NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID483]

Dear [redacted],

The Evidence Review Group, **BMJ Group**, and the technical team at NICE have now had an opportunity to take a look at the submission received on the **29th May 2014** by **Boehringer Ingelheim**. 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** on **4th July 2014**. 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], Technical [redacted]. Any procedural questions should be addressed to [redacted], Project Manager **XXXXXXXXXXXXX** in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Encl. checklist for in confidence information

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Section A: Clarification on effectiveness data

A1. **Priority Question**: Please clarify how dabigatran will be used in clinical practice, including:

- Whether there will be any overlap with LMWH treatment;
- The expected duration of secondary prevention after acute treatment for people presenting with a) DVT and b) PE, and how this is determined. If a range of expected treatment durations exist, please describe these and confirm the typical duration;
- whether dabigatran would be prescribed for acute treatment at recurrence of DVT or PE.

A2. Please provide an updated version of Table 19 in the submission to include the rationale for deviating from the NICE final scope in relation to:

- Comparison with fondaparinux;
- Comparison with rivaroxaban in relation to the subgroup of patients with active cancer.

Dabigatran trials

A3. **Priority Question:** Please provide details of the percentage time in therapeutic range (TTR) by warfarin treatment group for the individual geographic regions evaluated for the full randomised (ITT), full analysis and per protocol populations of RE-COVER I, RE-COVER II, and REMEDY.

A4. **Priority Question:** Please complete the following table for RE-COVER I, RE-COVER II, REMEDY, and RESONATE for the listed subgroups in the full randomised, full analysis and per protocol populations (that is, 16 tables):

a. Western Europe region;

b. INR control as measured by percentage time in therapeutic range (TTR) for centres in the warfarin group with TTR <60%;

c. INR control as measured by percentage time in therapeutic range (TTR) for centres in the warfarin group with TTR ≥60%.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

	Dabigatran			Warfarin			Dabigatran vs. Warfarin	
	n	N	Event rate (100 pt-year)	n	N	Event rate (100 pt-year)	Hazard Ratio (95% CI)	p-value
Composite of recurrent symptomatic VTE and deaths related to VTE								
Symptomatic PE								
Symptomatic DVT								
Deaths related to VTE								
All deaths								
Major bleed								
Clinically relevant bleed								
Composite of all major and clinically relevant bleeding events								
Any bleeding event								
ICH								
GI bleed								

A5. **Priority Question:** Please complete the table below to provide details on the number of events (n) and number of people analysed (N) for the outcomes of headache and gastrointestinal bleeding for the full randomised, full analysis and per protocol populations of RE-COVER I, RE-COVER II, REMEDY, and RESONATE (3 tables). Please also provide a reference to where this data is available in the clinical study reports for these trials.

	Dabigatran		Warfarin		Placebo		Dabigatran vs comparator	
	N	N	N	N	n	N	Hazard Ratio (95% CI)	p-value
Headache								
RE-COVER I					–	–		
RE-COVER II					–	–		

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

	Dabigatran		Warfarin		Placebo		Dabigatran vs comparator	
	N	N	N	N	n	N	Hazard Ratio (95% CI)	p-value
REMEDY					–	–		
RESONATE			–	–				
GI bleeding								
RE-COVER I					–	–		
RE-COVER II					–	–		
REMEDY					–	–		
RESONATE			–	–				

A6. Please provide the definition of active cancer used in RE-COVER I, RE-COVER II, RESONATE, and REMEDY (for each trial separately).

A7. Please complete the table below to provide a breakdown of the patients with cancer at baseline in RE-COVER I, RE-COVER II, and REMEDY for the randomised population:

	Dabigatran		Warfarin	
	n	N	N	N
Cancer under active treatment or with ≤1year remission				
RE-COVER I				
RE-COVER II				
REMEDY				

A8. Please provide a definition for “equipoise” as used in RESONATE and details of inclusion/exclusion criteria specifically pertaining to “equipoise”. Please clarify whether the reasons for inclusion in the trial were similar across treatment groups.

A9. Please provide a definition for “high risk” as used in REMEDY and details of inclusion/exclusion criteria specifically pertaining to “high risk”. Please clarify whether the reasons for inclusion in the trial were similar across treatment groups.

A10. Please clarify how many UK centres participated in RE-COVER I, RE-COVER II, RESONATE, and REMEDY (for each trial separately) and how many patients from the UK were randomised in each trial.

A11. Please provide details of the randomised population (ITT) treatment discontinuation rates by treatment group for RE-COVER I, RE-COVER II, RESONATE, and REMEDY

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

(for each trial separately) for: 1) the whole trial population and 2) centre's with TTR ≥60%. Please provide reasons for treatment discontinuation, with total number of patients discontinuing in each group for that reason. If this information is available in the CSRs, please also provide the page and table numbers.

A12. Please complete the table below to provide a breakdown of the types and frequency of adverse event that led to treatment discontinuation in each of the RE-COVER I treatment groups for the ITT population. Please complete similar tables for RE-COVER II, REMEDY and RESONATE. If this information is available in the CSRs, please also provide the page and table numbers.

	ITT Population					
	Rivaroxaban			**Warfarin**		
	n	**N**	**Event rate (100 pt-year)**	**n**	**N**	**Event rate (100 pt-year)**
Adverse event (please specify [add additional table rows below as necessary]):						
Adverse event:						

A13. Please provide details of any protocol amendments made in RE-COVER I, RE-COVER II, RESONATE, and REMEDY (for each trial separately) and give the reasons for any amendments.

A14. The NICE final scope lists post thrombotic syndrome, heart failure and chronic thromboembolic pulmonary hypertension as important outcome measures to be considered in the STA. Please clarify the rationale for not including data on these outcomes from the dabigatran trials included in the submission. Where possible, for these outcomes, please provide the number of events (n) and the number of people analysed in RE-COVER I, RE-COVER II, RESONATE, and REMEDY (for each trial separately) for the full randomised, full analysis and per protocol populations.

A15. Please clarify the rationale for conducting analyses by centre TTR using quintiles rather than quartiles.

A16. Please present the data in tables 51, 52, 82 and 83 broken down by centre TTR using quartiles.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Meta analyses

A17. **Priority Question**: Please provide the inclusion/exclusion criteria and the patient characteristics for all studies included in the meta-analyses discussed in the submission. Please also provide all Review Manager files for these meta-analyses.

A18. **Priority Question** Please clarify which trials were used in the AIC for dabigatran versus warfarin versus placebo described on page 145 that resulted in an RR 0.65 (95% CI: 0.15 to 2.87).

A19. Please clarify how the subgroup of "Time in INR" presented in Table 59 (pg 162) of the submission has been defined for the purposes of the analysis reported.

Clinical effectiveness systematic review

A20. Page 50 of the submission states that the searches for the systematic review of the literature on clinical effectiveness were carried out in two distinct phases. Please clarify the rationale for this.

A21. Warfarin appears to have been omitted as a comparator of interest in some of the literature searches. Please clarify whether warfarin was included as a comparator of interest in the search terms for both acute and secondary prevention. If warfarin was omitted as a term from either search, please clarify the rationale for the omission.

A22. Please provide the citations for the 35 studies included from the systematic review in the "qualitative synthesis"(MS; pg 55 and pg 154).

A23. Please indicate which study was excluded "because the results are difficult to interpret" (MS; pg 154) and clarify the reason(s) for exclusion of this study.

<u>Section B: Clarification on cost-effectiveness data</u>

B1 **Priority question:** Please describe the rationale for the following assumptions within the economic model:

a) all patients who experience a major bleeding event will stop treatment and not restart acute or preventative treatment for venous thromboembolism (VTE) after their bleeding event;

b) neither rivaroxaban nor dabigatran are prescribed at 1st or 2nd VTE recurrence;

c) at 1st or 2nd VTE recurrence, patients with active cancer are prescribed low-molecular-weight heparin (LMWH) plus warfarin, rather than LMWH monotherapy;

d) at 1st or 2nd VTE recurrence, a patient will receive acute treatment for VTE, but will not receive secondary prevention for future VTE.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

B2 **Priority question:** Within the model, it is stated that the probability of recurrent VTE for people treated with dabigatran is estimated using data from RECOVER I and II at 6-months plus 30 days post treatment, rather than data at 6-months. Please describe the rationale for choosing the data set including 30 days post treatment.

B3 **Priority question**: Please describe the rationale for using the combined clinical endpoint of "major or clinically relevant bleeding" to estimate incidence of bleeds within the economic model, rather than analysing "major bleed event" incidence and "clinically relevant non-major bleed event" incidence separately.

B4 **Priority question**: In the economic model, the probability of a "major or clinically relevant bleeding" (cell Probs!E18) for people treated with warfarin was estimated to be 8.5% based upon a figure of 217 patients out of the treated set (2554 patients) experiencing either a major bleed or a clinically relevant non-major bleed. The ERG has been unable to verify the 217 figure using the CSRs for RECOVER I and RECOVER II:

- For RECOVER I, treated set, the CSR (page 224 table 12.2.2.1:1) reports 111 people with major or clinically relevant bleeds, or 122 events;
- For RECOVER II, treated set, the CSR (page 170 table 12.2.2.1:1) reports 102 people with major or clinically relevant bleeds, or 120 events.

Please clarify how the figure of 217 people with "major or clinically relevant bleeding events" was estimated with reference to the relevant tables and specific numbers within the CSR.

B5 Please clarify how the following papers were identified and why they were selected:

- Prandoni et al 2007 (probability of recurrent VTE off treatment)
- Pengo et al 2004 (incidence of CTEPH)
- Prandoni et al 1997 (incidence of severe PTS)
- Keogh et al 2007 (CTEPH utility decrement)

B6 In Figure 29 of the submission (page 230) chronic ischemic heart disease is presented as a health state; however, in Table 96, the chronic ischemic heart disease health state is not described. Similarly, in Table 96 a health state of "dyspepsia" is described; however, this health state is not presented in Figure 29. Please confirm which of these health states are modelled in the sensitivity analysis.

B7 The adjustment for warfarin time in therapeutic range described in Section 7.3.1 page 241-242 was calculated using GPRD data. Was a similar analysis completed in which rates of VTE recurrence and major or clinically relevant bleeds were evaluated at

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

different % times in therapeutic range using data from either RECOVER I or II or REMEDY? If so, please provide this analysis.

B8 Results of one-way sensitivity analysis for the full list of parameters contained within the economic model were not presented within the submission.

- If this analysis was completed but not presented within the submission, please provide this analysis.
- If data is not available, please describe, for each analysis, the top ten variables that model results are most sensitive to. Please present total costs, total QALYs, and ICERs for the upper and lower value for each variable.

B9 Please run the following scenario analyses and present total costs, total QALYs and ICERs for each relevant comparison:

- LMWH plus warfarin and rivaroxaban are treatment options at 1st or 2nd VTE recurrence;
- for treatment and secondary prevention analyses, patients experiencing a 1st or 2nd VTE recurrence will receive acute treatment and secondary prevention;
- treatment duration for secondary prevention is set to lifetime for all analyses;
- patients who experience a major bleeding event will be reinstated on acute treatment and/or secondary prevention.

B10 Please provide the references for the studies identified and included from the systematic review of the economic evidence.

B11 With reference to the systematic review of cost-effectiveness evidence, please describe the rationale for including only economic evaluations which assessed at least one of the following therapies: dabigatran, rivaroxaban, edoxaban or apixaban.

B12 Please describe the rationale for estimating the cost of clinically relevant non-major bleeds that require hospitalisation using a weighted average of the following reference costs: MA22Z Lower Genital Tract Minor Procedures - Category 1, MA23Z Lower Genital Tract Minor Procedures - Category 2, MA25Z Upper Genital Tract Minor Procedures - Category 1, MA26Z Upper Genital Tract Minor Procedures - Category 2.

Section C: Textual clarifications and additional points

C1 Some discrepancies have been identified between outcomes reported within the submission compared with those reported in the model; these are listed in the tables below.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Please review Tables 1 to 4 below to confirm whether the submission or the model values are correct. If both values are correct, please explain the reason for the difference.

Please update the economic model and final results, if appropriate, should any of the discrepancies be in error.

Table 1. Acute treatment of DVT and PE; dabigatran versus rivaroxaban

Overview	Parameter	Value in submission	Location in submission	Value in model	Location in model
Summary of resources consumed, LMWH plus dabigatran	Total drug costs	£408	Table 134, page 351	£487	'Results!E12'
	Investigational treatment, drug	£323		£354	'Results!E13'
	Re-treatment with warfarin, drug	£8		£17	'Results!E15'
	Re-treatment with warfarin, acute parenteral drug	£31		£70	'Results!E16'
	Total monitoring (administration) costs	£244		£520	'Results!E17'
	Investigational treatment, admin	£22		£24	'Results!E18'
	Re-treatment with warfarin, admin	£210		£476	'Results!E19'
	Re-treatment with warfarin, acute parenteral admin	£5		£12	'Results!E20'
Summary of resources consumed, rivaroxaban	Total drug costs	£1,260	Table 134, page 351	£488	'Results!F12'
	Investigational treatment, drug	£1,222		£393	'Results!F13'
	Re-treatment with warfarin, drug	£7		£17	'Results!F15'
	Re-treatment with warfarin, acute parenteral drug	£31		£70	'Results!F16'
	Total monitoring (administration) costs	£911		£515	'Results!F17'
	Investigational treatment, admin	£700		£25	'Results!F18'
	Re-treatment with warfarin, admin	£206		£476	'Results!F19'
	Re-treatment with warfarin, acute parenteral admin	£5		£12	'Results!F20'
Total costs, rivaroxaban, deterministic results	Total costs	£7,523	Table 16, page 26 and Table 145, page 356	£7,532	'Results!F39'

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Table 2. Acute treatment of DVT and PE, dabigatran versus LMWH in the subgroup of patients with active cancer

Overview	Parameter	Value in submission	Location in submission	Value in model	Location in model
Summary of resources consumed, dabigatran	Total drug costs	£372	Table 135, page 352	£408	'Results!E12'
	Re-treatment with warfarin, drug	£1		£8	'Results!E15'
	Re-treatment with warfarin, acute parenteral drug	£2		£31	'Results!E16'
	Total monitoring (administration) costs	£45		£244	'Results!E17'
	Investigational treatment, admin	£22		£22	'Results!E18'
	Re-treatment with warfarin, admin	£15		£210	'Results!E19'
	Re-treatment with warfarin, acute parenteral admin	£0		£5	'Results!E20'
Summary of resources consumed, LMWH	Total drug costs	£1,224	Table 135, page 352	£1,260	'Results!F12'
	Re-treatment with warfarin, drug	£0		£7	'Results!F15'
	Re-treatment with warfarin, acute parenteral drug	£2		£31	'Results!F16'
	Total monitoring (administration) costs	£709		£911	'Results!F17'
	Investigational treatment, admin	£700		£700	'Results!F18'
	Re-treatment with warfarin, admin	£9		£206	'Results!F19'
	Re-treatment with warfarin, acute parenteral admin	£0		£5	'Results!F20'

Table 3. Acute treatment and secondary prevention of DVT / PE, dabigatran versus rivaroxaban

Overview	Parameter	Value in submission	Location in submission	Value in model	Location in model
Summary of resources consumed, rivaroxaban	Total drug costs	£793	Table 143, page 354	£801	'Results!F12'
	Total monitoring costs	£508		£510	'Results!F17'
Total costs, deterministic results, rivaroxaban	Total costs	£7,852	Table 17, page 27 and Table 146, page 356	£7,862	'Results!F39'

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Table 4. Acute treatment and secondary prevention of DVT and PE, dabigatran versus LMWH in the subgroup of patients with cancer

Overview	Parameter	Value in submission	Location in submission	Value in model	Location in model
Incremental life years gained, LMWH	Life years	Two values presented: 0.0119 0.0090	Table 126, page 348; Table 17, page 27; Table 146, page 356	0.0090	'Results!M28'
Incremental QALYs, LMWH	QALYs	Two values presented: 0.0197 0.0282	Table 126, page 348; Table 17, page 27; Table 146, page 356; Table 151, page 368	0.0197	'Results!M29'

C2 The CTEPH utility decrement described within the submission (0.12, page 302) does not match with the value for CTEPH decrement in the model (0.10, 'Utilities'!F75). Please confirm whether the 0.10 or 0.12 value is correct.

C3 For the probability of recurrent VTE used within the economic model for the warfarin arm of RECOVER I and II, cell 'Probs'!N17 states that the value is based upon the intent to treat (ITT) dataset; however, the sample size appears to be that of the treated set. Please confirm which dataset has been used.

C4 Please confirm which databases were searched for the cost-effectiveness literature review. Page 219 of the submission states "MEDLINE, MEDLINE In-Process, Embase, Econ-Lit, BIOSIS and the Cochrane Library including the NHSEED", compared with page 453 Section 8.17.1 which states "Medline, Embase, Medline (R) In-Process, EconLIT, NHS EED".

C5 Please clarify the potential discrepancy around comparison of data for rivaroxaban and dabigatran in the acute treatment of venous thromboembolic events (VTEs). A statement in Section 6.7.2 (pg 147) suggests that rivaroxaban was evaluated in only the secondary prevention of VTE, but data on use of rivaroxaban in acute treatment of VTE are presented and discussed.

C6 Within the economic model, the calculation within cell NHSRC 2013!T332 subtracts Unit costs!N429 from a weighted average reference cost; however, there is no value in Unit costs!N429. Please confirm whether the intention of this calculation was to subtract 'Unit costs'!N135 from NHSRC 2013!T332 (to mimic the calculation for DVT).

C7 In the economic model, the cost reported for parenteral treatment for UH Regimen 1 and 2 are £21.58 and £7.05 respectively (Unit costsN102:103 and Unit costsN125:126). These correspond to a daily cost of £4.32 and £1.41 respectively. In

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

the submission, Table 115, the daily costs are reported to be £4.67 and £1.76. Please confirm whether the submission or model costs are correct.