

Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation

Technology appraisal guidance

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Your responsibility

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This guidance should be read in conjunction with NG196.

1 Recommendations

- 1.1 Edoxaban is recommended, within its marketing authorisation, as an option for preventing stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors, including:
- congestive heart failure
 - hypertension
 - diabetes
 - prior stroke or transient ischaemic attack
 - age 75 years or older.
- 1.2 Decide whether to start treatment with edoxaban after an informed discussion with the person about its risks and benefits compared with warfarin, apixaban, dabigatran etexilate and rivaroxaban. For people taking warfarin, consider the potential risks and benefits of switching to edoxaban taking into account their level of international normalised ratio (INR) control.

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. It is administered orally. Edoxaban has a marketing authorisation for the 'prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAf) with one or more risk factors, such as congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).' The summary of product characteristics states that the recommended dose is 60 mg once daily. The recommended dose is 30 mg once daily in people with one or more of the following clinical factors: moderate or severe renal impairment (creatinine clearance 15 to 50 ml/min); body weight of 60 kg or less; concomitant use of the P-glycoprotein inhibitors ciclosporin, dronedarone, erythromycin or ketoconazole.
- 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 £58.80 for a 28-tablet pack (60 mg or 30 mg) and the daily cost of treatment is £2.10 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The [Appraisal Committee](#) considered evidence submitted by Daiichi Sankyo and a review of this submission by the [Evidence Review Group](#) (ERG).

Clinical effectiveness

Overview of clinical trials

- 3.1 The primary source of evidence was ENGAGE AF-TIMI 48, a randomised, international (46 countries, including 31 centres in the UK) double-blind, double-dummy, parallel-group, non-inferiority trial comparing edoxaban with warfarin. It included a total of 21,105 people with non-valvular atrial fibrillation and a moderate-to-high risk of stroke, defined as a CHADS₂ score of 2 or more (CHADS₂ is a scoring system that measures risk factors associated with congestive heart failure, hypertension, age, diabetes and stroke). People were randomly assigned to treatment with low-dose edoxaban (30 mg, n=7,034), high-dose edoxaban (60 mg, n=7,035) or warfarin (n=7,036). People randomised to edoxaban who were at increased risk of bleeding because of higher drug exposure (those weighing 60 kg or less, with creatinine clearance 30 to 50 ml/min, or having concomitant treatment with potent permeability glycoprotein inhibitors) had the dose reduced, either at randomisation or during the study, to 15 mg in the low-dose group and to 30 mg in the high-dose group. The clinical trial results presented below focus on the higher dose treatment arm because this is the recommended dose in the marketing authorisation. This is referred to throughout as the 60 mg/30 mg treatment arm because it included people who were given 30 mg because of clinical factors. The dose in the warfarin group was adjusted to maintain an international normalised ratio [INR] of 2.0 to 3.0, and people in the trial were 'well controlled' on warfarin (median time spent in the therapeutic range [TTR] was 68.4%).
- 3.2 Patient characteristics were similar between the treatment groups including age, sex, ethnicity, risk factors, CHADS₂ score and renal function. The mean CHADS₂ score was 2.8 and approximately 53% of patients had a CHADS₂ score of 3 or more, indicating that the patient population was at a moderate-to-high risk of

stroke. The median age of people in the study was 72 years and 62% were male.

- 3.3 The primary efficacy outcome was time to the first stroke (ischaemic or haemorrhagic) or systemic embolic event. People in the trial continued treatment and were followed up until approximately 672 primary efficacy endpoint events had been collected, which provided 87% power for confirming non-inferiority for each edoxaban regimen. A non-inferiority test using the modified intent-to-treat (mITT) population for the on-treatment period was pre-specified in the statistical analysis plan. To satisfy non-inferiority, the upper boundary of the one-sided 97.5% confidence interval for the hazard ratio of the primary efficacy endpoint comparing edoxaban with warfarin could not exceed 1.38, which was an estimate that preserved at least 50% of the benefit of warfarin over placebo. If edoxaban was shown to be statistically significantly non-inferior to warfarin, a superiority test would be performed using the intent-to-treat (ITT) population and the overall study period.

Clinical trial results

- 3.4 For the primary efficacy outcome (prevention of stroke or systemic embolic event) in the mITT analysis set (on-treatment and overall study period), edoxaban 60 mg/30 mg met the criteria for non-inferiority compared with warfarin. Stroke or a systemic embolic event occurred in 182 people in the edoxaban 60 mg/30 mg arm of the trial (1.18% per year) compared with 232 people in the warfarin arm (1.50% per year, hazard ratio [HR] 0.79, 97.5% confidence interval [CI] 0.63 to 0.99, $p < 0.001$ for non-inferiority). In the pre-specified superiority analysis performed in the ITT analysis set (overall study period), the rate of stroke or systemic embolic event was 1.57% per year in the edoxaban 60 mg/30 mg arm compared with 1.80% in the warfarin arm (HR compared with warfarin 0.87; 97.5% CI 0.73 to 1.04, $p = 0.08$ for superiority). Results for the mITT overall study period were consistent with those in the ITT overall study period.
- 3.5 The company presented results for the analyses of the components of the primary endpoint (stroke and systemic embolism) and the subcomponents of stroke (ischaemic, haemorrhagic, fatal and disabling) for the mITT analysis set (on-treatment period, and overall study period) and the ITT analysis overall study period. For the mITT overall study period, edoxaban was shown to be superior to

warfarin for haemorrhagic stroke ($p=0.001$). The results were similar for the mITT population, the on-treatment period analysis and the ITT population analysis.

- 3.6 The company presented analyses for the primary efficacy results using the mITT analysis set (overall study period) for subgroups according to risk of stroke (defined by CHADS₂ score) and renal function (creatinine clearance). The subgroup analysis for risk of stroke demonstrated that, compared with warfarin, the hazard ratio for the edoxaban 60 mg/30 mg dose was stable and non-inferior across CHADS₂ scores of 2 to 6. The subgroup analysis for renal function across 3 categories of creatinine clearance (normal renal function 80 ml/min or more; mild renal impairment more than 50 to less than 80 ml/min; and moderate renal impairment 30 to 50 ml/min), suggested that renal function had a significant impact on the efficacy of edoxaban in comparison to warfarin ($p=0.0042$). This result was shown to be consistent across analysis sets. The hazard ratios for the primary efficacy endpoint were 0.68 (95% CI 0.54 to 0.85) and 0.86 (95% CI 0.63 to 1.17) for the subgroups of people with mild or moderate renal impairment, respectively. In contrast, the relative risk of stroke or systemic embolic event was higher with edoxaban than with warfarin in the subgroup of people with normal renal function (HR 1.31, 95% CI 0.96 to 1.79). The company noted that this analysis should be treated with caution because a variety of factors (including an unusually low event rate in the warfarin group, and potential imbalances between treatment groups because of randomisation not being performed within subgroups) could have contributed to the observed hazard ratio for stroke or systemic embolic event compared with warfarin in the subgroup of people with normal renal function.
- 3.7 The company also did an analysis comparing centre-level TTR above and below 60%. The p value for interaction was 0.0361 which indicated that in centres with a TTR above 60% edoxaban had a similar effect compared with warfarin to that observed in the total study population, but there was a significant reduction in risk of stroke and systemic embolism in the subgroup with a centre-level TTR of less than 60%. When the TTR data were examined by quartiles, however, the p value for interaction was 0.50.

Health-related quality of life

- 3.8 Health-related quality of life data were collected in ENGAGE AF-TIMI 48 using the self-administered EQ-5D questionnaire at baseline and then every 3 months, until the end of the study. Approximately 60% of patients (11,995 patients) provided quality-of-life data; 164 (1.4%) patients were from the UK.

ERG comments on the clinical effectiveness data

- 3.9 The ERG noted that the statistically significant result for non-inferiority in ENGAGE AF-TIMI 48 was driven largely by a reduction in haemorrhagic stroke events in patients treated with edoxaban, but there was no statistically significant difference between edoxaban and warfarin for any other listed component or subcomponent.
- 3.10 The ERG commented that the estimate of treatment effect (hazard ratio) for the primary outcome may not be reliable because the assumption of proportional hazards between treatment with edoxaban or warfarin for haemorrhagic stroke (one of the components of the primary outcome) appeared to be violated. The hazard trend in the warfarin group changed sharply at 6 months, in comparison with a smooth hazard trend over time in the edoxaban group.
- 3.11 The ERG noted that the results of the analysis for centre-level TTR suggested that the efficacy of edoxaban in comparison to warfarin is significantly greater in the subgroup of centres achieving TTR of less than 60%, but this was not consistent across all analysis sets. There was no significant difference in the results from centres with a TTR of less than or greater than 60% when the analysis was conducted using the mITT population and the on-treatment observation period. The ERG therefore suggested that the finding that centre-level TTR may affect the efficacy of edoxaban in comparison to warfarin may be spurious.
- 3.12 The ERG stated that the health-related quality of life data provided during the clarification process were difficult to interpret because of the low response rate and incomplete analysis. The ERG therefore suggested that it was difficult to draw any firm conclusions about any differences in patients' experiences that are

attributable to the choice of treatment.

Adverse effects of treatment

- 3.13 The company presented the results of the safety analyses, which included all people who had at least 1 dose of study drug for the on-treatment period in ENGAGE AF-TIMI 48. In the principal safety analysis for the edoxaban 60 mg/30 mg arm compared with warfarin, the company stated that edoxaban had a significantly reduced rate of major bleeding (HR 0.80, 95% CI 0.71 to 0.91; $p < 0.001$) and of several secondary bleeding endpoints including intracranial, fatal, clinically relevant non-major and life-threatening bleeds ($p \leq 0.01$ for all comparisons). However, the company highlighted that major gastrointestinal bleeding occurred slightly more frequently in the edoxaban 60 mg/30 mg arm than in the warfarin arm (annualised rate of 1.51% compared with 1.23%, respectively; HR 1.23 [1.02 to 1.50]; $p = 0.03$).
- 3.14 The company stated that the 5 most frequent treatment-emergent adverse events in the edoxaban or warfarin groups were urinary tract infections, nasopharyngitis, bronchitis, dizziness and peripheral oedema. The company presented subgroup analyses for the primary safety outcome by centre-level TTR and by risk of stroke (as defined by CHADS₂), which were consistent with the overall population.

Network meta-analysis

- 3.15 The company did not find any head-to-head studies that compared edoxaban with rivaroxaban, dabigatran etexilate or apixaban so it did a network meta-analysis to estimate the relative efficacy and safety of edoxaban for treating atrial fibrillation, that included 4 trials: ENGAGE AF-TIMI 48, and 3 trials of other newer oral anticoagulants (apixaban 5 mg twice-daily [ARISTOTLE]; dabigatran etexilate 150 mg twice-daily or 110 mg twice-daily [RE-LY]; and rivaroxaban 20 mg once-daily [ROCKET-AF]). All 4 RCTs had a warfarin treatment arm. Because of significant differences in the patient characteristics and trial design between the 4 trials (for example, ARISTOTLE and RE-LY included people with a CHADS₂ score of 1 or more, whereas the CHADS₂ score was 2 or more in

both ENGAGE AF-TIMI 48 and ROCKET-AF) only data from patients with a CHADS₂ score of 2 or more from RE-LY and ARISTOTLE were used in the network meta-analyses.

- 3.16 The results of the meta-analysis demonstrated that for the composite endpoint of stroke and systemic embolism, efficacy was similar for high-dose edoxaban compared to other newer oral anticoagulants, but edoxaban significantly reduced major bleeding risk by 24%, 28%, and 17% compared to rivaroxaban, dabigatran etexilate 150 mg and dabigatran etexilate 110 mg, respectively. Major bleeding rates were similar between high-dose edoxaban and apixaban.

Evidence Review Group's comments on the network meta-analysis

- 3.17 The ERG considered that the key characteristics of the trials (study population, design, outcome measures; and effect modifiers such as age, disease severity, and duration of follow-up) included in the network meta-analyses were sufficiently similar to justify combining the results. The company's approach used annualised event rates and the ERG considered that this approach minimised any potential bias resulting from differences in trial duration, which ranged from 1.8 years in ARISTOTLE (apixaban) to 2.8 years in ENGAGE AF-TIMI 48 (edoxaban).
- 3.18 The ERG noted that in addition to the violation of the proportional hazards assumption for some end points within ENGAGE AF-TIMI 48, it was also violated within trials of the other 3 newer oral anticoagulants, and in the warfarin groups of the 4 trials included in the evidence network. The ERG highlighted that this meant the hazard ratios from the network meta-analysis were not reliable and should not be used to inform the company's economic model.

Cost effectiveness

- 3.19 The company developed a Markov cohort model to compare edoxaban with warfarin, apixaban, rivaroxaban and dabigatran etexilate for preventing stroke

and systemic embolism in people with non-valvular atrial fibrillation with 1 or more risk factors, such as congestive heart failure, hypertension, age 75 years or more, diabetes, previous stroke or transient ischaemic attack, and a CHADS₂ score of at least 2 (the baseline characteristics of ENGAGE AF-TIMI 48). The model consisted of 18 health states (patients entering the model with 'stable AF'), with 1-month cycles and a 30-year (remaining lifetime) time horizon from a starting age of 71 years. 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%. A half-cycle correction was applied to both costs and QALYs (with the exception of drug costs). The model design was based on previous economic analyses that were submitted to NICE (for example, [apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation](#)).

- 3.20 The health states in the company's model were defined by the clinical events considered to have a permanent impact on patients and were assumed to have an initial, as well a long-term, impact on costs, quality of life and mortality. The health states captured the main thrombotic events and adverse events of treatment including haemorrhagic and ischaemic stroke (separated into mild, moderate and severe), systemic embolism and myocardial infarction. Health states were further subdivided into an initial health state (in which costs and quality of life associated with the acute event and the case fatality rate were applied in the month after the initial event), and a long-term health state in which ongoing event costs, quality of life and mortality were applied in each monthly cycle. Events that were considered to have no long-term impact in the model were other intracranial haemorrhage, non-intracranial haemorrhage major bleeds, clinically relevant non-major bleeds, and transient ischaemic attack. In the model, these events incurred costs and a disutility for the length of the event.
- 3.21 The monthly probability of each clinical outcome for edoxaban was estimated from annual event rates from ENGAGE AF-TIMI 48. The transition probabilities for the comparators were obtained by applying the hazard ratio from the network meta-analysis for the intervention to the baseline probability. When there were no available data for a clinical outcome, it was assumed that the hazard ratio was equivalent to the hazard ratio estimated in the 'all patients' analysis. If there were no available data in the 'all patients' analysis, the hazard ratio was assumed to be 1.

- 3.22 In the model, people could permanently stop or switch treatment after an ischaemic stroke or a haemorrhagic stroke. After stopping treatment and switching to a new therapy, the transition probability (of health state and event) did not change to reflect the new therapy. The company assumed that people could not stop or switch treatment for any other reason because there would be no difference between treatment groups.
- 3.23 The adverse events considered in the company's model were non-intracranial haemorrhage major bleed, clinically relevant non-major bleeds, other intracranial haemorrhage, and transient ischaemic attack (assumed to be transient on clinical advice).

ERG comments

- 3.24 The ERG considered that the assumption of proportionality that underpinned the network meta-analysis had been shown to be violated both within and between trials (see also sections 3.10 and 3.18). The ERG highlighted that this meant the hazard ratios used to inform the company's economic model were therefore unreliable.
- 3.25 The ERG highlighted that the model predicted that, of a cohort of 1000 people with non-valvular atrial fibrillation having warfarin, there will be 157 stroke events. Using the company's approach to applying the risk of acute-stroke mortality, approximately 15 (9.6%) of these would be fatal, which is substantially less than the 16.8% reported in the study by Janes. The ERG assessed the impact of applying the acute mortality rates reported by Janes to all patients experiencing a stroke (ischaemic stroke and haemorrhagic stroke analysed separately; see sections 3.40 and 3.41). The ERG noted that mortality data from ENGAGE AF-TIMI 48 were not used in the model and no rationale for this was given by the company. The ERG considered it more appropriate to use mortality data from ENGAGE AF-TIMI 48. Therefore, in its exploratory analyses, the ERG extracted acute mortality data for ischaemic stroke and haemorrhagic stroke from the clinical study report (CSR50, page 132) and pooled it across the warfarin and edoxaban groups of the trial (see sections 3.40 and 3.41).
- 3.26 The ERG highlighted that the model overestimated overall survival for both

treatment groups compared with ENGAGE AF-TIMI 48, and that this potentially underestimated the relative effectiveness of edoxaban compared to warfarin.

Utility values

- 3.27 The baseline quality of life for the health state of stable atrial fibrillation in the company's model (0.78) was taken from a study of patients with atrial fibrillation having warfarin in the UK (Khan, 2004). In the sensitivity analyses, health-related quality of life data from ENGAGE AF-TIMI 48 were used (0.836). Health-related quality of life declined over time based on an adjustment for cohort aging (-0.00029 per year) to reflect the impact of age and thrombotic events on a patient's quality of life. Utility estimates for mild, moderate and severe stroke were derived from a published study by Gage (1996). The company assumed that patients who have a stroke, myocardial infarction or systemic embolic event experience a permanent decrement to their health-related quality of life.

ERG comments

- 3.28 The ERG noted that the base case utility value for the stable atrial fibrillation health state had been derived from a UK study by Khan which had a modest sample size of 125 patients, with a low response rate, and was designed to assess the effectiveness of an anticoagulation education programme and self-monitoring of patients with atrial fibrillation taking warfarin. The ERG did not consider this to be representative of a general atrial fibrillation population and it preferred the use of EQ-5D data collected in ENGAGE AF-TIMI 48.
- 3.29 The ERG highlighted that the age-related utility decrement in the model (-0.00029 per annum) based on self-reported health status of a US population and valued using the UK tariff may not be generalisable to a UK population. The ERG preferred to use EQ-5D data from the Health Survey for England in its analysis, because this was a more representative population for the UK. This produced an estimated annual utility decrement of -0.00646.

Resource use

- 3.30 The company used the BNF 68 (July 2014) to obtain drug costs in the model. All costs for the health states of ischaemic stroke, haemorrhagic stroke and systemic embolic events were based on the Oxford Vascular study (OXVASC, 2013), a large study of healthcare costs after stroke in patients with atrial fibrillation. Costs associated with myocardial infarction were based on NHS reference costs. Post-myocardial infarction costs were based on the Electronic Drug Tariff and the BNF 68 (July 2014).
- 3.31 The monitoring costs for warfarin patients were adapted from the unit cost of anticoagulation monitoring used in the NHS Costing Template for dabigatran etexilate, which was also used in the apixaban technology appraisal. These costs were inflated to 2013 costs using the Personal Social Services Research Unit Hospital and Community Services Health Index (HCHS). The model assumed that 34% of patients will be seen in a secondary care setting (at a cost of £323.10) with the remaining 66% seen in primary care (£235.11) giving a weighted average annual cost of £265.03.

ERG comments on resource use

- 3.32 The ERG noted that although the cost of warfarin used in the company's model (£0.11 per day) was estimated using the list prices reported in the BNF, it is widely available to the NHS at discounted prices. The ERG did an exploratory analysis using the warfarin cost estimated from figures reported in the Department of Health's eMit database (£0.0375).

Company's base-case results and sensitivity analysis

- 3.33 In the company's deterministic base case analysis (based on people with CHADS₂ ≥2), edoxaban, dabigatran etexilate 110 mg, apixaban and rivaroxaban were strictly dominated (less effective and more costly) by dabigatran etexilate 150 mg, which had an incremental cost-effectiveness ratio (ICER) of £7,645 per additional QALY gained compared to warfarin (table 1).

Table 1 Company's incremental base case (deterministic results)

Technology	Total costs	Total QALYs*	Inc costs	Inc QALYs	ICER vs warfarin (QALYs)	ICER per QALY gained (£)
Warfarin	£13,413	6.32	–	–	–	–
Dabigatran etexilate 150 mg	£15,563	6.60	£2,150	0.28	£7,645	£7,645
Apixaban	£15,940	6.59	£377	-0.01	£9,383	Strictly dominated
Edoxaban	£15,957	6.52	£17	-0.07	£12,881	Strictly dominated
Dabigatran etexilate 110 mg	£16,074	6.51	£117	0.00	£13,565	Strictly dominated
Rivaroxaban	£16,744	6.44	£670	-0.08	£28,180	Strictly dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; QALYs, quality-adjusted life years.

- 3.34 The company presented cost-effectiveness acceptability curves for the incremental analysis, which showed that the probability of edoxaban being cost effective was 2.9% at a maximum acceptable ICER of £20,000 per QALY gained, and 3.4% at a threshold of £30,000 per QALY gained. Warfarin had the highest probability (36.8%) of being the most cost-effective option at a threshold of £20,000 per QALY gained. At a maximum acceptable ICER of £30,000 per QALY gained, apixaban had the highest probability of being the most cost-effective option (32.6%). In the pairwise comparison of edoxaban compared with warfarin, the probability of edoxaban being cost effective was 47.1% at a maximum acceptable ICER of £20,000 per QALY gained and 57.1% at a maximum acceptable ICER of £30,000 per QALY gained.
- 3.35 The company did 14 pairwise deterministic sensitivity analyses. It highlighted that the variables that had the most impact on the deterministic base case results were patients' starting age (lower limit 52.1 years, upper limit 89.1 years), cost of treatment, monitoring costs for patients treated with edoxaban (baseline £0, upper limit £26.50), and the utility values of stable atrial fibrillation, post-event myocardial infarction and haemorrhagic stroke.

3.36 The company presented results of subgroup analyses for people with a CHADS₂ score of 3 or more, or with a centre-level TTR of 60% or more. In people with a CHADS₂ score of 3 or more edoxaban, dabigatran etexilate 110 mg, and rivaroxaban were strictly dominated (less effective and more costly) by apixaban and dabigatran etexilate 150 mg. For the subgroup of people with a centre-level TTR of 60% or more, edoxaban, dabigatran etexilate 110 mg, apixaban and rivaroxaban were strictly dominated by dabigatran etexilate 150 mg, which had an ICER of £11,738 per additional QALY gained compared to warfarin.

ERG's comments on the company's cost-effectiveness model results

3.37 Results from the company's base case probabilistic analysis were not explicitly included in the submission. However, they were calculated by the ERG using the company's model (table 2). Edoxaban, dabigatran etexilate 110 mg and rivaroxaban were strictly dominated by dabigatran etexilate 150 mg and apixaban extendedly dominated dabigatran etexilate 150 mg (more effective and less costly) with an ICER of £13,036 per QALY gained compared to warfarin.

Table 2 ERG's calculation of the probabilistic base case results (extracted from the company's model)

	Costs	QALYs	Incremental Cost	Incremental QALY	ICER
Warfarin	£12,868	6.56	–	–	–
Rivaroxaban	£16,313	6.65	–	–	Dominated
Dabigatran etexilate 110 mg	£15,732	6.66	–	–	Dominated
Edoxaban	£15,451	6.72	–	–	Dominated
Dabigatran etexilate 150 mg	£15,293	6.75	£2,425	0.185	Extendedly dominated
Apixaban	£15,531	6.77	£2,662	0.204	£13,036

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; QALYs, quality-adjusted life years.

3.38 The ERG highlighted that in the company's probabilistic and deterministic

analyses edoxaban was dominated (less effective and more costly than at least one alternative treatment). However, in the deterministic analysis dabigatran etexilate 150 mg dominated (was less costly and more effective than) the other, newer, oral anticoagulants, whereas in the probabilistic analysis apixaban dominated dabigatran etexilate 150 mg. The ERG considered that this was because of the very small differences in QALYs between dabigatran etexilate 150 mg and apixaban in all analyses. In addition, the ERG noted that the results of the probabilistic analysis were not completely stable (repeated runs of the same analyses gave slightly different results).

- 3.39 The ERG considered that because the subgroup analyses for patients with a CHADS₂ of 3 or more and for centre-level TTR of 60% or more were based on very limited data, the extent to which these results were truly representative of effects in these subgroups is unclear.

ERG's exploratory analyses

- 3.40 The ERG noted that the economic model appeared to be robust to the sensitivity analyses carried out by the company. The ERG carried out 17 individual exploratory scenarios, which used its preferred alternative parameter values or formulae. The ERG also combined multiple parameters to give their preferred base case, which included:

- corrected implementation of age-related utility adjustment
- ERG-sourced utility values for systemic embolism
- alternative utility values for myocardial infarction, transient ischaemic attack and ERG-sourced utility values for acute and post-stroke health states
- assumption regarding the method used to switch patient medication from dabigatran 150 mg to 110 mg at age 80
- assumption regarding treatment discontinuation after haemorrhagic stroke
- acute stroke fatality rate applied to all stroke events (16.8% for ischaemic and 31.6% for haemorrhagic stroke)

- trial data on acute stroke case fatality rates used for all ischaemic and haemorrhagic strokes
- age-adjusted utility decrement per year amended to -0.00646 instead of -0.00029
- the daily cost of warfarin amended
- the ENGAGE trial HR applied for haemorrhagic stroke.

3.41 None of the ERG's amendments to the company's model changed the results of the full incremental analyses; edoxaban was more expensive and less effective than at least one of the alternative treatments. When all of the ERG's preferred values were used in the model the pairwise deterministic ICER for the comparison of edoxaban with warfarin was £16,008 per QALY gained, and the probabilistic ICER was £22,079 per QALY gained. When additional alternative amendments were included to reconcile the model survival outputs with the trial data, and to reflect the changing age and sex distribution over time, this changed the deterministic pairwise ICER to between approximately £15,176 and £15,807, and the probabilistic ICER to between £21,728 and £23,634 per QALY gained.

3.42 [See the committee papers for full details of the evidence.](#)

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 non-valvular atrial fibrillation 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 heard from clinical and patient experts that the current standard treatment for non-valvular atrial fibrillation is warfarin, although there is increasing use of newer agents. The Committee was aware that non-valvular atrial fibrillation is well-managed with warfarin for many people, but is associated with a number of problems including the need for regular monitoring and dose adjustment, and it has multiple food and drug interactions. The Committee heard from the patient and clinical experts that the number of people being prescribed anticoagulation treatment for atrial fibrillation is increasing following publication of the NICE guideline on managing atrial fibrillation. This does not recommend aspirin for the treatment of non-valvular atrial fibrillation, which has led to a higher uptake of both warfarin and the newer oral anticoagulants. The Committee concluded that both warfarin and the newer oral anticoagulants are relevant comparators for edoxaban. The Committee accepted the limitations of warfarin therapy and the considerable impact it may have on people who take it, and recognised the potential benefits of edoxaban for people with non-valvular atrial fibrillation.

Clinical effectiveness

- 4.2 The Committee considered the clinical-effectiveness data from ENGAGE AF-TIMI 48, that compared edoxaban with warfarin. It considered that this trial was of good quality and discussed whether the results were generalisable to people with atrial fibrillation in the UK. The Committee noted that ENGAGE AF-TIMI 48, like other trials of newer anticoagulants, used CHADS₂ to assess the risk of stroke rather than CHADS₂-VASc, which is now used in clinical practice, as recommended in the NICE guideline on managing atrial fibrillation. The

Committee understood from the clinical expert that the CHADS₂-VASc scoring system was developed to better define those who would benefit from anticoagulation because a number of people with a CHADS₂ score of 1 would still benefit. It also heard that although these people were not included in ENGAGE AF-TIMI 48, a lower baseline risk of stroke would not be expected to reduce the relative efficacy of the treatment. In clinical practice, edoxaban is expected to be offered in the same place in the treatment pathway as other anticoagulants (that is, to women with a CHADS₂-VASc score of 2 and above, and to men with a score of 1 or above), while taking bleeding risk into account. The Committee concluded that the trial was well designed and generalisable to clinical practice.

- 4.3 The Committee considered the results of ENGAGE AF-TIMI 48. It noted that the primary efficacy outcome was a composite of stroke (both ischaemic and haemorrhagic) and systemic embolism. However, ischaemic stroke and systemic embolism could be considered direct treatment effects, whereas haemorrhagic stroke was a bleeding outcome and therefore an adverse event. The Committee noted that for the composite primary outcome, edoxaban was non-inferior to, but not superior to, well-controlled warfarin (which was defined in the trial as a median time in therapeutic range [TTR] of 68.4%). The Committee noted that when the individual components of the primary outcome were considered separately, there was only a statistically significant reduction in haemorrhagic stroke with edoxaban compared with warfarin. The Committee concluded that edoxaban was as clinically effective as warfarin for the primary efficacy outcome of reducing stroke (ischaemic and haemorrhagic) and systemic embolism, and had nearly half the rate of haemorrhagic stroke events compared to warfarin.
- 4.4 The Committee considered the results of the company's subgroup analyses, which used data from ENGAGE AF-TIMI 48. It noted that the company presented data for subgroups based on international normalised ratio (INR) control, that compared the efficacy of edoxaban and warfarin in relation to the median TTR for the study centre. One of the analyses showed that the relative benefits of edoxaban compared with warfarin were greater in centres where the centre-level TTR was less than 60%. The Committee noted comments from the company and the Evidence Review Group (ERG) that this was not consistent across all analysis sets. The Committee concluded that there was insufficient evidence to consider different treatment effects according to centre-level TTR.

- 4.5 The Committee noted that the company's subgroup analyses for risk of stroke (as defined by CHADS₂ score) showed that the hazard ratio for edoxaban compared with warfarin was stable and non-inferior across CHADS₂ scores of 2 to 6. The Committee concluded that there was no biologically plausible reason to indicate that the relative treatment effect would be dependent on the baseline risk of stroke.
- 4.6 The Committee discussed the subgroup analysis based on renal function, which used 3 categories of creatinine clearance (normal renal function, and mild or moderate impairment). It noted that the results of this analysis suggested a trend towards decreasing efficacy of edoxaban with increasing creatinine clearance (see [section 3.6](#)). The Committee heard from a clinical expert that this was likely to be because with better renal function edoxaban is removed by the kidneys more quickly, leading to a reduction in treatment effect. It also heard that this may apply to all newer oral anticoagulants, but data need to be re-evaluated to confirm this. It heard from the clinical experts that the proportion of people with good renal function (measured by creatinine clearance) who would be eligible for treatment with edoxaban was in the region of 5% to 10%, and that these are often younger people. The Committee noted the company's rationale that the results of this sub-group analysis should be interpreted with caution (see [section 3.6](#)). It also noted the summary of product characteristics which states that, in people with non-valvular atrial fibrillation and high creatinine clearance, edoxaban should only be used after careful evaluation of a person's thromboembolic and bleeding risk. The Committee concluded that if edoxaban is used in accordance with the summary of product characteristics, there is no reason to make differential recommendations based on creatinine clearance.
- 4.7 The Committee considered the adverse events reported in ENGAGE AF-TIMI 48. It noted that for the primary safety outcome of major bleeding, edoxaban resulted in statistically significantly fewer bleeds than warfarin. Edoxaban also had statistically significantly fewer other bleeding events including fatal, intracranial and clinically relevant non-major bleeds. The Committee recognised the particular importance of the reduction in intracranial bleeding compared with warfarin. It also noted the statistically significantly higher numbers of gastrointestinal bleeds in people treated with edoxaban compared with warfarin. The Committee was aware that this is not unique to edoxaban, and that clinicians are now more experienced in using the newer oral anticoagulants and in

managing the adverse events. It also heard from the clinical experts that administration of 4-factor prothrombin complex concentrate has been shown to reverse the effects of edoxaban. The Committee concluded that the risk–benefit profile of edoxaban was acceptable.

- 4.8 The Committee discussed the data for edoxaban compared with rivaroxaban, apixaban, dabigatran etexilate (110 mg twice daily and 150 mg twice daily) and rivaroxaban, that were used in the company's network meta-analysis. The Committee noted that the trials included in the network meta-analysis were not directly comparable; for example, they had different baseline risks of stroke (with different CHADS₂ inclusion criteria and mean CHADS₂ scores) and differences in time in the therapeutic range in the warfarin groups. The Committee also noted the ERG's concerns about the violation of the proportional hazards assumption in data from ENGAGE AF-TIMI 48, from the trials of the other 3 newer oral anticoagulants, and in the warfarin groups of the 4 trials included in the network meta-analysis. It understood from the ERG that this meant that the hazard ratios produced by the network meta-analysis were not sufficiently robust to compare the relative clinical effectiveness of the newer oral anticoagulants. The Committee considered the results of the network meta-analysis in the light of the methodological issues and noted that all the newer oral anticoagulants appeared to have comparable efficacy for the composite primary and bleeding outcomes. The Committee concluded that the network meta-analysis results should be interpreted with caution, but edoxaban is unlikely to be different from rivaroxaban, apixaban and dabigatran etexilate in clinical practice.

Cost effectiveness

- 4.9 The Committee considered the company's economic model. It noted that the economic analysis was largely based on the model used in [NICE's technology appraisal guidance on apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation](#), which captured the main efficacy and adverse events of treatment. The Committee agreed that the model structure, perspective and time horizon were appropriate, although it questioned the relevance of the inclusion of myocardial infarction. It concluded that the analysis was consistent with the NICE reference case.

- 4.10 The Committee considered the clinical-effectiveness estimates used in the company's model. It noted that the comparison of edoxaban with warfarin used direct evidence from ENGAGE AF-TIMI 48 to inform the company's economic model. The Committee was aware of the ERG's concern that the assumption of proportional hazards for edoxaban and warfarin for haemorrhagic stroke (one of the components of the primary outcome) appeared to be violated in ENGAGE AF-TIMI 48. However, the Committee considered that the general modelling approach and the pairwise comparison with warfarin were appropriate. The Committee noted that for the comparison of edoxaban with the other newer oral anticoagulants, hazard ratios obtained from the network meta-analysis were used in the economic model and that these estimates were considered unreliable by the ERG (see section 4.8). The Committee concluded that data from ENGAGE AF-TIMI 48 were appropriate for calculating the cost effectiveness of edoxaban compared with warfarin, but the estimates of the cost effectiveness of edoxaban compared with dabigatran etexilate, apixaban and rivaroxaban were based on data that were associated with a high degree of uncertainty.
- 4.11 The Committee heard from the ERG that there were differences in the utility values used in the economic model, compared with other NICE technology appraisals for atrial fibrillation (apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation; rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation; dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation). It noted that even though EQ-5D data were collected at baseline in ENGAGE AF-TIMI 48, the baseline utility value for stable atrial fibrillation used in the model was from another small UK study. The Committee noted that the ERG had identified a number of inconsistencies and had raised concerns about some of the sources of data used in the company model. However, the Committee noted that when the ERG's suggested revisions (alternative utility estimates for systemic embolism, myocardial infarction, and transient ischaemic attack) were applied, together with an amended age-adjusted utility decrement per year of -0.00646 instead of -0.00029 (see sections 3.40 and 3.41), they had only a minor impact on the incremental cost-effectiveness ratio (ICER). The Committee concluded that the utility values used in the model, although open to debate, were not key drivers of the cost effectiveness.
- 4.12 The Committee considered the costs used in the company's model. It noted that

costs for ischaemic stroke, haemorrhagic stroke, and systemic embolism were based on the Oxford Vascular Study (a cohort study of a UK population) and the costs were similar to those used in other NICE technology appraisals for atrial fibrillation ([apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation](#); [rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation](#); [dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation](#)). The Committee also noted that an INR monitoring cost of £265 was used by the company, and that this fell within a range previously accepted in NICE technology appraisals. The Committee concluded that the costs used in the model were appropriate.

- 4.13 The Committee considered the cost effectiveness of edoxaban compared with warfarin. It noted that the company's base-case deterministic and probabilistic ICERs for edoxaban compared with warfarin were £12,900 and £16,900 per QALY gained respectively. The Committee noted that the ERG considered the economic model to be robust to all of the company's sensitivity analyses, and to most of those done by the ERG. The Committee further considered the ERG's exploratory analyses. It noted that the change which had the largest single impact on the ICER was applying the hazard ratio from ENGAGE AF-TIMI 48 for haemorrhagic stroke (which increased the ICER to £17,100 per QALY gained). The Committee noted that the inclusion of all the ERG's preferred values in the model (see [sections 3.40 and 3.41](#)) resulted in a deterministic ICER of £16,000 per QALY gained and a probabilistic ICER of £22,100 per QALY gained. The Committee concluded that taking all of the analyses into account, edoxaban was cost effective compared with warfarin and could be recommended as an alternative to warfarin for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation who have 1 or more risk factors for stroke.
- 4.14 The Committee noted that the cost effectiveness of edoxaban compared with other newer oral anticoagulants was calculated using hazard ratios from the network meta-analysis, which the Committee considered to lack robustness (see [section 4.8](#)). In the full incremental analysis edoxaban, dabigatran etexilate 110 mg, apixaban and rivaroxaban were strictly dominated by dabigatran etexilate 150 mg, which had an ICER of £7,645 per additional QALY gained compared to warfarin. However, there were very small differences in QALYs and costs between the newer oral anticoagulants. The Committee concluded that there was insufficient evidence to distinguish between the clinical and cost effectiveness of

edoxaban and the newer oral anticoagulants recommended in previous appraisals (apixaban, dabigatran etexilate and rivaroxaban). Therefore, edoxaban could be recommended as a cost-effective treatment for non-valvular atrial fibrillation in people who have 1 or more risk factors for stroke.

- 4.15 The Committee concluded that the decision about whether to start treatment with edoxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of edoxaban compared with warfarin, apixaban, dabigatran etexilate and rivaroxaban. For people considering switching from warfarin to edoxaban, the potential risks and benefits of edoxaban should be considered in the light of their level of international normalised ratio (INR) control.
- 4.16 The Committee was aware of NICE's position statement with regard to the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising edoxaban. It 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 everolimus. It therefore concluded that the PPRS payment mechanism was irrelevant for the consideration of the cost effectiveness of edoxaban.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 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 non-valvular atrial fibrillation and the healthcare professional responsible for their care thinks that edoxaban is the right treatment, it should be available for use, in line with NICE's recommendations.

6 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

Professor Iain Squire (Vice-Chair)

Consultant Physician, University Hospitals of Leicester

Dr Graham Ash

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant

GP, Swadlincote, Derbyshire

Professor Aileen Clarke

Professor of Public Health and Health Services Research, University of Warwick

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Ms Pamela Rees

Lay Member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Ms Ellen Rule

Director of Transformation and Service Redesign, Gloucestershire Clinical Commissioning Group

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

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

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.

Christian Griffiths

Technical Lead

Eleanor Donegan

Technical Adviser

Bijal Joshi

Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Greenhalgh J, Longworth L, Crossan C, et al., Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation: A Single Technology Appraisal, March 2015.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Companies were also invited to make written submissions. Professional or expert and patient or carer groups gave their expert views on edoxaban by making a submission to the Committee. Companies, professional or expert and patient or carer groups, and other consultees, have the opportunity to appeal against the final appraisal determination.

Company

- Daiichi Sankyo UK (edoxaban)

Professional or expert and patient or carer groups:

- AntiCoagulation Europe (ACE)
- Arrhythmia Alliance
- Association of British Neurologists
- Atrial Fibrillation Association
- British Society for Haematology
- British Thoracic Society
- Clinical Leaders of Thrombosis (CLOT)
- Royal College of Pathologists

- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

- Bayer (rivaroxaban)
- Boehringer Ingelheim (dabigatran etexilate)
- Bristol–Myers Squibb, Pfizer (apixaban)
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Improvement Scotland
- Liverpool Reviews & Implementation Group, University of Liverpool
- National Institute for Health Research Health Technology Assessment Programme

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 Ameet Bakhai, Consultant Cardiologist and Clinical R&D Deputy Director, nominated by organisation representing Daiichi Sankyo UK – clinical expert
- Miss Nazish Khan, Principal Pharmacist Cardiac Services, nominated by organisation representing United Kingdom Clinical Pharmacy Association – clinical expert
- Miss Laura Wood, nominated by organisation representing Arrhythmia Alliance – patient expert
- Miss Vicki Hill, nominated by organisation representing Atrial Fibrillation Association –

patient expert

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 UK

Update information

July 2021: Section 1.2 updated to include the other anticoagulants approved by NICE.

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