17 page number not applicable:

Please provide a model with all the changes outlined above, together with a univariate and PSA analysis. Please provide tables of results including all sensitivity analysis.

1. Caprini JA, Botteman MF, Stephens JM *et al*. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. *Value.Health* 2003;6(1):59-74.