

Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism

Technology appraisal guidance
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1 Guidance

- 1.1 Rivaroxaban is recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

2 The technology

- 2.1 Rivaroxaban (Xarelto, Bayer) is indicated for the 'treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults'. For the initial treatment of acute pulmonary embolism, the recommended dosage of rivaroxaban is 15 mg twice daily for the first 21 days followed by 20 mg once daily for continued treatment and prevention of recurrent venous thromboembolism.
- 2.2 Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism (NICE technology appraisal guidance 261) recommends rivaroxaban as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults.
- 2.3 The duration of treatment recommended in the summary of product characteristics depends on bleeding risk and other clinical criteria. Short-term treatment (at least 3 months) is recommended for people with transient risk factors such as recent surgery and trauma. Longer treatment is recommended for people with permanent risk factors, or idiopathic (unprovoked) deep vein thrombosis or pulmonary embolism. A reduced dosage of 15 mg twice daily for 21 days followed by 15 mg once daily should be used in people with moderate (creatinine clearance 30–49 ml/min) or severe (creatinine clearance 15–29 ml/min) renal impairment if their risk of bleeding outweighs the risk of recurrent deep vein thrombosis or pulmonary embolism.
- 2.4 The summary of product characteristics lists the following adverse reactions for rivaroxaban: anaemia, dizziness, headache, fainting, bleeding events, tachycardia (rapid heartbeat), low blood pressure, haematoma, stomach pain, dyspepsia (heartburn), nausea, constipation, diarrhoea, vomiting, pruritus (itching), rash, bruising, pain in the extremities, fever, and swelling, especially of the ankles and feet. For full details of side effects and contraindications, see the summary of product characteristics.

- 2.5 Rivaroxaban costs £2.10 per 15-mg or 20-mg tablet ('British national formulary' edition 65). The cost of treatment is estimated to be £235.86, £427.61 and £811.13 for 3, 6 and 12 months of treatment respectively. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of rivaroxaban and a review of this submission by the Evidence Review Group (ERG; [section 10](#)).

- 3.1 The key clinical evidence in the manufacturer's submission came from EINSTEIN-PE, an international, event-driven, open-label, assessor-blind, non-inferiority study. The study included 4832 people in an intention-to-treat population. Treatment duration was 3, 6 or 12 months and this was determined by a study investigator before randomisation based on the risk profile of each person and local preferences. Patients were randomised to either rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily for the intended treatment duration, or to enoxaparin (a low molecular weight heparin [LMWH]) 1.0 mg/kg twice daily until anticoagulation was established plus a vitamin K antagonist (either warfarin or acenocoumarol), which was dose adjusted to maintain the international normalised ratio (INR) within a therapeutic range of 2.0 to 3.0 with a target of 2.5. Enoxaparin was administered for at least 5 days and was stopped when the INR was more than 2.0 on 2 consecutive measurements at least 24 hours apart. There was an advised overlap with the vitamin K antagonist of 4 to 5 days. Patients were assessed during their intended treatment duration, followed by a 30-day observation period. The manufacturer noted that there was a difference in the dose of enoxaparin used in the trial and the dose covered by the European and UK licence (that is, 1.5 mg/kg once daily for at least 5 days and until adequate oral anticoagulation is established).
- 3.2 Out of the whole study population, 5.2% were allocated to receive 3 months of treatment, 57.4% to 6 months of treatment and 37.4% to 12 months of treatment. The median time from onset of symptoms to randomisation was 4 days. The EINSTEIN-PE study allowed a limited amount of treatment before randomisation. A similar proportion of patients in the rivaroxaban arm (92.5%) and the LMWH/VKA arm (92.1%) received pre-randomisation anticoagulation ($p=0.62$, post-hoc binomial test). Among those who received pre-randomisation anticoagulation, 62.5% of patients received anticoagulation for 1 day (the maximum

duration permitted was 48 hours).

- 3.3 In the intention-to-treat population, the mean age was 58 and approximately 53% of the patients were male. Around 25% of patients in both treatment arms had a concurrent deep vein thrombosis. Pulmonary embolism was unprovoked in 65% of patients receiving rivaroxaban and 64% of patients receiving LMWH with a vitamin K antagonist (hereafter referred to as LMWH/VKA). Approximately 5% of people in both treatment arms had active cancer, and 19% and 20% of people in the rivaroxaban and LMWH/VKA treatment arms respectively had experienced a previous venous thromboembolism. EINSTEIN-PE excluded people with a creatinine clearance of less than 30 ml/min and people for whom rivaroxaban was not suitable or who had contraindications to enoxaparin, warfarin or acenocoumarol. A total of 555 (11.5%) patients discontinued treatment; the number of people who discontinued was similar in both treatment groups ($p=0.07$).
- 3.4 The primary efficacy end point for EINSTEIN-PE was symptomatic recurrent venous thromboembolism, which was a composite end point comprising recurrent deep vein thrombosis or pulmonary embolism. This included both fatal and non-fatal pulmonary embolism, and unexplained death for which a pulmonary embolism could not be ruled out. In the intention-to-treat population (rivaroxaban $n=2419$; LMWH/VKA $n=2413$), rivaroxaban met the pre-specified non-inferiority criterion, which required the upper bound of the 95% confidence interval of the hazard ratio to be less than 2. Symptomatic recurrent venous thromboembolism events occurred in 50 (2.1%) patients in the rivaroxaban arm compared with 44 (1.8%) patients in the LMWH/VKA arm (hazard ratio [HR] 1.12; 95% confidence interval [CI] 0.75 to 1.68).
- 3.5 The primary safety outcome for EINSTEIN-PE was clinically relevant bleeding, that is, major bleeding and clinically relevant non-major bleeding in the safety population, which consisted of all patients who had received at least 1 dose of the study drug (rivaroxaban $n=2412$; LMWH/VKA $n=2405$). There was no difference between rivaroxaban and LMWH/VKA in clinically relevant bleeding that was experienced by 249 (10.3%) and 274 (11.4%) patients in each treatment arm respectively (HR 0.90, 95% CI 0.76 to 1.07). The proportion of patients who

experienced major bleeding was statistically significantly lower with rivaroxaban (1.1%) than with LMWH/VKA (2.2%) (HR 0.49, 95% CI 0.31 to 0.79, $p=0.003$). In the intended treatment period, there were a similar number of deaths in the rivaroxaban arm (58 deaths) and the LMWH/VKA arm (50 deaths) (HR 1.13, 95% CI 0.77 to 1.65). Treatment-emergent adverse events (other than bleeding and recurrent venous thromboembolism) were similar between the treatment arms. Approximately 5% of patients in the rivaroxaban arm and 4% in the LMWH/VKA arm discontinued treatment because of an adverse event.

- 3.6 The manufacturer reported a time in therapeutic range for the comparator LMWH/VKA of 62.7% across all centres. The manufacturer highlighted that guidelines from the National Patient Safety Agency and the Scottish Executive Health Department recommend a time in therapeutic range of at least 60%. It also noted there was no statistical interaction observed in EINSTEIN-PE between time in therapeutic range and treatment effect.
- 3.7 Health-related quality of life was not measured in EINSTEIN-PE. The manufacturer described 2 measures of treatment satisfaction that had been measured: the Anti-Clot Treatment Scale (ACTS) and the Treatment Satisfaction Questionnaire (TSQM). Treatment satisfaction was not used to derive any of the utility values used in the economic analysis.
- 3.8 The manufacturer presented the results for a number of subgroups considered in EINSTEIN-PE, which included the 3 subgroups specified in the final scope issued by NICE. These were groups based on underlying risk of bleeding, provoked compared with unprovoked venous thromboembolism, and the presence or absence of cancer. The manufacturer used the intended treatment duration as a proxy for bleeding risk. The manufacturer tested for a statistically significant interaction between each subgroup and the primary efficacy and safety outcomes. The outcomes of the statistical interaction tests are academic in confidence, so the results cannot be presented in this document. The manufacturer also presented graphically the relative efficacy across subgroups, including the 3 subgroups specified in the final scope issued by NICE. The manufacturer presented similar results for the major and clinically relevant non-major bleeding outcome (with the exception of the

idiopathic and non-idiopathic groups). The 95% confidence intervals surrounding the hazard ratios for all outcomes overlapped across the subgroups, suggesting a consistency of effect.

- 3.9 The manufacturer highlighted that in the comparator arm of the trial, patients with cancer had received LMWH/VKA, whereas standard care in the UK is LMWH alone. The manufacturer did not consider it appropriate to conduct a network meta-analysis to estimate the relative effectiveness of rivaroxaban compared with LMWH in people with cancer who had experienced a pulmonary embolism. This was because of the heterogeneity of the studies assessing long-term treatment of venous thromboembolism in people with cancer, which the manufacturer had identified and presented in its submission for [NICE technology appraisal guidance 261](#).
- 3.10 The manufacturer constructed a Markov model to evaluate the consequences of 3-, 6- and 12-month, and lifelong, treatment with rivaroxaban for preventing recurrent venous thromboembolism in people who experience an acute pulmonary embolism. The model used a time horizon of 40 years and a cycle length of 3 months. To reflect the change in the risk patients experience over time, different risks were applied in cycle 1 (months 0–3), 2 (months 3–6), 3 and 4 (months 6–12) and 5 onwards (12 months onwards). The evaluation was undertaken from an NHS and personal social services perspective, and costs and utilities were discounted at 3.5% per year after the first year.
- 3.11 For people initially treated for 3, 6 or 12 months, there were 13 health states including death. The lifelong treatment model contained an additional state. People entered the model after their index pulmonary embolism to an on-treatment state in which they received 3-, 6-, 12-month or lifelong treatment with rivaroxaban or LMWH/VKA. They then either stayed on treatment, experienced a recurrent venous thromboembolism (pulmonary embolism or deep vein thrombosis), experienced an adverse event (clinically relevant non-major bleed, major intracranial bleed, or major extracranial bleed), moved to an off-treatment health state, entered a long-term complication state (for example, chronic thromboembolic pulmonary hypertension), or died. The additional state in the lifelong treatment model was for people who had

experienced a deep vein thrombosis in the timeframe of the model and who had not stopped treatment for other reasons. All patients who experienced a deep vein thrombosis after their index pulmonary embolism were at risk of post-thrombotic syndrome. There was not a separate health state for post-thrombotic syndrome, rather the consequences of post-thrombotic syndrome were applied as disutilities and costs to patients in both the on- and off-treatment post-deep vein thrombosis health states.

- 3.12 The modelled cohort was adults with an acute pulmonary embolism who matched the licensed indication, the EINSTEIN-PE trial population and the stated decision problem. Data from EINSTEIN-PE were used to inform the clinical effectiveness of treatments and to derive the transition probabilities used in the model; this was supplemented with data from the manufacturer's systematic reviews. All drug acquisition costs and resources associated with acute treatment hospital stay, monitoring, recurrent thromboembolic events and adverse events (that is, bleeding events) were included in the model.
- 3.13 A validated preference-based measure of quality of life was not measured in EINSTEIN-PE; the manufacturer derived the utility values used in the model through systematic review. The manufacturer assigned a baseline utility value of 0.825 to all patients with pulmonary embolism entering the model, which was taken from a survey of the UK general population using a visual analogue scale rating and adjusted with disutility values for deep vein thrombosis, pulmonary embolism, extracranial bleed, intracranial bleed and post-thrombotic syndrome. All people who had an intracranial bleed moved to a post-intracranial bleed health state in the next cycle of the model after their bleed. The utility value assumed for an intracranial bleed was 0.33, which increased to 0.71 in the post-intracranial bleed state. A disutility due to warfarin therapy of 0.012 was applied in the LMWH/VKA arm.
- 3.14 Base-case results were presented for the 3-, 6-, 12-month and lifelong treatment durations. For the 3-, 6- and 12-month treatment durations, rivaroxaban dominated LMWH/VKA, that is, rivaroxaban was less costly and more effective (0.027, 0.013 and 0.019 incremental quality-adjusted life years [QALYs] and a £395.80, £213.21 and £133.13 reduction in total

costs for the 3-, 6- and 12-month treatment groups respectively). In the lifelong treatment analysis, rivaroxaban was associated with an incremental cost-effectiveness ratio (ICER) compared with LMWH/VKA of £13,252 per QALY gained (0.104 incremental QALYs for an extra £1374.73).

- 3.15 The manufacturer performed 123 deterministic sensitivity analyses for each of the 4 durations of treatment. For the 3-, 6- and 12-month treatments, the net monetary benefit for rivaroxaban compared with LMWH/VKA was positive for all analyses if the maximum acceptable ICER was £20,000 per QALY gained. Cost effectiveness of lifelong treatment with rivaroxaban was most sensitive to changes in the frequency of INR-monitoring visits, where the ICER increased from £13,252 per QALY gained to £27,914 per QALY gained if people have 3, rather than 5, visits in each quarter after the first. The manufacturer conducted 1 scenario analysis, in which the time horizon was reduced from 40 to 5 years. With a 5-year time horizon, rivaroxaban continued to dominate LMWH/VKA for the 3-, 6- and 12-month treatment durations. For the lifelong treatment duration, reducing the time horizon to 5 years decreased the ICER of rivaroxaban compared with LMWH/VKA to £12,282 per QALY gained. Probabilistic sensitivity analysis demonstrated that there was a 99.9%, 95.9%, 93.7% and 59.1% probability that the base-case ICER for the 3-, 6-, and 12-month and lifelong treatments was lower than £20,000 per QALY gained.
- 3.16 The ERG considered that overall, the manufacturer's submission provided an unbiased estimate of the treatment effect of rivaroxaban. The ERG stated that it was based on a well-conducted systematic review of clinical effectiveness, which identified 1 relevant randomised controlled trial. It considered the trial to be of reasonable quality with a low risk of bias.
- 3.17 The ERG raised concerns that the patient population in the trial may not be fully representative of the treatment population in the UK. In particular, it stated that patients with severe renal impairment (a creatinine clearance of 15–29 ml/min) were excluded from the trial. The ERG noted that the summary of product characteristics specifies that rivaroxaban can be used with caution with dose reductions if needed in

this group of patients. The ERG stated that as these patients are at higher risk of bleeding and were excluded from the trial, it is possible that the trial may have underestimated the rate of bleeding that may be seen in clinical practice with rivaroxaban.

- 3.18 The ERG noted that the trial only assessed outcomes up to a 12-month treatment period; therefore, effectiveness and safety of long-term treatment with rivaroxaban is unknown. The ERG stated that the manufacturer's Kaplan-Meier plot of cumulative venous thromboembolism rates suggested a worsening of the relative hazard of recurrent venous thromboembolism while on rivaroxaban, compared with LMWH/VKA, towards the end of the 12-month treatment period. The ERG commented that it is plausible that the hazard of recurrent venous thromboembolism might worsen further if treatments are compared in the longer term, particularly if adherence to rivaroxaban (which does not need the regular monitoring of vitamin K antagonists) declines. The ERG suggested that the long-term adherence to rivaroxaban may be lower than the 80% plus observed in most of the patients in EINSTEIN-PE.
- 3.19 The ERG considered the manufacturer's subgroup analyses. The ERG suggested that the outcomes may be worse in the active cancer group than those seen for other patients because of increased bleeding risk. The ERG noted that the manufacturer's presentation of subgroup data suggested consistency across the subgroups in terms of the relative safety and efficacy. It considered that because of the small numbers of people in the trial who had cancer, differences in the incidence of bleeding may not have been apparent because of the small number of events recorded in each treatment arm. The ERG also noted the 95% confidence intervals around the hazard ratio for recurrent venous thromboembolism in patients with active cancer presented by the manufacturer were wide, and suggested this indicated that there is uncertainty around where the true effect lies and that the manufacturer's analysis of efficacy in the cancer subgroup should be interpreted with caution. The ERG had concerns that the manufacturer had used intended treatment duration as a proxy for both underlying risk of bleeding and provoked or unprovoked pulmonary embolism. However, it suggested that there are no robust markers for determining length of treatment in advance, which suggests that pre-specified treatment durations may not

be a good proxy for other variables.

- 3.20 The ERG considered the structure adopted for the economic model to be reasonable, consistent with current clinical understanding of pulmonary embolism and consistent with the previous economic evaluations of treatments for venous thromboembolism, such as the submission for [NICE technology appraisal guidance 261](#). The ERG also considered that the parameters used in the model were generally appropriate and that the population used in the model, drawn from EINSTEIN-PE, is broadly representative of the pulmonary embolism population in the UK (with the exception that it did not include people for whom rivaroxaban is contraindicated or people with severe renal impairment who may still be eligible for rivaroxaban).
- 3.21 The ERG noted that all transition probabilities were treatment-specific in the lifelong model but that there appeared to be an error in the model, because after 36 months, the probability of recurrent venous thromboembolism and bleeding events were the same for rivaroxaban and LMWH/VKA. The ERG stated that the probabilities of these events after 36 months were not explicitly stated in the manufacturer's submission. The ERG believed this to be an unintended error and corrected the model so that the treatment effect of rivaroxaban after 36 months was applied to the LMWH/VKA transition probabilities. After this amendment, the ICER for rivaroxaban compared with LMWH/VKA in the lifelong treatment analysis was reduced from £13,252 per QALY gained to £7072 per QALY gained. For all of the subsequent analyses, the ERG incorporated this correction and referred to this as the amended base case. The amended probabilistic base-case ICER for rivaroxaban compared with LMWH/VKA was £7019 per QALY gained.
- 3.22 The ERG had concerns about some of the utility values used in the manufacturer's model, particularly as some of the sources of utility values identified and used by the manufacturer were small studies or did not use the EQ-5D instrument that is the preferred measure of health related quality of life in adults in NICE's reference case. The ERG considered the utility value of 0.33 for an intracranial bleed, based on a study of 129 people that had used time trade off rather than the EQ-5D to derive the utility value that the manufacturer had applied for 3 months

in the intracranial bleed state model, to be low. The ERG identified a prospective, longitudinal study that suggested a utility value of 0.31 immediately after an intracranial bleed (stroke), increasing to 0.55 after 1 month and to 0.61 by 3 months. As the manufacturer had estimated that rivaroxaban was associated with fewer intracranial bleeds than LMWH/VKA, the ERG stated that a mid-value of 0.55 for the intracranial bleed health-state utility value would be a more conservative assumption. The ERG also questioned the manufacturer's choice of utility values for post-thrombotic syndrome. The manufacturer had used a study of 30 healthy volunteers that had used a standard gamble approach to derive a utility value of 0.93 for severe post-thrombotic syndrome. However, the ERG stated that the study of 129 people, which the manufacturer had used to obtain utility values for some of the health states in its model including the utility value for an intracranial bleed, gave a utility value of 0.86 for post-thrombotic syndrome. The ERG did not consider the manufacturer's choice of utility value for post-thrombotic syndrome to be a conservative assumption.

3.23 The ERG was satisfied that the unit costs used in the economic model were relevant and had been obtained using suitable methods. However, it noted that the costs of reversing the effects of rivaroxaban and warfarin in the case of major bleeding or elective surgery had not been included and that these may be significant. The ERG stated that vitamin K, fresh frozen plasma and prothrombin complex concentrate (PCC) are used to reverse bleeding events on warfarin but there is no specific antidote for rivaroxaban. The ERG commented that either activated recombinant factor VIIa or PCC may be considered to manage severe and life-threatening bleeding in patients on rivaroxaban. The ERG's clinical adviser considered that the reversal of bleeding on warfarin is likely to need less PCC than rivaroxaban, and that recombinant factor VIIa may be more effective for reversing rivaroxaban than PCC. The ERG estimated that the cost of treating a patient weighing 70 kg with recombinant factor VIIa is £19,303. The ERG also estimated that the cost of treating a bleed while receiving rivaroxaban with PCC would be £1680, and the maximum cost for treating a bleed on warfarin with PCC concentrate would be £1260.

3.24 The ERG conducted the following exploratory analyses:

- reduction in assumed frequency of INR-monitoring visits
- reduction in mean LMWH treatment length
- reduction in the efficacy of rivaroxaban after 12 months in the lifelong treatment analysis in preventing recurrent venous thromboembolism
- higher hazard of major bleed on rivaroxaban in the lifelong treatment analysis
- higher utility values for the intracranial bleed state
- higher mean age of model population
- costs of emergency anticoagulant reversal taken into account in all cases of major bleeding
- a multiple assumption scenario (reduction in assumed frequency of INR monitoring visits, with a greater proportion of these in secondary care and a greater proportion of the primary care monitoring visits led by nurses; reduction in mean LMWH treatment length; reduction in the efficacy of rivaroxaban after 12 months in the lifelong treatment analysis; higher hazard of major bleed).

3.25 The ERG noted that the manufacturer had assumed 9 INR-monitoring visits in the first quarter for people receiving LMWH/VKA and 5 in each subsequent quarter, and that this was consistent with what the manufacturer presented for [NICE technology appraisal guidance 261](#). The ERG highlighted that in NICE technology appraisal guidance 261, the Committee had concluded that a less intensive INR-monitoring programme of 6 visits in the first 3 months followed by 3 visits every quarter thereafter was reasonable and relevant (when a deep vein thrombosis was the index thromboembolism). The ERG reduced the frequency of INR-monitoring visits to 6 visits in the first quarter and 3 in each subsequent quarter. The ICER for rivaroxaban compared with LMWH/VKA increased from £7072 in the base case to £17,857 per QALY gained in the lifelong treatment duration analysis, and went from dominating LMWH/VKA in the 12-month treatment duration analysis to having an ICER of £3542 per QALY gained. Rivaroxaban continued to dominate LMWH/VKA in the 6-month treatment analysis. The ERG did not present the effect of a reduced INR-monitoring frequency scenario on the 3-month treatment analysis. For the lifelong treatment duration

analysis, the ERG assessed a further scenario of 6 visits in the first quarter and 2 in each subsequent quarter. This assumption increased the ICER for rivaroxaban compared with LMWH/VKA from £7072 to £22,912 per QALY gained.

- 3.26 Assuming a shorter treatment duration with LMWH from the manufacturer's estimate in the base case (derived from the academic-in-confidence average duration in EINSTEIN-PE) of either 9, 8 or 6 days was found to have a minimal cost-saving effect in the 6-month treatment duration analysis. Rivaroxaban continued to dominate LMWH/VKA regardless of treatment duration with LMWH. The ERG did not present the effect of assuming the shorter treatment duration with LMWH on the 3-, 12-month or lifelong treatment duration analyses.
- 3.27 As there was uncertainty surrounding the long-term efficacy and safety of rivaroxaban, the ERG performed scenario analyses that assessed varying efficacy and safety effects of rivaroxaban. The hazard ratio for recurrent venous thromboembolism for rivaroxaban compared with LMWH/VKA was 1.123 for the entirety of the lifelong treatment base case. The ERG assessed 2 scenarios in which the hazard ratio was increased to either 1.5 or 2.0 after 12 months (that is, rivaroxaban was assumed to be increasingly less effective relative to LMWH/VKA). Assuming a hazard ratio of 1.5 for venous thromboembolism after 12 months for the population in the lifelong treatment analysis increased the ICER for rivaroxaban compared with LMWH/VKA from £7072 to £9043 per QALY gained. When a hazard ratio of 2.0 was assumed, the ICER for rivaroxaban compared with LMWH/VKA increased to £14,090 per QALY gained.
- 3.28 In the manufacturer's base-case analyses, the hazard ratio for major bleed for rivaroxaban compared with LMWH/VKA was 0.493. The ERG assessed 2 scenarios in the lifelong treatment duration analysis in which the hazard ratio for major bleeds was increased. In the first scenario, the ERG used a hazard ratio for major bleeds of 0.65. This was taken from the EINSTEIN-DVT trial (one of the key trials supporting the clinical effectiveness of rivaroxaban in the manufacturer's submission for [NICE technology appraisal guidance 261](#)) that compared rivaroxaban with LMWH/VKA in preventing recurrent venous thromboembolism in people

who had experienced a deep vein thrombosis. In this scenario, the ICER for rivaroxaban compared with LMWH/VKA increased from £7072 to £10,070 per QALY gained for the lifelong treatment duration. In the second scenario, the ERG used a hazard ratio for major bleeds of 0.79, which was the upper limit of the 95% confidence interval surrounding the hazard ratio for a major bleed seen in EINSTEIN-PE. Applying this hazard ratio, the ICER for rivaroxaban compared with LMWH/VKA increased from £7072 to £14,177 per QALY gained for the lifelong treatment duration.

- 3.29 Assuming an increased utility value in the intracranial bleed state from 0.33 in the base case to 0.55 (see section 3.22) did not appreciably change the total QALYs and the model outcomes were hardly altered: rivaroxaban continued to dominate LMWH/VKA for 6- and 12-month treatment durations, and in the lifelong treatment analysis the ICER increased from £7072 to £7098 per QALY gained. The ERG did not present the effect of assuming a higher utility value in the intracranial bleed state on the 3-month treatment analysis.
- 3.30 The ERG noted that the base-case analyses used a population with a mean age of 58 years, which is lower than the mean age of some other pulmonary embolism and deep vein thrombosis patient populations described in the literature. However, assuming a higher mean age of the model population from 58 years in the base case to 65 years did not have a large effect on the cost-effectiveness estimates: rivaroxaban continued to dominate LMWH/VKA for 6- and 12-month treatment durations, and for a lifelong treatment, the ICER increased from £7072 to £7911 per QALY gained. The ERG did not present the effect of assuming a higher mean age of the model population on the 3-month treatment analysis.
- 3.31 The ERG assessed 3 scenarios in which the costs of emergency anticoagulant reversal were taken into account. The first scenario assumed that all people received PCC in all cases of major bleeding. This scenario had a modest effect on the base-case analyses for the 12-month and lifelong treatment durations: rivaroxaban continued to dominate LMWH/VKA in the 12-month treatment analysis and the ICER decreased from £7072 to £6868 per QALY gained in the lifelong treatment analysis. The second scenario assumed that people who had a

bleed while taking LMWH/VKA received PCC, whereas those taking rivaroxaban received recombinant factor VIIa. This scenario resulted in an ICER for rivaroxaban compared with LMWH/VKA of £2328 per QALY gained for the 12-month treatment duration, and increased the ICER from £7072 to £19,642 per QALY gained for the lifelong treatment duration. The third scenario assumed the same as the second scenario in terms of treatments received to reverse major bleeding but also assumed that the risk of a major bleed with rivaroxaban was more similar to the risk experienced on LMWH/VKA (HR 0.65 from EINSTEIN-DVT) and the frequency of INR monitoring for people receiving LMWH/VKA to be 6 in the first quarter and 3 in each subsequent quarter. In this scenario, the ICER increased for the 12-month treatment cohort to £23,364 per QALY gained and to £44,046 per QALY gained for lifelong treatment.

3.32 The ERG's multiple assumption scenario included a reduction in the frequency of INR-monitoring visits with a greater proportion occurring in secondary care (a 50:50 split rather than the 66 primary care to 34 secondary care split as in the manufacturer's base case); a greater proportion of primary care monitoring visits led by nurses (75% rather than 50%); a reduction in LMWH treatment length; a reduction in rivaroxaban efficacy after 12 months in the lifelong treatment duration analysis; and a raised hazard of major bleed. After applying these assumptions, rivaroxaban continued to dominate LMWH/VKA for the 6-month treatment duration. For the 12-month treatment duration, the ICER for rivaroxaban compared with LMWH/VKA was £11,590 per QALY gained, and for the lifelong treatment duration the ICER was £35,909 per QALY gained. The ERG did not present the effects of these multiple assumptions on the 3-month treatment analysis.

3.33 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of rivaroxaban, having considered evidence on the nature of pulmonary embolism and recurrent thromboembolism and the value placed on the benefits of rivaroxaban by people with the condition, those who represent them and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed the clinical management of pulmonary embolism. It noted the statements received from the clinical specialists, which stated that people with suspected pulmonary embolism are generally treated with immediate parenteral anticoagulation, most commonly with a low molecular weight heparin (LMWH) delivered by subcutaneous injection, and when the diagnosis has been confirmed, an oral vitamin K antagonist such as warfarin. The LMWH is continued for at least 5 days or until the patient's international normalised ratio (INR) has been within the therapeutic range for at least 24 hours, at which point it is stopped. The Committee also heard that a minority of people receive unfractionated heparin or fondaparinux instead of LMWH. People presenting with pulmonary embolism and haemodynamic instability may receive thrombolysis (or undergo embolectomy if thrombolysis is contraindicated) before receiving a vitamin K antagonist. The Committee discussed the manufacturer's decision problem, noting that the manufacturer had excluded fondaparinux as a comparator even though it was specified in the final scope issued by NICE. The Committee noted the comments from the manufacturer and the ERG highlighting that fondaparinux is rarely used in UK clinical practice. The Committee accepted that fondaparinux is rarely used and agreed that it was appropriate to consider only LMWH and a vitamin K antagonist as the comparator as listed in the manufacturer's decision problem.
- 4.3 The Committee considered the treatment duration with anticoagulation. The Committee was aware that the NICE clinical guideline 144 on [Venous thromboembolic diseases](#) recommends 3 months' anticoagulation with a vitamin K antagonist for people with confirmed pulmonary embolism, with treatment continued beyond 3 months for those with permanent risk

factors for venous thromboembolism recurrence, taking into account individual risk factors such as bleeding. However, it noted that approximately 95% of people in EINSTEIN-PE received anticoagulation for 6 months or more. The Committee heard from the clinical specialists that anticoagulation therapy is often started with an expected duration of therapy, but that clinical evaluation is usually carried out at 3 or 6 months, when a decision is made as to whether or not therapy should be continued long term. It also heard that pulmonary embolism is a potentially life-threatening event, and that it would be unusual for people to be treated for less than 6 months. The clinical specialists also explained that people who have had a massive pulmonary embolus, recurrent venous thromboembolism, or are considered to be at significant risk of recurrence would usually receive lifelong anticoagulation. The clinical specialists estimated that overall, as many as 50% of people with pulmonary embolism would subsequently receive lifelong anticoagulation. The Committee accepted that although [NICE clinical guideline 144](#) recommends an initial treatment duration of 3 months, the usual duration of treatment in UK practice was 6 months or more.

- 4.4 The Committee heard from the patient expert about the perceived benefits of rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolic events over the standard care of LMWH with a vitamin K antagonist (such as warfarin). The patient expert highlighted the disadvantages of warfarin, including the need for regular monitoring of INR, and dose adjustment. Monitoring, which needs regular visits to hospital or GP appointments, can be costly and inconvenient, and means some people may have to take time off work. The patient expert said young people of school or university age may also experience clots and INR monitoring can lead to disruption of education. The patient expert further explained that the burdens of monitoring and dose adjustments with warfarin may also affect carers of people who have had a pulmonary embolus and they may have to make adjustments to their own schedules to enable the person for whom they are caring to monitor their INR. As warfarin has many drug interactions, it may be unsuitable for people with comorbidities, and because of various food interactions, people may need to adjust and monitor their diet and lifestyle. The patient expert said that there are some people whose INR is

unstable on warfarin or who are allergic to it, for whom an alternative is needed. The patient expert highlighted that rivaroxaban can be used at the onset of pulmonary embolism in primary or secondary care. Rivaroxaban has the advantage that it avoids injections, regular blood tests and the diet and lifestyle considerations necessary with the combination of heparin and warfarin. The patient expert said that patients are very interested in rivaroxaban and other newer anticoagulants, but noted that a small proportion of patients are concerned about these new agents and find regular monitoring of INR reassuring to confirm that they are adequately anticoagulated. The patient expert expressed the view that rivaroxaban should be made available as an additional treatment option. The Committee accepted the limitations of treatment with LMWH and a vitamin K antagonist and acknowledged the potential benefits of rivaroxaban.

- 4.5 The Committee considered the clinical management of bleeding resulting from treatment with anticoagulants. The clinical specialists highlighted that there are currently no validated guidelines on how to treat bleeding experienced while taking the new anticoagulants. The clinical specialists stated that people who have a bleed while taking a vitamin K antagonist may receive vitamin K, which takes 8–12 hours to reverse the effect of the vitamin K antagonist. One clinical specialist estimated that approximately 0.1% of people receiving warfarin experience a major bleed and for major bleeds needing rapid reversal, the most effective treatment is prothrombin complex concentrate (PCC) that provides correction for 12 hours. However, PCC would only be considered appropriate for a proportion of people with a major bleed. The Committee noted that the Evidence Review Group (ERG) had suggested that recombinant factor VIIa may be used to reverse a bleed. The clinical specialists agreed that recombinant factor VIIa may be used, but as it has a very short duration of action of approximately 2 hours, and is extremely expensive, they considered that PCC would be used in preference. The Committee further noted that recombinant factor VIIa is not licensed for the reversal of bleeding experienced on the new anticoagulants. It heard from the clinical specialists and the patient expert that there is no established antidote for rivaroxaban but because of its relatively short half-life, some bleeds can be managed simply by discontinuing rivaroxaban. The Committee concluded that there are standard approaches to stop

bleeding experienced while on standard vitamin K antagonists such as warfarin, but there is uncertainty about the best approach to reverse bleeding experienced while taking rivaroxaban.

- 4.6 The Committee considered the generalisability of the EINSTEIN-PE trial to UK clinical practice. It discussed whether the population in the trial reflects those seen in UK clinical practice. The Committee noted that the mean age of the population in the trial was 58 years. The clinical specialists highlighted that the incidence of deep vein thrombosis and pulmonary embolism increases with age, but EINSTEIN-PE included few people over 80 years. The clinical specialists considered that the proportion of people in the trial with provoked and unprovoked pulmonary embolism was similar to that observed in clinical practice. The Committee noted the ERG's concern that EINSTEIN-PE excluded people with severe renal impairment, even though they may be eligible for treatment with rivaroxaban with dose adjustment if needed. The clinical specialists stated that rivaroxaban would probably not be used in routine clinical practice for people with severe renal impairment. The Committee heard from the clinical specialists that in their opinion, the population in EINSTEIN-PE generally reflected the corresponding UK patient population. The Committee concluded that the baseline characteristics of the population in EINSTEIN-PE were generalisable to UK clinical practice.
- 4.7 The Committee discussed the comparator used in EINSTEIN-PE and its relevance to UK clinical practice. The clinical specialists stated the LMWH used in the trial, enoxaparin, has the largest evidence base of all the LMWHs. The clinical specialists also stated that there were no known differences in the clinical effectiveness of the different available LMWHs. The Committee considered whether the dosage of enoxaparin used in EINSTEIN-PE is applicable to UK clinical practice. It noted that in EINSTEIN-PE, the US licensed dose of enoxaparin was used (that is, 1.0 mg/kg twice a day), whereas the dose used in the UK is 1.5 mg/kg once a day. The Committee heard from the clinical specialists that the 2 dosages are similar in terms of efficacy, and although people in EINSTEIN-PE received a higher overall daily dose of enoxaparin than would be seen in UK clinical practice, this is not expected to have affected the generalisability of the trial to the UK. The Committee

accepted that the differences in the dosage did not appear to be clinically significant and was satisfied that the comparators used in the trial represented routine and best practice.

- 4.8 The Committee considered the time in therapeutic range in the enoxaparin and vitamin K antagonist arm of the trial. It noted that the average time in therapeutic range for people receiving enoxaparin with a vitamin K antagonist was 62.7%. The clinical specialists stated that time in therapeutic range varies, but a range of between 60% and 70% would be expected in UK clinical practice. The Committee therefore concluded that the data from the enoxaparin with a vitamin K antagonist arm in the trial were applicable to routine clinical practice.
- 4.9 The Committee considered the generalisability of the EINSTEIN-PE trial to the subgroup of patients who have active cancer. The Committee noted that EINSTEIN-PE included a small proportion of people with cancer. The clinical specialists stated that people with cancer who experience venous thromboembolism would currently receive extended treatment with a LMWH alone, as evidence has shown that LMWH is more effective than warfarin for this group of people, and has been shown to reduce mortality. The Committee noted that the manufacturer had not presented any clinical evidence for a comparison of LMWH alone with rivaroxaban. The clinical specialists suggested that, without evidence from a direct comparison, it was unlikely that clinicians would offer rivaroxaban as an alternative treatment to LMWH for people with cancer. The Committee agreed that the comparator treatment in EINSTEIN-PE that included a vitamin K antagonist did not reflect UK clinical practice for people with cancer, and there was no evidence for the relative efficacy of rivaroxaban compared with long-term LMWH, the standard treatment for these patients. The Committee concluded that without direct evidence of the relative efficacy of rivaroxaban compared with LMWH alone, it would be inappropriate to make a recommendation for this group.
- 4.10 The Committee considered the trial design and the clinical-effectiveness results of the EINSTEIN-PE trial. It noted that the trial was designed to assess whether rivaroxaban was non-inferior to LMWH with a vitamin K antagonist for preventing recurrent thromboembolism after pulmonary

embolism and that the manufacturers had also tested for statistical superiority for the primary efficacy outcome. The Committee noted that for the whole trial population, the rates of recurrent venous thromboembolism were not statistically significantly different in the rivaroxaban and LMWH with a vitamin K antagonist arms in the trial. The Committee concluded that rivaroxaban has acceptable clinical effectiveness compared with low molecular weight heparin and a vitamin K antagonist.

- 4.11 The Committee discussed the safety data from EINSTEIN-PE. It noted that there was no statistically significant difference in the composite end point of major bleeding and clinically relevant non-major bleeding between rivaroxaban and LMWH with a vitamin K antagonist, but that the incidence of major bleeds was statistically significantly lower with rivaroxaban. The Committee concluded that rivaroxaban has an acceptable safety profile compared with low molecular weight heparin and a vitamin K antagonist.
- 4.12 The Committee considered the results from the treatment duration subgroups and noted that groups were based on clinical criteria. It discussed the level of uncertainty around the hazard ratios and noted that the confidence intervals surrounding the hazard ratio for recurrent thromboembolism overlapped. It was aware that the confidence intervals were particularly wide for the 3-month treatment duration subgroup and noted the analysis was based on a small number of people recruited to the group (around 5% of the study population) and on a small number of events in both treatment arms. In addition, the Committee heard from the clinical specialists that they were not aware of any biological reason to expect a differential effect in the 3-month treatment duration subgroup. The Committee therefore concluded that evidence of treatment effect should be based on the whole trial population of EINSTEIN-PE.
- 4.13 The Committee considered the issue of long-term or lifelong treatment with rivaroxaban. It noted that the maximum length of treatment in EINSTEIN-PE was 12 months, but was mindful that it had heard from the clinical specialists that some people will need longer treatment durations in clinical practice (section 4.3). In the absence of long-term data, the Committee considered the plausibility of the effects of rivaroxaban being

maintained beyond 12 months. The clinical specialists stated that there is no biological or pharmacological reason why the effects of rivaroxaban should not be maintained over time but noted that there was uncertainty about how people would adhere to treatment with rivaroxaban over the long term. The Committee accepted that there was no biological or pharmacological reason why the effects of rivaroxaban would not be maintained over the long term.

- 4.14 The Committee noted that the manufacturer had presented 4 base-case scenarios for 3-, 6-, 12-month treatments and a lifelong treatment analysis. It noted that the economic model used clinical-effectiveness data from EINSTEIN-PE and utility data derived through systematic review. The Committee noted that rivaroxaban dominated treatment with LMWH and a vitamin K antagonist, that is, was less costly and more effective in the manufacturer's deterministic analysis of 3-, 6- and 12-month treatment durations. It noted that for lifelong treatment, the manufacturer's base case incremental cost-effectiveness ratio (ICER) was £13,300 per quality-adjusted life year (QALY) gained but after the corrections made to the model by the ERG, the base case for lifelong treatment was reduced to £7070 per QALY gained. The Committee noted that this figure was calculated using the manufacturer's estimate of INR-monitoring costs.
- 4.15 The Committee discussed the estimate of the cost of INR monitoring. It heard from the clinical specialists that although there is a trend towards more monitoring being performed in primary care, some people still receive monitoring in secondary care. The clinical specialists also stated that there is huge variation in the frequency of INR monitoring for people receiving a vitamin K antagonist; some people may need weekly visits, particularly at the beginning of therapy, and some people may only need INR monitoring twice a year. The clinical specialists estimated that, as a guide, on the basis of 1 audit, INR monitoring once every 5–6 weeks might be a reasonable average estimate. The patient expert also highlighted that there is interest from patients in self-monitoring of INR, but there is variation in the availability of INR-home monitoring machines. The Committee concluded that there is considerable variability and uncertainty surrounding service provision and the frequency of INR monitoring that makes determining an accurate cost of INR monitoring

problematic. It noted that the ERG had assumed fewer INR-monitoring visits than the manufacturer, which the ERG confirmed resulted in lower first year monitoring costs of between £304 and £379. The application of these scenarios to lifelong treatment increased the ICER from £7070 per QALY gained in the base case to £17,900 and £22,900 per QALY gained respectively. The Committee considered how INR-monitoring costs had been estimated in previous appraisals. In [Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism](#) (NICE technology appraisal guidance 261) the Committee had considered that after deep venous thrombosis, an INR-monitoring frequency of 6 visits in the first quarter and 3 in each subsequent quarter, resulting in first-year costs of £320, to be reasonable. The Committee took into account the clinical specialists' estimates of average INR-monitoring frequency (that is, every 5–6 weeks) and also the deliberations during technology appraisal 261 and concluded that the ERG's scenarios were reasonable estimations of the impact of INR monitoring on the cost effectiveness of rivaroxaban, and that the manufacturer's estimate of frequency of monitoring visits was too high.

- 4.16 The Committee discussed the health-related quality of life data used in the economic model. It noted that health-related quality of life had not been measured in EINSTEIN-PE and that the manufacturer had obtained the utility values used in its model through systematic review. The Committee was aware that the ERG had considered the utility values used in the economic model to be generally appropriate; however, the Committee considered that some of the studies that the manufacturer had used to obtain the utility values were too small and did not meet the reference case outlined in NICE's [Guide to the methods of technology appraisal](#). The Committee expressed its disappointment that the manufacturer had not followed the reference case to derive the utility values. In particular, it noted that only 1 study fully met NICE's reference case criteria (that is, the source of data for measurement of health-related quality of life was reported directly by patients or carers, the source of preference data for valuation of changes in health-related quality of life was a representative sample of the public, and the preferred measure of health-related quality of life, the EQ-5D, had been used). The Committee noted that similar utility values had been used by

the manufacturer in its economic model for [NICE technology appraisal guidance 261](#) and it also noted that in the scenario analysis carried out by the ERG in which the utility value for the intracranial bleed state was increased from 0.33 to 0.55, there was only a minimal effect on the ICER. The Committee concluded that although the health-related quality of life studies selected by the manufacturer to obtain utility values for its economic model did not meet the NICE reference case, the cost-effectiveness estimates did not appear to be sensitive to the utility values used.

- 4.17 The Committee considered the 2 additional scenario analyses performed by the ERG for lifelong treatment that addressed the impact of an increase in the risk of a thromboembolic event or a bleeding event for rivaroxaban after 12 months. The Committee noted that the worst-case ICER for rivaroxaban compared with LMWH and a vitamin K antagonist was £14,100 per QALY gained when the hazard ratio for a recurrent venous thromboembolism was increased from 1.12 to 2, and £14,200 per QALY gained when the hazard ratio for a major bleed was increased from 0.49 to 0.79 (the upper limit of the 95% confidence interval for the major bleed hazard ratio seen in EINSTEIN-PE). The Committee noted that the ERG had also carried out a multiple assumption scenario that resulted in an ICER of £35,900. This included the assumption that both the effectiveness of rivaroxaban in preventing venous thromboembolic events decreased and the risk of bleeds increased relative to conventional therapy after 12 months compared with the base case. The Committee heard from the clinical specialists that if an anticoagulant was less effective in preventing venous thromboembolic events, then it would be expected to have a lower rate of bleeds. The clinical specialists stated that a scenario in which both the risk of venous thromboembolism and bleeding increased was clinically implausible. The Committee concluded that the ERG's multiple assumption scenario was not plausible and the resulting ICER was not appropriate or relevant for this appraisal.
- 4.18 The Committee considered the 3 scenario analyses undertaken by the ERG in which the costs of reversing a major bleed had been incorporated and had been assessed in the 12-month and lifelong treatment analyses. The Committee noted that in these scenarios, the ERG had assumed that all people who had a major bleed would receive either treatment with

PCC or recombinant factor VIIa; however, it was mindful of the testimony from the clinical specialists that only a proportion of people who had a major bleed would receive these treatments and PCC would preferentially be used over recombinant factor VIIa (see section 4.5). The Committee noted that recombinant factor VIIa is a particularly expensive drug and that the manufacturer did not consider the costs used by the ERG for recombinant factor VIIa to be relevant to patients in the decision problem. The Committee stated that consideration of bleeding reversal costs was relevant but that the ERG had presented extreme scenarios because it assumed that all people who had a major bleed would receive PCC or recombinant factor VIIa. The Committee agreed that there was too much uncertainty surrounding the treatment of bleeds experienced while on anticoagulants to reliably estimate the impact of treatment costs for reversing bleeding on the cost-effectiveness estimates. The Committee therefore concluded that the ICERs presented by the ERG for the 12-month analysis (worst-case scenario £23,400 per QALY gained) and the lifelong analysis (worst-case scenario £44,000) were not relevant for this appraisal.

- 4.19 The Committee considered that in all scenarios assessed for the 3-, 6- and 12-month treatment durations, rivaroxaban either continued to dominate, or the ICER compared with LMWH and a vitamin K antagonist could be considered a cost-effective use of NHS resources. The Committee concluded that rivaroxaban was cost effective for treating pulmonary embolism for 3, 6 or 12 months.
- 4.20 For lifelong treatment, the Committee considered the ERG's assumptions about the frequency of INR monitoring to be valid and concluded that the most plausible ICER for lifelong treatment with rivaroxaban compared with lifelong treatment with a vitamin K antagonist after initial treatment with a LMWH was between £17,900 and £22,900 per QALY gained. The Committee concluded that rivaroxaban is a cost-effective treatment option for the lifelong treatment of pulmonary embolism and prevention of recurrent thromboembolism for people in whom long-term treatment is indicated.

Summary of Appraisal Committee's key conclusions

TA287	Appraisal title: Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism	Section
Key conclusion		
Rivaroxaban is recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.		1.1
In all scenarios assessed for the 3-, 6- and 12-month treatment durations, rivaroxaban either continued to dominate or the ICER compared with LMWH and a vitamin K antagonist could be considered a cost-effective use of NHS resources. The Committee concluded that rivaroxaban was cost effective for treating pulmonary embolism for 3, 6 or 12 months.		4.19
For lifelong treatment, the Committee considered the ERG's assumptions about the frequency of INR monitoring to be valid and concluded that the most plausible ICER for lifelong treatment was between £17,900 and £22,900 per QALY gained. The Committee concluded that rivaroxaban is a cost-effective treatment option for the lifelong treatment of pulmonary embolism and prevention of recurrent thromboembolism for people in whom long-term treatment is indicated.		4.20
Current practice		
Clinical need of patients, including the availability of alternative treatments	People with suspected pulmonary embolism are generally treated with immediate parenteral anticoagulation, most commonly with a low molecular weight heparin (LMWH) delivered by subcutaneous injection, and when the diagnosis has been confirmed, an oral vitamin K antagonist such as warfarin. Duration of treatment is based on individual risk of recurrent venous thromboembolism and bleeding. The usual duration of treatment in UK practice is 6 months or more.	4.2, 4.3
The technology		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>Disadvantages of long-term anticoagulation with warfarin include the need for regular monitoring of INR, dose adjustment, multiple food and drug interactions and the impact on people's lifestyle including cost and inconvenience.</p> <p>Rivaroxaban avoids injections, regular blood tests and the diet and lifestyle considerations necessary with the combination of heparin and warfarin. It can be used at the onset of pulmonary embolism in primary or secondary care.</p>	<p>4.4</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>Rivaroxaban is indicated for the 'treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults'.</p>	<p>2.1</p>
<p>Adverse reactions</p>	<p>There was no statistically significant difference in the composite end point of major bleeding and clinically relevant non-major bleeding between rivaroxaban and LMWH with a vitamin K antagonist, but that the incidence of major bleeds was statistically significantly lower with rivaroxaban. The Committee concluded that rivaroxaban has an acceptable safety profile compared with LMWH and a vitamin K antagonist.</p>	<p>4.11</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The EINSTEIN-PE trial was the key trial supporting the clinical effectiveness of rivaroxaban in the manufacturer's submission.</p>	<p>4.10</p>

Relevance to general clinical practice in the NHS	The baseline characteristics of the population in EINSTEIN-PE were generalisable to UK clinical practice.	4.6
Uncertainties generated by the evidence	The manufacturer had not presented any clinical evidence for a comparison of rivaroxaban with LMWH alone for people with cancer to reflect UK clinical practice for this group of patients. Therefore, the Committee concluded it would be inappropriate to make a recommendation for this group.	4.9
	The maximum length of treatment in EINSTEIN-PE was 12 months, but some people will need longer treatment durations in clinical practice. The Committee accepted that there was no biological or pharmacological reason why the effects of rivaroxaban would not be maintained over the long term.	4.13
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	It was noted that treatment duration was assigned based on clinical criteria. The Committee noted that the confidence intervals surrounding the hazard ratio for recurrent thromboembolism overlapped.	4.12
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The primary efficacy outcome in EINSTEIN-PE was symptomatic recurrent venous thromboembolism. The Committee noted that for the whole trial population, the rates of recurrent venous thromboembolism were not statistically significantly different in the rivaroxaban and LMWH with a vitamin K antagonist arms in the trial. The Committee concluded that rivaroxaban had acceptable clinical effectiveness compared with LMWH and a vitamin K antagonist.	4.10
Evidence for cost effectiveness		

Availability and nature of evidence	The manufacturer presented an economic model, which used clinical-effectiveness data from EINSTEIN-PE and utility data derived through systematic review, and presented 4 base-case scenarios for 3-, 6-, 12-month treatments and a lifelong treatment analysis.	4.14
Uncertainties around and plausibility of assumptions and inputs in the economic model	There is considerable variability and uncertainty surrounding service provision and the frequency of INR monitoring that makes determining an accurate cost of INR monitoring problematic. The Committee took into account the clinical specialists' estimates, the deliberations during technology appraisal 261 and the ERG's scenarios and concluded that the manufacturer's estimate of frequency of monitoring visits was too high and the ERG's scenarios were reasonable estimates.	4.15
	The Committee considered that some of the studies that the manufacturer had used to obtain the utility values were too small and did not meet the reference case outlined in NICE's Guide to the methods of technology appraisal . It concluded that the cost effectiveness of rivaroxaban did not appear to be sensitive to the utility values used.	4.16

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>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?</p>	<p>The Committee heard from the patient expert who confirmed regular monitoring of INR, dose adjustment, multiple food and drug interactions with warfarin can impact on people's lifestyle can be costly and inconvenient. The manufacturer applied a disutility due to warfarin therapy of 0.012 in the LMWH/VKA arm.</p>	<p>4.4, 3.13</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>None identified</p>	

What are the key drivers of cost effectiveness?	INR monitoring costs. In the manufacturer's sensitivity analyses the cost effectiveness of lifelong treatment with rivaroxaban was most sensitive to changes in the frequency of INR-monitoring visits, where the ICER increased from £13,252 per QALY gained to £27,914 per QALY gained if people have 3, rather than 5, visits in each quarter after the first. For lifelong treatment, the Committee considered the ERG's assumptions about the frequency of INR monitoring to be valid resulting in the ICER for lifelong treatment with rivaroxaban compared with lifelong treatment with a vitamin K antagonist after initial treatment with a LMWH increasing from £7070 in the ERG's amended base case to between £17,900 and £22,900 per QALY gained.	3.15, 4.15, 4.20
Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered that in all scenarios assessed for the 3-, 6- and 12-month treatment durations, rivaroxaban either continued to dominate or the ICER compared with LMWH and a vitamin K antagonist could be considered a cost-effective use of NHS resources. The most plausible ICER for lifelong treatment with rivaroxaban compared with lifelong treatment with a vitamin K antagonist after initial treatment with a LMWH was between £17,900 and £22,900 per QALY gained.	4.19, 4.20
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 raised.	

5 Implementation

- 5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has a pulmonary embolism and the doctor responsible for their care thinks that rivaroxaban is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.3 NICE has developed tools to help organisations put this guidance into practice (listed below).
- Costing template and report to estimate the national and local savings and costs associated with implementation.

6 Recommendations for further research

- 6.1 There have been no head-to-head trials of rivaroxaban compared with a low molecular weight heparin for people who have cancer and experience an acute pulmonary embolism or deep vein thrombosis. As in [NICE technology appraisal guidance 261](#) it is recommended that further research should be carried out.
- 6.2 Research into the long-term treatment effects of rivaroxaban is needed.

7 Related NICE guidance

Published

- [Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing](#). NICE clinical guideline 144 (2012).
- [Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism](#). NICE technology appraisal guidance 261 (2012).
- [Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults](#). NICE technology appraisal guidance 245 (2012).
- [Venous thromboembolism: reducing the risk of venous thromboembolism \(deep vein thrombosis and pulmonary embolism\) in patients admitted to hospital](#). NICE clinical guideline 92 (2010).
- [Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults](#). NICE technology appraisal guidance 170 (2009).
- [Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults](#). NICE technology appraisal guidance 157 (2008).

NICE pathways

- [Venous thromboembolism](#). NICE pathway (2011).

NICE quality standards

- [Venous thromboembolism prevention](#). NICE quality standard 3 (2010).
- [Management of venous thromboembolic diseases](#). NICE quality standard 29 (2013).

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review in May 2015 alongside the review of [NICE technology appraisal guidance 261](#). The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrews Dillon
Chief Executive
June 2013

9 Appraisal Committee members and NICE project team

9.1 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

Professor Iain Squire (Vice Chair)

Consultant Physician, University Hospitals of Leicester

Professor A E Ades

Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Professor Thanos Athanasiou

Professor of Cardiovascular Sciences and Cardiac Surgery and Consultant Cardiothoracic Surgeon, Imperial College London and Imperial College Healthcare NHS Trust

Dr Gerardine Bryant

General Practitioner, Heartwood Medical Centre, Derbyshire

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Andrew England

Lecturer in Medical Imaging, NIHR Fellow, University of Liverpool

Professor Jonathan Grigg

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Brian Hawkins

Chief Pharmacist, Cwm Taf Health Board, South Wales

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital

Dr Sharon Saint Lamont

Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Mohit Misra

General Practitioner, Queen Elizabeth Hospital, London

Ms Sarah Parry

CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Dr Ann Richardson

Lay Member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Ms Ellen Rule

Programme Director, NHS Bristol

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit

Dr Peter Sims

General Practitioner, Devon

Mr David Thomson

Lay Member

Dr John Watkins

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

Dr Olivia Wu

Reader in Health Economics, University of Glasgow

9.2 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

Nicola Hay

Technical Adviser

Bijal Joshi

Project Manager

10 Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre (SHTAC):

- Copley V, Pickett K, Cooper K et al. Rivaroxaban for the treatment of pulmonary embolism and the prevention of recurrent venous thromboembolism. A single technology appraisal. February 2013

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

I. Manufacturer/sponsor

- Bayer (rivaroxaban)

II. Professional/specialist and patient/carer groups:

- AntiCoagulation Europe (ACE)
- British Society for Haematology
- British Society for Haemostasis and Thrombosis
- 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
- Vascular Society

III. Other consultees:

- Department of Health
- Welsh Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Clinical Guidelines Centre
- National Institute for Health Research Health Technology Assessment Programme
- Southampton Health Technology Assessment Centre, University of Southampton

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

- Dr David Bevan, Consultant Haematologist and Clinical Lead in Haemostasis, nominated by organisation representing Royal College of Pathologists and British Society for Haematology – clinical specialist
- Dr Mark Crowther, Consultant Haematologist, nominated by organisation representing British Society of Haemostasis and Thrombosis – clinical specialist
- Mrs Annya Stephens-Boal, Executive Officer of Lifeblood: The Thrombosis Charity, nominated by organisation representing Lifeblood: The Thrombosis Charity – patient expert

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

- Bayer

Changes after publication

January 2014: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

It has been incorporated into the NICE pathway on [venous thromboembolism](#) along with other related guidance and products.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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