NICE National Institute for
Health and Care Excellence

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

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

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

2 Information about dabigatran etexilate

2.1 Dabigatran etexilate (Pradaxa, Boehringer Ingelheim) is an oral direct thrombin inhibitor that specifically and reversibly inhibits thrombin, a key enzyme in blood clot formation. It is licensed for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. The recommended dosage of dabigatran etexilate is 300 mg (150 mg twice daily) following treatment with a parenteral anticoagulant for at least 5 days. For people aged 80 years or older and for people having verapamil, the recommended dose is 220 mg (110 mg twice daily). In people aged 75 to 80 years, people with moderately reduced kidney function, people with gastritis, esophagitis or gastroesophageal reflux, and people at increased risk of bleeding, either dose (300 mg or 220 mg) can be given based on an individual assessment. Dabigatran etexilate is contraindicated in people with severely reduced kidney function.

2.2 The most common adverse reaction to dabigatran etexilate is bleeding, although indigestion is also common. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Dabigatran etexilate costs £65.90 for a 60-capsule pack of the 150 mg or 110 mg doses (excluding VAT; BNF 67) and costs £2.20 per day of treatment. Costs may vary in different settings because of negotiated procurement discounts.

3   The company's submission

The appraisal committee considered evidence submitted by the company for dabigatran etexilate and a review of this submission by the Evidence Review Group (ERG). See the committee papers for full details of the evidence.

3.1   The company presented data from the RE-COVER and RE-COVER II trials on the effectiveness of dabigatran etexilate for treating deep vein thrombosis (DVT) and pulmonary embolism (PE). The RE-COVER trials were multicentre, randomised, double-blind, double-dummy controlled studies which were identical in design. The trials were designed to test the non-inferiority of 150 mg twice-daily dabigatran etexilate compared with adjusted-dose warfarin (with a target international normalised ratio [INR] of 2.0 to 3.0) in 5,153 patients with confirmed acute symptomatic venous thromboembolism (VTE), for whom the investigator considered at least 6 months of anticoagulant treatment to be appropriate. In the dabigatran etexilate arm, patients were given a parenteral anticoagulant for at least 5 days; in the warfarin arm, patients were also given parenteral anticoagulant and warfarin was added to achieve an INR of 2.0 to 3.0 patients were then given dabigatran etexilate or continued warfarin for 6 months with a 30-day follow-up after treatment had ended. The primary outcome was recurrent symptomatic VTE and VTE-related deaths in 6 months. VTE was defined as the combined incidence of DVT (detected by venous compression ultrasonography or venography) and PE (detected by ventilation-perfusion lung scan, pulmonary angiography or spiral [helical] CT). The average age of patients in the RE-COVER trials was around 55 years. patients in the warfarin arm had an INR of 2.0 to 3.0 (were in the appropriate therapeutic range) for between 57% and 60% of the time across the trials.

3.2   The company presented data from 2 trials that assessed dabigatran etexilate for secondary prevention: RE-MEDY and RE-SONATE. RE-MEDY was a randomised, double-blind trial designed to test the non-inferiority of 150 mg twice-daily dabigatran etexilate compared with warfarin (target INR 2.0 to 3.0) in 2,866 patients with confirmed acute VTE which had been successfully treated with an anticoagulant for 3 to 12 months. Of these patients, 1,141 (40%) had previously participated in the RE-COVER trials. patients in the RE-MEDY trial had increased risk of recurrent VTE (as determined by a study investigator);

according to the company, these patients represented a 'more severely affected patient group than other trial populations'. It was originally planned that patients in RE-MEDY should have dabigatran etexilate or warfarin for 18 months. However, the protocol was amended to extend the treatment period because a lower-than-projected event rate was observed, and patients instead had 6 to 36 months of treatment with a 30-day follow-up after the end of the course of treatment. The primary outcome in RE-MEDY was recurrent symptomatic and objectively confirmed VTE or death associated with VTE (excluding unexplained death). Clinically suspected DVT was objectively verified using pre-specified imaging studies. The average age of patients in the trial was around 55 years. patients having warfarin had an INR of 2.0 to 3.0 around 62% of the time.

3.3   RE-SONATE was a randomised controlled trial that compared 150 mg twice-daily dabigatran etexilate with placebo in 1,353 patients who had completed 6 to 18 months of treatment with a vitamin K antagonist for confirmed acute symptomatic VTE. Of this population, 27 (2%) had previously participated in the RE-COVER trials. RE-SONATE only included patients for whom there was uncertainty about the need for continued anticoagulation treatment (termed 'clinical equipoise'), indicating that the risks and benefits of extended treatment were unclear. The original study protocol for RE-SONATE stated that patients should be treated for 6 months, but because the number of VTE events necessary for statistical analysis was reached before some patients had completed 6 months of treatment, patients included in the analysis had dabigatran etexilate or placebo for between 3 and 6 months. All patients in the trial were also followed up for 12 months after treatment ended. The primary efficacy outcome in RE-SONATE was recurrent symptomatic and objectively confirmed VTE or death associated with VTE (including unexplained death). The average age of patients in the trial was around 56 years.

3.4   In the analyses of primary and secondary outcomes in the RE-COVER, RE-MEDY and RE-SONATE trials, the company used what it termed the 'full analysis set'. This comprised patients who were both randomised and had taken at least 1 dose of the study drug (5107 of the 5153 patients randomised in the RE-COVER trials, 2856 of 2866 in RE-MEDY and 1343 of 1353 in RE-SONATE). The company tested for the non-inferiority of dabigatran etexilate compared with warfarin using a non-inferiority margin for the upper boundary of the 95% confidence

interval (CI) around the hazard ratio (HR) of 2.75, and a margin for the upper boundary of the 95% CI around the difference in risk of 3.6 percentage points at month 6 in the RE-COVER trials; in RE-MEDY the corresponding margins were defined as 2.85 for the HR and 2.8% for the risk difference at month 18. In the pooled analysis of the RE-COVER trials, 60 patients (2.4%) in the dabigatran arm and 55 (2.2%) in the warfarin arm had a recurrent VTE (HR 1.09, 95% CI 0.76 to 1.57, $p<0.001$ for non-inferiority). In RE-MEDY, 26 patients (1.8%) in the dabigatran arm and 18 (1.3%) in the warfarin arm had a recurrent VTE (HR 1.44, 95% CI 0.78 to 2.64, $p=0.01$ for non-inferiority). In RE-SONATE, 3 patients (0.4%) in the dabigatran arm and 37 (5.6%) in the placebo arm had a recurrent VTE (HR 0.08, 95% CI 0.02 to 0.25, $p<0.001$ for superiority).

3.5   In its safety analysis, the company used data from all randomised patients who received at least 1 dose of the study medication. The analysis was based on which drug they took; this meant that it may not have been the drug to which they were randomised. Numerous bleeding outcomes were measured in the 4 trials. Tables 1 to 3 summarise the bleeding events reported throughout the company's submission.

Table 1 Summary of adverse events in the RE-COVER trial

–	Dabigatran N=2,553	Warfarin N=2,554
Major bleeding event, N (%)	37 (1.4%)	51 (2.0%)
Hazard ratio (95% confidence interval [CI])	0.73 (0.48 to 1.11), p value not reported	0.73 (0.48 to 1.11), p value not reported
Major or clinically relevant bleeding, N (%)	136 (5.3%)	217 (8.5%)
Hazard ratio (95% CI)	0.62 (0.50 to 0.76), p value not reported	0.62 (0.50 to 0.76), p value not reported
Any bleeding event, N (%)	411 (16.1%)	567 (22.2%)
Hazard ratio (95% CI)	0.70 (0.61 to 0.79), p value not reported	0.70 (0.61 to 0.79), p value not reported
Intracranial haemorrhage (ICH), N (%)	2 (0.1%)	5 (0.2%)

–	Dabigatran N=2,553	Warfarin N=2,554
Gastrointestinal (GI) bleed, N (%)	101 (4%)	68 (3%)

Table 2 Summary of adverse events in the RE-MEDY trial

–	Dabigatran N=1,430	Warfarin N=1,426
Major bleeding event, N (%)	13 (0.9%)	25 (1.8%)
Hazard ratio (95% confidence interval [CI])	0.52 (0.27 to 1.02), p value not reported	0.52 (0.27 to 1.02), p value not reported
Major or clinically relevant bleeding, N (%)	80 (5.6%)	145 (10.2%)
Hazard ratio (95% CI)	0.54 (0.41 to 0.71), p<0.001	0.54 (0.41 to 0.71), p<0.001
Any bleeding event, N (%)	277 (19.4%)	373 (26.2%)
Hazard ratio (95% CI)	0.71 (0.61 to 0.83), p<0.001	0.71 (0.61 to 0.83), p<0.001
Intracranial haemorrhage (ICH), N (%)	2 (0.1%)	4 (0.3%)
Gastrointestinal (GI) bleed, N (%)	45 (3.1%)	32 (2.2%)

Table 3 Summary of adverse events in the RE-SONATE trial

–	Dabigatran N=681	Placebo N=662
Major bleeding event, N (%)	2	0
Hazard ratio (95% CI)	Hazard ratio not calculable	Hazard ratio not calculable
Major or clinically relevant bleeding, N (%)	36 (5.3%)	12 (1.8%)

–	Dabigatran N=681	Placebo N=662
Hazard ratio (95% CI)	2.92 (1.52 to 5.60), p=0.001	2.92 (1.52 to 5.60), p=0.001
Any bleeding event N (%)	72 (10.5%)	39 (5.9%)
Hazard ratio (95% CI)	1.82 (1.23 to 2.68), p=0.0027	1.82 (1.23 to 2.68), p=0.0027
Intracranial haemorrhage (ICH), N (%)	None reported	None reported
Gastrointestinal (GI) bleed, N (%)	5 (0.7%)	2 (0.3%)

3.6 Across the RE-COVER trials, 9 patients (0.4%) in the dabigatran arms and 5 (0.2%) in the warfarin arms had an acute coronary syndrome event. Of these, 8 patients (0.3%) in the dabigatran arms and 4 (0.2%) in the warfarin arms had a myocardial infarction. In RE-SONATE, 1 patient in each of the dabigatran and placebo arms had a myocardial infarction. Two patients in the dabigatran arm had a transient ischaemic attack and 1 in the placebo arm had an ischaemic stroke. In RE-MEDY, 13 patients (0.9%) in the dabigatran arm and 3 (0.2%) in the warfarin arm had an acute coronary syndrome event. Of these, 9 patients in the dabigatran arm and 1 in the warfarin arm had myocardial infarction, and 3 patients in the dabigatran arm and 1 in the warfarin arm had ischaemia or unstable angina.

3.7 The company did not identify any head-to-head trials comparing dabigatran etexilate with rivaroxaban for treating DVT and PE. The company carried out a meta-analysis of data from 2 trials, EINSTEIN-DVT and EINSTEIN-PE, to estimate the effectiveness of rivaroxaban in treating DVT and PE. EINSTEIN-DVT and EINSTEIN-PE were open-label trials that randomised patients to either rivaroxaban (15 mg twice daily for the first 3 weeks followed by 20 mg once daily) or low molecular weight heparin (LMWH; enoxaparin 1 mg/kg twice daily for at least 5 days) plus a vitamin K antagonist (warfarin or acenocoumarol) for the treatment of recurrent symptomatic DVT or PE (patients in EINSTEIN DVT had an index event of DVT; those in EINSTEIN PE had an index event of PE). Treatment length was 3, 6 or 12 months depending on risk of recurrent VTE, as judged by an

investigator at the start of treatment. In the meta-analysis of the 2 EINSTEIN trials, rivaroxaban was associated with a similar number of recurrent VTE events to LMWH followed by a vitamin K antagonist (HR 0.88, 95% CI 0.54 to 1.43), fewer major bleeds (HR 0.54, 95% CI 0.36 to 0.79), and a similar number of clinically relevant bleeds (HR 0.92, 95% CI 0.8 to 1.06). The company used these estimates of the efficacy and bleeding rates of rivaroxaban (relative to LMWH followed by a vitamin K antagonist) to perform a meta-analysis of data from the RE-COVER trials using an adjusted indirect comparison. The confidence intervals for recurrent VTE and major bleeding crossed 1. At the time of the appraisal the company stated that the numerical results of its indirect comparison are academic in confidence and therefore cannot be presented here. The company also presented information on the methods it used to do a network meta-analysis, but did not present the results in its submission because the evidence network did not include a mixture of head-to-head trials and indirect evidence. It therefore did not add additional information to the adjusted indirect comparison.

3.8   For the prevention of recurrent VTE indication ('secondary prevention'), the company presented an adjusted indirect comparison of dabigatran etexilate compared with rivaroxaban using data from RE-SONATE and EINSTEIN-EXT, because both trials compared the active treatment with placebo. RE-MEDY was not included because warfarin was the comparator. EINSTEIN-EXT was a randomised, placebo-controlled trial to assess the efficacy and safety of rivaroxaban 20 mg for the prevention of recurrent symptomatic DVT or PE in patients who had had 6 to 12 months of rivaroxaban or vitamin K antagonist treatment for an acute episode of VTE. In the trial, the rate of recurrent VTE was lower with rivaroxaban than with placebo (HR 0.18, 95% CI 0.09 to 0.39), but the rates of major or clinically relevant bleeding were higher with rivaroxaban than with placebo (HR 5.19, 95% CI 2.30 to 11.70). At the time of the appraisal the company stated that the numerical results of its adjusted indirect comparison of dabigatran etexilate and rivaroxaban were academic in confidence and therefore are not presented here.

3.9   Around 4% of patients in the RE-COVER and RE-MEDY trials had active cancer at baseline. In the RE-COVER trials, 10 of the 173 patients (5.8%) in the dabigatran arms with active cancer and 12 of the 162 (7.4%) people in the warfarin arm with active cancer had VTE or VTE-related death (HR 0.76, 95% CI 0.33 to 1.76). The

company did not present the rate of recurrent VTE for patients with active cancer in RE-MEDY. There were also no trial data for dabigatran etexilate compared with LMWH or rivaroxaban in patients with active cancer. The company presented a direct meta-analysis of 5 trials comparing treatment of DVT and PE with LMWH or a vitamin K antagonist in people with active cancer. LMWH was associated with fewer recurrent VTE events than a vitamin K antagonist (relative risk [RR] 0.49, 95% CI 0.34 to 0.70) and a similar number of major bleeds (RR 1.05, 95% CI 0.53 to 2.10). The company also presented results from the Cancer DACUS extension study, which compared LMWH with a vitamin K antagonist for prevention of recurrent VTE. In this study LMWH was associated with a similar number of recurrent VTE events and major bleeds to a vitamin K antagonist (RR 0.63, 95% CI 0.34 to 1.18 for recurrent VTE; RR 2.58, 95% CI 0.51 to 13.06 for major bleeds).

3.10   The ERG commented on the characteristics of patients in the 4 dabigatran trials (RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE). It noted that the mean baseline ages in the 4 dabigatran trials were between 53 and 56 years, but that clinical advisers would expect most patients with VTE to be over 65 years, and some to be over 80 years (and so having the 110 mg twice-daily dose). The ERG commented that few, if any, patients in the dabigatran trials were aged over 80 years, and according to the trial protocols their VTE would be treated with the 150 mg twice-daily dose. The ERG concluded that there were no clinical trial data for people aged over 80 years receiving 110 mg dabigatran etexilate twice daily for this indication.

3.11   The ERG considered that the 'clinical equipoise' population in RE-SONATE was difficult to define in clinical practice, but that it was likely to comprise patients who were not having ongoing treatment for prevention of recurrent VTE. This population would be considered a different population to that currently treated for secondary prevention in the UK.

3.12   The ERG commented on the treatment regimen in the dabigatran trials and noted that there were limited data for patients treated continuously with dabigatran etexilate, starting from the acute phase of VTE through to long-term secondary prevention. It noted that the company had assumed equal efficacy for the different parenteral therapies in the dabigatran and warfarin arms. The ERG noted that according to NICE's final scope, the analysis should consider both patients who need a limited period of anticoagulation (3 to 6 months) and those who need

long-term anticoagulation (usually life-long). It noted that the mean duration of treatment in the RE-COVER trials was 164 days, and that no data were available for patients needing only 3 months of anticoagulation. In the RE-MEDY AND RE-SONATE trials, assessing long-term prevention of recurrent VTE, mean treatment duration was around 16 months and 6 months respectively. Because of this, the ERG noted that long-term data for safety and efficacy were limited by the varying trial lengths.

3.13 The ERG commented that the company had used data from the full analysis set rather than the intention-to-treat population, but noted that the patient numbers in both populations were similar. The ERG also commented that the results for the primary outcome in the intention-to-treat population in the RE-COVER and RE-MEDY trials (provided by the company in response to the clarification questions) were similar to those in the full analysis set population. The ERG noted that less than 10% of patients were lost to follow-up in the 4 dabigatran trials, and the numbers of discontinuations were well balanced between treatment groups.

3.14 The ERG considered the safety profile of dabigatran etexilate to be generally comparable with that of warfarin. The ERG noted that, for the RE-MEDY trial, the company reported a slightly higher baseline prevalence of cardiovascular risk factors in the dabigatran arm than in the warfarin arm. However, it was unclear whether these small differences in baseline characteristics were linked to the overall incidence of acute coronary syndrome events in RE-MEDY.

3.15 The ERG carried out its own network meta-analyses for the purpose of comparing dabigatran etexilate with rivaroxaban for acute treatment and for secondary prevention based on the trials presented in the company's submission. For all outcomes, the ERG used data assessed at the end of treatment rather than at the end of the observed period in the trial, and where possible used intention-to-treat data in its analysis. The ERG preferred the fixed-effects model over the random-effects model, and the odds ratio was used as a summary statistic for all analyses. Over the acute treatment period, rivaroxaban was associated with a similar number of VTE events and major bleeds to dabigatran etexilate (odds ratio [OR] for VTE events 0.837, 95% CI 0.516 to 1.299; OR for major bleeds 0.763 95% CI 0.402 to 1.320). Rivaroxaban was associated with statistically significantly more clinically relevant non-major bleeds than

dabigatran etexilate (OR 1.647, 95% CI 1.234 to 2.114). Over the secondary prevention treatment period, there were no statistically significant differences in the odds of a VTE, major bleeding, or a clinically relevant non-major bleed between rivaroxaban and dabigatran etexilate (recurrent VTE OR 1.744, 95% CI 0.510 to 4.388; major bleed OR 42, 95% CI 0.329 to 113; clinically relevant non-major bleed OR 2.133, 95% CI 0.681 to 5.303).

3.16   The ERG commented on the subgroup of patients with active cancer in the clinical trials. It noted that the definition of active cancer used in the RE-COVER and RE-MEDY trials included some people who may have been in remission for up to 5 years and who would not usually be considered to have active cancer in UK clinical practice. The ERG also noted that in the RE-COVER and RE-MEDY trials, people in the control arm with active cancer had a parenteral anticoagulant followed by warfarin. This differs from standard clinical practice in England, whereby these patients would continue treatment with LMWH. The ERG noted that the number of patients with active cancer was small and the event rates low. The ERG carried out a network meta-analysis for acute treatment in a population with active cancer, but there were no data for clinically relevant non-major bleeds for any of the comparisons and no data for major bleeding events when comparing rivaroxaban with dabigatran etexilate. The meta-analysis provided no statistically significant results. The ERG also stated that there were insufficient data to perform an analysis of secondary prevention of VTE in patients with active cancer. As such, the ERG considered that only limited conclusions can be made for the subgroup of patients with active cancer.

3.17   The company developed a Markov model with a 1-month (30-day) cycle length and a lifetime time horizon (60 years). A 3.5% discount rate was applied for costs and consequences, and the model was from an NHS and personal social services perspective. Patients entered the model after an initial VTE event and had treatment. If a patient had a recurrent VTE, they stopped current treatment and had 6 months' treatment with LMWH followed by warfarin (regardless of their initial treatment). They did not have continued anticoagulation for secondary prevention. Treatment was stopped completely if there was an intracranial haemorrhage, other major bleeding event, or for other reasons (such as end of planned treatment duration, worsening of other pre-existing conditions or adverse events other than bleeding). In the 'off treatment' health state, patients were assumed to have no risk of bleeding but were at continued risk of recurrent

VTE. patients in the model could have up to 2 recurrent VTE events. Those who had a PE (either as the initial, index event or a recurrent PE) could develop chronic thromboembolic pulmonary hypertension; the risk of this complication remained for 2 years after the PE. patients who had a DVT (either as the initial, index event or a recurrent DVT) could develop post-thrombotic syndrome, the risk for which remained for 5 years after their DVT. The model only included patients with severe post-thrombotic syndrome; the company stated that the mild form of the syndrome has little detrimental effect on quality of life. patients could die from any cause while in any of the health states. The model used age- and gender-specific UK mortality rates from the Office for National Statistics (2010). The cardiovascular health states (myocardial infarction and unstable angina) and a health state for dyspepsia (indigestion) were only modelled in the sensitivity analyses.

3.18 In the model, the average age of the cohort at baseline was 55 years. On entry, 69% of patients had an initial DVT, and 31% had an initial PE (data from pooled RE-COVER trials). The company modelled 2 base cases: acute treatment of VTE only, and treatment and long-term prevention of recurrent VTE (secondary prevention). In the acute treatment base case, patients only had acute treatment for initial or recurrent DVT/PE, and did not have any further treatment if they had a recurrent VTE. In the treatment and secondary prevention base case, people had acute treatment and secondary prevention for initial DVT/PE and acute treatment only (with LMWH/warfarin) for recurrent DVT/PE.

3.19 The company modelled the risk of the combined outcome of recurrent VTE and VTE-related death, and then split this risk by the proportion that was attributable to DVT, fatal PE and non-fatal PE. Similarly, it modelled the risk of the composite outcome of major or clinically relevant non-major bleeds, and split this total incidence by the proportion attributable to extracranial major bleeding events, intracranial major bleeding events, fatal major bleeding events and clinically relevant non-major bleeding events.

3.20 The company used clinical data from the pairwise comparisons in the clinical trials, and did not use the adjusted indirect comparisons or data from a network meta-analysis in its model. For the acute treatment phase, the company assumed that the baseline risk of each VTE and bleeding composite outcome was the incidence observed in the warfarin arm in the RE-COVER trials. It multiplied these

baseline risks by the hazard ratio from RE-COVER to derive incidence of each outcome with dabigatran etexilate, or multiplied these baseline risks by the hazard ratio for warfarin compared with rivaroxaban from the pooled EINSTEIN DVT/PE trials to derive the incidence of each outcome with rivaroxaban. To derive the proportion of people having each type of recurrent VTE event or bleeding event, the company applied the proportions observed in the warfarin arm of the RE-COVER trial, the dabigatran arm in the RE-COVER trials, and the rivaroxaban arm of the pooled EINSTEIN DVT/PE trials. For the risks of these outcomes during secondary prevention, the company used a similar approach. However, because the rivaroxaban secondary prevention trial EINSTEIN EXT compared rivaroxaban with placebo, the company instead took the baseline risk to be that observed for placebo in RE-SONATE. It then multiplied this baseline risk by the hazard ratios from RE-SONATE and EINSTEIN-EXT, to find the risk of these outcomes while taking dabigatran etexilate and rivaroxaban respectively. The company modelled the risk of these outcomes for dabigatran etexilate compared with warfarin based on the treatment effect and baseline risks observed in RE-MEDY. As a consequence of this approach, the risks of recurrent VTE or bleeding with dabigatran etexilate during long-term treatment for secondary prevention differed, depending on whether rivaroxaban or warfarin was the comparator. It also affected other assumptions in the model: for example, dabigatran etexilate treatment compared with warfarin for secondary prevention lasted 18 months (reflecting treatment length in RE-MEDY), and dabigatran etexilate treatment compared with rivaroxaban for secondary prevention lasted 6 months (reflecting treatment length in RE-SONATE). The length of acute treatment was 6 months in all comparisons. The company derived the risks of non-fatal PE, proximal DVT, VTE-related death and distal DVT after therapy discontinuation from a study by Pradoni et al.

3.21　　During the acute treatment period, the risk of a recurrent VTE or bleeding was assumed to decrease over time. This was based on the results of the dabigatran trials, which showed that rates of recurrent VTE and bleeds were higher in the months immediately after the index event and gradually declined thereafter. The risk of recurrent VTE and bleeding events was assumed to be constant over the secondary prevention treatment period and in the post-treatment period. Probabilities of events other than VTE or bleeding in the model were assumed to remain constant over time.

3.22   Chronic thromboembolic pulmonary hypertension, or CTEPH, is a complication of PE associated with considerable morbidity and mortality. The probability of CTEPH in the model was taken from a study by Pengo et al. Although post-thrombotic syndrome was not reported in the trials, its incidence in the model was assumed to be the same for all comparators (based on data from a study by Pradoni et al.).

3.23   The company used baseline age- and gender-specific utility values in its model, and adjusted for decreases in quality of life associated with treatment and each health state. The decrement in utility of -0.25 with a recurrent DVT or PE was assumed to be 6 weeks. For any type of bleeding event, a 1-month decrement in utility was assumed (-0.13 for a major bleed and -0.04 for a minor bleed). An additional decrement in utility of -0.5 was applied for a patient's lifetime if they were disabled as a result of an intracranial haemorrhage. A reduced utility of -0.12 was assumed for 1 month for patients not having treatment and who had CTEPH. patients who had severe post-thrombotic syndrome while off treatment were assumed to have a reduced utility of -0.07 for their remaining lifetime. The company assumed that taking warfarin would decrease quality of life and so applied a utility decrement of -0.012 while patients had warfarin. Similarly, the company assumed a utility decrement of -0.008 for people having LMWH.

3.24   The company assumed that patients having warfarin would have an initial anticoagulation clinic visit with a consultant at a cost of £62.56 (NHS reference costs 2012/13), 4 anticoagulation clinic visits during the warfarin titration period, and monthly follow-up visits during treatment with warfarin. Subsequent visits to the anticoagulation clinic were assumed to cost £27.99 (based on NHS reference costs 2012/13), and were weighted to take into account consultant-led and non-consultant-led appointments. Based on these assumptions, warfarin monitoring over the first year of treatment costs £482.41 (assuming 1 consultant-led visit and 15 further follow-up visits to the anticoagulation clinic). patients having dabigatran etexilate or rivaroxaban were assumed to visit an anticoagulation clinic just once.

3.25   The company presented base-case results for the cost effectiveness of dabigatran etexilate compared with LMWH followed by warfarin, for both treating VTE only and for the treatment and prevention of recurrent VTE (secondary prevention). In the deterministic base case for treating VTE, dabigatran etexilate

was associated with additional costs of £20 for 0.0239 more quality-adjusted life years (QALYs) compared with warfarin. This equated to an incremental cost-effectiveness ratio (ICER) of £862 per QALY gained. Dabigatran etexilate dominated rivaroxaban (that is, was both cheaper and more effective than rivaroxaban; dabigatran etexilate cost £20 less for 0.0003 more QALYs). In the treatment and secondary prevention base case, the company presented 2 pairwise comparisons: 1 for dabigatran etexilate compared with LMWH followed by warfarin, and 1 for dabigatran etexilate compared with rivaroxaban. The deterministic ICER for dabigatran compared with warfarin was £8,319 per QALY gained (incremental costs £458, incremental QALYs 0.0551). Rivaroxaban was dominated by dabigatran etexilate (dabigatran etexilate cost £67 less for 0.002 more QALYs). The company's probabilistic results were similar to the deterministic results.

3.26   The company carried out 9 scenario analyses:

- making adjustment for time in therapeutic range while taking warfarin

- allowing patients having rivaroxaban to have initial treatment with LMWH

- removing the utility decrement assumed for warfarin

- shortening the time horizon to 1 year or 6 months

- excluding bleeds while on LMWH before warfarin or dabigatran etexilate

- including the costs and utility decrement of dyspepsia (indigestion)

- including the costs and utility decrement of myocardial infarction and unstable angina

- including data for rivaroxaban from 6-months' treatment only

- including unexplained deaths in the model.

Of note, removing the utility decrement assumed for warfarin treatment increased the ICER in the treatment-only base case from £862 per QALY gained to £1,217 per QALY gained. The same scenario increased the treatment and secondary prevention base case ICER from £8,319 per QALY gained to £14,947 per QALY gained. The overall effect of these scenarios

was modest, and none increased the ICER for dabigatran etexilate compared with warfarin to over £20,000 per QALY gained.

3.27 The ERG had concerns about a number of the assumptions in the model relating to how patients would be treated in clinical practice. In the company's analyses, the length of acute treatment was 6 months. Although the ERG's clinical experts considered this to reasonably reflect clinical practice, the ERG acknowledged that, following publication of NICE's guideline on venous thromboembolic diseases, acute treatment of 3 months is increasingly common. The ERG noted that in the company's model, patients had treatment for prevention of recurrent VTE (secondary prevention) for 6 to 18 months (dependent on the comparator), but some patients in clinical practice in England may receive life-long anticoagulation treatment. The ERG also noted that in the model, patients with a recurrent VTE did not have secondary prevention; rather, they had only acute treatment. Based on clinical advice, the ERG considered it more likely that a patient with multiple VTE events would receive life-long secondary prevention unless precluded by the risk of bleeding. The ERG also disagreed that the only anticoagulation treatment option for a recurrent VTE would be LMWH followed by warfarin. It thought that some patients may have rivaroxaban and that patients with cancer would have LMWH. In the model, patients having a major bleeding event stopped treatment permanently. The ERG considered this to mean that patients would not re-start anticoagulation treatment if they had a recurrent VTE, which may not reflect UK clinical practice. It noted that in NICE technology appraisal guidance on rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE and rivaroxaban for treating PE and preventing recurrent VTE, patients with a major bleeding event could restart anticoagulation treatment after 1 to 3 months.

3.28 The ERG stated that it was appropriate to exclude cardiovascular health states from the base case because they are not of direct relevance to the condition of interest for this appraisal. However, it believed that dyspepsia (indigestion) should have been included in the base case due to its being an important side effect associated with dabigatran etexilate treatment.

3.29 The ERG noted that the company analysed the data through a series of head-to-head and indirect comparisons. The limitation of this approach for the secondary prevention analyses was that the data for dabigatran etexilate varied

in each comparison, resulting in a lack of comparability across scenarios. The ERG did not consider that treatment length would differ by intervention, and also noted that discontinuation on dabigatran etexilate for secondary prevention varied if warfarin or rivaroxaban was the comparator.

3.30   The ERG noted that the proportions of patients having each type of recurrent VTE event (DVT or PE), type of bleeding event (intracranial and extracranial major bleeding events and clinically relevant non-major bleeds), and whether a major bleed was fatal differed by treatment arm. This was because the proportions of patients experiencing each outcome were taken directly from observations in each separate clinical trial. The ERG consulted with clinical experts as to whether a difference in these outcomes should be expected with different treatments, and was advised that there was no clinical basis for such a difference.

3.31   The ERG noted that in its model the company had used the same decrement in utility associated with DVT and PE as that derived from EQ-5D data collected in the RE-COVER trials (-0.25). It noted that this was unexpected, as PE is a more serious condition which might be expected to lead to a larger decrease in quality of life than DVT. It further noted that in NICE technology appraisal guidance on rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE and rivaroxaban for treating PE and preventing recurrent VTE, the utility values estimated for PE and DVT were 0.63 and 0.84 respectively. However, the ERG agreed that it was appropriate to use EQ-5D data collected from the RE-COVER trials in the model, rather than other published estimates of utility.

3.32   The ERG noted that the company had assumed a utility decrement for a patient taking warfarin based on data from a study of just 48 patients. It estimated that the utility value of -0.012 may not be robust or generalisable due to the small sample size from which it was derived. Furthermore, an estimate of the utility associated with dabigatran etexilate treatment was not provided by the company. The ERG noted that a head-to-head comparison of warfarin and dabigatran etexilate from RE-LY (a trial of stroke prevention in people with atrial fibrillation) indicated that there was no long-term difference in the EQ-5D scores for patients having warfarin or dabigatran etexilate. However, it also noted that the utility decrement used by the company in the current submission was the same as that used in the company submissions for rivaroxaban in NICE technology appraisal guidance for the drug. The ERG concluded that although there may be a

difference in utility associated with warfarin, the disutility is likely to be small and may reduce over time as patients adjust to their treatment regimen. It acknowledged, however, that there is a great degree of uncertainty around estimates of disutility while on warfarin.

3.33   The ERG noted that for patients with an initial VTE who were treated with dabigatran etexilate, rivaroxaban or LMWH monotherapy, the company had not included an initial appointment where people are prescribed treatment and receive any training on how to take their medication. In contrast, all patients having warfarin were assumed to have an initial appointment at which treatment would be initiated, even those who had been admitted to hospital for their first VTE. The ERG therefore considered that the company had both overestimated the number of appointments for admitted patients who had warfarin (because they will not need an initial anticoagulation visit) and underestimated the number of appointments needed for dabigatran etexilate, rivaroxaban and LMWH monotherapy (because patients diagnosed with VTE outside of hospital will need an initial appointment to discuss anticoagulation treatment). Consequently, the ERG considered that the cost of administering dabigatran etexilate compared with warfarin may be underestimated.

3.34   The ERG noted the company's assumption that after an initial titration period in the first month, people taking warfarin would visit an anticoagulation clinic once a month for the remainder of treatment. The ERG heard from clinical experts that although this frequency of monitoring visits may be appropriate for initial acute treatment, visits would be less frequent for people continuing to take warfarin long-term for secondary prevention (typically once every 3 months). The ERG's clinical experts considered the monitoring schedule for dabigatran etexilate and rivaroxaban to be reasonable, but noted that patients receiving either drug may return to their GP each year. The ERG noted that the company's estimated cost for follow-up visits to an anticoagulation clinic (£27.99) assumed that some visits would be consultant-led. The clinical experts advised that in clinical practice, it is typical for nurses to provide the majority of contact at follow-up visits. The ERG assumed that such visits would instead cost £10.61.

3.35   The ERG commented that in the company's acute treatment deterministic base-case analysis, costs and QALYs varied between all 3 treatment strategies (by £40 and 0.02 per patient respectively). In particular, for dabigatran etexilate

compared with rivaroxaban, the estimated total QALYs differed by 0.0003. From this, the ERG reasoned that although dabigatran etexilate dominated rivaroxaban in the company's acute treatment base case, the company's estimates of average total costs and QALYs imply that all 3 treatments strategies would result in similar costs and consequences.

3.36   The company did not present a fully incremental analysis for the treatment and secondary prevention base case. The ERG stated that the main disadvantage of using different model parameters for dabigatran etexilate when comparing it with warfarin or rivaroxaban was that the results of each analysis cannot be compared: the costs and QALYs associated with dabigatran etexilate will differ in each case. Although dabigatran etexilate dominated rivaroxaban in the treatment and secondary prevention base case, the ERG noted that there was a QALY difference of less than 0.002 per patient and a cost difference of just £67. These results implied that the treatments are similar.

3.37   The ERG identified errors in the company's model. When it presented the company's base-case analysis with these errors corrected, there was only a modest difference in the resulting ICERs for dabigatran etexilate compared with warfarin. In the acute treatment base case, the corrected errors resulted in an ICER of £831 per QALY gained for dabigatran etexilate compared with warfarin, and dabigatran etexilate was less costly and less effective than rivaroxaban (dabigatran etexilate cost £22 less for 0.0003 fewer QALYs than rivaroxaban). In the treatment and secondary prevention base case, the ICER for dabigatran etexilate compared with warfarin was £9973 per QALY gained and dabigatran etexilate was less costly and less effective than rivaroxaban (dabigatran etexilate cost £23 less for 0.0013 fewer QALYs than rivaroxaban).

3.38   To derive exploratory base cases, the ERG combined 16 of the 42 scenarios it had tested (with the exception of 3 for the acute treatment exploratory base case, because they were only relevant to the secondary prevention treatment phase). The scenarios were:

- assuming that 50% of patients with a major bleeding event would return to treatment at a later date

- a 50-year rather than 60-year time horizon

- use of the ERG network meta-analysis for probability of VTE events and probability of bleeding

- assuming a constant proportion of VTE event types across treatments

- assuming a constant proportion of bleeding event types across treatments

- a death rate from intracranial haemorrhage of 39.5%

- an average age of 65 years across the model cohort

- patients had a utility decrement of 0.265 if they had a PE

- the disutility associated with DVT and PE was applied for 30 days

- the initial anticoagulation appointment for warfarin was removed

- monitoring visits assumed to cost £10.61

- cost of intracranial haemorrhage set at £14,777.

   In addition, in the treatment and secondary prevention base case the following scenarios were included:

- assumed life-long treatment for secondary prevention

- monitoring appointments in the secondary prevention period reduced from once a month to once every 3 months

- dabigatran etexilate discontinuation rate assumed to be the same as in RE-MEDY.

3.39   In the ERG's exploratory base case for acute treatment, dabigatran etexilate was associated with an additional cost of £223 and 0.012 more QALYs compared with warfarin (ICER of £18,240 per QALY gained). Dabigatran etexilate dominated rivaroxaban, costing £3 less per patient for an additional 0.0018 QALYs. In the exploratory base case for treatment and secondary prevention, dabigatran etexilate was associated with an additional cost of £3331 per patient and 0.093 more QALYs compared with warfarin (ICER of £35,768 per QALY gained). Rivaroxaban was extendedly dominated by dabigatran etexilate (compared with warfarin, rivaroxaban had additional costs of £2710 and QALYs of 0.020;

compared with rivaroxaban, dabigatran etexilate had incremental costs of £620 and QALYs of 0.073).

3.40 The ERG commented that for its exploratory acute treatment base-case analysis, the main factor increasing the ICER for dabigatran etexilate compared with warfarin was the lower costs associated with warfarin monitoring as a result of assuming that follow-up visits would all be nurse-led. The cost of a warfarin monitoring appointment was also an important factor in the exploratory base case for treatment and secondary prevention, as was the assumed frequency of warfarin monitoring in the secondary prevention period (once every 3 months rather than once monthly). The ERG commented that a company scenario analysis in which there was no utility decrement associated with warfarin showed that warfarin disutility was a major factor in the company's model. The ERG noted that if, in addition to the assumptions in its exploratory base case, it also assumed no disutility with warfarin in the secondary prevention period, the ICER for dabigatran etexilate compared with warfarin would be £90,000 per QALY gained. This would have such a large effect on the ICER because the ERG's model incorporating its preferred scenarios is increasingly sensitive to changes in QALYs.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dabigatran etexilate, having considered evidence on the nature of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the value placed on the benefits of dabigatran etexilate by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.2 The Committee discussed the clinical management of DVT and PE. It was aware that the NICE guideline on venous thromboembolic diseases: diagnosis, management and thrombophilia testing recommends that DVT and PE are treated with immediate parenteral anticoagulation, most commonly with a low molecular weight heparin (LMWH) delivered by subcutaneous injection together with an oral vitamin K antagonist such as warfarin. Both treatments are continued for at least 5 days or until the person's international normalised ratio (INR) has been within the therapeutic range for at least 24 hours, at which point the LMWH is stopped. The Committee was also aware that a minority of people have unfractionated heparin or fondaparinux instead of LMWH. The Committee heard that following publication of NICE technology appraisal guidance on rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE and rivaroxaban for treating PE and preventing recurrent venous thromboembolism, rivaroxaban is now recommended as an option for treating and preventing recurrent venous thromboembolism (VTE). However, it heard that the uptake of rivaroxaban varies widely. The clinical expert explained that the use of rivaroxaban depends to a certain extent on the arrangements and local infrastructure for warfarin treatment and monitoring. The Committee heard from the clinical expert that unlike both warfarin and dabigatran etexilate, with rivaroxaban initial treatment with LMWH is not needed. This could be an advantage for people treated as outpatients because injected treatment is not needed. However, the clinical expert stated that for people who need to be admitted to hospital, particularly for a PE, treatment is often started with LMWH before a decision is made about which oral anticoagulant to use.

4.3 The Committee considered the length of treatment with anticoagulation. It noted that the NICE guideline on venous thromboembolic diseases recommends that

the risks and benefits of continuing anticoagulation following a DVT or PE should be assessed at 3 months. The Committee heard from the clinical expert that the decision to continue or discontinue treatment at this point is based on whether the person's VTE event could be attributed to a transient risk factor or whether it was unprovoked. People with a transient risk factor that has resolved by 3 months may stop anticoagulation treatment at this stage, whereas people who still have a VTE risk factor or who had an unprovoked event would normally continue treatment. The clinical expert stated that clinical data for anticoagulation for longer than 12 months were limited. However, they stated that people taking anticoagulants are typically reviewed at 12 months to assess the efficacy of the treatment, bleeding risk, number of nuisance bleeds experienced, any other adverse events and the convenience to the person of taking the anticoagulant. People who do not experience any significant problems on anticoagulants may continue to take them. The clinical expert stated that the risks and benefits of continuing treatment vary between patients, but that a significant proportion of people who continue treatment for longer than 12 months would continue treatment for the rest of their lives. The Committee concluded that there was variation in the length of treatment with anticoagulants, and the decision to continue was dependent on the risks and benefits for the patient as well as their own choice. It further concluded that there are some people who may have life-long anticoagulation following a DVT or PE.

4.4   The Committee heard from the patient expert about the current treatment options for DVT and PE. The Committee heard that warfarin monitoring takes place in a number of different settings including hospital clinics, at GP appointments and community services. Furthermore, some people self-monitor their INR and adjust their warfarin doses accordingly. Some people may encounter a seamless monitoring service which has a negligible effect on their life, whereas others may be inconvenienced by appointments at times which are inflexible. The patient expert explained that the support given to people is highly variable. People are given a protocol for monitoring and dose adjustment to which they must adhere, but feedback suggests that people's experience and satisfaction with anticoagulation services varies. The Committee understood that dabigatran etexilate and rivaroxaban do not need monitoring and dose adjustments, and that some people appreciate the additional choice and reassurance of efficacy without monitoring. The patient expert explained that there has been gradual uptake of the new oral anticoagulants across the

indications for which they are licensed, but in some cases, they are being prescribed with no follow-up. The patient expert added that having no definitive antidote or protocol for rapid reversal of bleeding when using dabigatran etexilate is a concern, but that further research is underway. The Committee concluded that people welcome having the choice of new oral anticoagulants such as rivaroxaban and dabigatran etexilate, because they avoid the need for the monitoring and dose adjustments associated with warfarin.

Clinical effectiveness

4.5 The Committee considered the 4 dabigatran trials included in the company's submission: RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE. The Committee was aware that although the marketing authorisation for dabigatran does not require routine monitoring, press reports and an article published in the British Medical Journal had suggested that lower rates of bleeding could be achieved if dabigatran levels in the blood were monitored with subsequent dose-adjustment if needed. The company representatives stated that there were no other data on the safety or efficacy of dabigatran etexilate that were relevant to the Committee's appraisal of dabigatran etexilate for the treatment and secondary prevention of DVT and PE, and that it had fully disclosed all relevant data to the European Medicines Agency. The Committee accepted the company's statement that all relevant data had been submitted for the appraisal.

4.6 The Committee considered the trials and their generalisability to clinical practice in England. It noted that people taking warfarin in the RE-COVER trials and RE-MEDY had an INR in the therapeutic range 57% to 60% of the time, and that 60% is considered to be at the lower limit of the acceptable time in therapeutic range. However, it also noted that the time in therapeutic range had been calculated early on in the warfarin treatment phase when the dose was still being titrated, which may have resulted in the average time in therapeutic range being lower. The Committee further noted the Evidence Review Group's (ERG's) concerns that people in the trials were younger than would be expected in clinical practice in England. The Committee went on to note that all people in the dabigatran arms of the 4 trials had the 150 mg twice-daily dose, despite the summary of product characteristics stating that people aged over 80 years and people taking verapamil should have a lower dose of 110 mg twice daily. The

Committee was concerned that there were no clinical trial data on the 110 mg dose for the treatment and secondary prevention of DVT and PE. It heard from the company that the European Medicines Agency requested pharmacokinetic data on plasma levels of dabigatran in people having the 150 mg or 110 mg doses in the RE-LY trial for atrial fibrillation, and pharmacokinetic data from the trials for DVT and PE. Safety data for the 110 mg dose were available from the RE-LY trial. The company stated that the European Medicines Agency had approved the use of the lower dose for certain people based on these data. The Committee concluded that the dabigatran trials were generalisable to people who would have the 150 mg dose of dabigatran etexilate in clinical practice in England. Although there was some uncertainty as to whether the 110 mg dose would be equally effective in treating and preventing recurrent VTE in those people for whom it is recommended, the Committee concluded that dabigatran etexilate should be appraised in accordance with its marketing authorisation.

4.7   The Committee considered the effectiveness of dabigatran etexilate for the treatment and prevention of recurrent VTE (secondary prevention). It noted that in the RE-COVER and RE-MEDY trials similar numbers of people had a recurrent VTE in the warfarin and dabigatran arms, and that dabigatran etexilate was statistically non-inferior to warfarin for both acute treatment and secondary prevention. The Committee noted that in the RE-SONATE trial (which included people for whom there was uncertainty about their need for continued anticoagulation), statistically significantly fewer people had a recurrent VTE when taking dabigatran etexilate compared with placebo. The Committee noted that there were no head-to-head trials comparing dabigatran etexilate with rivaroxaban and that the company had performed an adjusted indirect comparison. The Committee noted that there was no clear difference between dabigatran etexilate and rivaroxaban in preventing recurrent VTE during acute treatment or when continued longer term for secondary prevention, because the 95% confidence intervals surrounding the hazard ratio were wide and crossed 1. The Committee also noted that the ERG had performed a network meta-analysis which showed no difference between dabigatran etexilate and rivaroxaban and that the 95% credible intervals surrounding the estimate were also wide. The Committee concluded that no difference had been demonstrated between dabigatran etexilate, warfarin and rivaroxaban in treating VTE and preventing recurrent events.

4.8   The Committee considered the effectiveness and safety of dabigatran etexilate in people with active cancer. It was aware that in clinical practice in England, standard care for people with active cancer who have a DVT or PE is at least 6 months' treatment with LMWH, with a review about whether to continue treatment at that point. It was also aware that LMWH is used rather than warfarin, because LMWH has been demonstrated to be more effective than warfarin in people with cancer. The Committee noted that only around 4% of people in the RE-COVER and RE-MEDY trials had active cancer, and agreed with the ERG's view that the definition of active cancer used in the trials was broader and would include more people than the definition of active cancer used in clinical practice in England. The Committee further noted that there were no head-to-head data comparing dabigatran etexilate with LMWH in people with active cancer available. The Committee concluded that there were insufficient data to assess the effectiveness and safety of dabigatran etexilate in people with active cancer who had a DVT or PE, and that it was not possible to make a specific recommendation for this group of people.

4.9   The Committee considered the rates of adverse events in people taking dabigatran etexilate. It noted that fewer people taking dabigatran etexilate in the RE-COVER and RE-MEDY trials had a major bleeding event compared with warfarin, but the confidence intervals surrounding the estimates crossed 1. The rate of major or clinically relevant bleeding, or any bleeding, was lower in these trials in people having dabigatran etexilate compared with warfarin (tables 1 to 3, section 3.5). The Committee also highlighted that there were fewer people in the trials who had an intracranial haemorrhage while taking dabigatran etexilate than while taking warfarin. It noted, and the clinical expert agreed, that the trial data suggest there is a tendency towards lower risk of intracranial haemorrhage in people taking the new oral anticoagulants (dabigatran etexilate, rivaroxaban, and apixaban) compared with warfarin across the indications for these drugs. The Committee noted that there were no significant differences between rates of major bleeds in either the company's adjusted indirect comparison or the ERG's network meta-analysis comparing dabigatran etexilate with rivaroxaban. The Committee observed that more people had an acute coronary syndrome event when having dabigatran etexilate compared with warfarin in RE-MEDY, but understood that this has been thought to reflect a protective effect of warfarin, rather than an adverse effect of dabigatran etexilate. It concluded that dabigatran etexilate had an acceptable safety profile compared with warfarin and

rivaroxaban.

Cost effectiveness

4.10   The Committee noted that the company had presented 2 base-case analyses: 1 for acute treatment and 1 for treatment and prevention of recurrent VTE ('secondary prevention'). It noted that the ERG had made a series of corrections to errors in the model which the company had agreed were appropriate. The Committee noted that in the acute treatment base case, the company had assumed that treatment would last for 6 months. In the treatment and secondary prevention base case, people were assumed to receive anticoagulation treatment for 6 to 18 months, depending on whether rivaroxaban or warfarin was the comparator. The Committee heard from the clinical expert that the risks and benefits of continuing treatment vary between people, but that a significant proportion of people continue treatment for the rest of their lives (see section 4.3). It considered that a large percentage of people needing long-term anticoagulation would have it indefinitely, but the company had not tested the effect of life-long treatment in its base case or sensitivity analyses. The Committee noted the ERG's scenario for life-long treatment, which increased the company's base-case incremental cost-effectiveness ratio (ICER) for dabigatran etexilate compared with warfarin (with ERG model corrections included) from £9973 to £15,634 per quality-adjusted life year (QALY) gained. The Committee further noted that the company had not included the cost and utility decrement of myocardial infarction and dyspepsia (indigestion) in its base case, but tested the effect of cardiac events in a sensitivity analysis which resulted in only a modest increase in the ICER for dabigatran etexilate compared with warfarin. The Committee concluded that it was appropriate to present base cases for acute treatment and treatment with secondary prevention separately, but that it should be assumed in the secondary prevention base case that treatment would be life-long for most people whose condition needs treatment beyond 6 months.

4.11   The Committee noted the company's assumption that there would be a disutility associated with warfarin therapy of -0.012. It noted that this disutility had also been applied for warfarin therapy in NICE technology appraisal guidance on rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE and rivaroxaban for treating PE and preventing recurrent VTE. The Committee

understood the ERG's concerns that the utility decrement was derived solely from a small study including just 48 people. The Committee heard that qualitative research on warfarin treatment suggested that people were anxious about being in the appropriate INR therapeutic range and whether they were taking the correct dose of warfarin. They also found warfarin monitoring visits to be inconvenient, and the dietary considerations associated with taking warfarin had a detrimental effect on their quality of life. The Committee noted that in the company's model, the utility decrement associated with warfarin was greater than that associated with injections of LMWH. It heard from the patient expert that this was reasonable, because people are willing to accept the negative effects of LMWH as a part of initial short-term treatment. In contrast, because warfarin is taken for a longer time, the cumulative effect on quality of life would likely be greater. The Committee concluded that warfarin treatment, particularly if life-long, could be expected to reduce quality of life but the extent to which it did so was uncertain. It further concluded that although the company's estimate of utility decrement was based on limited evidence, it was the best estimate available and had been accepted as reasonable in previous appraisals.

4.12   The Committee discussed the company's assumptions relating to the frequency and cost of warfarin monitoring. It noted that the company assumed all people having warfarin would have an initial appointment with a consultant, 4 monitoring visits while their dose of warfarin was titrated, and then monthly visits to check that their INR was within the therapeutic range for the remainder of treatment. The company had assumed that the initial consultant-led visit would cost £62.56, and estimated that follow-up INR visits would cost on average £28 per visit. This resulted in a monitoring cost of £482.41 for the first year of treatment. The Committee noted that the ERG had assumed that the cost of INR follow-up visits would be lower (£10.61 per visit) because they would all be done by a nurse, rather than some being consultant-led. The ERG's assumptions on INR visit costs resulted in a first-year cost of £221.71, less than half the company's original estimate. The Committee also noted that the ERG believed that people would have fewer warfarin monitoring visits (once every 3 months) than the company had suggested during the secondary prevention period. The Committee heard from both the patient expert and clinical expert that it was difficult to give a precise estimate of the cost of warfarin monitoring, because the structure of warfarin monitoring services varies widely and there is no definitive average monitoring cost available for the NHS. The Committee understood from previous

technology appraisals of dabigatran etexilate, rivaroxaban and apixaban that the estimates of warfarin monitoring costs from the companies and ERGs varied widely. It noted that in NICE technology appraisal guidance on rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE, the ERG's estimate of £320 for 15 visits in the first year had been considered more reasonable than the company's estimate of £656 for 24 visits. Similarly, in NICE technology appraisal guidance on rivaroxaban for treating PE and preventing recurrent VTE, the ERG's estimate of £304 to £379 for 12 to 15 visits had been considered more reasonable than the company's estimate of £607 for 24 visits in the first year. The Committee noted that some people need more frequent monitoring than others because their INR is more difficult to control. This combined with the variable warfarin monitoring arrangements throughout the NHS meant that estimating the average cost was very difficult. The Committee concluded that the company's estimate was higher than figures previously accepted as reasonable, but that the ERG's was lower.

4.13   The Committee discussed the ERG's exploratory base case for acute treatment, noting that it included 13 scenarios. The ICER for dabigatran etexilate compared with warfarin increased from £831 per QALY gained in the company's corrected base case to £18,240 per QALY gained in the ERG's exploratory analysis (incremental cost £223, incremental QALYs 0.012). The main reason for this higher ICER was the warfarin monitoring costs assumed by the ERG (see section 4.12). The Committee concluded that the most plausible ICER could not be determined for dabigatran etexilate compared with warfarin for acute treatment, but even if it accepted the ERG's exploratory analysis the ICER remained in the range which could be considered a cost-effective use of NHS resources. In the comparison with rivaroxaban, both the company and the ERG calculated that dabigatran etexilate dominated rivaroxaban (that is, dabigatran etexilate was both less costly and more effective than rivaroxaban). However, the Committee noted that neither the company nor the ERG had found any significant difference in efficacy between the 2 treatments in their indirect comparisons, and that the costs were also very similar. This would result in the ICER estimates being sensitive to small changes in the costs or QALYs having a large effect on the ICER. Therefore, the Committee accepted that dabigatran etexilate could be recommended as an option for the acute treatment of DVT and PE as an alternative to warfarin or rivaroxaban.

4.14   For the combined treatment and secondary prevention of VTE the ERG presented an exploratory base case and an incremental analysis. The Committee noted that the ICER for dabigatran etexilate compared with warfarin was £9973 per QALY gained in the company's corrected base case, and £35,786 per QALY gained in the ERG's exploratory analysis. The Committee was aware that the ERG had included 16 scenarios in its exploratory base case, and the main factors increasing the ICER were: assuming life-long secondary prevention for all patients (section 4.9), resulting in an ICER of £15,634 per QALY gained; assuming that warfarin monitoring in the secondary prevention period was less frequent (once every 3 months rather than monthly), resulting in an ICER of £15,208 per QALY gained; and assuming a lower cost of each warfarin monitoring visit (section 4.12), resulting in an ICER of £17,419 per QALY gained. The Committee noted that the scenarios included in the ERG exploratory base case interacted, and it was difficult to determine the ICER if the Committee did not accept all of the assumptions that the ERG had included. In particular, the Committee considered that the ERG's assumptions surrounding frequency and cost of warfarin monitoring visits were more conservative than assumptions accepted as reasonable in previous appraisals (see section 4.12). Combining these assumptions had a cumulative effect, driving the ICER towards £35,000 per QALY gained, but applying them separately resulted in ICERs of less than £20,000 per QALY gained. The Committee concluded that the ICER for dabigatran etexilate compared with warfarin for the treatment and secondary prevention of VTE was uncertain because of the lack of an average NHS warfarin monitoring cost, as well as uncertainty about the proportion of people who would stay on treatment for the rest of their lives. Although the company's base case was likely to be too low, the ERG's exploratory base case for treatment and secondary prevention, including conservative assumptions surrounding warfarin monitoring costs, may have overestimated the ICER. The Committee was prepared to accept that the ICER probably lay somewhere between the 2 estimates. In the comparison with rivaroxaban, the Committee noted that rivaroxaban was extendedly dominated by dabigatran etexilate. The Committee also noted that dabigatran etexilate and rivaroxaban had not been shown to have different efficacy, and their costs were very similar. This resulted in an ICER that was highly sensitive to changes in costs and QALYs. The Committee concluded that, on balance, dabigatran etexilate could be considered a clinically and cost-effective option for the treatment and secondary prevention of VTE.

Summary of appraisal committee's key conclusions

TA327	Appraisal title: Dabigatran etexilate for treating and preventing recurrent deep vein thrombosis and pulmonary embolism	Section
Key conclusion		
Dabigatran etexilate is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.		1.1
The most plausible ICER for dabigatran etexilate compared with warfarin for acute treatment could not be determined, but both the company's and the ERG's exploratory ICER remained in the range which could be considered a cost-effective use of NHS resources that is, both were under £20,000 per QALY gained. Neither the company nor the ERG had found any significant difference in efficacy between dabigatran etexilate and rivaroxaban for acute treatment of venous thromboembolism in their indirect comparisons, and the costs were also very similar between these 2 treatments.		4.13
For combined treatment and secondary prevention of VTE, the Committee considered that although the company's base case ICER for dabigatran etexilate compared with warfarin was likely to be too low (£9973 per QALY gained), the ERG's exploratory base case for dabigatran etexilate compared with warfarin (£35,786 per QALY gained) may have overestimated the ICER. The Committee was prepared to accept that the ICER probably lay somewhere between the 2 estimates. The Committee also noted that dabigatran etexilate and rivaroxaban had not been shown to have different efficacy, and their costs were very similar.		4.14
Current practice		

Clinical need of patients, including the availability of alternative treatments	DVT and PE are treated with immediate parenteral anticoagulation, most commonly with a low molecular weight heparin (LMWH) delivered by subcutaneous injection together with an oral vitamin K antagonist such as warfarin. Warfarin treatment can be continued for secondary prevention of recurrent DVT or PE. Rivaroxaban, an oral anticoagulant is an alternative treatment option for treating DVT and PE and prevention of recurrent DVT and PE.	4.2
	People welcome having the choice of new oral anticoagulants such as rivaroxaban and dabigatran etexilate, because they avoid the need for the monitoring and dose adjustments associated with warfarin.	4.4
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?	People welcome having the choice of new oral anticoagulants such as rivaroxaban and dabigatran etexilate, because they avoid the need for the monitoring and dose adjustments associated with warfarin.	4.4
What is the position of the treatment in the pathway of care for the condition?	Dabigatran etexilate is taken following treatment with a parenteral anticoagulant for at least 5 days.	2.1
	There is variation in the length of treatment with anticoagulants following an initial deep vein thrombosis or pulmonary embolism and the decision to continue is dependent on the risks and benefits for the patient as well as their own choice. There are some people who may have life-long anticoagulation following a DVT or PE.	4.3

Adverse reactions	There were no differences between dabigatran etexilate and warfarin and rivaroxaban in the rates of major bleeds. The Committee observed that more people had an acute coronary syndrome event when having dabigatran compared with warfarin in RE-MEDY, but understood that this has been thought to reflect a protective effect of warfarin, rather than an adverse effect of dabigatran. It concluded that dabigatran had an acceptable safety profile compared with warfarin and rivaroxaban.	4.9
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	There were 4 dabigatran trials included in the company's submission: RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE. The Committee accepted the company's statement that all relevant data had been submitted for the appraisal.	4.5
	The Committee concluded that the dabigatran trials were generalisable to people who would receive the 150 mg dose in clinical practice in England. Although there was some uncertainty as to whether the 110 mg dose (because there were no clinical data) would be equally effective in treating and preventing recurrent VTE in those people for whom it is recommended, the Committee concluded that dabigatran etexilate should be appraised in accordance with its marketing authorisation.	4.6

Relevance to general clinical practice in the NHS	The dabigatran trials were generalisable to people who would receive the 150 mg dose in clinical practice in England. The Committee was concerned that there were no clinical trial data on the 110 mg dose for the treatment and secondary prevention of DVT and PE. It heard from the company that the European Medicines Agency requested pharmacokinetic data on plasma levels of dabigatran in people having the 150 mg or 110 mg doses in the RE-LY trial for atrial fibrillation, and pharmacokinetic data from the trials for DVT and PE. Safety data for the 110 mg dose were available from the RE-LY trial.	4.6
Uncertainties generated by the evidence	The 95% confidence intervals surrounding the estimates of the relative efficacy of dabigatran etexilate compared rivaroxaban presented by the company and the ERG were wide.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee concluded that there were insufficient data to assess the effectiveness and safety of dabigatran etexilate in people with active cancer who had a DVT or PE, and that it was not possible to make a specific recommendation for this group of people.	4.8
Estimate of the size of the clinical effectiveness including strength of supporting evidence	In the dabigatran trials comparing dabigatran etexilate with warfarin and in the company's adjusted indirect comparison of dabigatran etexilate with rivaroxaban no difference was demonstrated between dabigatran etexilate and warfarin and dabigatran etexilate and rivaroxaban in treating VTE and preventing recurrent events.	4.7
Evidence for cost effectiveness		

Availability and nature of evidence	The Committee noted that the company had presented 2 base-case analyses: 1 for acute treatment and 1 for treatment and prevention of recurrent VTE ('secondary prevention'). The Committee considered it was appropriate for the company to present base cases for acute treatment and treatment with secondary prevention separately, but that it should be assumed in the secondary prevention base case that treatment would be life-long for most people who require treatment beyond 6 months.	4.10
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee heard that it was difficult to give a precise estimate of the cost of warfarin monitoring, because the structure of warfarin monitoring services varies widely and there is no definitive average monitoring cost available for the NHS. The Committee concluded that the company's estimate of warfarin monitoring costs was higher than figures previously accepted as reasonable in previous appraisals, but that the ERG's was lower.	4.12
	Warfarin treatment, particularly if life-long, could be expected to reduce quality of life but the extent to which it did so was uncertain. The Committee concluded that although the company's estimate of utility decrement was based on limited evidence, it was the best estimate available and had been accepted as reasonable in previous appraisals.	4.11

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?	None identified.	
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	
What are the key drivers of cost effectiveness?	The acute treatment base case ICER for dabigatran etexilate compared with warfarin was sensitive to the warfarin monitoring costs assumed by the ERG.	4.13
	In the ERG's exploratory base case for treating and preventing recurrent VTE and the main factors increasing the ICER for dabigatran etexilate compared with warfarin were: assuming life-long secondary prevention resulting in an ICER of £15,634 per QALY gained; assuming that warfarin monitoring in the secondary prevention period was less frequent (once every 3 months rather than monthly), resulting in an ICER of £15,208 per QALY gained; and assuming a lower cost of each warfarin monitoring visit resulting in an ICER of £17,419 per QALY gained.	4.14

	For both acute treatment and secondary prevention of VTE, the Committee noted that neither the company nor the ERG had found any difference in efficacy between the dabigatran etexilate and rivaroxaban treatments in their indirect comparisons, and that the costs were also very similar. This resulted in the ICER estimates being sensitive to small changes in the costs or QALYs.	4.13, 4.14
Most likely cost-effectiveness estimate (given as an ICER)	The most plausible ICER for dabigatran etexilate compared with warfarin for acute treatment was uncertain, but both the company's and the ERG's exploratory ICER remained in the range which could be considered a cost-effective use of NHS resources that is, both were under £20,000 per QALY gained. Neither the company nor the ERG had found any significant difference in efficacy between dabigatran etexilate and rivaroxaban for acute treatment of venous thromboembolism in their indirect comparisons, and the costs were also very similar between these 2 treatments.	4.13

	For combined treatment and secondary prevention of VTE, the Committee considered that although the company's base case ICER for dabigatran etexilate compared with warfarin was likely to be too low (£9973 per QALY gained), the ERG's exploratory base case for dabigatran etexilate compared with warfarin (£35,786 per QALY gained) may have overestimated the ICER. The Committee was prepared to accept that the ICER probably lay somewhere between the 2 estimates. The Committee also noted that dabigatran etexilate and rivaroxaban had not been shown to have different efficacy, and their costs were very similar.	4.14
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No equalities issues were discussed.	

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 deep vein thrombosis or pulmonary embolism and the doctor responsible for their care thinks that dabigatran etexilate 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)
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 Gerardine Bryant
GP, Swadlincote, Derbyshire

Matthew Campbell-Hil

Lay member

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital, Bristol

Dr Sharon Saint Lamont
Head of Clinical Quality, NHS England (North)

Mr Cliff Snelling
Lay member

Dr Ian Lewin
Honorary Consultant Physician and Endocrinologist, North Devon District Hospital

Dr Louise Longworth
Reader in Health Economics, HERG, Brunel University

Dr Alec Miners
Senior Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Pamela Rees
Lay member

Dr Ann Richardson
Lay member

Dr Paul Robinson
Medical Director, Merck Sharp & Dohme

Ellen Rule
Director of Transformation and Service Redesign, Gloucestershire CCG

Stephen Sharp
Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Peter Sims
GP, Devon

Dr John Watkins

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

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

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.

Mary Hughes

Technical Lead

Fay McCracken

Technical Adviser

Bijal Joshi

Project Manager

7 Sources of evidence considered by the committee

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

- Edwards S, Wakefield V, Thurgar, et al., dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism, August 2014

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 and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Boehringer Ingelheim (dabigatran etexilate)

II. Professional/specialist and patient/carer groups:

- AntiCoagulation Europe (ACE)

- British Cardiovascular Society

- British Society for Haematology

- Clinical Leaders of Thrombosis (CLOT)

- Lifeblood: The Thrombosis Charity

- Royal College of Nursing

- Royal College of Pathologists

- Royal College of Physicians

- 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 and Social Services and Public Safety, Northern Ireland (DHSSPSNI)

- Healthcare Improvement Scotland

- LEO Pharma (tinzaparin)

- National Institute for Health Research Technology Assessment Programme

- Sanofi (enoxaparin)

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 dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism by attending the initial Committee discussion and providing written evidence to the Committee.

- Dr Peter MacCallum, Senior Lecturer and Honorary Consultant Haematologist, nominated by organisation representing British Cardiovascular Society – clinical expert

- Ms Diane Eaton, Project Manager for ACE, nominated by organisation representing AntiCoagulation Europe (ACE) – patient expert

E. 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.

- Boehringer Ingelheim

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