NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Single Technology Appraisal (STA)

Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID662]

Dear Adrian,

The Evidence Review Group, BMJ Technology Assessment Group, and the technical team at NICE have now had an opportunity to take a look at the submission by Daiichi Sankyo received on the 13 February 2015. 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 **Wednesday 25 March 2015**. 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 uploaded to NICE Docs/Appraisals.

If you have any further queries on the technical issues raised in this letter then please contact Carl Prescott, Technical Lead (carl.prescott@nice.org.uk). Any procedural questions should be addressed to Bijal Joshi, Project Manager (bijal.joshi@nice.org.uk) in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A – clarifications of the clinical data

A1. **Priority question:** Please provide the details in section 1.3, page 14 of the company submission (CS) for the UK marketing authorisation of edoxaban for its use in the treatment and secondary prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). The current information refers to a different indication.

A2. **Priority question:** Please clarify how many patients had their edoxaban dose adjusted in the Hokusai-VTE trial in the following analysis sets and a breakdown of when during the trial the dose adjustments took place:

a) modified intention-to-treat (mITT) analysis set, overall study period;

b) mITT analysis set, on treatment period ;

c) safety analysis set overall study period;

d) safety analysis set on-treatment period.

A3. **Priority question:** Please clarify the source of the data and the analysis sets used for each of the studies in the network meta-analysis (NMA) for all outcomes (CS, Tables B 31 to B 40, pages 87–90).

A4. **Priority question:** Please provide working WinBUGS code files including the priors, initial values, and the formatted data used for all NMAs (including sensitivity/subgroup analyses) presented in the submission.

A5. Please provide further details of the criteria used to determine the treatment duration (minimum 3 months, maximum 12 months) for patients in the Hokusai-VTE.

A6. Please clarify the type and frequency of monitoring performed in the Hokusai-VTE trial? (e.g. were patients weighed at each visit?)

A7. Please provide an explanation for [redacted] (CS, page 64).

A8. Please provide a further breakdown of when in the time “from index event to 14 days” the recurrent VTE events occurred in each of the edoxaban and warfarin groups for the safety analysis set, on-treatment period reported in Table B 57 (page 131) of the company submission and Table 1.4.9.4.2 of the Hokusai-VTE post-hoc analysis.

A9. Please provide the equivalent data already provided in Table B 57 (CS, page 131) on recurrent VTE as a function of the time period based on Hokusai-VTE using the mITT analysis set, on-treatment period for both the edoxaban arm and warfarin arm.

A10. Please provide the definition of “Temporary baseline risk factors” used in the subgroup analysis presented in Figure B 7 (CS, page 66).

A11. Please provide details of any subsequent treatment received by the subjects in each treatment arm after permanent study drug discontinuation (CS, Table B 17, page 71).

A12. Please clarify the rationale for the per protocol analysis of recurrent VTE during the treatment + 30 days study period presented in Appendix 14, page 38.

A13. Please provide the Deviance Information Criterion (DIC) and a comparison of the residual deviance with the number of unconstrained data points for each outcome when using a fixed and random effects model for the NMA (CS, Tables B 41 to B 50).

A14. Please populate the table below with the results only from patients who were still on treatment at 6 months.

Hokusai-VTE trial			
Efficacy endpoint		n/N intervention1	n/N intervention2
Recurrence at 6 months	VKA regimen vs edoxaban 60mg od		
Safety endpoints	VKA regimen vs edoxaban 60mg od		
Composite bleeding	VKA regimen vs edoxaban 60mg od		
Major bleeding	VKA regimen vs edoxaban 60mg od		
Non-major bleeding	VKA regimen vs edoxaban 60mg od		
VTE related death	VKA regimen vs edoxaban 60mg od		

A15. Please re-run the NMA using the results provided in A14.

<u>Section B – clarifications of the economic data</u>

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

a) The duration of the model cycles is 2 weeks. Previous VTE models have used 1-month cycles.

b) The risk of further complications like chronic thromboembolic pulmonary hypertension (CTEPH), post-thrombotic syndrome (PTS), recurrent VTE and mortality do not change with the number of VTE events experienced by individuals.

c) Please provide the rationale for aggregating the PE and the DVT states together in the overall VTE state.

d) For recurrent VTE, all patients are assumed to be hospitalized but are not on any anticoagulation treatment (HRG codes used to estimate the cost of

recurrent VTE are based on the costs of hospitalisation which do not include diagnosis and treatment). Please justify why all patients are hospitalised and why no patients receive anticoagulation treatment while in hospital.

e) After recurrence of VTE, patients go back to their original anticoagulation therapy. Please provide your justification for assuming that patient revert to their original treatment after a VTE event.

f) Please explain why patients are not at risk of PTS in all health states?

g) Please justify why patients off treatment receive no further anticoagulation treatment?

h) Please explain why patients are not at risk of CTEPH or stroke when off treatment?

i) Please justify why patients with CTEPH receive no further anticoagulation treatment?

j) Inclusion of the stroke health state in the model. The ERG is concerned with the inclusion of the stroke health state in the model as it seems to include haemorrhagic strokes. These are also included in the major bleed (MB) health state as they are effectively a bleeding event. Please explain the rationale for having a discrete stroke health state and clarify if any adjustments were made to account for the apparent double counting of haemorrhagic strokes in the model.

k) No rationale was provided as to why stroke was included but myocardial infarction (MI) and systemic embolic events were not?

l) Please provide justification that 40% of patients discontinue due to heparin-induced thrombocytopenia (HIT)?

B2. **Priority question:** The percentage of patients experiencing PTS, taken from Prandoni *et al.* 1997, is based on the number of severe cases of PTS. The same paper reports the average probability of experiencing PTS (across mild, moderate and severe categories) of 18%. Please explain why the probability for severe cases was used in the economic model?

B3. **Priority question:** Regarding the mortality estimates used in the model (Table 1) could you please:

a) Provide the rationale for using the mITT analysis set (overall study period) for the estimation of VTE related death when the safety analysis set (on treatment period) was used for all the other estimates.

b) Please provide the rationale for using the Prandoni *et al*. 2015 paper to estimate the mortality associated with HIT. The odds ratio used in your analysis (and reported in Prandoni *et al*. 2015) represents the probability of HIT patients developing thromboembolic complications (VTE, ischemic stroke, MI and arterial embolism) compared with patients who did not

experience HIT and not the probability of dying from HIT. Please also note that the estimate used reflects a 1 year analysis.

c) Explain why the probabilities used for MB-related death, stroke related-death and recurrent VTE-related death were not adjusted to reflect the 2-week cycle length?

d) Provide the rationale for using the 11.3% estimate for the probability of dying associated with VTE recurrence (Table 4 in Carrier *et al.* 2010) throughout the different periods of the analysis when you could have used more accurate data from the same study to reflect the 6 month-probability of dying from recurrent VTE?

e) Can you also please provide the rationale for using the VTE estimate instead of the PE and DVT estimates to create a weighted average as you have done with several other estimates in the model?

Table 1. Probabilities of disease-related death used in the economic model

Event	N	n	Increase in mortality risk	P used in the model (2- weeks)	Source	Analysis set
VTE-related death	8,240	48	0.58%	0.022%	Hokusai-VTE CSR, table 11.10	mITT Analysis Set - Overall Study Period (1 year = 26 cycles)
CRNMB related death	666	0	0%	0%	Hokusai-VTE post-hoc analysis, table 1.4.3.6.2	Safety Analysis Set – On-Treatment Study Period
MB related death	124	12	9.7%	9.7%	Hokusai-VTE post-hoc analysis, table 1.4.6.5	Safety Analysis Set – On-Treatment Study Period
Stroke related death	52	2	3.85%	3.85%	Hokusai-VTE CSR, table 12.15	Safety Analysis Set – On-Treatment Study Period
HIT related death	-	-	16.6%	0.0372%	Prandoni et al 2015	LMWH population, over 1 year
VTE recurrence related death	-	-	11.3%	11.3%	Carrier et al, 2010	VTE population, over 3 months

B4. **Priority question:** Please provide the rationale for splitting the utility associated with the “recurrent VTE” state between DVT utility and PE utility, when the health state “on treatment/index VTE” considers the overall VTE utility and doesn’t desegregate between PE and VTE.

B5. **Priority question:** Given that the PTS condition is associated with specific costs and QALYs, modelling PTS as a separate health state would have increased

model transparency and avoided potential formulae mistakes. The ERG has identified several errors in the calculation of the PTS utility. For example, looking at the “warfarin engine” tab, column F7 and H7 – the probability of PTS is not changing from year 1 onwards as it is meant to be but more fundamentally, the formulae is overestimating the total utility experienced in the on treatment and off treatment states since it takes the weighted average of: (2-week probability of PTS)*PTS utility + [1- (2-week probability of PTS)]*utility norm. The same problem applies to all the other engines in the model (i.e. non-vitamin K antagonist oral anticoagulants [NOACs]). The ERG suggests that the correct formula should be (2-week probability of PTS)*PTS utility + [(1- raw annual probability of having PTS) adjusted to reflect the 2 week period)]*utility norm. Please make the appropriate adjustments to the calculation of PTS utility.

B6. **Priority question:** It seems that costs have not been updated to reflect the same cost year. Please clarify if this is the case. If costs have not been adjusted to reflect the same year please adjust all costs in the economic analysis to 2014 costs and present the revised results for the base case analysis, subgroup analysis and sensitivity analysis.

B7. **Priority question:** Please clarify what was the assumed average weight of patients in the calculation of heparin costs. If this hasn’t been considered, can the company please adjust the cost so it reflects this?

B8. **Priority question:** Please revise the PTS cost calculations. There seems to be a significant underestimation of the costs since these are not capturing the bi-weekly proportion of patients who would develop PTS at every cycle (and their respective costs). The way in which the costs are calculated would only make sense if the annual probability of PTS was being used in the calculations.

B9. **Priority question:** The diagnostic outpatient costs (applied to the first cycle only) include a doppler ultrasound, CT angiography, electrocardiogram and d-dimer. Please explain why:

a) Only 50% of patients receive these tests.

b) The costs, which relate to diagnostic tests, are not also incurred during a recurrent VTE event when a second diagnosis of DVT or PE will need to be made.

c) The costs are not applied according to the type of VTE event.

d) A chest x-ray and echocardiogram have not been included.

e) An outpatient appointment or emergency admission has not been included.

B10. **Priority question:** Please explain the rationale for assuming that the same proportion of patients (25%) receives unfractionated heparin, dalteparin, tinzaparin and enoxaparin.

B11. **Priority question:** On page 190 of the company submission it is stated that "evidence did not allow for subgroup analyses in the DVT population (with respect to the NMA), therefore no results for a DVT-only subgroup are presented". Can the company please clarify why this subgroup analysis would not be possible given that such data were available at least for warfarin and rivaroxaban?

B12. **Priority question:** The ERG identified mistakes in the PE subgroup model. Some of the model estimates, for example the probability of experiencing CTEPH, are adjusting the total population to reflect the proportion of patients with DVT only and the proportion of patients with PE. This is incorrect as everyone is the PE subgroup model should be exposed to the probability of developing CTEPH. Please amend this and check that no other errors similar to this have occurred.

B13. **Priority question:** Please run the following scenario analyses and present total costs, total quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for each relevant comparison:

a) Subgroup analysis for patients with index PE (with or without DVT) using the Hokusai-VTE trial data (mITT, overall treatment) for each subgroup, thus comparing edoxaban with warfarin.

b) Subgroup analysis for patients with DVT only using the Hokusai-VTE trial data (mITT overall treatment) for each subgroup, thus comparing edoxaban with warfarin.

c) Base-case analysis comparing edoxaban with warfarin, using the Hokusai-VTE trial data for the mITT population, overall treatment period.

B14. **Priority question:** The ERG was unable to identify several model parameters in the respective sources provided (Table 2) and also identified several discrepancies between values reported in the model and values reported in the submission (Table 3). Therefore, could the company please:

a) For the values presented in Table 2 , pinpoint where in the sourced documents the estimates are located (and in the case where additional analysis was done to obtain these, please present the analysis and the raw data).

b) Which values in Table 3 are the correct ones.

B15. The ERG was unable to identify several model parameters in the respective sources provided for the PE subgroup model (Edoxaban VTE_PE subgroup_FINAL_13 02 15_AIC CIC). Can the company please, for the values presented in Table 4, pinpoint where in the sourced documents the estimates are located and provide any missing sources?

Table 2: Discrepancies between the model and submission with the source provided

Parameter	Value in the model and submission	Location in submission	Value in source	Source	Location in source (to be completed by the company)
Utility inputs					
Recurrent VTE	-0.1047 = (-0.17 * (1 - Settings!$C$18) - 0.06*Settings!$C$18) where 'Settings'!$C$18 refers to the proportion of DVT patients	Table B79	Recurrent DVT, -0.17; recurrent PE, -0.06. The ERG believes the company has switched these values for a recurrent PE and DVT in the model.	Sullivan *et al.* 2011 (112)	
CRNMB	0.648*		Median valuation (IQR) 0.76 (0.59-0.95) for muscular bleeding health state.	Locadia *et al.* 2004 (119)	
MB	0.494*		Median valuation (IQR) 0.65 (0.49-0.86) for gastro-intestinal bleeding health state.		
PTS	0.673*		Median valuation (IQR) 0.82 (0.66-0.97) for PTS health state.		
VTE index event	[redacted]		Unable to verify [redacted] in the source provided. The ERG has identified a baseline mean value of [redacted]	Hokusai VTE HRQoL data	
VTE index event (PE subgroup)	[redacted]**	NR	Unable to verify [redacted] in the source provided. The ERG is unclear as to why a European subgroup would be used to inform the utility for the PE subgroup when the type of VTE is not reported separately.	Hokusai VTE EQ-5D analysis European data Table 3.2.1	

Cost inputs					
Daily cost of warfarin	£0.06	Table B81 and Table B83	Unable to verify with the BNF. The ERG notes eMIT should be used as the source cost for warfarin based on the recommendations in NICE Guides to Methods of Technology Appraisal 2013.	BNF price: Dose: 5–10 mg ,28-tab pack = 88p; 5mg	
Electrocardiogram	£31	Table B83	Unable to verify/ find the HRG codes provided. HRG identified by the ERG: EA47Z, Electrocardiogram Monitoring and stress testing, service code 324, Anticoagulant Service,17, £74 (£25 to £157)	NHSRC 2012-2013 "DA01 CECG [12 Lead]": 241,662 £31	
INR monitoring cost	£24	Table B81 and Table B83	Unable to verify/find the HRG codes provided. HRGs identified by the ERG: WF01A, Non-consultant led, Non-Admitted Face to Face Attendance, Follow-up, 324, Anticoagulant Service, 833,218 stays, £21 (£9 to £28) WF01A, Consultant led, Non-Admitted Face to Face Attendance, Follow-up, 324, Anticoagulant Service, 1,515,603 stays, £28 (£14 to £29)	NHSRC 2012-2013: "324 Non-consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,149,507 stays £18 "324 Consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,588,225 stays £29	
Diagnosis and treatment of PE, inpatient costs	£1,500	Table B83	Unable to verify/ find the HRG codes provided. The ERG found these codes which seem to be the appropriate ones to use for PE: DZ09D, Pulmonary Embolus with CC Score 12+, 1,174 stays £4,011 DZ09E, Pulmonary Embolus with CC Score 9-1,1 2,973 stays £2,862 DZ09F, Pulmonary Embolus with CC Score 6-8, 7,160	NHSRC 2012-2013: DZ09A “Pulmonary Embolus with Major CC":15,799 stays £1,876 DZ09B "Pulmonary Embolus with CC":15,404 stays	

			stays £2,025 DZ09G, Pulmonary Embolus with CC Score 3-5, 15,283 stays £1,429 DZ09H, Pulmonary Embolus with CC Score 0-2, 17,007 stays £981	£1,354 DZ09C "Pulmonary Embolus without CC":6,330 stays £920	
Cost of vascular surgery outpatient appointment (first)	£162	Table B83	Unable to verify £162 with NHSRC. HRG identified by the ERG: WF01B, Non-Admitted Face to Face Attendance, First, service code 10, Vascular Surgery, £163 (£107 to £211)	NHSRC 2012-2013, HRG codes not reported	
Cost of vascular surgery outpatient appointment (following)	£111	Table B83	Unable to verify £111 with NHSRC. HRG identified by the ERG: WF01A, Non-Admitted Face to Face Attendance, Follow-up, service code, 107, Vascular Surgery, 132, £133 (£90 to £158)		
Cost of one GP visit	£36	Table B83	Unable to verify £36 with NHSRC. Cost identified by the ERG: Unit Costs of Health and Social Care 2013, 11.7 minute visit including direct staff care and qualification costs, £45 per visit		

*Used to calculated the relative decrement at 55 years of age
**Edoxaban VTE_PE subgroup_FINAL_13 02 15_AIC CIC
Abbreviations used in the table: CRNMB, clinically relevant on-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ERG, Evidence Review Group; GP, general practitioner; HRG, Health Resource Group; INR, international normalised ratio; MB, major bleed; NHSRC, NHS Reference Costs; PE, pulmonary embolism; PTS, post thrombotic syndrome

Table 3: Discrepancies between the value reported in the model and the value reported in the submission

Parameter	Value in the model	Location in the model	Location in the submission	Value in the submission	Correct value (to be completed by the company)
Total cost of edoxaban (first cycle)	£114.04	'Inputs Costs'E43	Page164, Table B81 and Table B83	Values in the submission refer to a cost of £138.00 (page164) and £114.04.	
Rivaroxaban (first cycle)	£73.50	'Inputs Costs'E51	Page165, Table B82 and Table B83	£88.20	
Rivaroxaban (following cycles)	£29.40	'Inputs Costs'E52	Page165, Table B82 and Table B83	£30.76 and £29.40	
Number of INR monitoring visits	1.1	'Inputs Costs'E15	Table B81 and Table B83	Rivaroxaban submission: 9 visits in first three months, then 5 visits per quarter (=24 per year) 24/26 = 0.9 visits per cycle; 1.1 visits per month would imply 28.6 visits per year.	
LT CTEPH total QALYs, warfarin	0.0207	'Warfarin engine'CR24	Table B87	11.7432	
Post stroke total QALYs, warfarin	0.0710	'Warfarin engine'CR26		0.0024	
LT CTEPH total QALYs, edoxaban	0.0208	'Edoxaban engine'CR24		11.7483	
Post stroke total QALYs, edoxaban	0.0712	'Edoxaban engine'CR26		0.0019	
LT CTEPH total QALYs, dabigatran	0.0208	'Dabigatran engine'CR24		11.7433	
Post stroke total QALYs, dabigatran	0.0713	'Dabigatran engine'CR26		0.0014	
LT CTEPH total QALYs, rivaroxaban	0.0208	'Rivaroxaban engine'CR24		11.7563	

Post stroke total QALYs, rivaroxaban	0.0711	'Rivaroxaban engine'CR26		0.0026	
Probability of CTEPH 4 months-12 months	0.0195 (calculated from Guérin et al, 2014, 4.8%)	'Inputs – Clinical'C19	Table B64	0.0155 (calculated from Pengo et al. 2004, 3.8%)	
Abbreviations used in the table: CRNMB, clinically relevant on-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; INR, international normalised ratio; LT, long term; PTS, post thrombotic syndrome					

Table 4. Discrepancies between the model values and source provided in PE model

Parameter	Value in the model	Location in model	Value in source	Source	Correct value/location in source (to be completed by the company)
Probability of VTE Recurrence 1-14 days	0.0048 = 8/1669	'Inputs – Clinical'C6	Unable to verify. Table 1.4.9.4.2 reports the the composite of DVT, non-fatal PE, and fatal PE	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.9.4.2	
Probability of VTE Recurrence 15 days-3 months	0.0095 = 15/1586	'Inputs – Clinical'C7			
Probability of VTE Recurrence 4 months-12 months	0.0056 = 8/1441	'Inputs – Clinical'C8			
Probability of CRNMB	0.1001 = 167/1669	'Inputs – Clinical'C13	Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2	
Probability of MB	0.0138 = 23/1669	'Inputs – Clinical'C14			
Probability of stroke	0.0077 = 13/1679	'Inputs – Clinical'C20	Source not provided	Hokusai EUR0060 Subgroup Analysis Page 16	
Probability of death due to	0.0072 = 12/1669	'Inputs – Clinical'C25	Source not provided	Hokusai Post-Hoc	

VTE				analysis for NMA Table 1-7.1.2	
Probability of death due to recurrence	0.113	'Inputs – Clinical'C26 'Inputs – Clinical'I26	The ERG is unclear why the total VTE event rate has been used in the PE subgroup model. Fatality event rate reported in the source for a PE at 3 months, 30.1%; 6 months, 20.6%.	Carrier *et al*. 2010	
Probability of going off treatment after CRNMB	Number of permanent discontinuations=8	'Inputs – Clinical'C45	Unable to verify. Table 1.4.3.7 reports 19 patients discontinued permanently from warfarin treatment and this is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.3.7	
	N = 1669, Subjects with CRNMB=167		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2	
Probability of going off treatment after MB	Number of permanent discontinuations=6	'Inputs – Clinical'C49	Unable to verify. Table 1.4.6.7 reports 26 patients discontinued permanently from warfarin treatment and this is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.6.7	
	N = 1669, Subjects with MB=23		Source not provided	OKUSAI Post-Hoc analysis for NMA Table 1-3.2	
Probability of death after MB	Total number of fatal events= 3+1	'Inputs – Clinical'C50	Unable to identify, Table 1.4.6.6.2 is not restricted to PE patients	DS internal statistical analysis - post hoc for model. Table 1.4.6.6.2	
	Subjects with MB=23+25		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2	
Probability of HIT	0 = 0/1650	'Inputs – Clinical'I12	Unable to verify. Table 1.4.2.4.1 is	DS internal statistical	

			not restricted to PE patients	analysis - post hoc for model. PE Population Table 1.4.2.4.1	
Probability of stroke	0.00419 = 7/1671	'Inputs – Clinical'I20	Source not provided	Hokusai EUR0060 Subgroup Analysis Page 16	
Probability of going off treatment after CRNMB	Number of permanent discontinuations=10	'Inputs – Clinical'I45	Unable to verify. Table 1.4.3.7 reports 25 patients discontinued permanently from edoxaban treatment and this is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.3.7	
	N = 1650, Subjects with CRNMB=144		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2	
Probability of going off treatment after MB	Number of permanent discontinuations=6	'Inputs – Clinical'I49	Unable to verify. Table 1.4.6.7 reports 17 patients discontinued permanently from edoxaban treatment and this is not restricted to PE patients	DS internal statistical analysis - post hoc for model. PE Population Table 1.4.6.7	
	N = 1650, Subjects with MB=25		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2	
Probability of death after MB	Total number of fatal events=3+1	'Inputs – Clinical'I50	Unable to verify. Table 1.4.6.6.2 is not restricted to PE patients	DS internal statistical analysis - post hoc for model. Table 1.4.6.6.2	
	Subjects with MB= 23+25		Source not provided	Hokusai Post-Hoc analysis for NMA Table 1-3.2	
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ERG, Evidence Review Group; MB, major bleed; NMA, network meta-analysis; PE, pulmonary embolism; PTS, post thrombotic syndrome					

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

B16. Please explain the rationale for using the safety analysis (on treatment) for the efficacy outcomes used in the economic model? Please explain why other analyses (for example, mITT, overall treatment, etc.) were not deemed appropriate.

B17. Please explain the difference in the Hokusai-VTE trial outcomes between the mITT on treatment set and the safety analysis on treatment set, given that there were no treatment misallocations (as reported in page 61 of the submission). More precisely, please explain why the total number of events differs from Table B 10 (CS, p65) to Table 1.4.9.4.2 (post-hoc analysis, p 620), respectively.

B18. Please populate Table 5 below with the data for the primary efficacy endpoint for the mITT population (on treatment and overall treatment period).

Table 5.Primary efficacy endpoint: adjudicated symptomatic recurrent VTE (mITT analysis set, on-treatment study period)

Time period	N	n	p	95% CI
From index event to 14 days				
From 15 days to 98 days				
From 99 days to 364 days				
Total				

B19. Please explain the discrepancies between the safety population and mITT population given there were no study misallocations for:

a) VTE- related deaths in Table 12.21 (page 155) in the CSR and Table 11.10 (page 115) in the same document.

B20. Please explain the discrepancies between:

a) The number of MB events in Table 12.10 (CSR, page 135) and Table 1.4.6.5 (post-hoc analysis, page 510).

b) The number of patients experiencing a clinically relevant non-major bleed (CRNMB) event is different for the warfarin treatment group in the post-hoc analysis (n=371) (Table 1.4.3.7, page 381) and in the Hokusai-VTE CSR (n=368) (Table 12.6, page 160).

c) The number of patients experiencing a CRNMB event is different for the edoxaban treatment group in the post-hoc analysis (n=304) (Table 1.4.3.7, page 381) and in the Hokusai-VTE CSR (n=298) (Table 12.6 , page 160)

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

B21. Please provide the rationale for assuming that the probability of discontinuation after CRNMB and MB are the same across all NOACs.

B22. Please explain why the total number of adjudicated confirmed fatal major intracranial bleeding events (n=23) is greater than the number of adjudicated confirmed fatal MB events (n=12) in the post-hoc analysis report (Table 1.4.5.5 page 450 and Table 1.4.6.5 page 511).

B23. Please provide the rationale for using the probability of PTS reported in Prandoni *et al*. 1997 in the PE subgroup model, when the proportion of patients in this study with PE is only 14%.

B24. Please justify the reason for including a decrement associated with a CRNMB event given that previous STAs (TA261 and TA287) did not include a decrement for CRNMB and this decrement was removed in the ERG analysis for TA327.

B25. Within the model, the utility associated with the CRNMB, MB, CTEPH (including long-term), stroke (including long-term) and PTS states is calculated as a relative decrement compared with the UK population norm at 55 years. The company has assumed that the baseline age is the 55-64 age range for all the studies, which is incorrect for some studies like for example Locadia *et al.* 2004 where the baseline age is 53 years. Can the company please adjust all estimates so they accurately reflect the baseline age of the respective studies, by using the appropriate population norm to estimate the relative utility loss for each health state?

B26. Please explain how the following sources were identified and selected given that these are used in the economic model but are not reported in the studies included for data extraction (CS, Table B 79, page 157) resulting from the company's systematic review:

a) Marchetti *et al*. 2001 (107), warfarin treatment;

b) Gould *et al*. 1999 (123), HIT;

c) Meads *et al*. 2008 (124), CTEPH;

d) Lunde, 2013 (125), post stroke.

B27. Please provide more details on the rationale for choosing the sources for all QoL values presented in Table B 79 (CS, page 157). For example, why was Locadia *et al.* 2004 chosen to inform the value for PTS related utility instead of Enden *et al.* 2013 and why was the utility for VTE taken from the Hokusai VTE EQ-5D analysis rather than Cohen *et al*. 2014 (which was identified in the systematic search).

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

B28. Please explain why, for the purpose of estimating the cost of DVT, day cases, regular day/night admissions and procedures in outpatients were included when all patients are assumed to be hospitalized (i.e. inpatients) in the model?

B29. Please provide the rationale for assuming that the proportion of patients receiving drug therapy is equal for a CTEPH and LT-CTEPH.

B30. Out of the proportion of CTEPH or CTEPH long-term patients receiving drug therapy (50%), the proportion of patients receiving sildenafil or bosentan does not add up to 100%. Please explain why or what other drug therapy those remaining patients should receive.

B31. Can the company please provide the missing estimates from Table 84 (CS, page 177) for the number of HIT and CTEPH events in the economic model?

B32. On page 177 of the company submission it is reported that Markov traces are presented in Appendix 19 and Appendix 20. However, the ERG could not find these. Could you please provide them?

B33. On page 183 of the company submission, it is mentioned that because edoxaban is dominant compared with warfarin in the base-case analysis, it is not possible to generate a tornado diagram. The ERG does not agree with this statement. It is possible to produce tornado diagrams when base case ICERs are dominant or dominated. Since some of the ICERs resulting from the sensitivity analysis will be dominant whilst others can reach values such as £43,743 (as per page 183 in the submission), the ERG requests that the company presents tornado diagrams in terms of the net monetary benefit (NMB, evaluated at a £20,000 threshold value). Using the NMB overcomes the problem of some of the ICERs resulting from sensitivity analysis being negative. Tornado diagrams are crucial to understand what the key model drivers are in a systematic and unbiased manner. If this is not possible, 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.

B34. In the probabilistic sensitivity analysis, a normal distribution was used to model cost and utility data. Please provide the rationale for using the normal distribution instead of the gamma distribution for costs and the beta distribution for utilities.

B35. Please confirm if the results presented for a lifelong treatment duration in Tables B 102 and B 103 are erroneously presenting the base case results (treatment duration = 12 months) and if the results presented in Table 6 and

B36. Table 7 are the correct ones.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Table 6: Incremental results (treatment duration = lifelong), ERG results

	Edoxaban	Warfarin	Dabigatran	Rivaroxaban
Cost per QALY gained	NA	£3,860	£111,610	Dominated
Incremental QALYs	NA	0.1838	-0.0071	-0.0743
Incremental costs	NA	£709	-£789	£25

Table 7: Cost-effectiveness analysis (treatment duration = lifelong), ERG results

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Warfarin	£21,068.4	12.492	-	-	-
Rivaroxaban	£21,752.5	12.750	£684.1	0.258	2,651
Edoxaban	£21,777.9	12.676	£25.3	-0.074	Dominated
Dabigatran	£22,567.4	12.683	£789.5	0.007	Dominated

B37. Please run the following scenario analyses and present total costs, total QALYs and ICERs for each relevant comparison:

a) Base-case analysis comparing edoxaban with warfarin, using the Hokusai-VTE trial data for the safety population, overall treatment period.

b) Base-case analysis comparing edoxaban with warfarin, using the Hokusai-VTE trial data for the safety population, on treatment period.

c) Base-case analysis comparing edoxaban with warfarin, using the Hokusai-VTE trial data for the mITT population, on treatment period.

Section C: Search strategies, textual clarifications and additional points

C1. Regarding the cost-effectiveness search:

a) Please explain the rationale for not searching the HTA database within the Cochrane search to identify cost-effectiveness studies and resource use data.

b) According to Appendix 10, the search was conducted in December 2014 alone. Please clarify why it is suggested on page 111 of the submission that the initial search was conducted in May 2014, and why the results from this search are not presented in Appendix 10.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

c) The ERG has also found a discrepancy between the number of records identified from the search in the main body of the submission and the number reported in Appendix 10. Please explain this discrepancy.

C2. Regarding the search for the measurement and valuation of health effects:

a) Please explain the rationale for not searching the HTA database within the Cochrane search to identify studies on the measurement and valuation of health effects.

b) The ERG is unclear how Figure 24 in the main body of the submission relates to the number of records reported in Appendix 12; please clarify if this includes records identified from the initial and updated search. Please also present the number of records identified in the initial and updated search from Medline, Cocharne, Embase and Econlit separately.

c) Please present the intended footnote for the * presented in Figure 24 which relates to “records identified from other sources”

d) Please explain why the actual number of records identified from the update does not correspond to the difference in the number of records identified.

C3. Please clarify how inputs for the model (probabilities, costs, utilities) relating to the complications associated with VTE events and the adverse effects of treatment such as stroke, major bleeding, clinically relevant non-major bleeding and HIT were intended to be captured in the searches performed as the search terms restricted the VTE population.

C4. Please clarify the numerical discrepancy between the number of studies included for data extraction in Figure B 1, page 39 of the company submission (n = 2 [1 trial]) and the text on page 40 of the company submission (“The only source for the edoxaban phase 3 trial is its peer-reviewed publication.”).

C5. Please clarify the numerical data to support the statement “...with significantly less clinically relevant bleeding in a broad spectrum of VTE subjects including high-risk subgroups (elderly, fragile and cancer subjects) as reported on page 107 of the company submission.