10/08/2011

NHS
National Institute for
Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

Dear [redacted]

Re: Single Technology Appraisal – Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery

The Evidence Review Group Kleijnen Systematic Reviews Ltd and the technical team at NICE have now had an opportunity to take a look at submission received on the 19 July 2011 by Bristol-Myers Squibb Pharmaceuticals and Pfizer. 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 **17:00, Wednesday 24 August 2011**. 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 to [redacted] in the first instance.

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1 **Priority request:** Please provide a complete set of data for all comparisons of all outcomes estimated using Winbugs. This should be in a format that can be run immediately (i.e. without any editing) in WinBUGs. It also shoul be accompanied by a complete set of comments showing the study from which the data was obtained. This will enable the ERG to check the results of the mixed treatment comparison (MTC).

A2 **Priority request:** Please provide, for THR and TKR, an overview of the studies used in the indirect comparison and, separately, in the MTC for group 2. Please provide justification if any studies are excluded from these analyses.

A3 **Priority request:** It is expected that the MTC and the indirect comparisons should produce the same results given that all three comparisons are estimated via the same common comparator, which is enoxaparin 40mg od i.e. there are no head to head comparisons between these comparators. Please explain why the results for the MTC are different from the results of the indirect comparisons for apixaban 2.5mg bd with the other comparators, dabigatran 220mg od and rivaroxaban 10mg od.

A4 **Priority request:** A possible typographical error was identified by the ERG for fondaparin* in line #9 of the Medline search strategy for clinical effectiveness where it appears as fonadaparin*. The error appears to have been repeated across all strategies containing comparison drugs. When the ERG repeated the searches using the correct spelling they noticed considerable differences in the number of records identified. Please check that no relevant fondaparinux trials were missed in your search strategy.

A5 Please explain why the abbreviation LMWH was not used in the search strategy for the mixed treatment comparison and all subsequent searches for low molecular weight heparin. Please clarify whether this could have influenced the results.

A6 Please explain the rationale behind not including the following LMWH listed on Emtree as free text searches as you have done with other LMWHs: livaraparin-calcium; tafoxiparin; idrabiotaparinux; rd-11885;; idraparinux; semuloparin; cy-222; deligoparin; antixarin. The ERG noted that the scope for the mixed treatment comparison methodology (Appendix 16 in the manufacturer's submission) states that "low molecular weight heparins other than enoxaparin were included in the MTC analyses where these were available at relevant licensed doses". The ERG considers that any issues surrounding licensing would not be a reason for their exclusion. Could you confirm if these LMWHs were also excluded during screening?

A7 On page 85 of the manufacturer's submission, it states: "The adjusted indirect comparison is regarded as the most appropriate analysis for informing the clinical efficacy and safety of apixaban versus relevant treatment comparators in this submission, since the MTC results were inconsistent with some of the head-to-head RCT data." Please explain which results were inconsistent; and provide an explanation for these inconsistencies.

A8 On page 132, the manufacturer's submission states "For simplicity a comparison with enoxaparin only is made in the base case, as it is the most widely used LMWH. Therefore, the **indirect** comparison results for apixaban versus enoxaparin are used only. This approach assumes that LMWHs are broadly clinically equivalent, which was an assumption also made in the NICE appraisal of dabigatran for VTE prevention in orthopaedic patients (64) and is consistent with the analyses underpinning the VTE prevention NICE guidelines too" The ERG is unclear why a reference to the indirect comparison has been made here when direct evidence is available. Please clarify this statement.

A9 On page 133 (table 58), baseline risks cannot be found in the publications regarding Advance 2 (Lancet 2010) and Advance 3 (NEJM 2010). Please clarify these risks.

A10 Please explain why Medline, Cinahl & Cochrane searches for clinical effectiveness and the MTC used the term Arthro**scopy** rather than Arthro**plasty** (as in the Embase search for these sections and all other searches) and clarify whether the inclusion of arthroplasty in the search is likely to result in additional relevant publications being identified.

Section B: Clarification on cost-effectiveness data

B1 **Priority request:** The model structure does not seem to allow for transition between mild to moderate post thrombotic syndrome in year 1 to severe post thrombotic syndrome in year 2 and beyond. Please justify this assumption and advise whether it is supported by any evidence.

B2 **Priority request:** The model does not distinguish between types of bleed and types of VTE for each comparator individually (they are all the same). However, as an example, apixaban has fewer total bleeds, but more major bleeds compared with enoxaparin in THR. This assumption may favour apixaban, therefore please adjust the model to allow for differences in type of bleed and type of VTE.

B3 **Priority request:** The cost-effectiveness model does not allow a full incremental analysis (only 2 comparators at the time). Because of this, it is not possible to run a PSA for all comparators simultaneously, as should be done. Please adapt the model in order to perform an incremental analysis and PSA for all comparators simultaneously.

B4 **Priority request:** Please explain why, for THR, fondaparinux 2.5 mg od was not included in the indirect comparison, as used in the CEA model? Please re-run the indirect comparison and include fondaparinux 2.5 mg od. The ERG notes that for THR the only trial (Lassen et al 2002) fondaparinux 2.5mg od is compared with enoxaparin 40 mg od, however the composite outcome (any VTE+death) is not reported. However, the study does report any VTE (PE or

DVT) and death separately. Although there could be overlap between these two outcomes, the number of deaths is small (fondaparinux (n=2) and enoxaparin (n=4)). Therefore, if it is assumed that there is perfect overlap (that is, composite = any VTE) then the OR=0.416; or if it is assumed that there is no overlap (i.e. composite=any VTE+death) then the OR=0.418. Asthere is little difference between these two results please include fondaparinux 2.5 mg od data from the indirect comparison analysis in the CEA model for THR and conduct sensitivity analyses where appropriate.

B5 **Priority request:** The manufacturer's submission suggests that apixaban may be associated with improved treatment compliance (pg 14) because it is an oral medication as opposed to an injection. However, it is possible that the reverse could be true given that compliance with oral medication depends largely on the individual, whereas compliance with injection might depend at least partly on others, including carers, who might be more motivated than the individual. In light of this, please provide estimates of compliance for each of the comparators and incorporate these in the cost effectiveness model.

B6 **Priority request:** On page 86 (Table 36), results are reported as Odds Ratios (ORs). However on page 132 the manufacturer's submission states: "Relative risks (RR) are used in the economic model rather than odds ratios (OR) because they can be applied directly to an absolute probability of an event to generate the absolute event rate for the comparator treatment." It is unclear whether the ORs and RRs match, without full data extraction of included studies. Please provide tables with numbers of events and total number analysed for each outcome included in the economic model, together with the corresponding ORs and RRs.

B7 **Priority request:** A possible typographical error was identified for the word analy* in line #74 of the Medline search for cost-effectiveness, where it appears as anlay*. The error appears to have been repeated in all subsequent strategies using this filter. Please clarify whether this could have influenced the results.

B8 **Priority request**: Please explain why Medline Mesh terms were used to search Embase in lines #76-97 of the Embase cost-effectiveness strategy, and why the appropriate Emtree translations were not used.

B9 On page 154 (section 6.4.7) of the manufacturer's submission, please clarify which instruments were used for the different utility inputs, and justify if different instruments in addition to EQ-5D were used and for which estimates?

B10 On page 154 (section 6.4.7) of the manufacturer's submission the ERG has noted that the standard errors for utilities and the utility decrements are all set to 10%, and considers that it would have been more appropriate to use estimates based on empirical evidence. Please amend the standard errors and utility decrements in line with the available evidence.

B11 Please use standard deviation instead of standard error for the distribution of treatment duration in the model.

B12 On page 127, patients in the THR trial are described as being slightly younger than those in clinical practice. In the TKR trial, patients are described as being slightly less often male. Are sex and age predictors of bleeding and VTE? If so, please use adjusted baseline risks and relative risks in the model.

B13 In table 81 of the manufacturer's submission, the results of the trial and the model do not exactly match. Please justify why recalibration has not been undertaken.

B14 In table 81 of the manufacturer's submission, results are provided for enoxaparin and apixaban. Please provide results for the other comparators as well.

B15 Please amend the cost per course of dabigatran (for THR) from £1324.40 to £134.40 in table 77.

B16 It is unclear to the ERG how the costs in tables 91 and 92 relate to those in 93 and 94 in the manufacturer's submission. For example, in table 91 apixaban is £58 less costly than enoxaparin. In table 93 the difference in mean total treatment costs is £54. Please clarify the difference between these numbers.

B17 The distributions (lognormal) for the relative risk model parameters for the comparators underestimate the uncertainty as observed in the trials. For instance, for rivaroxaban THR the 95% confidence interval (CI) in the trial was 0.18-0.51, while the distribution in the model results in a 95% CI of 0.26-0.35. Please adjust the distributions used in the model for the relative risks, in order to properly reflect uncertainty.

B18 The RE-MODEL and RE-NOVATE trials do not present relative risks. Please clarify how the data inputs for the relative risks and uncertainty for dabigatran in the model were determined.

B19 A disparity between the dates listed for the Embase “Measurement and Valuation of Health Effects” was noted. Section 9.12.1 in the manufacturer’s submission records that Ovid Embase 1980 to present day was searched, but in section 9.12.4 the strategy records 1996 to week 27 2010. Please confirm the start date of the search strategy and explain whether the discrepancy in start dates could have influenced the results?

B20 On page 182 (table 92) should be amended to Tables 91 and 92

B21 On page 15 in the last sentence, THR should read TKR and vice versa.

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