17 December 2012

NHS
National Institute for Health and Clinical Excellence

NICE
British Council Offices
10 Spring Gardens
London
SW1A 2BU

[redacted]

www.nice.org.uk

Dear [redacted],

Re: Single Technology Appraisal – Rivaroxaban for the treatment of pulmonary embolism and prevention of recurrent venous thromboembolism

The Evidence Review Group (Southampton Health Technology Assessment Centre) and the technical team at NICE have now had an opportunity to take a look at submission received on the 21st November 2012 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, 7th January 2013**. 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.

[redacted]

[redacted]

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

General request

1. **Priority request:** Please supply the Clinical Study Report for EINSTEIN PE

2. **Priority request:** Please supply the CHMP assessment report for rivaroxaban in the treatment of pulmonary embolism.

Literature searching

3. In section 7.1.1, the search strategy for cost effectiveness studies is described. On page 106 of the submission it states that "horizon scanning using key words" was performed. Please clarify how this was done (e.g. using the National Horizon Scanning Centre database).

<u>Section A: Clarification on effectiveness data</u>

EINSTEIN-PE population

A1. The SmPC for rivaroxaban states that rivaroxaban can be used with caution in patients with severe renal impairment, defined as a creatinine clearance of 15-29 mL/min. Patients with a creatinine clearance of < 30 mL were excluded from the EINSTEIN –PE trial. Despite this exclusion criterion, 6 people with a creatinine clearance of <30 mL/min were included in EINSTEIN-PE.

- Please clarify why patients with a creatinine clearance of <30 mL were excluded from the trial.

- Please clarify what evidence there is for the efficacy of rivaroxaban for the treatment of PE and prevention of recurrent venous thromboembolism in a population with severe renal impairment?

A2. On page 99 it states that 62.5% of people received just one day of pre-randomisation anticoagulation whereas in the NEJM article (Table 2) the corresponding percentages are slightly lower: (n=1389/2419 [57.4%] rivaroxaban; n=1400/2413 [58.0%] standard therapy).

- The denominator in the NEJM article is the ITT population, whereas it appears that the denominator in the submission is the total number who received pre-randomisation treatment. Please clarify this apparent discrepancy.

- Please clarify whether all treatments used prior to randomisation were LMWH as implied by the denominator in Figure 7 (page 73 of the submission), or whether unfractionated heparin and fondaparinux was also used, as implied by Table 2 of the NEJM article?

A3. Pre-randomisation LMWH is listed as one of the pre-specified subgroups in Figure 7 (page 73 of the submission). However, a reference to this subgroup could not be found in the trial protocol. Please clarify whether use of pre-randomisation LMWH was a pre-specified subgroup.

A4. The publication from the EINSTEIN-PE trial notes in its discussion (NEJM article page 1296, paragraph 3), that the study population was representative of the spectrum of patients who present with symptomatic pulmonary embolism, with the exception of those for whom fibrinolytic therapy was planned. Please explain how the exclusion of people for whom fibrinolytic

therapy was planned in EINSTEIN PE would affect the generalisability of EINSTEIN PE to a UK population?

Subgroups in EINSTEIN PE

A5. **Priority question:** The percentages for unprovoked/ provoked 'index event' for the ITT population (15.8% and 84.2% respectively) presented on page 72 of the submission are different to the proportions presented in Table 9 (approximately 64.5 unprovoked) and Table 10 (49.3% idiopathic DVT/PE) in the submission (pages 56 and 57 respectively) and Table 1 in the NEJM publication (where the proportion of unprovoked and provoked PE was 64.5% and 35.5%, respectively).

- Please explain the reason (s) for these differences.
- Please provide the definition used to include people in the provoked or unprovoked index event subgroups.

A6. **Priority question:** Please clarify the rationale for the subgroups considered in the subgroup analysis of safety outcomes (Figure 10, page 77 of the submission) and those considered for efficacy outcomes (Figure 7, page 73 of the submission).

Statistical analysis in EINSTEIN PE

A7. Please provide a citation for the meta-analysis of historical trials used to inform the non-inferiority margin (page 62 of the submission).

A8. It is noted that page 97 of the submission states that the non-inferiority margin was pre-specified as per EMA guidance. However, please provide further information about the pre-specified decision that for non-inferiority to be concluded, rivaroxaban had to retain at least 50% of the efficacy of enoxaparin/VKA (that is, the upper 95% CI needed to below the hazard ratio margin of 2.0)? Specifically, please clarify why this fraction of efficacy (i.e. at least 50%) was considered appropriate for this indication.

A9. On page 72 of the submission, results are reported for the primary efficacy outcome in the ITT population, the PP population, and also the 'ITT on-treatment' and 'PP on-treatment' populations. Please define the ITT on-treatment' and 'PP on-treatment' populations, and provide the numbers of patients in each, according to trial arm.

EINSTEIN PE outcomes

A10. **Priority question:** The definition of bleeding events that are excluded from treatment-emergent adverse events on page 78 of the submission is unclear, as not all bleeds (e.g. epistaxis) are excluded. Please list the bleeding outcomes that were and were not included in the analysis of treatment-emergent adverse events described on table 18 and table 22 (on page 92 of the submission). For each bleeding outcome included in the treatment emergent adverse event please, provide numbers, proportions and P-values, risk ratios, absolute risk differences and associated 95% confidence intervals.

A11. The footnote to table 15 (page 70 of the submission) states that 'some patients may have experienced more than one event'. Please provide the number of patients experiencing more than one event and, which events were experienced together.

A12. **Priority Question:** It is not clear from the submission which outcomes were assessed by the blinded central independent adjudication committee (CIAC). For example Table 8 (page 52 of the submission) states that "all suspected outcome events were classified by a central independent adjudication committee (CIAC) who members were unaware of the treatment assignments", Appendix 3 (page 300) states that the blinded CIAC also assessed the "key safety outcomes according to pre-defined criteria" and the NEJM publication states "in the case of suspected venous thromboembolism, the protocol required objective testing" (page 1289) Please clarify precisely which outcomes were assessed by the CIAC.

A13. Please clarify the total the number of patients in each arm who were included in the adverse events analyses detailed in Table 18, page 79 of the submission.

A14. Page 96 of the submission reports percentages of patients with 'confirmed events' (VTE recurrence – 10.2% in the rivaroxaban group vs. 9.7% in the dual enoxaparin/VKA arm). These percentages do not appear to be consistent with those reported on page 69 of the submission, which states for the primary efficacy outcome "the outcome was confirmed in 50 (2.1%) patients in the rivaroxaban group and 44 (1.8%) patients in the dual enoxaparin/ VKA arm". Please clarify which of the figures are correct.

Discontinuations in EINSTEIN PE

A15. **Priority question** Page 62 of the submission states "when enrolment was discontinued, patients completed their assigned treatment except for those in the 12 month duration group who completed at least 6 months".

- Please clarify whether it was specified in the protocol for EINSTEIN-PE that people in the 3- and 6-month treatment groups must finish their treatment if they have not completed by the time of enrolment discontinuation, whilst people in the 12-month treatment group should continue until 6 months or whether all people in the 3- and 6-month treatment groups in EINSTEIN PE, but not the 12-month treatment group had completed their treatment at the time enrolment was discontinued.

- Please provide the number and proportion of patients overall and by each trial arm did not complete the full 12 months of treatment?

A16. **Priority question** Please clarify why the number of patients stated to have discontinued the study drug as a result of an adverse event in Table 18 page 79 of the submission differs to the number stated in Table 13 page 64 and Figure 5 page 65 of the submisson. Please clarify which data are correct.

Einstein-PE patient treatment satisfaction

A17. Please clarify how many patients from each trial arm were included in the analyses of patient treatment satisfaction and how the patients included in these analyses were selected.

A18. Please provide the rate of missing data across each trial arm in the patient satisfaction analyses (for the ACTS measure), and the strategy for dealing with missing data.

A19. Please clarify whether the TSQM analyses were performed for the ITT population, and if so, please provide the rate of missing data and the strategy for dealing with missing data as above.

A20. Please clarify the methods used to analyse the TSQM data. Please also provide the underlying data to support the final sentence in the third paragraph on page 38.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Table 28 on page 120 of the submission reports the probabilities of a VTE in patients on LMWH/VKA by patient treatment duration and period. Please provide the probabilities by period for rivaroxaban equivalent to the data in table 28, for LMWH/VKA.

B2. **Priority Question:** The treatment effect is applied in the model using a hazard ratio assuming a proportional hazard (page 120 of the submission).

- Please clarify whether a test was performed to support the assumption of proportional hazard? If so, please describe which test was used and provide the result of the test.

- Please clarify whether consideration was given to using separate probabilities or relative risk ratios for the rivaroxaban and the comparator arm, rather than a proportional hazard?

B3. The technology acquisition costs for rivaroxaban provided in Table 1 and subsequent tables for the base case cost-effectiveness analysis (£216.74, £392.52; £727.71 for 3, 6, 12 months, respectively) are slightly lower than those presented in Table 2 (£235.86, £427.61 or £811.13). Please clarify the discrepancy in these costs.

B4. **Priority question:** Please provide the mean (SD) number of INR monitoring visits for both arms of the EINSTEIN-PE trial for the first three months, and 3 month cycles thereafter.