NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Edoxaban is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

2 The technology

2.1 Edoxaban (Lixiana, Daiichi Sankyo) is an anticoagulant that directly inhibits factor X (factor Xa), which is a key component in the formation of blood clots. Edoxaban has a marketing authorisation for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. It is administered orally. The recommended dosage of edoxaban is 60 mg once daily, or 30 mg once daily in specific patient groups (people with renal impairment, low body weight [60 kg or less], or concomitant use of potent permeability glycoprotein [P glycoprotein] inhibitors), following treatment with a parenteral anticoagulant for at least 5 days.

2.2 The summary of product characteristics includes the following adverse reactions for edoxaban: bleeding, anaemia, nausea, rash, hepatobiliary disorders (increased blood bilirubin and gamma-glutamyl transferase) and

abnormal liver function test. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Edoxaban costs £2.10 per 15-mg, 30-mg or 60-mg tablet (excluding VAT) and the daily cost of treatment is £2.10. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Daiichi Sankyo and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

Overview of clinical trials

3.1 The company did a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of edoxaban for the treatment and secondary prevention of venous thromboembolism (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 that compared edoxaban against treatment with rivaroxaban, dabigatran etexilate, and warfarin. The company did not find any relevant non-randomised studies.

3.2 Hokusai-VTE was an international (37 countries including the UK) randomised, double-blind, non-inferiority trial. It compared initial treatment with heparin followed by edoxaban or warfarin for treating acute symptomatic VTE or preventing symptomatic recurrent VTE. Eligible adults were randomised in a 1:1 ratio with stratification by presenting diagnosis, temporary baseline risk factors (such as trauma, surgery or immobilisation) and the dose of edoxaban (which was reduced for patients with moderate renal impairment, those who were having concomitant treatment with potent permeability glycoprotein [P-glycoprotein] inhibitors,

or those who weighed 60 kg or less). A total of 8292 patients were randomly assigned to either the edoxaban group (n=4143) or the warfarin group (n=4149).

3.3 All patients had initial therapy with open-label heparin for at least 5 days. Edoxaban or warfarin was administered in a double-blind, double-dummy fashion:

- Patients in the edoxaban group had placebo warfarin during initial heparin therapy. After stopping heparin, they continued placebo warfarin (adjusted to maintain a sham international normalised ratio [INR] of 2.0 to 3.0) and started 60 mg of edoxaban once daily (or 30 mg once daily in patients who needed 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 to 3.0) and started placebo edoxaban.

Treatment with edoxaban or warfarin continued for at least 3 months and up to a maximum of 12 months, with treatment duration based on risk of recurrent VTE, risk of bleeding, and patient preference. The company noted that people who stayed in the trial for longer than 3 months were mostly those identified as being at higher risk of recurrence. In both groups, the median duration of treatment was about 260 days (8.5 months). Around 60% of patients had treatment for more than 6 months; 40% of patients continued treatment for 12 months.

3.4 Patient characteristics were similar between the treatment groups: mean age was 56 years, the majority of patients were male (57%) and patient ethnicity was reported as white (70%), Asian (21%), black (4%) or 'other' (5%). A total of 4921 patients presented with DVT only, and 3319 with PE (with or without DVT).

3.5 The primary efficacy outcome measure in the trial was the incidence of symptomatic recurrent VTE (a composite measure of recurrent DVT, new non-fatal symptomatic PE, and fatal PE) during the 12-month study period. Secondary outcomes included clinically relevant bleeding during treatment or within 3 days of interrupting or stopping the study drug (this was 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.

3.6 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 done in the modified intention to treat population (analyses based on randomised treatment, even if the patient did not receive this) for the overall study period, which included 4118 patients randomised to edoxaban and 4122 randomised to warfarin. Summary statistics were provided for the on-treatment period. The safety population (analyses based on treatment received) was used for outcomes related to safety; this population was identical to the modified intention to treat population, because all patients had the treatment to which they were randomised. The company did 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; n=1669 in the warfarin group), or DVT only (n=2468 in the edoxaban group; n=2453 in the warfarin group).

Clinical trial results

3.7 The company presented results for the primary efficacy outcome (symptomatic recurrent VTE) using a pre-specified 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). Edoxaban demonstrated statistically significant non-inferiority for the primary outcome when compared with warfarin (p<0.0001; Table 1). Similar results were obtained for the on-treatment period (HR,0.82; 95% CI, 0.60 to 1.14; p<0.0001 for non-inferiority).

Table 1 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

3.8 Some patients in Hokusai-VTE completed EuroQoL-5-Dimensions (EQ-5D) assessments and utility scores were determined for all patients using the UK time trade-off (TTO) value set, at baseline and then at 3-month intervals. 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.

Adverse effects of treatment

3.9 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. For the safety outcomes, results included:

- Bleeding (major or clinically relevant non-major bleeding, primary safety outcome): edoxaban was associated with fewer bleeding events (p=0.004 for superiority, see table 2). Major bleeding in critical sites

included 5 intracranial haemorrhage events (none of which were fatal) in the edoxaban group, and 18 (6 fatal) in the warfarin group. Major bleeding in non-critical sites included 27 gastrointestinal tract bleed events (1 fatal) in the edoxaban group and 18 (2 fatal) in the warfarin group.

- Mortality: the rate for VTE-related death, cardiovascular death and other known causes (cancer, bleeding, infectious disease or other) was 0.8% in both groups (no statistical analyses presented).

Table 2 Bleeding events (on-treatment study period)

	Edoxaban (n=4118)	Warfarin (n=4122)
Major and CRNM bleeding, n (%)	349 (8.5)	423 (10.3)
HR edoxaban versus warfarin (95% CI)	0.81 (0.705, 0.936)	
p value	0.004	
Major bleeding, n (%)	56 (1.4)	66 (1.6)
HR edoxaban versus 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 versus warfarin (95% CI)	0.80 (0.68–0.93)	
p value	0.004	
All bleeding, n (%)	895 (21.7)	1056 (25.6)

Key: CI, confidence interval; CRNMB, clinically relevant non-major; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; VTE, venous thromboembolism

Network meta-analysis

3.10 The company did a Bayesian network meta-analysis that compared edoxaban with warfarin, apixaban, dabigatran etexilate and rivaroxaban for the treatment and secondary prevention of VTE. The company stated that, to reduce heterogeneity between the trials, 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 were extracted). This led to the inclusion of

6 randomised controlled trials, all of which compared the treatment of interest with low-molecular-weight heparin plus warfarin.

3.11 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 in the company submission as odds ratios with 95% credible intervals [CrI] for ease of interpretation), using warfarin as the reference treatment. It did 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 of VTE recurrence at 6 months. The results demonstrated no large differences in treatment effects for the outcomes, and the odds ratios had wide credible intervals that approached or crossed '1' (that is, there was no difference in effect). Results for the PE subgroup were consistent with the main population.

3.12 The company did a qualitative assessment of the consistency of evidence generated by direct and indirect comparisons, and stated that the network meta-analysis results for each oral anticoagulant compared with warfarin were generally consistent with the direct evidence from the original trials.

3.13 The company did not quantitatively measure heterogeneity between the trials, because a low number of the trials had similar designs or comparators. Instead, it did a qualitative analysis of heterogeneity and found that there was variance across the trials in blinding, heparin lead-in

time, duration of treatment and the proportion of patients with extensive PE. The company concluded that there were substantial differences between the trial designs and the populations used for 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 did not include initial heparin therapy
- allowed the dosage of edoxaban to be reduced at any point, which was not allowed in other trials
- was the only trial to have a flexible treatment duration (so that later data included more high-risk patients who needed to remain on treatment for longer)
- did not allow for an extension, whereas patients in other trials were entered into extension studies
- was double-blind, whereas trials for rivaroxaban had open label designs.

Evidence Review Group's comments on the company's clinical effectiveness evidence

3.14 The Evidence Review Group (ERG) stated that the systematic review done by the company was reasonable, and that the identified trial (Hokusai-VTE) was well conducted and appropriately powered to demonstrate non-inferiority. However, the ERG stated that while the trial population was similar to trials for other newer anticoagulants, the generalisability of the trial to the UK population was uncertain because it included more people who were reported as 'Asian' and a younger population than would be expected in UK clinical practice. The treatment duration also suggested a higher-risk population (60% had treatment for longer than 6 months). The ERG noted that the design of Hokusai-VTE was different from other trials evaluating newer anticoagulants for this condition because patients could have their drug dosage altered at the

beginning of or during the trial. The ERG was unsure about whether the monitoring undertaken in the trial would be needed in clinical practice but it stated that, because the dose of edoxaban was related to variable patient factors, it should be expected that some periodic monitoring would be needed to check whether a patient's dose needed to be reduced.

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

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

3.16 The ERG noted 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.

3.17 The ERG considered the results of the trial, noting that recurrent VTE was more frequent for edoxaban in the first 30 days of the trial (21 events in the edoxaban group compared with 15 events in the warfarin group, in the DVT subgroup; and 9 events in the edoxaban group compared with 7 events in the warfarin group, in the PE subgroup). However, this difference was not statistically significant. Overall, the trial demonstrated statistically significant non-inferiority compared with warfarin for VTE recurrence. The company reported that edoxaban was statistically significantly superior (p=0.004) for the outcome of major and non-major bleeding. However, the ERG noted that this difference was driven by non-

major bleeding events (major bleeding events were not statistically significantly different for edoxaban compared with warfarin).

3.18 The ERG considered the approaches taken by the company 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 the patient's initial diagnosis (DVT or PE)
- the use of a fixed-effects model was reasonable because of the small number of studies included in the network and the lack of direct comparison of newer oral anticoagulants with any treatment other than warfarin
- the quality assessments of the trials included in the network were mostly adequate
- the indirect comparisons from the network meta-analysis were consistent with the direct evidence from the individual trials.

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

Cost effectiveness

3.20 The company identified 12 studies related to the comparators in the scope in its systematic review of cost-effectiveness analyses. The company found no studies evaluating the cost-effectiveness of edoxaban for treating and preventing VTE, and developed a new economic model.

3.21 The company developed a Markov model that compared edoxaban with warfarin, rivaroxaban and dabigatran etexilate for the treatment and secondary prevention of an acute VTE event. The model included 12 states representing treatment status (on-treatment or off-treatment health states), adverse events (post-thrombotic syndrome, heparin-induced thrombocytopenia, VTE recurrence, major bleeding, clinically relevant non-major bleeding, chronic-thromboembolic pulmonary hypertension, long-term chronic thromboembolic pulmonary hypertension, stroke, and post-stroke) and death. Each model cycle was 2-weeks long; the company stated that this cycle length was used to accurately model the effects of initial heparin for those treatments that needed it (edoxaban and dabigatran etexilate), and to more accurately model the costs and utilities associated with various adverse events represented in the model (which often occur within a short period of time 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 (0 to 2 weeks; 2 weeks to 3 months; 4 to 6 months; 7 to 12 months, and 12 months onwards); this allowed the use of different transition probabilities over time in order to capture the change in risk of having an event.

3.22 Patients entered the model in the ‘on treatment’ health state where they had initial anti-coagulation treatment. While having treatment, patients were at risk of having an adverse event and moving to the associated health state. In the adverse event health states of chronic-thromboembolic pulmonary hypertension and stroke, patients experienced the event and

accrued costs and utility values for 1 cycle only. After this, patients moved to post-chronic thromboembolic pulmonary hypertension and post-stroke health states. Patients could also only experience heparin-induced thrombocytopenia, VTE recurrence, and bleeding for 1 cycle. After this, most patients moved back to the on-treatment health state (that is, restarted their initial anticoagulation treatment), but a proportion of patients moved to the off-treatment health state. The off-treatment health state captured patients who had stopped anticoagulation treatment either as a result of an adverse event or because they had reached the end of a specific treatment duration (after 12 months in the base case). Patients could move to a death state at any point in the model.

3.23 Subgroup analyses varied the treatment length (from 12 months in the base case to 3 months, 6 months or lifelong [50 years]) or varied the initial VTE event (PE with or without DVT). The company did not include an analysis for people with active cancer, for whom warfarin would be unsuitable, because these patients were not included in studies of edoxaban.

3.24 The company modelled the interventions using the dosage described in the marketing authorisations. The company used the following sources to estimate data for the model: Hokusai-VTE (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 as a result of an adverse event, for all treatments); network meta-analysis (odds-ratios of edoxaban, dabigatran etexilate, and rivaroxaban compared with warfarin for VTE recurrence and bleeding); published literature (risk of initial and long-term chronic thromboembolic pulmonary hypertension, probability of death as a result of VTE recurrence, transition probabilities while off treatment, death as a result of heparin-induced thrombocytopenia, and risk of post-thrombotic syndrome).

3.25 The company conducted a systematic literature review (and further additional targeted searches) to identify sources for utility values for people with VTE. It identified 6 sources that were used to derive utility data for the model. Other than for the initial VTE event, it did not use the Hokusai-VTE trial quality-of-life data, because it stated that the sample size was too small and therefore the utility values were not reliable. At entry into the model, for the first cycle only, all patients had a utility value that reflected the disutility of the initial VTE (derived from Hokusai-VTE data, using the European population only). For all subsequent cycles, all patients in all treatment groups were assigned age-dependent baseline utility values from the general population without illness. When patients experienced adverse events in the model, the company applied a health-state-related utility decrement that was deducted from the baseline utility value. For the health states 'heparin-induced thrombocytopenia', 'VTE recurrence', 'bleeding', 'chronic-thromboembolic pulmonary hypertension' and 'stroke' disutility was applied for 1 cycle only; 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 was also applied to all patients having treatment with warfarin, to capture disutility associated with warfarin treatment such as frequent INR monitoring. No treatment-related disutility was assumed for other treatments. The company adjusted the modelled utility values over time to reflect increasing age, with most decrements taken from a population aged 55–64 years.

3.26 The company used drug costs from the British National Formulary (edition 68; 2014) and costs of hospitalisation from NHS reference costs 2013–14 in its model. It also conducted a systematic review of the literature for other costs such as those for treating stroke. For all 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 subsequent cycles; the first cycle included the drug and administration costs associated with low-molecular-weight heparin (for patients who had

warfarin, edoxaban and dabigatran etexilate). In the health states of heparin-induced thrombocytopenia, VTE recurrence, bleeding, chronic-thromboembolic pulmonary hypertension, and stroke, patients could accrue costs for 1 cycle only. For warfarin, the company included monitoring costs of £24.95 per cycle (a weighted average cost for INR testing of £27 from NHS reference costs, and a monitoring frequency of 0.9 per cycle from TA287 rivaroxaban, which assumed 9 visits in the first 3 months then 5 visits each quarter). No monitoring costs were assumed for any other treatment.

Company's base-case results and sensitivity analysis

3.27 The company's base case results for edoxaban (based on a model updated with corrections advised by the ERG, 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 incremental cost-effectiveness ratio (ICER) of £2451 per quality-adjusted life year (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 etexilate.

Company scenarios

One-way sensitivity analyses

3.28 The company conducted one way deterministic sensitivity analyses using upper/lower 95% confidence intervals for transition probabilities for warfarin, probabilities of complications while on warfarin or newer oral anticoagulant treatment, probability of death, hazard ratio for VTE recurrence compared with warfarin, and utility values and utility decrements. It also varied costs by plus or minus 20%. Compared with warfarin, the company stated that most ICERs for edoxaban were similar

to its base case of £2451 per QALY gained. The ICER increased to around £22,500 per QALY gained when it used high values for the probability of chronic thromboembolic pulmonary hypertension (between 3–12 months) or stroke with newer oral anticoagulants, and a low value for the probability of stroke with warfarin. When the company used the low value for the probability of chronic thromboembolic pulmonary hypertension between 3 months and 12 months with warfarin, the ICER for edoxaban increased to £10,377 per QALY gained. Compared with dabigatran etexilate, the scenarios that had the largest impact on ICERs were the higher value for 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 for dabigatran etexilate compared with warfarin (£45,755 per QALY gained). However, the company stated that most scenarios had a limited impact on the ICERs. Rivaroxaban dominated edoxaban in all scenarios.

Probabilistic sensitivity analyses

3.29 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% of simulations and dominated in 10% of simulations; it was more effective and more costly in 46% of simulations. Compared with rivaroxaban, edoxaban was dominated in 86% of simulations and more effective and more costly in 14% of simulations. Compared with dabigatran etexilate, edoxaban was dominant in 69% of simulations and less effective and less costly in 31% of simulations. The probability of edoxaban being cost effective at a maximum acceptable ICER of £20,000 per QALY gained compared with warfarin, rivaroxaban and dabigatran etexilate was approximately 70%, 8% and 75% respectively.

Evidence Review Group's comments on the company's cost-effectiveness model

3.30 The ERG noted several concerns about the model structure, but it stated that most of these issues did not have a substantial impact on the cost effectiveness estimates. The ERG's concerns included:

- If patients had a recurrent VTE, they returned to their original therapy. However, clinical experts advised the ERG that patients would switch to a higher dosage or change treatment because their original treatment had not prevented recurrence.
- If shorter cycles are used (in this instance a 2-week cycle was used) then the use of health states that have a fixed cycle duration needs to be carefully considered, because this may incorrectly estimate the impact of certain events on quality of life and costs. To overcome this, the company could have increased the length of the cycle, modelled the event without a fixed cycle duration, or used more post-event states (as it had done for chronic thromboembolic pulmonary hypertension).
- Patients were at risk of post-thrombotic syndrome when on- or off-treatment, but only at risk of chronic thromboembolic pulmonary hypertension and stroke when on treatment. However, clinical experts advised the ERG that these are all VTE-related complications. The ERG therefore stated that patients should be at risk of these outcomes at all times in the model.
- The inclusion of the stroke health state was methodologically flawed, so the ERG conducted a scenario analysis without this. Flaws noted were that:
  - the company had not included several 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 stopped (patients would temporarily stop after an ischaemic stroke, but permanently stop after intracerebral haemorrhage).
- In the major bleeding health state, the impact of intracerebral haemorrhage (which has a 40% mortality risk and a 60% disabling risk) on quality of life was underestimated.

3.31 The ERG considered the clinical-effectiveness estimates used in the model. It 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 treatments. To consider this, the ERG conducted a scenario analysis that assumed there were no differences between 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.

3.32 The ERG raised several concerns with the disease-specific mortality in the model. For example, the ERG noted that VTE recurrence data from the trial were used to model the initial event mortality, and not recurrence. For the recurrent-VTE mortality rate, clinical experts advised the ERG that the rate used (13.7%) was overestimated, with the rate in practice being closer to 3%. The ERG concluded that the mortality estimates for both initial and recurrent VTE were not appropriate, and conducted 2 scenario analyses; 1 using trial data, and 1 using NICE's technology appraisal guidance on dabigatran etexilate for treating and secondary prevention of DVT and/or PE estimate of 3% that was more consistent with expert opinion. For stroke, the ERG noted that the health state included both intracerebral haemorrhage and ischaemic stroke, but the mortality was derived from ischaemic stroke only. Clinical experts advised the ERG that intracerebral haemorrhage has a mortality of around 40%, therefore the modelled mortality rate for stroke (3.85%) was an underestimate.

3.33 The ERG made some revisions to the quality-of-life estimates used in the model (see section 3.38).

3.34 The ERG considered monitoring costs, stating that they appeared to be overestimated for warfarin and underestimated for the other oral anticoagulants. For warfarin, the ERG stated that in clinical practice most visits for international normalised ratio (INR) monitoring occur within the first 3 months, but 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. 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 needed 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 etexilate 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. The ERG conducted 3 scenario analyses to reflect different clinical opinions about monitoring of newer anticoagulants: a scenario in which patients have an annual visit where they have urea and electrolyte tests; a scenario in which patients have an annual appointment with their GP but they have no tests; and a scenario in which patients have an appointment twice a year where they have urea and electrolyte tests.

3.35 The ERG considered the one-way sensitivity analysis presented by the company, stating that it had concerns about its transparency, relevance and robustness. It stated that the company had not justified its choice of parameters and had presented only the 8 most influential parameters. The ERG stated that 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 with warfarin, and probability of stroke and chronic thromboembolic pulmonary hypertension with the other oral anticoagulants) were based on the assumption that the probability of these events might be different depending on the type of treatment, which did not have face validity. 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 it obtained the standard deviations in the calculation. For costs, the company had varied overall health state costs by plus or minus 20%. However, the ERG noted that this meant it was not possible to identify specific costs or resource use within each health state. The ERG stated that the company should have explicitly varied the resource use associated with warfarin monitoring, because this was expected to be a key model parameter.

3.36 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 newer anticoagulant 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 reduced the usefulness of the probabilistic results.

3.37 The ERG corrected technical errors in the company's model. After these corrections were applied the base case ICERs remained the same for edoxaban compared with warfarin, dabigatran etexilate and rivaroxaban. The ERG then provided scenario analyses based on this revised company base case. When compared with rivaroxaban, edoxaban was dominated in all scenarios. When compared with dabigatran etexilate, the key parameters were the odds ratio used to model the probability of VTE recurrence for dabigatran etexilate 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 NICE's technology appraisal guidance on dabigatran etexilate for treating and secondary prevention of DVT and/or PE 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, the ICERs were £18,953 per QALY gained in the scenario base case and £40,359 per QALY gained in lifelong duration scenario) and the level of newer oral anticoagulant monitoring assumed (£4,780 to £7,315 per QALY gained depending on the level assumed).

3.38 The ERG presented exploratory analyses that compared edoxaban with warfarin, using data from Hokusai-VTE rather than from the company's network meta-analysis. The ERG stated that it considered this approach and the associated ICERs to be the most robust because they were derived from direct comparisons in a randomised controlled trial. The ERG presented ICERs for each individual change to the model, and the cumulative effect of each change (Table 3), with a final ICER of £26,028 per QALY gained after all of the following changes were made:

- used VTE recurrence and bleeding odds ratios from Hokusai-VTE
- used phase-specific data for bleeding events and VTE-related mortality (not time-to-event data)
- increased the duration of the decrement in quality of life after recurring VTE and MB
- removed the disutility associated with non-major bleeding
- reduced the 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 the warfarin cost (£0.04)
- changed the duration of heparin treatment to reflect the Hokusai-VTE trial (7.5 days for edoxaban and 8.5 days for warfarin)

- assumed that 30% of recurrent DVT cases and 50% of recurrent PE cases need hospitalisation
- applied initial and recurrent VTE diagnostic costs to 100% of patients, according to the type of VTE event: DVT, £143.23; PE, £307.23
- used the estimate from NICE's guidance on venous thromboembolism for the long term chronic thromboembolic pulmonary hypertension cost (£1280 at 2014 prices), combined with anticoagulation treatment costs
- removed the stroke health state from the model
- assumed that patients having oral anticoagulants (except warfarin) have an annual appointment where they have urea and electrolyte tests.

Table 3 ERG's exploratory analyses

	Incremental	Cumulative
Company base case using trial ORs	£1958	£1958
Phase-specific data warfarin bleeding		
Costs	£46	
QALYs	0.022	
ICER	£2063	£2063
Phase-specific data recurrent VTE mortality		
Costs	£34	
QALYs	0.014	
ICER	£2433	£2551
Increased QALY decrement duration recurrent VTE + major bleed		
Costs	£43	
QALYs	0.022	
ICER	£1972	£2574
Removed disutility for clinically relevant non-major bleed		
Costs	£43	
QALYs	0.022	
ICER	£1968	£2593
Reduced warfarin monitoring (18 visits year 1)		
Costs	£349	
QALYs	0.022	
ICER	£15,739	£21,505
Warfarin costs £0.02 per day		
Costs	£36	
QALYs	0.022	
ICER	£1632	£21,057
Heparin duration 7.5 days edoxaban, 8.5 warfarin (Hokusai)		
Costs	£78	
QALYs	0.022	
ICER	£3522	£23,324
VTE hospitalisation: 30% DVT & 50% PE		
Costs	£45	
QALYs	0.022	
ICER	£2031	£23,352
VTE diagnostics: 100% (DVT, £143.23; PE, £307.23)		
Costs	£43	
QALYs	0.022	
ICER	£1960	£23,352
NICE CG92 estimate for long term CTEPH (£1,280 per month)		
Costs	£44	
QALYs	0.022	
ICER	£1997	£23,389
Stroke health state removed		
Costs	£42	
QALYs	0.02	
ICER	£1869	£23,251
Non-warfarin treatments: annual monitoring		
Costs	£88	
QALYs	0.022	
ICER	£3990	**£26,028**
Key: CTEPH chronic thromboembolic pulmonary hypertension, OR odds ratios		

3.39 Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of edoxaban, having considered evidence on the nature of venous thromboembolism (VTE) and the value placed on the benefits of edoxaban by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee considered the experience of people with VTE. It noted submissions from clinical and patient experts which stated that the impact of a deep vein thrombosis (DVT) or pulmonary embolism (PE) can be devastating, with patients often hospitalised, restricted in movement and unable to continue with previous activities. When recovering from VTE, patients may need further treatment and monitoring. It heard from the patient and clinical experts that the need for International Normalised Ratio (INR) checks when taking warfarin represents a major disadvantage, and the most important issue for patients is to have an effective treatment which minimises disruption to their day-to-day lives. The Committee was aware that various models of provision of INR monitoring are in use in England. It heard from the patient experts that some people taking warfarin monitor their own INR levels, but in some areas in the UK this was being made more difficult or phased out. The Committee heard that patients value newer oral anticoagulants such as edoxaban which do not need routine monitoring. In addition, the Committee noted that warfarin has many drug and food interactions which is not the case for the newer agents. The Committee heard from the patient and clinical experts that in the absence of regular monitoring, compliance with the newer anticoagulants would not be regularly checked, and good patient information was vital to help encourage compliance. However, they noted that this was not an issue for most patients, who were well aware of the importance of anticoagulation treatment. The Committee noted that edoxaban has a simple once-daily dosage, and

would usually only need 1 annual monitoring visit to check renal function. The Committee concluded that patients value newer oral anticoagulants such as edoxaban, which cause less disruption to their lives than warfarin.

4.2 The Committee considered the current treatment for people with VTE. It heard from the patient experts that there was variation in practice in the UK. Patients were sometimes not informed about the range of anticoagulants available, prescription of newer oral anticoagulants depended on local clinical leadership and policies, and prescribing rates for warfarin ranged from 0.6% to 56%. One expert stated that some clinicians consider it easier to reverse the effects of warfarin than the newer oral anticoagulants, and in some instances warned their patients about the lack of reversibility of newer agents. However, this concern was not necessarily justified because most of the newer anticoagulants can be reversed with prothrombin complex concentrates, and more specific reversing agents are awaiting marketing authorisation. The clinical and patient experts also stated that some hospitals restrict the choice of anticoagulants to minimise prescribing errors, and that rivaroxaban was currently the most widely used of the new oral anticoagulants. The clinical expert noted that there had been a recent drive to increase outpatient treatment for VTE and agents that do not need heparin to be given for a few days at the beginning of treatment would be preferable for the 30% to 40% of patients treated for VTE as an outpatient. However, the clinical expert noted that a large proportion of treatment for VTE is still started as an inpatient, when patients typically have parenteral heparin for several days. In this situation a drug such as edoxaban may be useful because of its simple dosing schedule. The Committee also heard from the clinical expert that having the option to use a lower dose of edoxaban was of value, and the availability of a range of anticoagulant agents was necessary because patients may be allergic to 1 or more agents. The Committee concluded that the choice of anticoagulant treatment would largely depend on the healthcare setting and local policies.

Clinical effectiveness

4.3 The Committee considered the Hokusai-VTE trial. It noted that it had an unconventional design in a number of ways; for example, patients could change dosage during the trial, there was a flexible treatment duration, and the primary efficacy outcome was measured at 12 months irrespective of the time when treatment stopped (which could have been as early as 3 months). The Committee noted that the trial therefore differed from VTE trials for other anticoagulants. The clinical expert agreed that it was unusual that the primary outcome was measured in patients who had potentially been untreated for up to 9 months (although the Committee noted that 60% of patients in the trial had treatment for at least 6 months). However, the company stated that this approach accurately reflected real-world clinical practice, and led to a more conservative estimate of efficacy, with which the clinical expert agreed. The Committee was aware that the design of the trial was not strictly comparable with other recent trials for newer anticoagulants, and that the value of assessing efficacy several months after some patients had stopped treatment was questionable. However, the trial did allow a choice of dosage, and did not predetermine the length of treatment at the start, both of which mirrored clinical practice. The Committee concluded that Hokusai-VTE was well designed and suitable for evaluating the clinical effectiveness of edoxaban.

4.4 The Committee considered the baseline characteristics of the patients in the trial. It noted the ERG's concerns about generalisability (section 3.14). However, it heard from the clinical and patient experts that they had no concerns about the generalisability of the trial, including the age of participants, with 1 expert explaining that people can experience VTE at any age. The Committee also noted that the patient population was comparable to that in other trials for newer anticoagulants. The Committee concluded that the results of the clinical trial were generalisable to people

with VTE in the NHS and were appropriate for decision making on the clinical effectiveness of edoxaban.

4.5 The Committee discussed the clinical efficacy results from Hokusai-VTE. It noted that the trial had shown a higher rate of VTE recurrence in the edoxaban group compared with warfarin in the first 30 days, but agreed that caution was needed in interpreting this difference because the numbers were small and the difference was not statistically significant. The Committee concluded that overall the trial had demonstrated that edoxaban was statistically non-inferior to warfarin for VTE recurrence.

4.6 The Committee considered the network meta-analysis presented by the company which compared edoxaban with warfarin, rivaroxaban and dabigatran etexilate. The Committee noted the wide credible intervals and the non-inferiority design of the trials in the network. It further noted that the unconventional design of Hokusai-VTE compared with the other trials in the network had led to heterogeneity. The Committee concluded that no clear differences between treatments for any outcome had been demonstrated, but that the comparative evidence was weak (because of the lack of direct evidence comparing the newer anticoagulants, and the issues noted with the network meta-analysis) and therefore the results needed to be interpreted with caution.

4.7 The Committee noted that a small number of people with cancer had been included in the trial but that no subgroup analysis results had been presented for these patients. The Committee heard from the clinical expert that the standard treatment for VTE in people with cancer is low-molecular-weight heparin. Hokusai-VTE did not include this as a comparator group, so there was no comparison of edoxaban with the current standard of care for these patients. The Committee concluded that the trial did not provide relevant data for people with cancer who experienced VTE, and it was unable to make any specific recommendation for this subgroup of patients.

4.8 The Committee discussed the adverse events associated with edoxaban. It noted that there were 18 primary intracranial haemorrhages in the warfarin group (of which 6 were fatal) and 5 in the edoxaban group, none of which were fatal (section 3.9). The Committee was aware that intracranial haemorrhage is considered to be the single most serious complication of anticoagulation treatment. It heard from the clinical expert that the reduced risk of intracranial haemorrhage is recognised as a benefit of newer oral anticoagulants in general and there is also the suggestion that, when intracranial haemorrhage does occur, the bleed may be less extensive than with warfarin. However, this benefit needs to be balanced against an increased risk of gastrointestinal bleeding as suggested in the trial; there were 9 more gastrointestinal bleeds in the edoxaban group than in the warfarin group (section 3.9). The Committee heard concerns from the ERG that although Hokusai-VTE demonstrated a statistically significant reduction in bleeding (major and clinically relevant non-major bleeding), the reduction for major bleeding alone was not statistically significant. The Committee concluded that there was no statistically significant difference for major bleeding for edoxaban compared with warfarin, but that a reduction in intracranial haemorrhage with edoxaban was a potential substantial benefit.

Cost effectiveness

4.9 The Committee considered the structure of the company's health economic model and the assumptions used. The ERG had raised a number of parameter and structural concerns about the model. The Committee generally agreed with these concerns, particularly:

- The assumption that some adverse events such as chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome were treatment-related rather than disease-related.
- The exclusion of treatment-switching after VTE recurrence (the Committee heard from the clinical expert that returning to a treatment that had failed to prevent recurrence was not clinically plausible).

- The inclusion of both ischaemic and haemorrhagic stroke within the stroke health state. Ischaemic stroke is not treatment-related whereas intracranial haemorrhage is; putting them together was an oversimplification and not clinically plausible. It also resulted in potential double-counting of intracranial haemorrhage because this was also included in the major bleeding health state.

Despite these and other concerns about the reliability of the model, the Committee heard from the ERG that flaws in the model, although important methodologically, did not have a substantial impact on the cost-effectiveness results, because they affected both arms equally, or because the probabilities of the associated adverse events were low. The Committee concluded that some of the assumptions in the model and model structure lacked clinical plausibility but, taking into account the ERG's comments and analyses, these flaws were not key drivers of cost-effectiveness.

4.10 The Committee considered the clinical-effectiveness estimates that had been used in the company's economic model, noting that the estimates were from a network meta-analysis which had limited capacity to demonstrate statistically significant differences between treatments. The Committee concluded that the efficacy data from the network meta-analysis contributed to uncertainty in the cost effectiveness results.

4.11 The Committee considered the warfarin monitoring-cost assumptions used in the company model. The Committee noted that the company had assumed an annual cost of warfarin monitoring of approximately £630. The Committee discussed whether this cost was reasonable. It heard from the ERG that according to their clinical experts the company had overestimated the costs of monitoring – the frequency was too high, and the monitoring would usually be done by a nurse rather than a consultant as assumed in the company base case. After reducing the frequency of visits and assuming monitoring would be nurse-led, the ERG had used a monitoring cost of £342 in the first year and £190 after that. The

Committee heard from the company that it had access to unpublished preliminary registry data suggesting that monitoring costs in clinical practice were substantially higher than the estimates used by the ERG. The Committee was aware that there is considerable variation in how warfarin monitoring is provided in the NHS, which would affect the costs, and that there is also individual variation (some patients have INR levels which are more unstable than others and need more frequent monitoring). The exact frequency and cost of warfarin monitoring is therefore unknown. The Committee referred to previous appraisals in its consideration of the very different estimates from the company and ERG. It noted that the cost assumed by the company was substantially higher than the range considered plausible in previous appraisals for VTE (£304 to £379). The Committee concluded that the company estimates were higher than had previously been accepted as plausible and the ERG estimates for the first year were closer to those previously accepted. However, the precise costs of warfarin monitoring remained uncertain.

4.12 The Committee considered the cost-effectiveness estimates generated by the company and ERG. It noted that the warfarin monitoring cost was the main driver of the cost-effectiveness estimates. The Committee agreed that the cost of monitoring in the first year in the ERG base case was more consistent with previous appraisals than the company's estimate. Therefore, it considered that the ICER relative to warfarin was likely to be closer to the ERG estimate of £26,000 per QALY gained than the company estimate of approximately £2500 per QALY gained. Nevertheless, it considered that both ICERs were subject to high levels of uncertainty because of the previously discussed flaws in the company model on which they were based, and the lack of definitive warfarin monitoring costs in the NHS. Noting these uncertainties, the Committee further considered the cost effectiveness of edoxaban compared with other anticoagulants that had been considered in previous appraisals for the treatment of VTE. The Committee accepted that the clinical effectiveness of edoxaban had been adequately demonstrated by the

clinical trial. It also noted that the price of edoxaban was similar to one of the other agents, rivaroxaban. Taking into account the lack of any clear trial evidence that edoxaban was substantially different from the other newer oral anticoagulants, and the testimony of the experts, the Committee concluded that the most plausible ICER was likely to be in line with that of the other oral anticoagulants already recommended in previous NICE guidance for the treatment of VTE. The Committee therefore concluded that edoxaban could be recommended as a cost-effective use of NHS resources.

4.13 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism, when appraising edoxaban. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of edoxaban. It therefore concluded that the PPRS Payment Mechanism was not relevant for its consideration of the cost effectiveness of edoxaban.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title:**	**Section**
Key conclusion		
Edoxaban is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults. Taking into account the similar price of edoxaban to rivaroxaban, the lack of any clear trial evidence that edoxaban was substantially		1.1 4.12

different from the other newer oral anticoagulants, and the testimony of the experts, the Committee concluded that the most plausible ICER was likely to be in line with that of the other oral anticoagulants already recommended in previous NICE guidance for the treatment of VTE. The Committee therefore concluded that edoxaban could be recommended as a cost-effective use of NHS resources.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee noted that the impact of a DVT or PE can be devastating, with patients often hospitalised, restricted in movement and unable to continue with previous activities. It heard from the patient and clinical experts that the need for International Normalised Ratio (INR) checks when taking warfarin represents a major disadvantage. The Committee noted that edoxaban has a simple once-daily dosage, and would usually only need 1 annual monitoring visit to check renal function. The Committee concluded that patients value newer oral anticoagulants such as edoxaban, which cause less disruption to their lives than warfarin.	4.1
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee noted that edoxaban has a simple once-daily dosage, and would usually only need 1 annual monitoring visit to check renal function.	4.1
What is the position of the treatment in the pathway of care for the condition?	The Committee heard from the clinical and patient experts that some hospital protocols limit the choice of anticoagulants to minimise prescribing errors. It heard from the clinical expert that agents that do not need heparin would be preferable for the 30% to 40% of patients treated for VTE as an outpatient. However, those treated for VTE as an inpatient typically have parenteral heparin for several days, and in this situation a drug such as edoxaban may be preferable, because of its simple dosing schedule. A range of anticoagulant agents is necessary because patients may be allergic to 1 or more agents. The Committee concluded that the choice of anticoagulant treatment would largely depend on the healthcare setting and local policies.	4.2

Adverse reactions	The Committee noted that there were fewer primary intracranial haemorrhages in the edoxaban group of the trial compared with the warfarin group. It heard from the clinical expert that this was recognised as a benefit of newer oral anticoagulants in general, but that this benefit needs to be balanced against an increased risk of gastrointestinal bleeding with the newer oral anticoagulants. The Committee concluded that there was no statistically significant difference for major bleeding for edoxaban compared with warfarin, but that a reduction in intracranial haemorrhage with edoxaban was a potential substantial benefit.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the Hokusai-VTE trial had an unconventional design; for example, the primary efficacy outcome was measured at 12 months irrespective of the time when treatment stopped. The Committee noted that the design of the trial was not strictly comparable with other recent trials for newer anticoagulants, and that the value of assessing efficacy several months after some patients had stopped treatment was questionable. However, the trial did allow a choice of dosage, and did not predetermine the length of treatment at the start of treatment, both of which mirrored clinical	4.3

	practice. The Committee concluded that Hokusai-VTE was well designed and suitable for decision making on the clinical effectiveness of edoxaban.	
Relevance to general clinical practice in the NHS	The Committee noted the ERG's concerns about the generalisability of Hokusai-VTE to the UK population. However, it heard from the clinical and patient experts that they had no concerns about the generalisability of the trial. The Committee also noted that the patient population was comparable to that in other trials for newer anticoagulants. The Committee concluded that the results of the trial were generalisable to people with VTE in the NHS and were appropriate for decision making on the clinical effectiveness of edoxaban.	3.14 4.4

Uncertainties generated by the evidence	The Committee noted the wide credible intervals and the non-inferiority design of the trials in the network meta-analysis. It further noted that the unconventional design of Hokusai-VTE had led to heterogeneity. The Committee concluded that no clear differences between treatments for any outcome had been demonstrated, but that the comparative evidence was weak (because of the lack of direct evidence comparing the newer anticoagulants, and the issues noted with the network meta-analysis) and therefore the results needed to be interpreted with caution.	4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that a small number of people with cancer had been included in the trial but that no subgroup analysis results had been presented for these patients. It heard from the clinical expert that the standard treatment for VTE in people with cancer is low-molecular-weight heparin. Hokusai-VTE did not include this as a comparator arm, so there was no comparison of edoxaban with the current standard of care for these patients. The Committee concluded that the trial did not provide relevant data for people with cancer who experienced VTE.	4.7

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that the trial was well designed, appropriately powered, and had demonstrated that edoxaban was statistically non-inferior to warfarin for VTE recurrence.	4.3 4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The company developed a new economic model that compared edoxaban with warfarin, rivaroxaban and dabigatran etexilate for the treatment and secondary prevention of an acute VTE event. The model included 12 states representing treatment status (on-treatment or off-treatment health states), adverse events, and death. The model had a lifetime time horizon (maximum 50 years) and each model cycle was 2-weeks long.	3.21 – 3.22
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the modelled clinical-effectiveness estimates were from a network meta-analysis which had limited capacity to demonstrate statistically significant differences between treatments. The Committee concluded that there was uncertainty about the cost-effectiveness results. The Committee noted and agreed with the parameter and structural concerns about the model noted by the ERG, particularly: the assumption that some adverse events were treatment-related rather than disease-related; the exclusion of treatment-switching after VTE	4.9 – 4.11

	recurrence; and the inclusion of both ischaemic and haemorrhagic stroke within the stroke health state. The Committee concluded that some of the assumptions in the model and the model structure lacked clinical plausibility but, taking into account the ERG comments and analyses, these flaws were not key drivers of cost-effectiveness. The Committee agreed that the cost-effectiveness results were largely driven by the estimates of warfarin monitoring costs, and noted that the costs of monitoring assumed by the company were substantially higher than the range considered plausible in previous appraisals for VTE (£304 to £379). The Committee concluded that the ERG estimates for the first year were closer to those previously accepted as plausible. However, the precise costs of warfarin monitoring remained uncertain.	

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	At entry into the model, for the first cycle only, all patients had a utility value that reflected the disutility of the initial VTE (derived from Hokusai-VTE data). For all subsequent cycles, all patients in all treatment groups were assigned age-dependent baseline utility values from the general population without illness. When patients experienced adverse events in the model, the company applied a health-state-related utility decrement that was deducted from the baseline utility value (derived from its systematic literature review).	3.25
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that the trial did not provide relevant data for people with cancer who experienced VTE, and it was unable to make any specific recommendation for this subgroup of patients.	4.7
What are the key drivers of cost effectiveness?	The Committee agreed that the cost-effectiveness results were largely driven by the estimates of warfarin monitoring costs.	4.9 4.12

Most likely cost-effectiveness estimate (given as an ICER)	The Committee agreed that the ICER was likely to be closer to the ERG estimate of £26,000 per QALY gained than the company estimate of approximately £2500 per QALY gained. Nevertheless, it considered that both ICERs were subject to high levels of uncertainty because of parameter and structural uncertainties in the model.	4.11 4.12
Additional factors taken into account		
Patient access schemes (PPRS)	N/A	
End-of-life considerations	N/A	
Equalities considerations and social value judgements	N/A	

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has deep vein thrombosis (DVT) or pulmonary embolism (PE) and the doctor responsible for their care thinks that edoxaban is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time the final appraisal determination goes out for appeal and will be removed when the final guidance is published. Further information is available on the NICE website.

- Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. NICE technology appraisal 341 (2015).

- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. NICE technology appraisal 327 (2015).
- The geko device for reducing the risk of venous thromboembolism. NICE medical technology guidance 19 (2014).
- Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. NICE technology appraisal 287 (2013).
- Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. NICE technology appraisal 261 (2012).
- Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. NICE clinical guideline 144 (2012).
- Venous thromboembolism: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline 92 (2010).

7 Review of guidance

7.1 The guidance on this technology will be considered for review 3 years after publication. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Jane Adam

Chair, Appraisal Committee

June 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant
General Practitioner, Swadlincote, Derbyshire

Dr Andrew England
Senior Lecturer, Directorate of Radiography, University of Salford

Dr Mohit Misra
General Practitioner, Queen Elizabeth Hospital, London

Ms Sarah Parry

Clinical Nurse Specialist - Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees

Lay Member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Mr Stephen Sharp

Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Carl Prescott

Technical Lead

Joanna Richardson

Technical Adviser

Bijal Joshi

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by BMJ Technology Assessment Group (BMJ–TAG):

- Edwards SJ, Crawford F, Wakefield V, et al. Edoxaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism: A Single Technology Appraisal. BMJ–TAG, April 2015.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on edoxaban by making a submission to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I. Company

- Daiichi Sankyo (edoxaban)

II. Professional/expert and patient/carer groups:

- AntiCoagulation Europe
- British Thoracic Society
- Clinical Leaders of Thrombosis
- Royal College of Nursing
- Royal College of Physicians
- Thrombosis UK
- United Kingdom Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Bayer (rivaroxaban)
- BMJ-TAG
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- LEO Pharma (tinzaparin)
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on edoxaban by providing oral evidence to the Committee.

- Dr Luke Howard, Consultant Respiratory Physician, nominated by organisation representing Daiichi Sankyo – clinical expert
- Mrs Diane Eaton, Project Development Manager for AntiCoagulation Europe, nominated by organisation representing AntiCoagulation Europe – patient expert
- Professor Beverley Hunt, Medical Director for Thrombosis UK, nominated by organisation representing Thrombosis UK – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Daiichi Sankyo (edoxaban)