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[redacted]
Boehringer Ingelheim Ltd

25 March 2008

Dear [redacted]

Dabigatran etexilate for the prevention of venous thromboembolism

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 first look at the submission document and economic model submitted by Boehringer Ingelheim Limited.

There are a number of issues relating to the clinical and cost effectiveness data on which we are seeking clarification at this stage. An overview of the key matters for clarification is provided in part A, overleaf. The ERG has provided detailed feedback, referring to specific locations in the submission. These specific points for clarification are provided in part B of this clarification letter. Please note that details regarding the key matters for clarification can be found in part B.

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 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, Tuesday **08 April 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 further queries on the technical issues raised in this letter than please contact Ruaraidh Hill or Helen Chung. Procedural questions should be addressed to Chris Feinmann in the first instance.

Regards

Meindert Boysen

Pharmacist MSc HPPF

Associate Director - Single Technology Appraisals

Encl.: checklist for in confidence information

A – Matters for clarification – overview of key issues

Clinical effectiveness

A1. Expand on description of evidence searches and study inclusion and exclusion in the clinical effectiveness review. This is necessary for the searches in the submission to be validated.

A2. Provide details of the status of the RE-MOBILIZE study, including justification for inclusion in the clinical effectiveness review.

A3. Provide further detail of trial flow and baseline characteristics of groups in the included studies. Identify and discuss any differences within studies and respond to all critical appraisal items included in the submission template.

A4. Provide both random effects and fixed effect results for all summative analyses.

A5. Provide pooled analyses for primary endpoints and safety data from studies, or an explanation for not doing so. Include analysis of bleeding outcomes. Full description of methodology should be provided.

A6. Provide further clarification of and justification for the modified intention to treat analysis. Reporting of this analysis seems inconsistent between different parts of the submission.

A7. Expand description of the mixed treatment comparison (MTC). Specify which studies have been included and explain process for estimation of adjusted indirect comparison.

A8. Provide results of further MTC:

a. including fondaparinux (see part B for detailed specification) and

b. excluding comparators which were not specified in the scope (such as aspirin and mechanical methods).

Cost effectiveness

A9. Report on pricing variations of comparators which may result from agreed discounts and explore the affect of varying comparator cost in the economic evaluation.

A10. Identify and discuss any differences in data inclusion or analysis between clinical effectiveness and economic evaluation. Justify combining of minor bleed and clinically relevant bleed in the economic evaluation.

A11. Provide incremental cost effectiveness ratios (ICERs) using both random effects and fixed effect results (as specified above).

A12. Provide ICERs combining data from RE-MODEL and RE-MOBILIZE).

B – Matters for clarification – detailed queries

Clinical effectiveness

Ref	Page	Question / clarification / requirement
B1	14	Please clarify why the RE-MOBILIZE study is included in effectiveness evaluation, yet not considered appropriate for economic evaluation. Please give clear explanations of inclusion and exclusion.
B2	26	Please give complete description of the 15 excluded studies listed. Please confirm that the 7 conference abstracts cited do report on trials that were subsequently published and clarify if these are early publications of the included RCTs or other citations.
B3	26	Please provide a list of all citations identified by the search in BILIT and pre-BILIT. This information is necessary to validate the searches described in the submission. The ERG have attempted to rerun the search described in the submission and only 10 items were found. It is assumed that the 9 further unique citations were identified in BILIT and pre-BILIT. In addition, it is assumed that the RE-MOBILIZE trial was identified from this source as it was not found in the publicly accessible databases named.
B4	26	Please be explicit that the RE-MOBILIZE trial is currently published as an abstract only. This is important since a great deal of the data reported to be from this study are marked confidential in the submission and cannot be verified with reference to a published paper. The absence of a published source also affects the ERG's capacity to critically appraise this RCT.
B5	40	Please give baseline demographic and clinical characteristics for all trial arms and highlight any differences. This level of presentation is in accordance with point 14 on the CONSORT checklist, and highlight any differences between these

		within-trial groups. The ERG note that presentation of overall trial demographic and clinical characteristics combined for all arms participants in a trial (as in Tables 13 and 14) is not sufficient.
B6	44, 45, 46	Please provide complete information on participant involvement in the trials. In accordance with the CONSORT flowchart, and point 13 on the CONSORT checklist, for example, please record: • *numbers of eligible patients* • *reasons for withdrawals between randomization stage and treatment stage* • *numbers analysed for both efficacy and safety endpoints, and numbers excluded from each analysis, with reasons*
B7	59	Please provide tabulated responses (in a single table) to all critical appraisal questions, as specified in in section 5.3.6 of the submission template, repeating information in other parts of the submission if necessary.
B8	62, 64, 66	Please describe the *modified ITT* (mITT) analysis fully. It is presented in the submission as the exact equivalent of the FAS, with only those with evaluable venographs. On page 60 the analysis is presented as something different. Therefore, please report numbers of participants analysed by FAS and analysed by mITT. If they identical, please state so explicitly Please also explain the rationale for exclusion of other treated patients from efficacy and safety analyses.
B9	70	Both fixed effect and random effects model based results are required for all analyses. Please provide results from random effects models for the relative risk for the primary efficacy endpoint of the combined European trials (RE-MODEL and RE-NOVATE).
B10	70	Please provide fixed effect and random effects models for relative risk for each dosing schedule for the combination of the two knee

		trials (RE-MODEL and RE-MOBILIZE). While is the ERG appreciate that the combination of the European trials is valuable because it has high generalisability to the UK setting, there is also a case for combining the two knee trials as they concern the same population, with a more similar risk of VTE (that is higher than and different from the hip population) and a similar treatment duration. The inclusion of these analyses will provide NICE with all available information on which to base a decision, especially since there is otherwise only a single relevant RCT for each population to support the submission.
B11	74	Please provide random effects models for relative risk for the secondary efficacy endpoint of the combined European trials (both fixed effect and random effects models are required for all analyses).
B12	78	Please conduct meta-analyses of risk difference on both the primary and secondary endpoints, using both fixed effect and random effects models.
B13	78	Please conduct additional meta-analyses of risk difference on the combination of the RE-MODEL and RE-MOBILIZE trials (both fixed effect and random effects models).
B14	79	Currently, pooled analyses have only been performed on the secondary efficacy endpoint and no explanation has been given for not performing this analysis on the primary efficacy endpoint (or safety endpoints). Also, the statistical model used in the analysis that is provided is not described. Please perform such analyses, as required.
B15	81	A mixed treatment comparison (MTC) has been performed including fondaparinux, a specified comparator of the submission, but this included 5 fondaparinux trials, 2 of which arguably should <u>not</u> be included, that is studies of hip fracture and abdominal surgery (It is unclear if the MTC is based on the NICE VTE guidance – although this is not made clear). If the MTC is to be retained:

	89	1a) Please specify exactly the trials (references) that have been included in the MTC for each endpoint; the number and details of included trials relating to each intervention is unclear 1b) Please remove references to comparators not specified in the scope *eg. aspirin, stockings* 1c) Please explain the process of "estimation by adjusted indirect comparison" used to generate RRs for DBG and extended LMWH versus nil in the single intervention meta-analyses, and why no adjustment was possible for RE-NOVATE The following addtional analyses are required in order for the ERG to evaluate the evidence presented in your submission: 2a) Please provide specific meta-analyses for an indirect comparison of relevant outcomes with fondaparinux, a specified comparator with DBG in this submission, in relevant combinations • *including but not restricted to 3 RCTs comparing fondaparinux with enoxaparin, the common comparator with DBG, 1 using the EU 40mg dose (elective hip), and* • *2 RCTs using the USA 30mg b.i.d dose (elective hip, and elective knee) eg. Lassen 2002, Bauer 2001, Turpie 2002).* • *Alternatively, explain why these indirect comparisons with fondaparinux have not been performed (this does not include the comparison with placebo or nil*). 2b) Please perform a search for trials involving the submission's stated comparators (LMWH and fondaparinux) and report the results of that search.
B16	93	Please perform relevant meta-analyses (as above) using fixed effect and random effects models for bleeding outcomes, as required The submission template requires: *"if trials are designed to test significant differences between treatments with respect to an adverse effect, it should be reported in same detail as previous [efficacy] sections"*

Cost effectiveness

B17	140	Table 57. Minor bleed = minor bleed + clinically relevant bleed. In the effectiveness section (pgs 94-95) major bleed is reported combined with clinically relevant bleed. Please provide a justification as to why minor bleed is combined with clinically relevant bleed in the cost-effectiveness section.
B18		Please repeat the cost-effectiveness analysis using estimates from a random effects model.
B19	70	Please repeat the cost-effectiveness analysis using RRs from the fixed and random effects models for each dose for the combination of the two knee trials (RE-MODEL and RE-MOBILIZE), as requested above.

Matters for clarification – further specific comments and queries

Ref	Page	Question / clarification / requirement
B20	12	Page number missing
B21	14	Please clarify the comparator status of enoxaparin as a LMWH (eg. what % of LMWH used is enoxaparin)
B22	14	Please clarify the statement that the rate of VTE and all-cause mortality in the comparator group in the RE-MOBILIZE trial was "uncharacteristically low"
B23	16	Please include the results of the indirect comparisons (Section 5.6)
B24	2	Please provide a detailed and accurate contents list
B25	23	Please check the dosing regimens and the differences between USA and EU according to the ACCP guidelines – the information given here differs from the information given on pp.36, 37
B26	25	Please list the data sources searched, including any restrictions, as required by the QUORUM checklist. Please justify any restrictions of date.
B27	25	Please give information on supplementary methods used to identify studies (other than the searching of electronic databases), as specified in the QUORUM checklist (such as handsearching of journals, reference and citation tracking). If no such methods have been employed, please explain why.
B28	25, 215	Appendix 2, section 9.2: Please recheck the date ranges for the databases listed in Table 110 – are these correct?
B29	25-26	It is stated that 2 reviewers screened all titles and abstracts "according to the inclusion and exclusion criteria as given below (section 5.2.2)". According to these criteria, only 3 RCTs would be included (the BISTRO II study would be excluded, for the reasons stated in 5.2.3). Please revise the numbers in 5.1, or explain the inclusion in 5.1 of the BISTRO II study according to the stated criteria

B30	26	Please explain the inclusion of the BISTRO II trial in 5.2.1 (i.e. compares intervention with comparator, therefore included here, but excluded from included list by dose)
B31	26	“The abstracts or papers . . . a further 15 were removed” – this sounds like a two-level screening process – please clarify exactly the process by which the 19 unique citations identified by the search were reduced to 4; also, does the generation of results not come BEFORE the selection by the 2 reviewers?
B32	27	Please give the rationale behind the inclusion and exclusion criteria stated in 5.2.2, as required in 5.1, p.25
B33	28	Please explain the processes by which data were extracted from the included studies, as required by the QUORUM checklist
B34	3	Please note that the submission should not usually exceed 75 pages
B35	30	Please explain the processes by which this trial was identified, and how any other studies were identified and excluded
B36	37	Please explain the differences, if any, between the populations receiving the different doses of DBG (Table 12)
B37	38	Please provide, if possible, the dates defining the periods of recruitment and follow-up, in accordance with point 14 on the CONSORT checklist, as required
B38	38	Please clarify any information given regarding points 9 and 10 on the CONSORT checklist, as required
B39	39	Please clarify whether, and how the blinding process was evaluated, in accordance with point 11 on the CONSORT checklist, as required
B40	39	Please explain why the justification of outcome measures appears under the section on trial methods (5.3.1), rather than Efficacy outcomes (5.3.4)
B41	39	Please confirm the statement that all patients receiving twice daily subcutaneous injections is correct
B42	40	Please explain the terms PK and PD

B43	44	Not all numbers are consistent with the published study, please check and revise flowchart or explain
B44	47	Please provide references for endpoints debate
B45	48	Please provide references on stated associations of asymptomatic VTEs
B46	61	Please justify the statement that VTE rates were “surprisingly low”, and favouring the comparator
B47	61	Please include median follow-up time of analysis, as required
B48	66	Please justify statement that levels of VTE in comparator were “surprising”
B49	68, 69	Please explain why secondary endpoints reported here do not correspond with the secondary endpoints as defined in Tables 15 and 16 previously
B50	71-80	Please be consistent in using either trial names or trial numbers to identify trials, as required (p.3). Up to this point, trial names have been used, only to be replaced by trial numbers here.
B51	79	Please explain the statement that the analyses “appear to favour enoxaparin” – they do favour enoxaparin, don’t they?
B52	8, 10, 13	Please justify both doses (220 mg and 150mg) – since the published RCTs do not distinguish between the populations receiving the two doses being evaluated, what is the evidence for the specified doses for the specific populations, that is, the lower dose level for moderate renal impairment and elderly populations?
B53	80	Please give more detail on the sensitivity analyses • numbers of missing events • highlight any significant differences between the therapies • explain why only the fixed effects model was chosen
B54	83	Please explain how the Cochrane library differs from CENTRAL, is CENTRAL not a component of the Cochrane library? Please clarify which components of the Cochrane library were searched. Please explain why, if looking for meta-analyses only, a register

		of controlled trials was searched (CENTRAL)?
B55	89, 92	Please clarify where the results are for the estimated pooled risk of HIT
B56	93	Please explain why extent of exposure is reported, it is not listed in the safety outcomes to be reported (p.49)
B57	94, 95	Please report absolute difference of DBG versus enoxaparin for major bleeding
B58	94, 95	Please report absolute difference of DBG versus enoxaparin for clinically-relevant bleeding alone
B59	94, 95	Please explain the inclusion of a reference to the BISTRO II trial here (the trial was excluded, and there is no other reference to it in the submission)
B60	103-104	Please provide references: • for 'endpoints debate' • for stated associations of asymptomatic VTEs • supporting the methodological approach adopted Please provide overview of results with reference to their critical appraisal