NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Edoxaban, like dabigatran but unlike rivaroxaban, requires 5 days of treatment with heparin before treatment begins. Is this an important issue for patients?
- Are the results generalisable to the UK population? Compared with the population that would be expected in UK clinical practice, the trial population had a younger age, more males, more people of Asian ethnicity, and may have had a longer treatment duration. The mean time in therapeutic range in the warfarin arm was 63.5%.
- In the first 30 days, the trial showed a non-statistically significant higher incidence of VTE recurrence in the edoxaban arm (21 edoxaban compared with 15 warfarin events in the DVT subgroup and 9 edoxaban compared with 7 warfarin events in

the PE subgroup). Is the Committee satisfied that edoxaban is non-inferior to warfarin for recurrent VTE?

- The Hokusai VTE trial had a unique design in that the primary efficacy endpoint of recurrent VTE was assessed at 12 months however long participants had been taking anticoagulants (and therefore after many people had stopped treatment) – is this data the most appropriate for decision making? Data was also presented for the 'on treatment' period. The trial had a flexible treatment duration, from 3 months up to 12 months depending on patient need, and dosage could be adjusted at the beginning of or during the trial.
- For adverse events the company used the safety population. Is this appropriate?
- The only direct evidence available is the comparison with warfarin; there is no direct evidence compared with other new oral anticoagulants. Does the network meta-analysis provide a robust estimate of the relative effectiveness of edoxaban compared with other anticoagulants?
  - For edoxaban the company did not use all available data, instead using only 6 month data for the on treatment period – is this the most appropriate population?
  - The company stated that the results should be interpreted with caution because of substantial heterogeneity between the trials.
  - The results of the network meta-analyses show odds ratios that have wide credible intervals that approach or cross '1'.
  - All trials in the network meta-analysis are non-inferiority trials – has this limited the ability to show meaningful differences between comparators?

Cost effectiveness

- The ERG noted a number of issues with the model structure, including:
  - Tunnel states: does the use of tunnel states together with the short cycle length properly represent the cost and utility impact of adverse events?
  - Assumptions: are the assumptions used in the model plausible? For example:
    - ◊ Would patients return to their original treatment even if they suffered a recurrent VTE while taking it?

    - ◊ Are chronic thromboembolic pulmonary hypertension and post thrombotic syndrome treatment related (as assumed in the model) or related to the underling disease (PE or DVT)?
    - ◊ Stroke is a treatment related event in the model but are only intracranial bleeds a complication of treatment, not all strokes?
- The company used effectiveness results from the network meta-analyses – is this data suitable and robust?
  - The odds ratios in the network meta-analyses showed wide confidence intervals that approached or crossed '1'.
  - When compared with trial data, the modelled risk of recurrence (based on the network meta-analysis) shows under and over estimates for recurrent VTE and bleeding.
- A number of methodological issues were noted with the utility values used, such as searches that were limited to VTE (and therefore not sensitive to capture values for adverse events) and the trial data were limited. Are the utility values appropriate for decision making?
- The ICERs suggest that edoxaban has similar costs and effectiveness when compared with warfarin. Edoxaban drug costs are (£2.10 per day) whereas warfarin drug costs are approximately £0.02 per day). The major cost offset for the higher drug costs of edoxaban is the warfarin monitoring costs. Have the warfarin monitoring costs been accurately captured?
  - For warfarin, the company assumed the frequency of visits would be 24 per year, with an average frequency of 0.9 visits per two-week cycle. This is associated with a cost of £24 every two weeks. Is this reasonable?
  - Are warfarin monitoring assumptions acceptable when compared with those considered in previous appraisals?
  - For edoxaban, the company's model assumes no monitoring is required – would monitoring costs be required in clinical practice?
- How robust are the company's sensitivity and scenario analyses?
  - The probabilistic analyses exclude key parameters (VTE recurrence and bleeding).

  - Do the one way sensitivity analyses have face validity (assuming that treatment type affects outcomes such as stroke)?
- Is the Committee confident that the model is suitable for decision making?
- Given the small differences in QALYs and costs between the different treatments, what is the Committee's view on the reliability of an incremental analysis?
- There have been several recent appraisals for oral anticoagulants – Does the Committee consider that information from these about relative costs and estimates of efficacy are helpful to inform this appraisal?
- What is the Committee's view of the ERG scenario analyses?

1 Remit and decision problem

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of edoxaban tosylate within its licensed indication for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People with deep vein thrombosis and/or pulmonary embolism	In line with the final NICE scope	None.	The pivotal trial population inclusion/exclusion were more restrictive: 1. Age > country specific minimum legal adult age 2. DVT presenting in the proximal vessels only (distal DVT excluded; clinical experts advised this is appropriate)
Intervention	Edoxaban tosylate	In line with the final NICE scope	None	The intervention is appropriate, however: 1. Dose adjustment makes comparison with other new oral anticoagulation trials difficult. 2. Fondaparinux was not an option for parenteral anticoagulant. The ERG is uncertain what effect this may have had on outcomes.
Comparators	• Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • Rivaroxaban • Dabigatran	In line with the final NICE scope. Note: the company stated there was no evidence available for edoxaban in patients for whom VKA is	The company stated that there was no evidence for the population for whom a vitamin K antagonist is unsuitable.	The company has included all key comparators, however: 1. Enoxaparin was the only low molecular weight heparin for parenteral therapy. The ERG is unsure what effect this would have

	For people for whom a vitamin K antagonist is unsuitable: • Low molecular weight heparin or fondaparinux alone • Rivaroxaban • Dabigatran	unsuitable. The company included apixaban in the network meta-analysis, however it was not in the final scope.		and therefore assumed all drugs for initial parenteral therapy have equal efficacy. 2. No direct comparisons of edoxaban with rivaroxaban or dabigatran, or any comparisons for people for whom vitamin K antagonists are not suitable, because of a lack of evidence.
Outcomes	The outcome measures to be considered include: • mortality • venous thromboembolism recurrence • complications following deep vein thrombosis or pulmonary embolism, including post thrombotic syndrome and chronic thromboembolic pulmonary hypertension • adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding) • health-related quality of life.	In line with the final NICE scope	None.	The outcomes are appropriate, however the submission does not present data for incidence of post thrombotic syndrome or chronic thromboembolic pulmonary hypertension from the trial.
Other considerations	If evidence allows, subgroups will be considered by type of venous thromboembolism (pulmonary embolism or deep vein	The company submission included subgroup analyses according to type of venous	The company stated that: • It had not provided specific subgroups	The ERG provided analyses for the missing DVT subgroup. The ERG noted patients with active cancer (n=208) were

	thrombosis). The analysis should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). If evidence allows, the analysis should also consider people for whom the need for long-term anticoagulation is uncertain and aspirin or no preventative treatment might be considered. If the evidence allows, the analysis should consider separately people with active cancer and include any effect on the person's cancer or cancer treatment.	thromboembolism (PE with or without PTE; a DVT-only subgroup was not presented).	aligned with different treatment durations but that duration of anticoagulation can be varied in the model • No evidence was available for patients for whom need for long-term anticoagulation is uncertain • No evidence about active cancer was available from the phase III trial	recruited to the trial and the submission reports a sub group analysis was planned, but no data are reported. The ERG agreed that the exclusion about a lack of long term anticoagulation was legitimate. The ERG noted that the flexible duration of the trial makes interpreting data for subgroups of people who require acute treatment and people needing long term treatment difficult. Whilst those patients still taking drugs at 12 months can be considered a proxy group for life-long therapy, the long-term safety and efficacy data for edoxaban are limited by the 12 month duration of the trial.

2 The technology and the treatment pathway

2.1 Venous thromboembolism (VTE) is a term used to describe deep vein thrombosis (DVT) and pulmonary embolism (PE). Deep vein thrombosis is the formation of a thrombus (blood clot) in a deep vein, most commonly located in the leg, but also the thigh, pelvis or arm. When deep vein thrombosis occurs, dislodged blood clots may travel to and block the blood vessel that carries blood from the heart to the lungs; this is called pulmonary embolism. VTE is associated with risk factors such as increasing age, surgery, pregnancy and cancer, but sometimes the cause is unknown. Approximately 8% of people experience a recurrence of VTE within 12 months of stopping treatment, and it is also associated with complications including stroke, post-thrombotic syndrome (a complication of DVT in the leg which causes aching, itching and varicose veins), and chronic thromboembolic pulmonary hypertension (a complication of PE where there is an increase in blood pressure in the pulmonary artery, which can increase the risk of heart failure).

2.2 NICE clinical guideline 144 states that patients with confirmed proximal DVT or PE should be offered a choice of low molecular weight heparin or fondaparinux (started as soon as possible) and a vitamin K antagonist (started within 24 hours). For people for whom a vitamin K antagonist is not considered an appropriate treatment, unfractionated heparin or low molecular weight heparin may be continued instead of a vitamin K antagonist. NICE technology appraisal guidance 261 and 287 also recommend rivaroxaban as an option for treating deep vein thrombosis and pulmonary embolism, respectively (both guidance also recommend rivaroxaban for VTE prevention). NICE technology appraisal guidance 327 recommends dabigatran etexilate as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults. Treatment options used in clinical practice for the long-term secondary prevention of venous thromboembolism include vitamin K antagonists, rivaroxaban, dabigatran and aspirin. Frequent monitoring and possible adjustment of dose is required with the use of vitamin K

antagonists. Table 2 shows the different drugs available for treating venous thromboembolism and preventing recurrent venous thromboembolism.

Table 2 Current anticoagulant pharmacotherapy for VTE

Type of therapy	Pharmaceutical class	Name
Parenteral therapies	Heparin group	Unfractionated heparin (e.g. calciparin)
		Low-molecular-weight heparin (e.g. enoxaparin)
	Factor Xa inhibitors	Fondaparinux
Oral therapies	Vitamin K antagonists	Warfarin, acenocoumarol, phanocoumarol and fluindione
	Non-vitamin K antagonist oral anticoagulants	Direct thrombin inhibitors (dabigatran)
		Direct factor Xa inhibitors (rivaroxaban)

Table A5 on page 24 of the company submission

2.3 Edoxaban tosylate (Lixiana, Daiichi Sankyo) is an anticoagulant that acts by direct inhibition of activated factor X (factor Xa). Factor Xa is a key component in the formation of blood clots. Edoxaban tosylate is administered orally. Edoxaban does not currently have a marketing authorisation in the UK for treating VTE. On 23rd April 2015 it received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) who have recommended edoxaban for the treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent DVT and PE in adults.

Table 3 Technologies

	Edoxaban	Dabigatran	Rivaroxaban	Warfarin
Marketing authorisation	The Committee for Medicinal Products for Human Use (CHMP) have recommended edoxaban for the treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent DVT and PE in adults.	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.	Prophylaxis and treatment of venous thrombosis and pulmonary embolism.
Administration	Oral	Oral	Oral	Oral
Dosing and cost	The recommended dose is 60 mg once daily following initial use of parenteral anticoagulant for at least 5 days. Treatment duration should be individualised after careful assessing of treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE. According to the company submission, edoxaban costs £2.10 per tablet (15 mg, 3 mg or 60 mg), meaning a 3-month course would cost £191.63. In the pivotal Hokusai-VTE trial, the dosage was reduced to 30 mg	The recommended daily dose is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. Treatment duration should be individualised after careful assessing of treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE. The British National Formulary states that dabigatran 150 mg costs £65.90 for a 60-capsule pack.	The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks then 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE. The British National Formulary states that rivaroxaban 20 mg costs £58.80 for a 28-tablet pack.	The typical induction dose is 10mg daily for 2 days but this should be individually tailored. The daily maintenance dose is usually 3–9 mg taken at the same time each day. The exact maintenance dose depends on the prothrombin time or other appropriate coagulation tests. Control tests should be made at regularly and the maintenance dose adjusted accordingly. Once the maintenance dose is established, it is rarely necessary to alter it. The British National Formulary states that a 28-tab pack of warfarin costs £1.03 and £1.05 for the 3- and 5-mg doses.

	if patients had one or more factors associated with edoxaban overexposure (patients with moderate renal impairment, or who were receiving concomitant treatment with potent P-glycoprotein inhibitors, or who weighed 60 kg or less).			

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 The patient and professional groups described the treatment pathway for people who have experienced VTE. They stated that most patients are initially treated with immediate parenteral anticoagulation for around 5 days, followed by a vitamin K antagonist such as warfarin on the same day or shortly after. They noted that this treatment combination is associated with several disadvantages, for example warfarin requires regular visits to health services for monitoring, which is resource intensive for the NHS and a time consuming burden at a stressful time for patients. Also, heparin is administered via injection which can be distressing for patients. Alternatively, new oral anticoagulants (NOACs) such as rivaroxaban, dabigatran and apixaban, may be offered, which are generally preferred by most patients because they work quickly, allow for fixed daily dosing which simplifies prescribing and administration, and usually do not require regular monitoring and dose adjustment. Rivaroxaban and apixaban also do not require a heparin lead in, although dabigatran does. One patient group stated treatment and monitoring may be initiated in secondary care with continuation of treatment in primary care after discharge from hospital, however one professional group stated that there is variation in practice, with some services such as monitoring and prescribing offered variably in either primary or secondary care. Edoxaban could also be used in both primary and secondary care. One professional group stated that rivaroxaban was being used in the ambulatory care setting to reduce inpatient admission.

3.2 The patient and professional organisations stated they were aware of inconsistencies nationally around access to NOACs. The patient groups stated they were aware of cases where patients had been denied choice of or access to NOACs in primary care on the grounds of costs. The professional group also stated that there was variation in care for those who required anticoagulation monitoring because of varying levels of local services available.

3.3 The patient organisations described living with the condition. They stated that experiencing VTE for the first time can be devastating. Patients may be hospitalised for periods of time, restricted in movement and unable to continue with previous activities. DVT can cause pain as circulation is impaired (which can affect mobility), swelling, warmth, heaviness, redness and tenderness, and can lead to post thrombotic syndrome (requiring further treatment for many years). PE can cause breathlessness, chest pain, sudden collapse, and death; those who survive may require intensive care for several months. People who develop VTE are at a heightened risk of further episodes which can cause further distress. Whilst recovering from VTE, patients may require further treatment and monitoring, therefore the most important issue for patients is receiving an effective treatment which is the easiest and least intrusive to minimise the impact on their day-to-day lives (some patients reported they had lost their jobs because they had taken too much time off work for treatment).

3.4 Patient and professional organisations considered the advantages of edoxaban. They stated that it provided a number of benefits when compared with warfarin and may bring some advantages over NOACs, for example edoxaban is administered once daily (dabigatran is taken twice daily) with no dose change (rivaroxaban is twice daily for 3 weeks then once daily) which may increase compliance and reduce dosing errors. However, they stated that overall edoxaban had similar benefits and disadvantages to other NOACs, and used a longer heparin lead-in in the trials (7 days) than the standard period (5 days), and therefore some clinicians would likely prefer rivaroxaban to avoid the heparin lead-in. The professional organisations stated that because of the similarity with other NOACs, implementation of edoxaban would be straightforward with staff and resources mostly already in place. For all NOACs, professional and patient organisations noted that a reversal agent was currently not available, although they stated that this is an active area of research. One professional organisation stated that new evidence is emerging for the existing NOACs about drug interactions, and that as edoxaban is a new

drug this information will not be initially known. Another disadvantage is that in some circumstances, for example to monitor adherence or because of reduced renal function, edoxaban may require anticoagulant monitoring. Overall a reduced need for monitoring with NOACs compared with warfarin was an advantage, but it would make monitoring adherence to treatment more difficult.

3.5 Patient and professional organisations described groups who may particularly benefit from edoxaban. They stated it would be an appropriate alternative to warfarin, for example for patients whose disease was not well controlled using warfarin, people who have impaired renal function and low body weight (who can have a lower dose option), and people who have difficulty attending clinics.

4 Clinical-effectiveness evidence

Overview of clinical trials

4.1 The company conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of edoxaban for the treatment and secondary prevention of VTE. It identified 1 relevant randomised clinical trial (Hokusai-VTE). The company did not find any head-to-head studies, so it conducted a network meta-analysis to compare edoxaban with initial low molecular weight heparin and continued VKA, rivaroxaban, dabigatran and apixaban. The company did not find any relevant non-randomised studies.

4.2 Hokusai-VTE was an international (37 countries including the UK) phase III, randomised, double-blind, double-dummy, parallel-group, non-inferiority trial. It compared initial heparin followed by edoxaban (hereafter referred to as edoxaban), with initial heparin overlapping with warfarin followed by warfarin only (hereafter referred to as warfarin), in treating acute symptomatic VTE and preventing symptomatic recurrent VTE (see section 4.3). Eligible adults with either acute symptomatic DVT or PE (with or without DVT) were stratified in a 1:1 ratio by presenting diagnosis,

temporary baseline risk factors (such as trauma, surgery or immobilisation) and need for dose reduction (patients with moderate renal impairment, or who were receiving concomitant treatment with potent P-glycoprotein inhibitors, or who weighed 60 kg or less). After stratification, a total of 8292 patients were randomly assigned to either the edoxaban group (n=4143) or the warfarin group (n=4149).

4.3 All patients received initial therapy with open-label heparin, either low molecular weight heparin (enoxaparin, either 1 mg/kg twice daily or 1.5 mg/kg once daily; administered subcutaneously) or unfractionated heparin (started with 5000 IU bolus and 1300 IU/hour infusion, activated partial thromboplastin time adjusted) for at least 5 days. Edoxaban or warfarin was administered in a double-blind, double-dummy fashion:

- Patients in the edoxaban group received placebo warfarin during initial heparin therapy. After stopping heparin, they continued placebo warfarin (adjusted to maintain a sham international normalized ratio [INR] of 2.0–3.0) and started 60 mg of edoxaban once daily (or 30 mg once daily in patients who required dose reduction at randomisation or during the study).
- Patients in the warfarin group started warfarin during initial heparin therapy. After stopping heparin, they continued warfarin (adjusted to maintain an INR of 2.0–3.0) and started placebo edoxaban.

Treatment with edoxaban or warfarin was continued for at least 3 months and up to a maximum of 12 months, with treatment length varied based on clinical judgement of risk of recurrent VTE, risk of bleeding, and also patient preference. The company noted this meant that people progressing beyond 3 months in the trial were mostly those identified as being at higher risk of recurrence – therefore as duration of treatment increases, the trial data is more concentrated with participants who are higher-risk. In both groups, the median duration of treatment was around 260 days (8.5 months) and 40% of patients continued treatment for 12 months.

4.4 Patient characteristics were similar between the treatment groups including age, gender, ethnicity, presenting diagnosis, VTE risk factors and baseline medical history. Mean age was 56 years, the majority of patients were male (57%) and patient ethnicity was white (70%), Asian (21%), black (4%) or 'other' (5%). Around 60% of patients received treatment for more than 6 months. A total of 4921 patients presented with DVT only, and 3319 with PE (with or without DVT). Please see tables B 6 and B 7 of the company submission for details of baseline characteristics.

4.5 The company reported their results as efficacy, safety and 'other' outcomes. The primary efficacy outcome was incidence of symptomatic recurrent VTE (a composite of recurrent DVT, new non-fatal symptomatic PE, and fatal PE) during the 12-month study period. Secondary outcomes included clinically relevant bleeding occurring during treatment or within 3 days of interrupting or stopping study drug (also referred to by the company as the primary safety outcome, a composite of major bleeding and clinically relevant non-major bleeding), and a composite clinical efficacy outcome of recurrent VTE and all-cause mortality during the 12-month study period.

4.6 The trial included 3 analysis sets (modified intention to treat, per protocol analysis, and safety analysis) and 2 study periods (overall study period and on-treatment period). The primary efficacy analyses were based on the modified intention to treat population for the overall study period, which included 4118 patients randomised to edoxaban and 4122 randomised to warfarin, with summary statistics also provided for the on-treatment period. The safety population, designed to capture and analyse patients by treatment actually received, was used for outcomes related to safety, and this population was identical to the modified intention to treat population (because all patients received the treatment to which they were randomised). The company conducted pre-specified subgroup analyses for the primary efficacy outcome for various patient and disease characteristics, including whether the presenting diagnosis was PE with or without DVT (n=1650 in the edoxaban group and n=1669 in the warfarin

group), or DVT only (n=2468 in the edoxaban group and n=2453 in the warfarin group).

ERG comments

4.7 The ERG stated that the systematic review done by the company was reasonable. The ERG noted that there was no direct evidence for edoxaban compared with other NOACs, but the identified trial, Hokusai-VTE, was well conducted and appropriately powered to demonstrate non-inferiority, with outcomes highly relevant to the secondary prevention and management of VTE. However, the ERG stated that the generalisability of the trial to UK practice was uncertain because the trial population was atypical of those who require treatment for VTE in the UK (although it noted that trials for other NOACs have included patients with similar demographic profiles):

- The number of participants from the UK was small (n=111)
- There were more males than females in the trial, and females have higher incidence of VTE
- The trial population included a higher proportion of people who are Asian (21%) than would be expected in UK clinical practice.
- The mean baseline age of 56 was younger than the age of over 65 years that would be expected for people who experience a VTE
- The treatment duration (60% received treatment for longer than 6 months) suggested a high risk population Clinical experts advised the ERG that DVT is typically treated for 3-6 months, PE for 6 months, and, if secondary prevention is required for VTE, treatment would be lifelong.

4.8 The ERG noted that the Hokusai-VTE trial design was different from other trials evaluating NOACs for this condition because patients could have their drug dose altered at the beginning of or during the trial, which meant that patients would potentially be treated with the study drugs for longer than they would in routine clinical practice. Further, the ERG was unsure about whether the monitoring undertaken in the trial would be required in

clinical practice, however it stated that because the dose of edoxaban was related to variable patient factors, it should be expected that some periodic monitoring would be required to check whether patients require dose reduction.

4.9 The ERG noted that the company had not presented evidence for the subgroups of:

- People with active cancer: The ERG noted that the Hokusai VTE trial had included people with a diagnosis of active cancer and an analysis had been planned but not conducted, which may be because of limited data (n=208)
- People for whom treatment with warfarin was not appropriate: the ERG agreed this exclusion was legitimate because of a lack of data
- People with DVT: the ERG disagreed with the exclusion of this subgroup. As the Hokusai VTE trial (warfarin and edoxaban) and the EINSTEIN DVT trial (section 4.20, rivaroxaban) included data for people with DVT, the ERG was able to conduct an analysis for this population.

Clinical trial results

4.10 For the trial results for the primary efficacy outcome, the company pre-specified a non-inferiority margin of 1.5 for the upper 95% confidence interval (CI) of the hazard ratio (HR) (that is, the non-inferiority analyses demonstrated statistically significant non-inferiority if the upper boundary of the 95% confidence interval for the outcome was below 1.5).

4.11 Symptomatic recurrent VTE, the primary outcome, occurred in 130 patients (3.2%) in the edoxaban group and 146 (3.5%) subjects in the warfarin group (hazard ratio 0.89, 95% confidence interval 0.703 to 1.128) during the overall study period. Because the upper limit of the 95% confidence interval (1.128) was below the pre-specified non-inferiority margin of 1.5, the difference between edoxaban and warfarin was statistically significant for non-inferiority ($p<0.0001$) (Table 4). Similar

results were obtained for the on-treatment period (hazard ratio 0.82, 95% confidence interval 0.60 to 1.14; p<0.0001 for non-inferiority).

Table 4 Adjudicated symptomatic recurrent VTE (overall study period)

	Edoxaban (n=4118)	**Warfarin (n=4122)**
All patients with recurrent VTE, n (%)	130 (3.2)	146 (3.5)
Hazard ratio for edoxaban versus warfarin (95% CI)	0.89 (0.703, 1.128)	
p-value (for non-inferiority)	<0.0001	
Type of first recurrent VTE, n (%)		
PE with/without DVT	73 (1.8)	83 (2.0)
PE-related deaths	24 (0.6)	24 (0.6)
Fatal PE	4 (<0.1)	3 (<0.1)
Non-fatal PE	49 (1.2)	59 (1.4)
Unexplained death (with VTE not ruled out)	20 (0.5)	21 (0.5)
DVT alone	57 (1.4)	63 (1.5)

Key: CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism
Source: table B9 on page 63 of the company submission

4.12 The company stated that the primary efficacy results were broadly consistent across the subgroups assessed, for example edoxaban was non-inferior to warfarin in the subgroup analyses according to age and presenting diagnosis (DVT or PE with/without DVT). For further details of the subgroup analyses, see pages 65–69 of the company submission.

4.13 The company presented results for secondary efficacy analyses. An analysis for the superiority of edoxaban compared with warfarin showed that there was no statistically significant difference in the composite endpoint of recurrent VTE and all-cause mortality, with events occurring in 228 patients (5.5%) in both the edoxaban and warfarin groups (HR 1.00, 95% CI 0.832 to 1.200; p=0.9933 for superiority). All-cause mortality was numerically slightly greater in the edoxaban group (n=122 [3.0%]) than in the warfarin group (n=106 [2.6%]). Please see section 4.16 for secondary outcomes related to safety.

4.14 A total of [redacted] patients in Hokusai-VTE completed a total of [redacted] EuroQoL-5-Dimensions (EQ-5D) assessments. Utility scores were determined for

all patients using the UK time trade-off (TTO) value set, at baseline and at 3-month intervals thereafter. The mean utility score was approximately [redacted] at baseline and [redacted], but the company reported that the results should be interpreted with caution because data were too limited to compare the effects of edoxaban and warfarin on health-related quality of life.

ERG comments

4.15 The ERG noted that the trial demonstrated that edoxaban was non-inferior to warfarin for the primary efficacy endpoint recurrent VTE. It stated that although health related quality of life data had been collected in the trial, the small number of respondents severely limited the usefulness of this information. The ERG also noted recurrent VTE was higher for edoxaban in the first 30 days of the trial (21 edoxaban compared with 15 warfarin events in the DVT subgroup and 9 edoxaban compared with 7 warfarin events in the PE subgroup), but this difference was not statistically significant. Please see section 4.18 and 4.19 for adverse event outcomes.

Adverse effects of treatment

4.16 The company presented the results of safety analyses, all of which related to adverse events, using the safety analysis set for the on-treatment population. Treatment duration was similar between arms, with approximate treatment durations as follows: less than 3 months (12%), 3-6 months (26%), greater than 6 months (60%) and greater than 12 months (40%). The median treatment duration in both arms was approximately 265 days. For the safety outcomes, results included:

- Bleeding: (major or clinically relevant non-major bleeding, primary safety outcome): Edoxaban was associated with fewer bleeding events (HR: 0.81; 95% CI: 0.705, 0.936; p = 0.004 for superiority) (Table 5). For subgroups the company reported that rates of bleeding events were numerically lower with edoxaban than with warfarin in the following groups associated with a higher risk of bleeding: age ≥75 years; fragile status (age ≥75 years, body weight ≤50 kg, or creatinine

clearance 30-50 mL/min); history of or active cancer; PE with/without DVT; female gender; creatinine clearance 30–50 mL/min; concomitant aspirin use.

- Permanent discontinuation of study drug because of adverse event: 5.7% for edoxaban and 5.4% for warfarin (no statistical analyses presented).
- Mortality: the rate for VTE-related death, cardiovascular death and other known causes (cancer, bleeding, infectious disease or other) was 0.8% in both arms (no statistical analyses presented).
- Major adverse cardiac event (composite of non-fatal myocardial infarction, non-fatal stroke, non-fatal systemic embolic events, and cardiovascular death) was 1.2% in the edoxaban group and 1.0% in the warfarin group (HR: 1.22; 95% CI: 0.804, 1.854; p = 0.35).

Table 5 Adjudicated bleeding events (on-treatment study period) (primary safety outcome)

	Edoxaban (n=4118)	Warfarin (n=4122)
Major and CRNM Bleeding, n (%)	349 (8.5)	423 (10.3)
HR Edoxaban vs. Warfarin (95% CI)	0.81 (0.705, 0.936)	
p-value	0.004	
Major Bleeding, n (%)	56 (1.4)	66 (1.6)
HR Edoxaban vs. Warfarin (95% CI)	0.84 (0.592, 1.205)	
p-value	0.3521	
Fatal, n (%)	2 (<0.1)	10 (0.2)
CRNM Bleeding, n (%)	298 (7.2)	368 (8.9)
HR Edoxaban vs. Warfarin (95% CI)	0.80 (0.68–0.93)	
p-value	0.004	
All Bleeding, n (%)	895 (21.7)	1056 (25.6)

Source: table B18, page 72 of the company submission

4.17 The company presented data on treatment emergent adverse events, which were further categorised as serious if they met criteria such as were life-threating or caused inpatient hospitalisation. The company stated these events were similar in both arms. Serious events in the on-

treatment period that caused permanent cessation of drug were 2.9% in the edoxaban group and 2.5% in the warfarin group. Common treatment emergent adverse events included [redacted].

ERG comments

4.18 The company reported that edoxaban was statistically significantly superior for the composite outcome of major and non-major bleeding, although the ERG noted that this difference was driven by the non-major bleeding outcome, with major bleeds numerically but not statistically significantly lower for edoxaban compared with warfarin. The ERG noted that edoxaban demonstrated a broadly consistent bleeding profile across pre specified sub groups, and had shown numerically lower rates of bleeding than warfarin for subgroups typically associated with high risk of bleeding. The ERG also noted that the company had asserted that there was no difference between edoxaban and warfarin for additional safety endpoints, including major adverse cardiac events, but this had not been explicitly demonstrated statistically.

4.19 The ERG noted that post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension were outcomes listed in the scope, were collected during the trial, and were outcomes used by the company in its cost effectiveness analyses. However, the company had not presented trial information for these outcomes in its submission.

Meta-analyses/indirect comparison/MTC

4.20 The company conducted a Bayesian network meta-analysis to compare edoxaban with warfarin, apixaban, dabigatran and rivaroxaban for the treatment and secondary prevention of VTE. The company stated it included only trials from which it could derive data for a fixed 6 month study period (that is, either the trial was fixed for 6 months, or, if the trial was longer than 6 months, only data up to 6 months was extracted), in order to reduce heterogeneity between the trials. This led to the inclusion

of 6 randomised controlled trials, all of which compared the treatment of interest with low molecular weight heparin plus a vitamin k antagonist:

- 3 trials had a fixed duration of 6 months:
  - AMPLIFY: apixaban, 5400 patients with VTE
  - RE-COVER I: dabigatran (plus low molecular weight heparin), 2564 patients with VTE
  - RE-COVER II: dabigatran (plus low molecular weight heparin), 2568 patients with VTE
- 3 trials with a fixed duration of 12 months, but 6-month data could be extracted:
  - Hokusai-VTE: edoxaban pivotal trial, see section 4.1-4.6.
  - EINSTEIN-PE: rivaroxaban, 4833 patients with PE
  - EINSTEIN-DVT: rivaroxaban, 3449 patients with DVT

4.21 The company used a fixed effects Bayesian model to synthesise the results for each outcome, and used the posterior distribution to derive comparative treatment effects (shown as odds ratios with 95% credible intervals [CrI] for ease of interpretation), using the VKA regimen as the reference treatment. It stated that it used a fixed effects model because of the small number of trials available per comparison, and that it was not possible to use a random effects model [redacted]. It conducted network meta-analyses for the whole VTE population, and also secondary analyses for the PE population only, for the following outcomes:

- VTE recurrence
- Bleeding (major bleeding, non-major bleeding and a composite of both outcomes)
- VTE-related death
- Net clinical benefit (composite of VTE recurrence, major bleeding and all-cause mortality).

The base case network meta-analysis was for the outcome 6 month VTE recurrence. Table 6 shows the results of the network meta-analysis, showing that rates were similar for edoxaban when compared with other treatments for VTE. Table 7 shows the results of the network meta-analysis, for edoxaban when compared with other treatments for the PE subgroup.

Table 6: Network meta-analyses (all patients), odds ratio and credible interval for edoxaban compared with all treatments

	VKA	Apixaban	Dab	Riva
VTE	[redacted]	[redacted]	[redacted]	[redacted]
Composite bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Non-major bleeding	[redacted]	[redacted]	[redacted]	[redacted]
VTE related death	[redacted]	[redacted]	[redacted]	[redacted]
Net clinical benefit	[redacted]	[redacted]	[redacted]	[redacted]
Note: Apixaban was not a comparator in the scope Net clinical benefit: composite of VTE recurrence and major bleeding				

Table 7 Network meta-analyses (PE subgroup), odds ratio and credible interval for edoxaban compared with all treatments

	VKA	Apixaban	Dabigatran	Rivaroxaban
VTE Recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Composite Bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Major Bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Non-major bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Note: Apixaban was not a comparator in the scope				

4.22 The company stated that it conducted a qualitative assessment of the consistency of evidence generated by direct and indirect comparisons and

stated that the network meta-analysis results for each NOAC versus warfarin were generally consistent with the direct evidence from the original trials.

4.23 The company stated that it did not quantitatively investigate heterogeneity between the trials because a low number of the trials had similar designs or comparators. It instead conducted qualitative analysis of heterogeneity and found that there was variance in blinding, heparin lead-in, duration of treatment and proportion of patients with extensive PE across the trials. The company concluded that there were substantial differences between the design and the populations of the network meta-analyses which meant that any results should be interpreted with caution. For example, Hokusai-VTE was designed differently to other studies because it:

- included initial heparin therapy for at least 5 days, whereas trials for rivaroxaban and apixaban were given as a single treatment
- allowed the dosage of edoxaban to be reduced at any point whereas other trials did not allow for this.
- was the only trial to have a flexible treatment duration (therefore later data included more high-risk patients who needed to remain on treatment).
- did not allow for an extension whereas patients in other trials were entered into extension studies
- was double-blind whereas EINSTEIN-DVT and EINSTEIN-PE had open label designs.

ERG comments

4.24 The ERG noted that the trials in the network meta-analysis did not appear to have large differences between patient baseline characteristics. It noted that the company had identified a high risk of bias in some trials because of a lack of blinding, but the ERG stated this is less of a concern for objective outcomes such as mortality or recurrent VTE.

4.25 The ERG considered the approaches taken for different aspects of the network meta-analysis. It stated that:

- the approach to reduce heterogeneity by including only trials with 6 month data was reasonable
- the qualitative approach to considering heterogeneity was pragmatic but the ERG would have preferred it if the company had performed 2 separate analyses based on index event (DVT or PE)
- the use of a fixed effects model was reasonable because of the small number of studies populating the network and the lack of direct comparison of NOACs with any treatment other than warfarin.
- the quality assessments of the trials included in the NMA were mostly adequate.
- the indirect comparisons from the network meta-analysis were consistent with the direct evidence from the individual trials.

4.26 The ERG stated that any differences in outcomes between the treatments in the network were small and more likely to be due to random chance, because the non-inferiority design of the original studies limited the opportunity for any treatment in the network to have demonstrated any statistically significant differences. Overall, there were no large differences in treatment effects for the outcomes, with odds ratios that had wide credible intervals that approached or crossed '1' (that is, no difference in effect), indicating a large amount of uncertainty. The ERG noted that results for the subgroups of DVT (conducted by the ERG as the company had not included this, shown in ERG report table 20 p.88) and PE showed results that were consistent with the main population.

5 Cost-effectiveness evidence

5.1 The company identified 12 studies related to the comparators in the scope in its systematic review of cost-effectiveness analyses (see company submission p.144, table B 54). As the company found no studies

evaluating the cost-effectiveness of edoxaban for treating and preventing VTE, it developed a new economic model.

Model structure

5.2 The company developed a new Markov model to compare edoxaban with warfarin, rivaroxaban and dabigatran for the treatment and secondary prevention of an acute VTE event. The model included 11 states representing treatment status (on treatment or off treatment health states), adverse events, and death. Model cycles were 2 weeks – the company stated this cycle length was used to accurately model the effects of initial heparin for those treatments that required it (edoxaban and dabigatran), and to more accurately model the costs and utilities associated with various adverse events represented in the model, which often occur acutely in clinical practice. The company conducted the analysis from the perspective of the NHS and Personal Social Services, and discounted costs and health effects at an annual rate of 3.5%. The model had a lifetime time horizon (maximum 50 years) with 5 key time points – this allowed the use of different transition probabilities over time to capture the change in risk of event:

- 0 to 2 weeks (days 1 to 14)
- 2 weeks to 3 months (days 15 to 98)
- 4 months to 6 months (days 99 to 183)
- 6 months to 12 months (days 184 364
- 12 months onwards (day 365 onwards)

5.3 Patients entered the model in the “on treatment” health state where they received initial anti-coagulation treatment. Whilst receiving treatment, patients were at risk of experiencing an adverse event and moving to the associated health state: transition to recurrent VTE and bleeding (major bleeding or clinically relevant non-major bleeding) health states depended on the anticoagulation treatment given, and transition to heparin induced thrombocytopenia (only for those who received heparin), stroke, and chronic thromboembolic pulmonary hypertension health states were

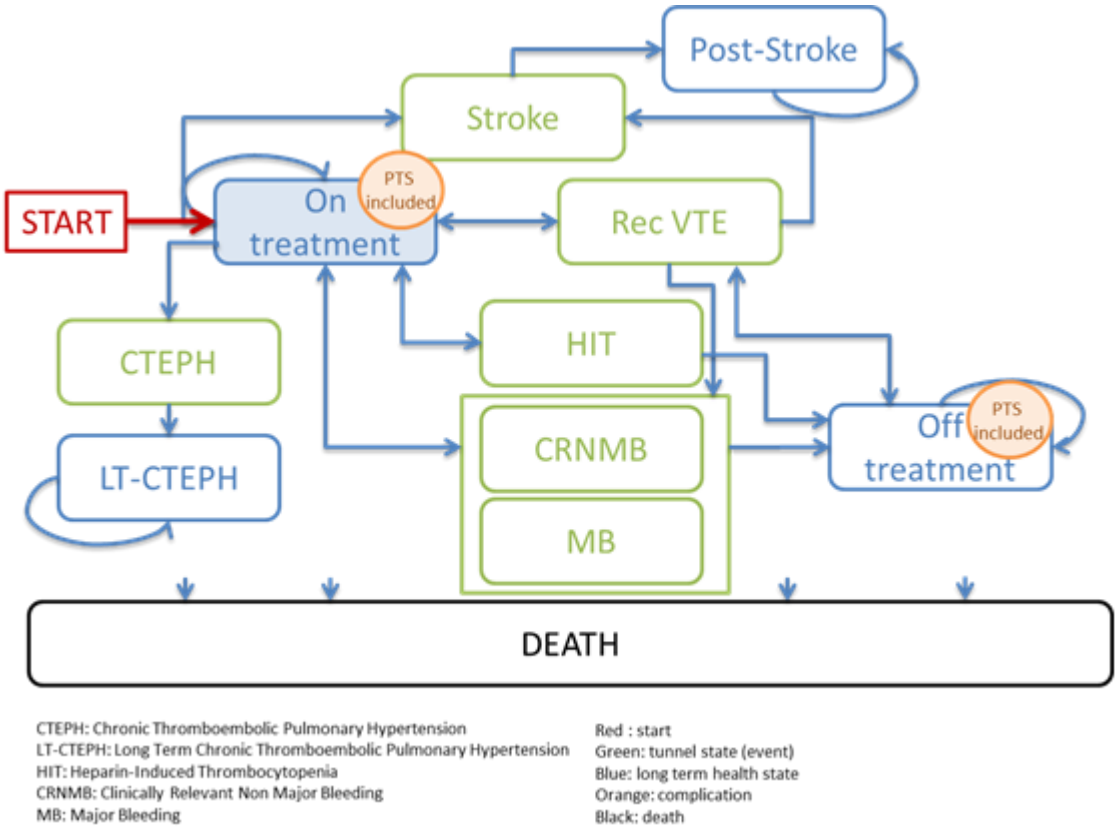
independent of the type of anticoagulation given. If patients experienced stroke or chronic thromboembolic pulmonary hypertension, they received no further anticoagulation treatment and could only move to the post-stroke or long term chronic thromboembolic pulmonary hypertension health states respectively, and remained there for the duration of the model.

5.4 The company modelled heparin induced thrombocytopenia, VTE recurrence, bleeding, chronic thromboembolic pulmonary hypertension and stroke as tunnel states. This meant that patients could not remain in the state for more than one consecutive cycle – patients experienced the event and accrued costs and utility values for one cycle only. In the heparin induced thrombocytopenia, VTE recurrence and bleeding health states, after the event had resolved (one cycle), most patients could transition back to the on-treatment health state (to reinitiate their initial anticoagulation treatment), but a proportion of patients moved to the off treatment health state. The off treatment health state captured any patient who had ceased anticoagulation treatment either because of an adverse event or because of the end of specific treatment durations (12 months in the base case), and it was assumed these patients were at a higher risk of VTE recurrence, but could not experience stroke or chronic thromboembolic pulmonary hypertension as these events were considered complications of treatment.

5.5 If VTE recurred (which could happen in on or off treatment health states), patients transitioned to the VTE recurrence health state, accrued costs of diagnosis and hospitalisation for VTE, and then transitioned back to the on treatment health state to reinitiate their initial anticoagulation treatment. The company noted that it assumed that the number of VTE recurrences did not affect the risk of further VTE recurrence (or any other adverse event), because of a lack of evidence, and also because this assumption simplified the model structure. Patients in the on and off treatment health states were also at risk of post thrombotic syndrome (not a separate health state in the original model [Figure 1] however following a

suggestion from the ERG it was included as a health state) which accrued costs and disutility values. Patients could move to a death state at any point in the model, either because of disease-related death (increased risk of mortality with index VTE event, VTE recurrence, bleeding, chronic thromboembolic pulmonary hypertension [long-term or not] and stroke) or age-dependent other-cause mortality.

Figure 1 Model structure



5.6 Subgroup analyses varied treatment length (from 12 months in the base case to 3 months, 6 months or lifelong [50 years]) or varied VTE event (patients with an index PE (± DVT). The company stated that it excluded people with active cancer for whom VKAs would be unsuitable because these patients were not included in studies of edoxaban.

ERG comments

5.7 The ERG stated that the search strategy used by the company to identify health economic studies was generally appropriate. However, it noted that

searches were not performed in the Health Technology Assessment database, which may have resulted in the omission of relevant publications. In addition, NICE clinical guideline 144, on the management of venous thromboembolic diseases, was not identified or included, which contained relevant information for this topic.

5.8 The ERG noted several concerns about the model structure

- If patients experienced a recurrent VTE, they returned to their original therapy, but clinical experts advised the ERG that patients would switch to a higher dosage or change treatment because their current treatment had not prevented recurrence.
- The ERG stated that if shorter cycles are used (in this instance a 2 week cycle was used) then the use of tunnel states (see section 5.4) needs to be carefully considered, because it can potentially misestimate the impact of certain events on quality of life and costs. To overcome this, the company could have increased cycle duration, modelled the event as a non-tunnel state, or used more post-event states (as had been done for chronic thromboembolic pulmonary hypertension).
- The ERG stated that treatment duration is variable and highly determined by whether the event was provoked or unprovoked, for example provoked DVT would only require treatment for 3-6 months, however in the base case patients had a fixed treatment duration of 12 months.
- Patients were only at risk of post-thrombotic syndrome when on or off treatment, and chronic thromboembolic pulmonary hypertension and stroke only when on treatment. However, clinical experts advised the ERG that these are VTE related complications. The ERG therefore stated that patients should be at risk of these outcomes at all times in the model (although this did not have a large effect on the ICER)
- 20% of modelled patients survived until the age of 90. This indicates that survival is potentially overestimated in the economic model.

5.9 The ERG noted the following issues with modelled health states, but stated that they did not have a large effect on the ICER:

- After experiencing chronic thromboembolic pulmonary hypertension, patients move into the long term chronic thromboembolic pulmonary hypertension health state and receive no further anticoagulation treatment, which was not clinically plausible.
- Clinical experts advised the ERG that the heparin-induced thrombocytopenia health state was not an important enough event to be included in the model
- The inclusion of the stroke health state was methodologically flawed and the ERG conducted a scenario analysis removing this. Flaws noted were:
  - The company had not included several other equally relevant cardiovascular events, for example myocardial infarction.
  - It included both intracerebral haemorrhages and ischaemic stroke, which meant that intracerebral haemorrhages, also included in the major bleeding health state, were double counted
  - Clinical experts advised the ERG that the type of stroke would affect whether treatment would be discontinued (patients would temporarily discontinue after an ischaemic stroke, but permanently discontinue after intracranial haemorrhage).
- The impact of intracranial haemorrhage (which has a 40% mortality risk and 60% disabling risk) in the major bleeding health state on quality of life was underestimated.

Model details

Clinical effectiveness

5.10 The company modelled the interventions using dosages described in the marketing authorisations (please see Table 3). The company used the following data sources to populate the model: Hokusai-VTE was used to estimate VTE recurrence (time dependent), bleeding, adverse events and

VTE related mortality for warfarin only; and heparin induced thrombocytopenia, stroke, probability of discontinuation after adverse event and mortality because of adverse event for all treatments. The network meta-analysis was used to estimate odds-ratios of edoxaban, dabigatran, and rivaroxaban compared with warfarin for VTE recurrence and bleeding. Published literature was used for risk of initial and long term chronic thromboembolic pulmonary hypertension, probability of death because of VTE recurrence, transition probabilities while off treatment, death because of heparin induced thrombocytopenia, and risk of post thrombotic syndrome.

Table 8: Modelled clinical effectiveness

Treatment	Days	Parameter	CI	Source
VTE recurrence				
Warfarin prob.	0-14	0.56%	0.331% - 0.785%	Hokusai trial
	15-98	1.083%	0.761% - 1.404%	
	99-364	0.447%	0.229% - 0.666%	
Edoxaban OR	All	[redacted]	(0.59-1.17)	Network meta-analysis HR applied to warfarin probability
Rivaroxaban OR	All	[redacted]	(0.6-1.1)	
Dabigatran OR	All	[redacted]	(0.75-1.58)	
Off treatment prob.	15-264	5.6%		Coleman (Markov model, rivaroxaban v placebo
	365 +	3.5%		
Clinically relevant non-major bleeding (CRNMB) incidence				
Warfarin prob	All	8.93%	8.06%-9.80%	Hokusai trial.
Edoxaban OR	All	[redacted]	0.66 - 0.93	Network meta-analysis HR applied to warfarin probability
Rivaroxaban OR	All	[redacted]	0.89 - 1.26	
Dabigatran OR	All	[redacted]	0.45 - 0.75	
Major bleeding (MB) incidence				
Warfarin prob	All	1.60%	1.22%-1.99%	Hokusai trial.
Edoxaban OR	All	[redacted]	0.62 - 1.37	Network meta-analysis HR applied to warfarin probability
Rivaroxaban OR	MB	[redacted]	0.37 - 0.83	
Dabigatran OR	MB	[redacted]	0.48 - 1.16	
Heparin-induced thrombocytopenia incidence				
All(rivaroxaban n/a)	0-14	0.02%	0.00%-0.07%	Hokusai trial
Stroke incidence				
All treatments	All	0.63%	0.39%-0.87%	Hokusai trial.
Chronic thromboembolic pulmonary hypertension (CTEPH) incidence				
All treatments	99 +	1.951%		Guérin (study of CTEPH incidence post PE).
Long term prob.	99+	33%		Expert opinion
Probabilities of discontinuation after heparin-induced thrombocytopenia (HIT)				
All	All	40%		Assumption
Probabilities discontinuation CRNMB				
Warfarin	All	5.2%	4.5%-5.8%	Hokusai trial
All other treatments		8.4%	7.5%-9.2%	Trial
Probabilities of discontinuation after MB				
Warfarin	All	38.8%	37.3%-40.3%	Hokusai trial
All other treatments	All	29.8%	28.4%-31.2%	
Probabilities of disease-related death (all treatments)				
VTE	0-365	0.58%	0.35%-0.81%	Hokusai trial
CRNMB	All	0%	NA	
MB	All	9.7%	8.8%-10.6%	
Stroke	All	3.85%	0.0%-0.09%	
HIT	All	1.7%		Joseph (bivalirudin for HIT)
VTE recurrence	All	13.7%		Carrier (systematic review, VTE recurrence)
Not disease related				Age/gender dependent UK life tables
Post-thrombotic syndrome				
All	0-364	2.7%		Prandoni (long term prospective f-up 528 DVT patients)
All	365+	5.4%		
Key: CI confidence interval; HR hazard ratio; OR odds ratio; f-up follow-up				

ERG comments

5.11 The ERG noted that the odds ratios derived from the 6-month meta-analysis for VTE recurrence used in the model had not shown any statistically significant differences between any treatment. To consider this, the ERG conducted a scenario analysis assuming there were no differences between the treatments in effectiveness for this outcome (that is, the odds ratios were set to '1'). The ERG also conducted an analysis setting the HR to '1' for bleeding. However, as a statistically significant difference for non-major bleeding between edoxaban and warfarin had been shown in the network, the ERG also conducted a scenario analysis where the odds ratio for major bleeding was set to '1' but non-major bleeding effectiveness was the same as in the base case.

5.12 The ERG noted that the company had implicitly assumed proportional hazards (Figure 2) for recurrent VTE. However, based on visual inspection (the ERG did not have the patient level data to confirm this statistically) of the Kaplan Meier curves showing actual VTE recurrence in the trial, proportional hazards had not been demonstrated. To further investigate the validity of the modelled edoxaban arm, the ERG compared the number of actual VTE recurrence events for edoxaban in the trial with the predicted number of events when using the network meta-analysis, and found there was an underestimation of recurrent events in the model. Overall the ERG concluded that assumptions about proportional hazards should have been validated and presented by the company, and the substantial discrepancy shown between the modelled and actual data (Figure 2 and Figure 3 below) cast doubt on the validity and the clinical plausibility of the modelled edoxaban arm. Further, the ERG stated they were unclear why the company had not extrapolated the trial data to estimate the recurrence of VTE.

Figure 2 VTE recurrence in the economic model (produced by the ERG)

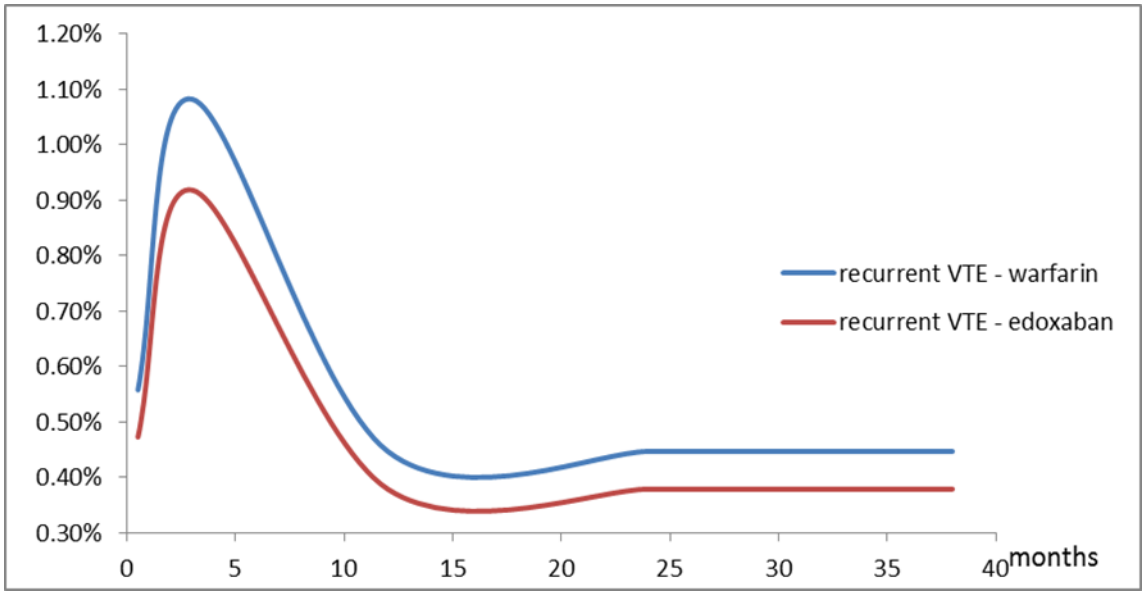
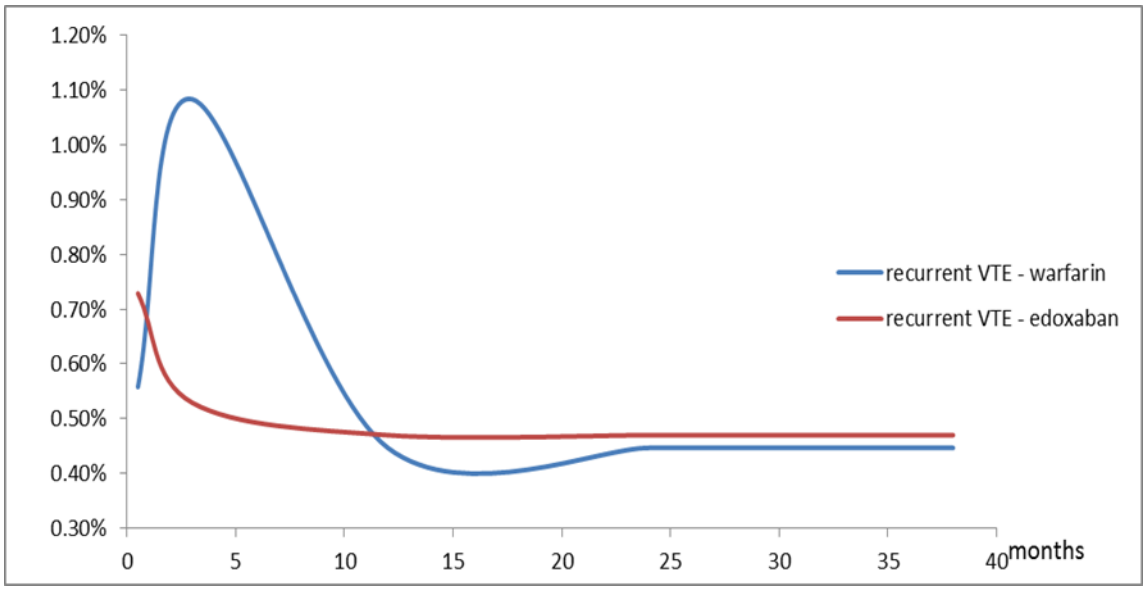


Figure 3 VTE recurrence in the Hokusai-VTE trial (produced by the ERG)



5.13 The ERG noted a discrepancy in the methodology used to model recurrent VTE and bleeding events. The effectiveness of VTE recurrence was modelled using phase specific data, however for bleeding events the company had used time to event data, despite having phase specific data available. The ERG stated this skewed the analysis and underestimated (substantially for non-major bleeding, less so for major bleeding) the number of bleeding events, because the phase specific data captured the first event in each treatment period (up to a maximum of 3 events were

captured, the first event in treatment periods day 1 to day 14, day 15 to day 98 and day 99 onwards), whereas the time to event data only captured the first event for the on treatment period. The ERG also noted that the company had assumed proportional hazards, which appeared to be valid based on visual data but should have been justified and presented by the company. Finally, the ERG compared the differences in the modelled data compared with both the time to event data and the phase specific data, noting under and overestimations of bleeding event data in the model (table 39 ERG report). Overall the ERG stated that phase-specific analysis data should have been used to obtain the warfarin baseline data as with VTE recurrence, and it presented a scenario analysis using these data.

5.14 The ERG noted the following issues but stated that they would not have a significant impact on the final ICER:

- The Hokusai VTE trial had captured chronic thromboembolic pulmonary hypertension (□ in the edoxaban arm over the 12 month follow up) and post-thrombotic syndrome (□ in the edoxaban arm and □ in the warfarin arm of the trial) but this information was not reported in the submission
- The model substantially overestimated chronic thromboembolic pulmonary hypertension events compared with trial data
- The modelled rate of post-thrombotic syndrome (2.7% in the first year and 5.4% thereafter) was underestimated. Clinical experts advised the ERG that post-thrombotic syndrome can affect up to 40% of patients and for moderate to severe can affect 25% to 40% of patients.

5.15 The ERG was generally satisfied with the data used to estimate the gender and age-related mortality in the model. However it raised several concerns with the disease-specific mortality in the model. For VTE, the ERG noted that VTE *recurrence* data from the trial was being used to model the *index* event mortality, and not recurrence. There also appeared to be an overestimation of VTE mortality in the trial; clinical experts

advised the ERG that, because 91% of VTE deaths in the trial were categorised as “unexplained deaths where VTE cannot be ruled out”, it was impossible to know whether these deaths were VTE related or not. Further, the company had used the modified intention to treat population for the overall study period (which included deaths when not on treatment) to model index VTE mortality, but had used the safety population for the on treatment period for all other mortality estimates derived from Hokusai VTE, which introduced inconsistency and potentially skewed the analysis. For the recurrent VTE mortality rate, clinical experts advised the ERG that the rate used (13.7%) was overestimated, with the rate in practice closer to 3%. The ERG concluded that the mortality estimates for both index and recurrent VTE were not appropriate, and conducted 2 scenario analyses, one using trial data and one using TA327 (dabigatran) estimates of 3% which was more consistent with expert opinion. For stroke, the ERG noted that the health state included both intracranial haemorrhage and ischaemic stroke, but the mortality was derived from ischaemic stroke only. Clinical experts advised the ERG that intracranial haemorrhage has a mortality of around 40%, therefore the modelled mortality rate for stroke (3.85%) was underestimated.

5.16 The ERG stated that it fundamentally disagreed with the methodology used to apply mortality in the first 12 months of the model. All patients had an increased risk of mortality (0.022%) for the 12 month period, which was applied additively to the risk of mortality in other health states. The ERG noted this was inconsistent with the way costs and benefits of index VTE and mortality risk for recurrent VTE had been estimated in the model (which could not affect patients for more than one consecutive cycle). Further, this approach led to a higher risk of death in the first 12 months in adverse event health states and a lower risk after this, even if a patient had experienced a recurrent event. Although the ERG stated this was unlikely to affect the final ICER, it stated that the index VTE mortality should be applied for 2 weeks only and should be the same value as the recurrent VTE estimate.

Utility values

5.17 The company conducted a systematic literature review to identify sources for utility values for people with VTE. Other than the VTE index event, it did not use the Hokusai trial data, because it stated the sample size was too small and therefore the utility values were not appropriate. The company identified 15 sources from the literature review, 2 of which were used to derive utility data for the model (Sullivan et al., 2011, and Locadia et al., 2004). Four further sources, not identified in the literature review, were also used to derive utility data for the model (Marchetti et al. 2007, Gould et al. 1999, Meads et al. 2008, and Lunde et al. 2013). The company did not describe how it identified these sources in the original submission, however following a request for clarification it stated that it had conducted additional targeted searches because their original searches were not targeted enough.

5.18 At entry in to the model, for the first cycle only, all patients began with a utility value of [redacted] to reflect the disutility of the initial VTE (derived from the Hokusai VTE trial, using the European population only). The company noted that this had no impact on the model as it was applied across treatment arms, but it was included for face validity. For all following cycles, all patients in all treatment arms were assigned age-dependent baseline utility values from the general population without illness. The company then applied a health state related utility decrement which was deducted from baseline utility value when patients experienced adverse events in the model. As health states heparin induced thrombocytopenia, VTE recurrence, bleeding, chronic thromboembolic pulmonary hypertension and stroke were tunnel states (see section 5.4), the disutility was applied temporarily for one cycle only, whereas post thrombotic syndrome, post stroke and long term chronic thromboembolic pulmonary hypertension were assumed to accrue the disutility for the lifetime of the model. A utility decrement (of 0.012) was also applied to all patients receiving treatment with warfarin, to capture disutility associated with warfarin treatment such as frequent INR monitoring. No treatment related

disutility was assumed for other treatments. VTE and heparin-induced thrombocytopenia were fixed value decrements, all other adverse events used percentage decrements. Table 9 shows the values used in the model. The utility decrements were applied for the duration of the event/for the associated cycle. The company made adjustments over time to modelled utility values to reflect increasing age, with most decrements taken from a population aged 55-64 years.

Table 9: Modelled quality-of-life values

State	Utility value	Disutility duration	Reference in submission	Justification	Source utility
VTE index event	[redacted]	1 cycle	**Hokusai-VTE sub-study** (European pop.): Used for face validity for all 1st cycles		[redacted]
Warfarin treatment	-0.0120	On treatment	**Marchetti**: Cost-utility study, LMWH vs OAC, captures warfarin disutilities e.g. INR monitoring, TTO. Used in TA327 dabigatran		
NOAC treatment	0.0		Assumed no treatment disutility		N/A
Recurrent VTE	-0.1253	1 cycle	**Sullivan**: HRQL RE-COVER trial		
HIT	-0.0712	1 cycle	**Gould**: cost-effectiveness study LMWH v UFH		0.00274
CRNMB	-19%	1 cycle	**Locadia**: observational study (n=124) HRQL and treatment preference for people with VTE, major bleeding, PTS. TTO utilities. Used in dabigatran & rivaroxaban appraisals for CRNMB and MB.		0.76
MB	-31%	1 cycle			0.65
PTS	-12%	Lifetime			0.82
Stroke	-59%	1 cycle			0.33
Post-stroke	-12%	Lifetime	**Lunde**: EQ5D 353 hospital stroke patients, Norway, TTO		0.70
CTEPH	-30%	1 cycle	**Meads:** Study of CAMPHOR Utility Index, 308 CTEPH patients, TTO.		0.56
LT CTEPH	-30%	Lifetime			0.56
Deaths	0				

CRNMB clinically relevant non-major bleed; CTEPH chronic thromboembolic pulmonary hypertension; HRQL health related quality of life; INR international normalised ratio; LT long term; LMWH low molecular weight heparin; NOAC new anticoagulant; MB major bleed; PTS post thrombotic syndrome; TTO time trade off; UCH unfractioned heparin

ERG comments

5.19 Overall the ERG stated it was reasonably satisfied with the estimation of quality of life in the model. Although it noted a number of methodological

issues (for example searches were limited to a VTE population, and therefore not sufficient to capture adverse effects of treatment), it stated that these issues were unlikely to have a large impact on the final ICER. To further consider issues identified with utility values, the ERG made adjustments and conducted scenario analyses as follows:

- Index and recurrent VTE:
  - Increased QALY loss duration to 1 month after recurrent VTE (because the base case was limited to a duration of 2 weeks which the ERG stated did not fully capture the disutility of recurrence)
  - Used alternative utility values from Cohen et al. 2014 (because the ERG was concerned about the accuracy of the values used in the base case: the company had used trial data despite noting it was inappropriate for use in cost effectiveness analyses; the company had modelled index VTE inconsistently as an absolute value rather than applying a decrement to population norms as with other values; also the values taken from Sullivan et al. appeared counterintuitive with PE utility higher than DVT)
- Warfarin treatment: removed the treatment associated decrement (the Committee for a previous VTE appraisal, TA327 [dabigatran] had agreed with the principle of a decrement, but was uncertain about the value of the decrement)
- Non-major bleeding: Removed the disutility for non-major bleeds (clinical experts advised the ERG that non-major bleeds would require medical attention but it would not affect quality of life)
- Major bleeding: doubled the disutility (to reflect a one month cycle, as clinical experts advised the ERG that this can affect quality of life of a month or more)
- Stroke: The ERG corrected the value which had not been adjusted for age by the company (this changed the decrement from 59% to 65%).

Resource use

5.20 The company used sources including the British National Formulary (drug costs) and NHS reference costs 2013-14 (hospitalisation costs) to populate costs in the model. It also conducted a systematic review of the literature for other costs such as the costs of stroke.

5.21 For all the treatments, the costs associated with the first cycle of treatment (that is, treatment for the initial VTE) were calculated independently of the costs of the following cycles. The first cycle included the costs associated with low molecular weight heparin (for warfarin, edoxaban and dabigatran). This cost was derived using an equally weighted (25% each) average cost of 4 technologies: dalteparin (£8.50), tinzaparin (£8.34), enoxaparin (£8) and unfractioned heparin (£7.60). This resulted in a daily heparin drug cost of £8.11. Additionally, costs of administration were included, as a weighted average of the following 2 administration costs: one-off self-administration training cost (£37) for 92% of patients, and daily cost of professional administration (£37) for 8% of patients for the duration of heparin treatment.

5.22 The company assumed the following for drug costs in the model:

- Warfarin: The company assumed that warfarin (daily cost £0.02) was co-administered with heparin for 8.5 days. This resulted in a first-cycle cost of £128.32 (to capture 8.5 days of heparin drug and administration costs, and £0.02 daily cost of warfarin for 14 days) and £0.23 (£0.02 daily warfarin cost for 14 days) for the following cycles. It was also assumed that people receiving warfarin required £24.95 costs of INR testing per cycle. This figure was derived using a weighted average cost of INR of £27 from NHS reference costs and frequency of monitoring of 0.9 per cycle from of monitoring from TA287 (rivaroxaban) which assumed 9 visits in first 3 months then 5 visits per quarter thereafter.
- Edoxaban: The company assumed that edoxaban treatment began after 5 days of treatment with low molecular weight heparin. The daily

cost of edoxaban was assumed to be £2.10. The cost of treatment associated with edoxaban during the first cycle was £108.27 (including heparin treatment and administration costs for 5 days and 14 days of edoxaban costs) and £29.40 for the following cycles.

- Rivaroxaban: Rivaroxaban has a twice-weekly initiation dose for the first 21 days (£4.20 per day), and after this the dosage is once daily (£2.10 per day). The company assumed twice-daily dosing in the first cycle and once daily thereafter because of the 2 week cycle structure. This assumption meant that the costs of week 3 dosing was too low and to account for this the company artificially increased the costs of the first cycle by the equivalent of 1 week of once daily dosing. The cost of rivaroxaban was therefore £73.50 during the first cycle, and £29.40 during subsequent cycles.
- Dabigatran: As with edoxaban, the company assumed a 5-day low molecular weight heparin lead-in. The daily cost of dabigatran was considered to be £2.20 resulting in a first-cycle cost of £109.14 and a following-cycle cost of £30.76.

5.23 The company presented costs which were accrued per health state. Hospital related costs were taken from NHS reference costs, using a weighted average in instances where there were multiple healthcare resource group (HRG) codes. As health states heparin-induced thrombocytopenia, VTE recurrence, bleeding, chronic thromboembolic pulmonary hypertension, and stroke were tunnel states (see section 5.4), patients could accrue costs for one cycle only in these health states.

- On treatment state
  - First cycle only (patients assumed to be hospitalised for 2 weeks):
    - Outpatient costs: Total diagnosis costs of £221.03, consisting of 100% patients accruing outpatient appointment or emergency admission cost (£65), and 50% of patients (based on rivaroxaban) accruing imaging and diagnosis costs for all of the following: doppler ultrasound (£49), CT angiography (£91),

electrocardiogram (ECG) (£118), chest X-ray (£106), echocardiogram, (£65), D-dimer (£13.06).

    - ◊ Inpatient costs: Diagnosis and treatment of VTE (£1071) based on diagnosis and treatment of DVT (£711.53) and PE (£1596), and assuming that 59.3% patients were DVT only.
    - ◊ Drug costs (see section 5.22)
  - Second cycle onwards
    - ◊ Drug costs (see section 5.22)
    - ◊ INR monitoring (warfarin only) £24.95 per cycle (see section 5.22)
    - ◊ Additional costs due to post-thrombotic syndrome: During the first year incidence of 2.7% of patients, where in cycles 2, 10 and 18 there were 3 appointments for vascular surgery, the first costing £161.76, and the following £135.50 each. During the following years, incidence of 5.4%, requiring 2 GP visits per year (£46 per visit). Frequency based on Goodacre et al. 2006 (a study of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis).
- VTE recurrence state:
  - As per index event first cycle.
- Off treatment state:
  - No costs are applied in the off-treatment state (however a proportion of patients are assumed to experience post-thrombotic syndrome, see above).
- Heparin-induced thrombocytopenia state:
  - Total cost per event: £617.61 (hospitalisation costs)
- CRNMB state:
  - Total cost per event: £149 (hospitalisation costs)
- MB state:
  - Total cost per event: £1136 (hospitalisation costs)
- Chronic thromboembolic pulmonary hypertension state:
  - Treatment costs including surgery and drug therapy, a total cost per event of £4394 based on:

    - ◊ 56.8% of patients (from Pepke-zaba et al., 2011, chronic thromboembolic pulmonary hypertension registry) with chronic thromboembolic pulmonary hypertension receive pulmonary endodartectomy (unit cost £7412.09)
    - ◊ 51.5% of patients receive drug therapy: either sildenafil (approximately 70% patients, £208 per cycle) or bosentan (approximately 30% of patients, £755 per cycle).
- Long term chronic thromboembolic pulmonary hypertension state:
  - Treatment costs per cycle: £184 based on:
    - ◊ 51.5% of patients receive drug therapy: either sildenafil (approximately 70% patients, £208 per cycle) or bosentan (approximately 30% of patients, £755 per cycle).
- Stroke state:
  - Total cost per event: £3182.41 (hospitalisation)
- Post-stroke state
  - Annual cost for stroke survivors was estimated to be £7485.54 (a cost per cycle of £288). Based on Lunego-Fernandez et al. 2013 (a study of the long term costs of stroke for people with atrial fibrillation)
- Death states: No costs are included in these states (disease-related death and other-cause mortality).

Table 10: Modelled health states and associated costs

Health state	Items	Cost (£)	Occurrence	Reference
On treatment (1st cycle only)	Costs of diagnosis including ECG	£13-118	50%	NHS ref costs & TA287 riva
	Outpatient admission	£65	100%	NHS ref costs
	Total Outpatient cost	**£221.03**	**Per event**	
	Hospitalisation DVT	£711.53	59% DVT	NHS ref costs
	Hospitalisation PE	£1596		NHS ref costs
	Total Inpatient costs	**£1071**	**Per event**	
	Drug costs			
	Warfarin/hep	£128.32	Per cycle	BNF
	Edoxaban/hep	£108.27	Per cycle	Daiichi Sankyo
	Dabigatran/hep	£109.14	Per cycle	BNF
	Rivaroxaban	£73.50	Per cycle	BNF
On treatment (>2nd cycle)	*Drug costs*			
	Warfarin	£0.23	Per cycle	Hokusai-VTE
	Edoxaban	£29.40	Per cycle	Daiichi Sankyo
	Dabigatran	£30.76	Per cycle	BNF
	Rivaroxaban	£29.40	Per cycle	BNF
	INR monitoring (warfarin)	£27	0.9 per cycle	NHS ref + TA287
	PTS costs (probability of PTS: 2.7% in first year and 5.4% thereafter)			
	1st Vascular surgery	£161.76	1 in 1st year	NHS ref costs + Goodacre
	F-up Vascular surgery	£135.50	2 in 1st year	
	Cost of one GP visit	£46	2 per year	
VTE recur.	**Total**	**£1292 (+drug)**	Per event	Index VTE 1st cycle
Off treatment	**Total**	**£0.00**		Assumption
HIT	**Total (hospitalisation)**	**£617.61**	Per event	NHS ref cost
CRNMB	**Total (hospitalisation)**	**£149**	Per event	NHS ref costs
MB	**Total (hospitalisation)**	**£1136**	Per event	NHS ref costs
CTEPH	Pulmonary endodartectomy	£7412.09	56.80% of patients	NHS ref costs + Pepke-Zaba
	Drug therapy (51.50% of patients, based on national audit)			
	Sildenafil	£208.00	69.40%	BNF
	Bosentan	£755.10	28.30%	BNF
	Total	**£4394**	**Per event**	
LT CTEPH	**Total (drug costs)**	**£184**	**Per cycle**	
Stroke	**Total (hospitalisation)**	**£3182.41**	**Per event**	NHS ref costs
Post stroke	**Total**	**£288**	**Per cycle**	Lunego-Fernandez
Death	**Total**	**£0.00**		Assumption

BNF British National Formulary; CRNMB clinically relevant non-major bleed; CTEPH chronic thromboembolic pulmonary hypertension; ECG electrocardiogram; HRQL health related quality of life; INR international normalised ratio; LT long term; LMWH low molecular weight heparin; NOAC new anticoagulant; MB major bleed; PTS post thrombotic syndrome;

ERG comments

5.24 The ERG noted that the company's searches for resource use data were limited to a VTE population, and therefore could possibly miss costs

associated with adverse effects of treatment including bleeding and heparin-induced thrombocytopenia.

5.25 For heparin, the ERG was not clear about the justification for the duration of heparin treatment and stated that the company should have modelled the treatment duration of heparin to reflect the Hokusai-VTE trial (7.5 days for edoxaban and 8.5 days for warfarin), or modelled the treatment duration with heparin according to NICE Clinical Guideline 144 (minimum of 5 days). The ERG modelled both options in scenario analyses and estimated the respective costs.

5.26 The ERG stated it was generally satisfied with the resource use and costs assumed for the administration of dabigatran and rivaroxaban. However it raised issues with the costs of edoxaban and warfarin. For edoxaban, the company had stated that the daily price of edoxaban was based on [redacted]. However, the company had not explicitly stated or costed the dosage for edoxaban. For warfarin, the company had only considered a dosage of 10mg daily, however clinical experts advised the ERG clinical that the dosage would be 5 mg daily, with a large variation from patient to patient and over time. Therefore the ERG weighted the estimated cost per mg using the quantity of warfarin items prescribed as reported in Prescription Cost Analysis data (PCA) 2014 for primary care in England (resulting in a cost of £0.04 per day); and presented an analysis for this.

5.27 The ERG considered monitoring costs, stating it appeared they were overestimated for warfarin and underestimated for NOACs. For warfarin, the ERG stated that in clinical practice most visits for international normalised ratio (INR) monitoring occur within the first 3 months, however the company had used an average number of visits per cycle in the model, which did not capture this. Clinical experts also advised the ERG that after 3 months the monitoring schedule would be closer to 3 visits per quarter, not 5; after 12 months it would be approximately 10 visits per year. Further, follow-up visits would likely be delivered by nurses. To

consider the impact of this the ERG conducted a scenario analysis to reduce the number of visits required in the first year (for the base case) to 3 visits per quarter after the initial 3 months, and 10 visits per year after the first year when assuming lifelong treatment, with follow-up visits based on non-consultant-led anticoagulation clinic attendance. For edoxaban, dabigatran and rivaroxaban, the ERG stated that in clinical practice there would be some monitoring costs expected beyond those considered standard monitoring for patients who have experienced VTE. Therefore the ERG conducted 3 scenario analyses to reflect different clinical opinions about NOAC monitoring: an average scenario (patients on NOACs receive an annual visit where they receive urea and electrolytes test); a conservative scenario (patients on NOACs have an annual appointment with their GP where they receive no tests) and; a less conservative scenario (patients receive biannual visits where they receive urea and electrolytes test).

5.28 The ERG considered the costs of hospitalisation and diagnosis. It noted several concerns with the company's calculation of costs associated with index and recurrent VTE. The company had assumed 100% of patients receive inpatient care, but clinical experts advised the ERG this was likely closer to 30% for DVT and 50% for PE, therefore the ERG conducted scenario analyses with these changes. The company had also assumed that 50% of patients would receive diagnostic tests, however clinical experts advised the ERG that all patients would require diagnostic tests, with different tests required depending on VTE type. This led to a cost of diagnosis of £143.23 per patient for DVT and £307.23 per patient for PE (see table 71 ERG report) and the ERG considered this in a scenario analysis.

5.29 The ERG discussed the costs associated with complications of VTE. For long term chronic thromboembolic pulmonary hypertension, the ERG stated the costs appeared to have been underestimated. The company had assumed that 50% of patients receive drug therapy, however clinical experts advised the ERG that this should be 100%. The ERG reviewed

previous appraisals (TA261, TA287 and TA327) for the ongoing costs of chronic thromboembolic pulmonary hypertension. The appraisals had used a cost of £1219 per month based on NICE CG92 (reducing the risk of VTE in patients in hospital) (2010 prices), which included the average cost of bosentan, sitaxentan and sildenafil. The ERG also believed the dose of bosentan for long term chronic thromboembolic pulmonary hypertension had been underestimated because the statement of product characteristics stated the dose should be doubled after week 4 (an increase in cost from £755 per cycle to £1,510). Finally, clinical experts advised the ERG that it would be inappropriate for patients not to receive anticoagulant treatment following chronic thromboembolic pulmonary hypertension because of the risk of further recurrence. Therefore the ERG conducted a scenario analysis in which the NICE CG92 estimate for long term chronic thromboembolic pulmonary hypertension was applied in the model (£1280 2014 prices).

5.30 For adverse effects of treatment, the ERG stated that overall the costs seemed reasonable.

Company's base-case results and sensitivity analysis

5.31 The company's base case results for edoxaban (based on a model updated with corrections advised by ERG in several areas including costs and utilities) were presented incrementally, and also as edoxaban compared with each comparator, and each comparator compared with warfarin. In the incremental analysis, edoxaban, and all other comparator treatments, were dominated by rivaroxaban (that is, all treatments were more expensive and less effective than rivaroxaban). Edoxaban had an ICER of £2451 per QALY gained (incremental costs £45.37, incremental QALYs 0.0185) compared with warfarin, and was dominant (that is, more effective and less costly) compared with dabigatran.

Table 11 Company base case, with corrections

Technology	Total cost	Total QALY	Inc. costs	% Inc. QALY	ICER vs warfarin	ICER (£) incremental
Rivaroxaban	£4,016	12.43	-	-	Dominant	-
Warfarin	£4,033	12.40	£16.88	-2.76%	-	Dominated
Edoxaban	£4,078	12.42	£45.37	1.85%	£2,451	Dominated
Dabigatran	£4,116	12.41	£38.32	-0.57%	£6,551	Dominated
Note: Incremental QALYs shown as % change. Incremental costs and QALYs are shown for incremental ICERs						

Company scenarios

One-way sensitivity analyses

5.32 The company conducted one way deterministic sensitivity analyses on the following:

- Using upper/lower 95% CI:
  - Transition probabilities for warfarin
  - Probabilities of complications while on warfarin or NOAC
  - Probability of death
  - Hazard ratio for VTE recurrence compared with warfarin
  - Utility values and utility decrement
- Costs with a variation of +/-20% (assumption)

5.33 Compared with warfarin, the company stated that most ICERs for edoxaban were similar to base case of £2451 per QALY gained. The ICER increased to around £22,500 per QALY gained when using high values of the probability of chronic thromboembolic pulmonary hypertension (between 3-12 months) or stroke with NOACs, and the low value of probability of stroke with warfarin. Compared with warfarin the low value of the probability of chronic thromboembolic pulmonary hypertension between 3 months and 12 months with warfarin increased the ICER to £10,377 per QALY gained. Compared with dabigatran the scenarios that had the largest impact on ICERs were the higher value of the odds ratio of VTE recurrence (for edoxaban compared with warfarin)

within 3 months (£180,870 per QALY gained) and the lower value of the same odds ratio of VTE recurrence (dabigatran compared with warfarin) (£45,755), although the company stated most scenarios had a limited impact on the ICERs. Compared with rivaroxaban, rivaroxaban dominated edoxaban in all scenarios. For all comparators, the company stated that the top variables with the largest effect on results included probabilities of stroke, probabilities and odds ratios for chronic thromboembolic pulmonary hypertension (3 months and 12 months), and odds ratios for major bleeding and VTE recurrence, with all other parameters having limited effect on the results.

ERG comments

5.34 The ERG stated it was concerned about the transparency, relevance and robustness of the one-way sensitivity analysis. It stated that the company had not justified their choice of parameters and had presented only the 8 most influential parameters. Further, the ERG stated the analysis was rendered largely irrelevant because the company included clinically implausible scenarios. For example the 3 inputs identified by the company as the key model drivers for edoxaban compared with warfarin (probability of stroke and chronic thromboembolic pulmonary hypertension with NOACs and probability of stroke with warfarin) were based on the assumption that the probability of these events might be different depending on the treatment received, which did not have face validity.

5.35 For utility values and decrements, the company had estimated 95% confidence intervals as the high and low values. However, the ERG stated that the company had not reported how they had obtained the standard deviations in the calculation. For costs, the company had varied overall health state costs by +/-20%. However, the ERG noted that this meant it was not possible to identify specific costs or resource use within each health state. Further, the ERG stated that the company should have explicitly varied the resource use associated with warfarin monitoring, as this was expected to be a key model parameter.

Scenario analysis

5.36 The company conducted one scenario analysis, using the odds ratio for VTE recurrence for edoxaban compared with warfarin from Hokusai VTE (rather than the network meta-analysis as in the base case). Compared with warfarin edoxaban had an ICER of £1948 per QALY gained (incremental costs £43.40, incremental QALYs 0.0222).

ERG comments

5.37 The ERG stated that the scenario using the odds ratios for edoxaban compared with warfarin from the Hokusai VTE trial was not informative because it raised the same concerns as those from the network meta-analysis about proportional hazards and non-statistically significant differences (see section 5.12).

Probabilistic sensitivity analyses

5.38 The company conducted probabilistic sensitivity analyses using 2000 simulations. Key parameters including event rates, costs, risks, utility values and population characteristics were varied simultaneously by sampling from various probability distributions. Compared with warfarin, edoxaban was dominant in 42% and dominated in 10% of simulations, and was more expensive and more costly in 46% of simulations. Compared with rivaroxaban, edoxaban was dominated in 86% of simulations and more costly and more effective in 14% of simulations. Compared with dabigatran, edoxaban was dominant in 69% of simulations and less effective and less costly in 31% of simulations. The probability of cost effectiveness when assuming a maximum acceptable ICER of £20,000 per QALY gained compared with warfarin, rivaroxaban and dabigatran was approximately 70%, 8% and 75% respectively.

ERG comments

5.39 The ERG was concerned with the validity of the probabilistic results. It noted that the company had assigned a non-parametric distribution to the odds ratios for NOAC treatment effectiveness (VTE recurrence and

bleeding events) therefore they were not included in the probabilistic sensitivity analysis. The ERG stated that the exclusion of key clinical parameter estimates calculated in the network meta-analysis considerably removed the usefulness of the probabilistic results.

5.40 The company considered only the overall costs associated with a health state (not the resource use and unit costs) therefore the ERG generated these probabilities from the model (see Table 84 p.227 ERG report for both the VTE population base case and the PE subgroup analysis). This showed that at a maximum acceptable ICER of £20,000 per QALY gained, edoxaban had approximately 70%, 10%, and 75% probability of being cost-effective when compared with warfarin, rivaroxaban and dabigatran respectively.

Subgroup analyses

5.41 The company conducted subgroup analyses for patients with an index PE (with or without DVT) and patients undergoing fixed durations of treatment (3 months, 6 months and lifelong). The company stated that it did not conduct analyses for patients with DVT only as there was not enough evidence in the network meta-analysis to allow for this. The results were as follows:

- Patients with an index PE (with or without DVT)
  - Rivaroxaban dominated all treatments in incremental analyses.
  - Edoxaban was dominant compared with warfarin and dabigatran
- Patients undergoing fixed durations of treatment (all patients):
  - For short-term treatment (3 months, 6 months), rivaroxaban was dominant compared with all treatments, and edoxaban dominated warfarin and dabigatran
  - For lifelong treatment, rivaroxaban dominated edoxaban and dabigatran. Compared with warfarin and dabigatran, edoxaban had ICERs of £7,608 and £312,568 per QALY gained respectively (note: the £312,500 ICER is based on a very slight reduction in both costs and QALYs for edoxaban compared with dabigatran).

- Patients undergoing fixed durations of treatment (PE subgroup):
  - Short term (3 months, 6 months), rivaroxaban dominated edoxaban, and edoxaban was dominant compared with dabigatran and warfarin
  - Lifelong – Edoxaban dominated warfarin, and had an ICER compared with rivaroxaban of £1996 per QALY gained. and £26,935.24 compared with dabigatran.

ERG comments

5.42 For the PE subgroup, the ERG identified and corrected 2 mistakes in the model (the company had used the odds for recurrent VTE from the network meta-analysis for the whole VTE population, not the PE subgroup, and had included some costs of hospitalisation for DVT).

5.43 For the analyses of different treatment durations, the ERG stated that these were of value because the duration of treatment depends on patients' individual risk factors, and whether the event was provoked or unprovoked. However, for the 3 month treatment scenario it stated that the frequency of INR monitoring was incorrect therefore it re-ran this scenario using 1.5 visits per cycle, where edoxaban remained dominant when compared with warfarin.

5.44 The ERG stated the results in the company base case seemed consistent across different treatment periods, apart from dabigatran, which changed from being dominated by edoxaban in 3, 6 and 12 month scenarios to an ICER of £312,569 per QALY gained for the lifetime treatment duration scenario. However, the ERG explained that this ICER should be interpreted with caution, because the ICER was caused by a decrease in incremental costs and a small loss of QALYs for edoxaban compared with dabigatran (0.003) and was close to a dominant ICER. The ERG also undertook additional analyses based on a DVT subgroup (please see ERG report section 6.2).

ERG exploratory analyses

5.45 The ERG corrected the following technical errors in the model: the stroke utility value reported within Locadia et al. 2004 was adjusted from 59% to 65%to reflect the age of the modelled patients (section 5.19), and the ERG corrected the utility decrement associated with heparin-induced thrombocytopenia which was adjusted twice instead of once for cycle duration. After these corrections were applied in the model, the base case ICERs remained the same for edoxaban compared with warfarin, dabigatran and rivaroxaban respectively. The ERG then provided the following scenario analyses based on this revised company base case:

- Changed the odds ratios comparing edoxaban with warfarin to ‘1’ for:
  - VTE recurrence
  - Major bleeding
- Used the company's phase-specific data instead of the time-to-event data used in base case to model the baseline probability of the following with warfarin:
  - Bleeding events
  - Recurrent VTE related mortality
- Used the recurrent VTE-related mortality estimate used in TA 327 (dabigatran, 3%)
- Increased the duration of the utility decrement to 1 month for MB and VTE recurrence
- Removed the disutility associated with CRNMBs
- Reduced the number of INR monitoring visits for warfarin patients from 24 visits in the first year to 18 visits
- Revised warfarin cost per day to £0.04
- Changed the treatment duration of heparin to:
  - reflect the Hokusai-VTE trial (7.5 days for edoxaban, 8.5 days for warfarin)
  - reflect clinical experts' advice (6.5 days for warfarin and 5 days for edoxaban)

- Assumed that 30% of recurrent DVT cases and 50% of recurrent PE cases require hospitalisation.
- Applied index and recurrent VTE diagnostic costs to 100% of patients, according to type of VTE event: (DVT £143.23; PE, £307.23).
- Applied the NICE CG92 estimate for long term chronic thromboembolic pulmonary hypertension cost (£1,280 at 2014 price-year), combined with anticoagulation treatment costs.
- Removed the utility decrement associated with warfarin from the economic analysis.
- Removed the stroke health state from the model.
- Varied NOAC monitoring using 3 different scenarios (section 5.27).
- Reduced the number of INR monitoring visits for warfarin from 24 visits in the subsequent years of treatment (for the company's scenario analysis of lifelong treatment) to 10 visits per year.

When compared with rivaroxaban, edoxaban was dominated in all scenarios. When compared with dabigatran, the key parameters were the odds ratio used to model the probability of recurrence for dabigatran compared with warfarin (£9678 per QALY gained) and the data used to model recurrent VTE related mortality (when using Hokusai-VTE phase-specific data the ICER was £15,111 per QALY gained and when using TA327 the ICER was £28,116 per QALY gained). When compared with warfarin the main parameters were INR monitoring (assuming 2 less visits per quarter in the final 3 quarters of the year, £18,953 per QALY gained in the scenario base case and £40,359 per QALY gained in lifelong duration scenario) and the level on NOAC monitoring assumed (£4,780 to £7,315 per QALY gained depending on the level assumed).

The ERG presented their consideration of an alternative base case ICER, based on warfarin based on warfarin only as their analyses used the Hokusai VTE trial. The ERG stated it ERG stated it considered this approach and the associated ICERs to be the most robust for the the most robust for the available evidence, because it was derived from direct comparisons in direct comparisons in a randomised controlled trial and because of the uncertainty in the company network meta-analysis.

5.46 Table 12 shows the ERG's alternative base case ICER which incorporates all the Hokusai-VTE trial estimates available in the model. The final ERG alternative base case ICER is £26,028, based on the following key assumptions:

- VTE recurrence and bleeding odds ratios from Hokusai-VTE;
- Phase-specific data used for bleeding events and VTE related mortality (not time-to-event);
- Increased the duration of the decrement in a quality of life after recurring VTE and MB;
- Removed the disutility associated with non-major bleeding;
- Reduced number of INR monitoring visits for warfarin from 24 visits in the first year to 18 visits, to reflect 3 instead of 5 visits per quarter (after the initial 9 visits in the first 3 months);
- Revised warfarin to reflect a cost for 5mg/day (£0.04);
- Heparin treatment duration changed to reflect the Hokusai-VTE trial (7.5 days for edoxaban and 8.5 days for warfarin);
- Assumed 30% of recurrent DVT and 50% of recurrent PE cases require hospitalisation;
- Index and recurrent VTE diagnostic costs applied to 100% of patients, according to the type of VTE event: DVT, £143.23; PE, £307.23;
- Used NICE CG92 estimate for the long term chronic thromboembolic pulmonary hypertension cost (£1,280 at 2014 price-year), combined with anticoagulation treatment costs;
- Removed the stroke health state from the model;
- Assumed that patients on NOACs have an annual appointment where they receive a U&E test.

Table 12 ERG's base case ICER (table 87 ERG report)

	Edoxaban	Warfarin	Incremental	Cumulative
Company's base case (with ORs from Hokusai-VTE)				
Total costs (£)	£4,076	£4,033	£43	
QALYs	12.42	12.4	0.022	
ICER			£1,958	£1958
Phase-specific trial data used to model baseline prob. warfarin bleeding				
Total costs (£)	£4,062	£4,016	£46	
QALYs	12.42	12.4	0.022	
ICER			£2,063	£2,063
Phase-specific trial data used to model recurrent VTE mortality				
Total costs (£)	£3,731	£3,697	£34	
QALYs	11.57	11.55	0.014	
ICER			£2,433	£2,551
QALY: Recurrent VTE (increased decrement duration); major bleed (from Sullivan)				
Total costs (£)	£4,076	£4,033	£43	
QALYs	12.44	12.42	0.022	
ICER			£1,972	£2,574
Disutility associated with clinically relevant non-major bleed removed				
Total costs (£)	£4,076	£4,033	£43	
QALYs	12.42	12.4	0.022	
ICER			£1,968	£2,593
International normalised ratio: Nurse-led, 9 visits in 1st 3 months, then 3 per quarter				
Total costs (£)	£4,076	£3,727	£349	
QALYs	12.42	12.4	0.022	
ICER			£15,739	£21,505
Revised 5mg/day warfarin cost using Prescription Cost Analysis 2014				
Total costs (£)	£4,076	£4,040	£36	
QALYs	12.42	12.4	0.022	
ICER			£1,632	£21,057
Heparin duration from Hokusai trial (7.5 days edoxaban, 8.5 warfarin)				
Total costs (£)	£4,111	£4,033	£78	
QALYs	12.42	12.4	0.022	
ICER			£3,522	£23,324
Hospitalisation Index/recurrent VTE: 30% DVT & 50% of PE				
Total costs (£)	£3,180	£3,135	£45	
QALYs	12.42	12.4	0.022	
ICER			£2,031	£23,352
Diagnostics Index/recurrent VTE: 100% (DVT, £143.23; PE, £307.23)				
Total costs (£)	£4,059	£4,015	£43	
QALYs	12.42	12.4	0.022	
ICER			£1,960	£23,352
NICE CG92 estimate for LT-CTEPH (£1,280 per month, 2014 prices)				
Total costs (£)	£4,528	£4,484	£44	
QALYs	12.42	12.4	0.022	
ICER			£1,997	£23,389
Stroke health state removed				
Total costs (£)	£3,282	£3,240	£42	
QALYs	12.43	12.41	0.02	
ICER			£1,869	£23,251
NOAC patients receive an annual visit where they receive U&E				
Total costs (£)	£4,141	£4,033	£88	
QALYs	12.42	12.4	0.022	
ICER			£3,990	**£26,028**
Key: CTEPH chronic thromboembolic pulmonary hypertension				

5.47 The ERG also presented different ICERs for when the NOAC monitoring regimen is varied in the model for the alternative base case. If patients visit their GP once a year without receiving any tests, the ICER is £25,910 per QALY gained. If the NOAC monitoring schedule consists of biannual visits with urea and electrolyte tests, the ICER increases to £28,805 per QALY gained. When assuming patients on NOACs do not need any extra monitoring beyond what would be expected for VTE patients, then the ICER is £23,251.Reducing the lead in time for heparin from 7.5 days to 5 days for edoxaban decreases the final ICER to £23,766.

5.48 The ERG also presented analyses incorporating all treatments by using the network meta-analysis assumptions, but also including some changes based on clinical expert opinion. The key assumptions underlying the alternative ICERs were:

- VTE recurrence and major bleeding odds ratio for edoxaban compared with warfarin changed to ‘1’;
- Phase-specific data used for bleeding events and VTE related mortality (not time-to-event);
- Recurrent VTE-related mortality estimate from TA 327 (3%);
- Increased the duration of the decrement in a quality of life after recurring VTE and MB;
- Removed the disutility associated with non-major bleeding;
- Reduced number of INR monitoring visits for warfarin from 24 visits in the first year to 18 visits, to reflect 3 instead of 5 visits per quarter (after the initial 9 visits in the first 3 months);
- Revised warfarin to reflect a cost for 5mg/day (£0.04);
- Heparin treatment duration changed to reflect clinical experts' advice (6.5 days for warfarin and 5 days for edoxaban);
- Assumed 30% of recurrent DVT and 50% of recurrent PE cases require hospitalisation;
- Index and recurrent VTE diagnostic costs applied to 100% of patients, according to the type of VTE event: DVT, £143.23; PE, £307.23;

- Used NICE CG92 estimate for the long term chronic thromboembolic pulmonary hypertension cost (£1,280 at 2014 price-year), combined with anticoagulation treatment costs;
- Removed the stroke health state from the model;
- Assumed that patients on NOACs have an annual appointment where they receive a U&E test.

When all changes were incorporated, the ICER was £35,899 per QALY gained compared with warfarin, dominant compared with dabigatran and dominated compared with rivaroxaban.

5.49 The ERG also presented an alternative base case ICER for different treatment durations (Table 89 ERG report), 3, 6, 12 months and lifetime, assuming 1 annual visit with U&E test done for NOACs. The ICERs increase with treatment duration, from £2221 per QALY gained at 3 months to £57,072 per QALY gained for lifelong treatment for edoxaban compared with warfarin.

Innovation

5.50 Justifications for considering edoxaban to be innovative:

- The company noted that, like the other new oral anticoagulants, edoxaban does not require any INR monitoring. It highlighted that edoxaban differed from the other NOACs in that can be taken with or without food (unlike rivaroxaban), that it is once-daily and stable outside its blister pack (unlike dabigatran). It also noted that its dose can be halved in specific patient groups at increased risk of edoxaban overexposure.

[redacted]

- The patient groups stated they considered edoxaban to be innovative. One patient group stated this was because edoxaban removes the need for frequent blood testing and dosage adjustment associated with warfarin, and self-injection associated with low molecular weight heparin. Another patient group stated that it offers similar benefits to existing treatments with the benefit of reducing fatal and intracranial bleeding, that treatment was extended past 6 months in the clinical trial which may be beneficial to patients requiring long term treatment, and that it increases clinician and patient choice by providing an alternative treatment to rivaroxaban and dabigatran.

6 Equality issues

6.1 No equalities issues have been identified.

7 Authors

Carl Prescott
Technical Lead

Joanna Richardson
Technical Adviser

with input from the Lead Team (Andrew England, Nerys Woolacott and David Thomson.

Appendix A: Clinical efficacy section of the draft European public assessment report

Not yet available.