

# Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism

Technology appraisal guidance

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# 1 Recommendations

- 1.1 Rivaroxaban is recommended 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 The technology

- 2.1 Rivaroxaban (Xarelto, Bayer) is indicated for the 'treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults'. For the initial treatment of acute deep vein thrombosis, 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 recurrence.
- 2.2 The duration of treatment recommended in the summary of product characteristics depends on bleeding risk and other clinical criteria: short-term treatment (3 months) is recommended for those with transient risk factors such as recent surgery and trauma, and longer treatment for permanent risk factors or idiopathic (unprovoked) deep vein thrombosis. The summary of product characteristics further states that experience with rivaroxaban in this indication for more than 12 months is limited. 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 to 49 ml/min) or severe (creatinine clearance 15 to 29 ml/min) renal impairment. For full details of side effects and contraindications, see the summary of product characteristics.
- 2.3 Rivaroxaban costs £2.10 per 15-mg or 20-mg tablet. 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 considered evidence submitted by the manufacturer of rivaroxaban and a review of this submission by the Evidence Review Group (ERG).

- 3.1 The key clinical evidence in the manufacturer's submission came from 2 trials (EINSTEIN-DVT and EINSTEIN-Ext). EINSTEIN-DVT was an open-label non-inferiority study that compared rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for 3, 6 or 12 months) with enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for treating patients with acute symptomatic deep vein thrombosis without any symptoms of pulmonary embolism, and for preventing recurrent deep vein thrombosis and pulmonary embolism. Enoxaparin was given until a vitamin K antagonist had brought the international normalised ratio (INR) into the target range, and was then stopped. Based on individual patient risk factors, patients were either assigned to 3, 6 or 12 months of treatment as determined by the treating physician. EINSTEIN-Ext was a randomised placebo-controlled superiority trial that compared rivaroxaban (20 mg once daily; n=602) with placebo once daily (n=594) in patients with confirmed symptomatic deep vein thrombosis or pulmonary embolism that had been treated for 6 or 12 months with a vitamin K antagonist (warfarin or acenocoumarol) or rivaroxaban up to the moment of randomisation. Patients were recruited if the risks and benefits of further anticoagulation were finely balanced, that is, there was 'clinical equipoise' for the decision to continue anticoagulation.
- 3.2 The manufacturer's submission noted that about 60% of patients recruited into EINSTEIN-Ext were assigned to 6 months of treatment, about 40% were assigned to 12 months of treatment and 28% had previously used rivaroxaban. The manufacturer also noted that some people were excluded from the EINSTEIN-DVT and EINSTEIN-Ext trials, such as those with a creatinine clearance of less than 30 ml/min, clinically significant liver disease, high blood pressure (systolic more than 180 mmHg or diastolic more than 110 mmHg), active bleeding or at high risk of bleeding.
- 3.3 The primary efficacy endpoint was a composite of deep vein thrombosis or pulmonary embolism (symptomatic, recurrent venous thromboembolism). Pulmonary embolism included both fatal and non-fatal pulmonary embolism. The

primary safety endpoint was a composite of major bleeding and other clinically relevant non-major bleeding ('clinically relevant bleeding') for EINSTEIN-DVT and major bleeding for EINSTEIN-Ext. A range of secondary composite endpoints were also included.

- 3.4 In EINSTEIN-DVT, the primary efficacy endpoint of symptomatic recurrent venous thromboembolism occurred in 2.1% (n=36) of patients in the rivaroxaban group compared with 3.0% (n=51) in the enoxaparin and vitamin K antagonist group (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.44 to 1.04,  $p < 0.001$  for non-inferiority and  $p = 0.076$  for superiority). The overall HR for rivaroxaban was 0.97 (95% CI 0.76 to 1.22,  $p = 0.77$ ) for the primary safety endpoint of clinically relevant bleeding and 0.67 (95% CI 0.44 to 1.02,  $p = 0.06$ ) for death from all causes. Recurrent deep vein thrombosis occurred less frequently in patients treated with rivaroxaban than with enoxaparin and a vitamin K antagonist (14 compared with 28). Pulmonary embolisms (fatal and non-fatal) did not differ between treatment groups.
- 3.5 The manufacturer reported a time in therapeutic range for the comparator enoxaparin and a vitamin K antagonist of 57.7% across all centres and 59.7% in western European 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-DVT between time in therapeutic range and treatment effect.
- 3.6 In EINSTEIN-Ext, patients taking rivaroxaban experienced fewer recurrences of venous thromboembolism (1.3%, n=8) than patients taking placebo (7.1%, n=42; HR 0.18, 95% CI 0.09 to 0.39,  $p < 0.0001$ ). The numbers of clinically relevant non-major bleeding events were significantly higher in the rivaroxaban arm than in the placebo arm (32 patients [5.3%] compared with 7 patients [1.2%],  $p < 0.001$ ). There were more major bleeding events in patients taking rivaroxaban (4 patients compared with no patients), although this did not reach statistical significance.
- 3.7 The manufacturer reported a mixed-treatment comparison for the subgroup of patients with cancer. This compared the relative effectiveness of rivaroxaban with dual low molecular weight heparin (LMWH) and a vitamin K antagonist, long-term LMWH compared with LMWH and a vitamin K antagonist, and rivaroxaban

compared with long-term LMWH. The manufacturer provided 3 analyses. The primary analysis used data from a systematic review of long-term anticoagulation in patients with cancer reported by Akl et al. (2011) and from the whole EINSTEIN-DVT trial population. Secondary analysis 1 used data from a trial by Lee et al. (2003) evaluating the LMWH dalteparin for the prevention of recurrent venous thromboembolism in patients with cancer and the data from the whole EINSTEIN-DVT trial population. Similarly, secondary analysis 2 used data from Akl et al. (2011) and effectiveness data from the cancer subgroup of EINSTEIN-DVT.

- 3.8 Results from the primary analysis indicated that for patients with active cancer, the venous thromboembolism recurrence hazard ratio for rivaroxaban compared with long-term LMWH was 1.44 (95% credible intervals 0.07 to 31.4). Secondary analysis 2 showed that rivaroxaban was less effective than LMWH at preventing venous thromboembolism recurrence (HR 1.32, 95% credible intervals 0.06 to 32.3) but induced fewer major bleeding events (odds ratio 0.24, 95% credible intervals 0.00 to 9.44). However, the manufacturer noted that the mixed-treatment comparison had credible intervals with wide margins for the efficacy and safety of rivaroxaban compared with long-term LMWH.
- 3.9 The manufacturer reported adverse events from EINSTEIN-DVT and EINSTEIN-Ext that were experienced in at least 4% of any treatment group. The most common adverse events across both EINSTEIN trials were headache, pain in extremity, nasopharyngitis and nosebleed. The reported incidences of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension were low in both arms of EINSTEIN-DVT and EINSTEIN-Ext.
- 3.10 The manufacturer's submission used a Markov-based model for the economic evaluation of rivaroxaban within its licensed indication for treating deep vein thrombosis and preventing recurrent thromboembolic events. Two analyses were presented: a primary analysis comparing rivaroxaban with LMWH and a vitamin K antagonist over 3, 6 and 12 months, and a cost-minimisation analysis for patients with active cancer, which used dalteparin (a LMWH) as the comparator. The manufacturer also presented a further exploratory cost-effectiveness analysis for patients with active cancer at the request of the ERG.
- 3.11 The Markov model comprised 11 health and treatment states and patients entered the model after a diagnosis of deep vein thrombosis. The model relied on

the control arm of EINSTEIN-DVT to derive the probabilities of recurrent venous thromboembolism, bleeding and discontinuation rates. The probabilities in the rivaroxaban arm were calculated by applying the appropriate hazard ratio or risk ratio to the probability in the control arm. The 3-month discontinuation rate was assumed to be 1.9%. Probabilities for long-term complications and risk of mortality were taken from both EINSTEIN-DVT and literature reviews. Drug and resource costs were derived from relevant UK sources (BNF, NHS Reference Costs 2009 to 2010 and Personal Social Services Research Unit [PSSRU] 2010) and generally reflected UK clinical practice. The model did not include monitoring for patients treated with rivaroxaban or LMWH. It assumed 9 visits in the first 3 months, followed by 5 visits thereafter (every 3 months) for patients treated with a vitamin K antagonist. It also assumed that 66% of visits for INR monitoring would take place in primary care and 34% in secondary care. For primary care, the manufacturer assumed INR monitoring would be delivered equally by a GP and a nurse (50/50 split). The estimated annual cost of INR monitoring, including transport costs, was £656 in the first year and £540 thereafter.

- 3.12 A validated preference-based measure of quality of life was not used in the EINSTEIN-DVT trial, so the economic model submitted by the manufacturer used utility values sourced from literature reviews. The manufacturer assigned a baseline utility value of 0.825 to all patients with deep vein thrombosis entering the model, which was taken from a survey of the UK general population using a visual analogue scale rating (Kind et al. 1998) and adjusted with disutility values for deep vein thrombosis, pulmonary embolism, extracranial bleed, intracranial bleed and post-thrombotic syndrome.
- 3.13 The base-case results included all the drug acquisition costs, resources associated with monitoring, and costs associated with adverse events (that is, bleeding events) and were presented by intended treatment durations (3, 6 and 12 months). Treatment with rivaroxaban dominated treatment with LMWH and a vitamin K antagonist across all treatment durations, that is, rivaroxaban was less costly and more effective compared with LMWH and a vitamin K antagonist (0.02 incremental QALYs for all treatment durations and cost savings of £163 at 3 months, £124 at 6 months and £33 at 12 months).
- 3.14 The manufacturer undertook a series of univariate and multivariate deterministic sensitivity analyses to test the robustness of the results by varying most of the

parameters used in the economic evaluation. The results were generally sensitive to the cost of monitoring and the hazard ratio for venous thromboembolism. The manufacturer also provided probabilistic sensitivity analyses. These showed that there was a 94.2% to 98.9% probability of rivaroxaban being cost effective at £20,000 per QALY gained for all treatment durations. The treatment duration of 3 months produced the most cost savings and increased incremental QALYs. The probability of rivaroxaban being the dominant treatment option was 97.1% in patients having 3 months of anticoagulation, 83.9% in those having 6 months and 53.0% in those having 12 months.

- 3.15 The manufacturer presented a cost minimisation analysis evaluating rivaroxaban in patients with cancer. Patients with cancer were assumed to be treated for 6 months. The cost of rivaroxaban was £4.20 per day for the first 21 days (2 tablets daily), followed by £2.10 per day (1 tablet daily). The cost of dalteparin was £8.47 per day for the first month and £7.06 per day for subsequent months. The total cost saving associated with rivaroxaban compared with LMWH (dalteparin) was £903 for patients with cancer.
- 3.16 The manufacturer also presented an exploratory cost-effectiveness analysis of the subgroup of patients with cancer. Using treatment effects from the mixed-treatment comparison, assuming no INR monitoring cost and using a 6-month treatment duration, rivaroxaban dominated dalteparin (0.0013 incremental QALYs and cost savings of £1,085).
- 3.17 The ERG raised concerns about the applicability of the EINSTEIN trials to UK clinical practice, including that the trials did not fully reflect the UK population with deep vein thrombosis because a number of important patient groups were excluded from both trials. These included patients with high risk of bleeding, creatinine clearance less than 30 ml/min (but not less than 15 ml/min), clinically significant liver disease, high blood pressure (systolic more than 180 mmHg or diastolic more than 110 mmHg) and non-proximal deep vein thrombosis. Specifically, the ERG noted that there are no data to inform decisions about patients with increased risk of bleeding. The ERG also noted that the EINSTEIN trials did not include patients for whom vitamin K antagonists are not appropriate, other than patients with cancer. It noted the population recruited into the EINSTEIN trials excluded a number of important groups relevant to the decision problem.

- 3.18 The ERG and its clinical advisers considered the comparator (enoxaparin) used by the manufacturer to be appropriate, although the dosage used in the EINSTEIN trials (1 mg/kg twice daily) was not in line with UK clinical practice (1.5 mg/kg once daily). Using the twice-daily dosage may have been unfavourable to rivaroxaban.
- 3.19 The manufacturer assumed the maximum treatment duration was 12 months for idiopathic deep vein thrombosis or in the presence of permanent risk factors. However, the clinical advisers to the ERG questioned this assumption and stated that it is now common for treatment to extend beyond 12 months, depending on patient characteristics and risk factors. The ERG's clinical advisers estimated that around 20% of people with deep vein thrombosis would have long-term treatment because of an ongoing risk of recurrence of venous thromboembolism.
- 3.20 The ERG raised concerns about the robustness of the mixed-treatment comparison in the cancer subgroup and the way the evidence was synthesised. The ERG noted that the included trials varied in the length of follow-up, and choice and dosage of LMWH also varied across studies. The ERG concluded that the mixed-treatment comparison did not provide good estimates of the uncertainty associated with the true treatment effect, but found the point estimate to be reasonable.
- 3.21 The ERG presented exploratory analyses that corrected certain errors in the model and took into account a less intensive INR monitoring strategy comprising 6 INR monitoring visits in the first 3 months and 3 visits every 3 months thereafter. The results indicated that enoxaparin and a vitamin K antagonist were dominated by rivaroxaban for the 3-month duration group (0.02 incremental QALYs and a cost saving of £51). Compared with enoxaparin and a vitamin K antagonist, the incremental cost-effectiveness ratio (ICER) of rivaroxaban was £3,247 per QALY gained for the 6-month treatment duration and £14,902 per QALY gained for the 12-month treatment duration.
- 3.22 The ERG revised the manufacturer's exploratory analysis in cancer patients to take into account what it considered to be a more plausible – and smaller – distribution of between-study standard deviations (as opposed to the alternative distributions used by the manufacturer). This found rivaroxaban to be less effective than LMWH at preventing venous thromboembolism recurrence. The

ERG raised concerns with the limited evidence available in the cancer subgroup, and with the modelling assumptions in the exploratory analysis. The ERG concluded any reliance on the results of the mixed-treatment comparison may lead to inaccurate estimates of mean ICERs because they are based on inflated expected values.

## Additional manufacturer analyses

- 3.23 After consultation, the manufacturer submitted additional analyses on the cost effectiveness of rivaroxaban in people in whom long-term anticoagulation is intended; that is, people who need anticoagulation for longer than 12 months. The manufacturer also commented further on the characteristics of patients in the 3-, 6-, and 12-month treatment duration groups in the EINSTEIN-DVT trial.
- 3.24 The manufacturer's new economic model for long-term use of rivaroxaban used event rates for venous thromboembolism recurrence and bleeding from the 12-month duration group of EINSTEIN-DVT for people treated with a LMWH and a vitamin K antagonist. The long-term risk of venous thromboembolism recurrence (after 1 year) was taken from a meta-analysis review, and results from the whole trial population of EINSTEIN-DVT were used to estimate the treatment effects. The manufacturer presented 2 scenarios. One took into account the manufacturer's assumed INR frequency of 9 visits in the first 3 months followed by 5 visits every 3 months thereafter (first-year costs £656). The other adopted a less intensive INR monitoring programme of 6 visits in the first 3 months followed by 3 visits every 3 months thereafter (first-year cost of £413). The model assumed a discontinuation rate of 3.6% every 3 months based on a review of long-term statin therapy because evidence on adherence to rivaroxaban for longer than 12 months of treatment was not available. The model also included a sensitivity analysis in which the 3-month discontinuation rate was varied from 1.9% to 6.9%.
- 3.25 The model applied a disutility of 0.012 to warfarin, which was sourced from a study by Marchetti et al. (2001) involving a small group of patients (n=48) attending an anticoagulation clinic. The manufacturer noted that a disutility would not apply to rivaroxaban, citing reasons that included raised levels of treatment satisfaction in comparison with LMWH and a vitamin K antagonist, and that no

clinically important adverse events were associated with rivaroxaban that had not already been taken into account in the model. The manufacturer also referred to NICE's technology appraisal guidance on dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation, in which a disutility was applied to dabigatran to account for dyspepsia, an adverse event not associated with rivaroxaban.

- 3.26 The results from the long-term anticoagulation model showed that the ICER for rivaroxaban compared with LMWH and a vitamin K antagonist was £6,037 per QALY gained under the manufacturer's assumed INR monitoring cost of £656 (0.16 incremental QALYs and additional cost of £953). Assuming a lower INR monitoring cost of £413, an ICER of £15,847 per QALY gained (0.16 incremental QALYs and additional cost of £2,502) was reported by the manufacturer. The probabilistic sensitivity analysis based on reduced INR monitoring showed that there was a 58% probability that rivaroxaban was cost effective at £20,000 per QALY gained and a 25% probability that rivaroxaban was dominant (more effective and less costly).
- 3.27 The ERG was generally satisfied with the assumptions made in the manufacturer's long-term economic model but noted that it is uncertain whether the treatment effects assumed in the model would remain fixed over a lifetime. The ERG explored several scenarios based on variations to the manufacturer's long-term anticoagulation model:
- Assuming treatment effect from the whole trial population over a lifetime horizon.
  - Assuming a lower INR cost of £320 for the first year followed by £248 annually thereafter, based on a reduced frequency of visits (6 visits in the first 3 months and then 3 visits every 3 months thereafter with a different GP/nurse consultation ratio than the 1 used by the manufacturer).
  - Varying the 3-month discontinuation rate for rivaroxaban from 3.6% as assumed in the manufacturer's long-term model to 1.9% as assumed by the manufacturer in the original submission.
  - Applying a 0.012 decrement in utility for warfarin and no decrement for rivaroxaban; 0.012 decrement in utility for warfarin and 0.006 decrement in utility for rivaroxaban; and assuming no decrement in utility for both warfarin

and rivaroxaban.

Taking into account the above assumptions, the results from the ERG's exploratory analyses yielded ICERs ranging from £19,381 to £38,837 per QALY gained. A deterministic calculation based on a whole-trial treatment effect, the lower cost of INR monitoring, and a utility decrement for warfarin only, indicated an ICER of £19,381 per QALY gained, assuming the same 3-month discontinuation rate of 3.6% for warfarin and rivaroxaban. The equivalent ICER when the discontinuation rate for rivaroxaban was lowered to 1.9%, while keeping the warfarin discontinuation rate at 3.6%, was £25,076 per QALY gained.

- 3.28 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 venous 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 heard from the clinical specialists that currently venous thromboembolism is initially treated with a LMWH (such as enoxaparin, dalteparin or tinzaparin) for rapid anticoagulation, overlapped with warfarin until an effective INR is achieved. The Committee also heard that treatment duration is based on an assessment of the benefit of continued anticoagulation compared with the risk of bleeding. The clinical specialists stated that treatment is often started with an expected duration of therapy, but that increasingly, a clinical re-evaluation is carried out at 3 or 6 months and a decision is made whether or not to continue therapy. The clinical specialists stated that in current UK practice, most people receive anticoagulation treatment for 6 months, which corresponds to the largest group in the EINSTEIN-DVT trial. However, the Committee heard that a NICE guideline in development on venous thromboembolic diseases is expected to recommend anticoagulation for 3 months in people with transient risk factors for deep vein thrombosis, and to recommend longer-term treatment in people with permanent risk factors and unprovoked deep vein thrombosis, taking into account individual risk factors such as risk of bleeding. The Committee concluded that although 6 months is currently the commonest duration of treatment in UK practice, this could change in light of the NICE guideline on venous thromboembolic diseases.
- 4.3 The Committee noted the written evidence from patient experts, which stated that many people find taking warfarin to be stressful, because of the necessary regular monitoring with blood tests, dosing adjustments, and because people must be careful about their diet because of warfarin's interaction with certain foods. The Committee heard from clinical specialists who agreed that warfarin is associated with a wide range of important and potentially dangerous drug interactions, and that warfarin can also negatively impact people's quality of life by preventing travel and other freedoms because of the need for regular

monitoring. The Committee also heard from the patient experts that rivaroxaban may improve the quality of life of people who currently take warfarin by removing the need for constant monitoring, frequent blood tests and visits to an anticoagulation clinic. It also heard that rivaroxaban is likely to benefit people who are needle phobic or who want to resume normal patterns of life without having to worry about the disruption associated with attending clinics. The use of rivaroxaban would also relieve the concern that people may have about not being on the correct warfarin dose to keep their INR well controlled. Additional advantages of rivaroxaban are the lack of need for INR monitoring, which could reduce the need for support services, and its oral formulation compared with LMWH, which is injected.

## Clinical effectiveness

- 4.4 The Committee discussed the clinical-effectiveness data from the EINSTEIN-DVT trial, which compared rivaroxaban with enoxaparin and a vitamin K antagonist in people with venous thromboembolism. The Committee heard from the clinical specialists that enoxaparin and a vitamin K antagonist is the key comparator. The Committee discussed whether the dosage of enoxaparin used in the EINSTEIN-DVT trial is relevant to UK clinical practice. The Committee heard from the clinical specialists that the dosage used in the UK (1.5 mg/kg once daily) and the dosage used in the EINSTEIN-DVT trial (1 mg/kg twice daily) are similar in efficacy and the difference is not expected to have affected the results of the trial. The Committee concluded that the difference in dosage did not appear to be clinically significant and was satisfied that the comparators used in the trial represented routine and best practice in the NHS.
- 4.5 The Committee considered the time in therapeutic range in the warfarin arm of the trial. It noted that the mean time in therapeutic range was 58%, which is lower than might be expected in routine UK clinical practice. However, the Committee heard from the clinical experts that control of INR is more difficult when warfarin is first started and before stabilisation on longer-term treatment. The Committee therefore concluded that for this patient population, the data from the warfarin arm in the trial was applicable to routine UK practice.
- 4.6 The Committee considered the trial design and results of EINSTEIN-DVT. The

Committee noted that EINSTEIN-DVT was a non-inferiority trial that compared rivaroxaban with enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol). The Committee heard that patients recruited into the trial were allocated to 3-, 6- and 12-month treatment durations by the treating physician, based on individual patient risk factors, before randomisation. The Committee noted that, for the whole trial population, rivaroxaban was at least as effective as the enoxaparin and a vitamin K antagonist regimen with respect to the primary efficacy endpoint of symptomatic recurrent venous thromboembolism and to the primary safety endpoint of clinically relevant bleeding. The Committee concluded that rivaroxaban was as effective as enoxaparin followed by a vitamin K antagonist for preventing recurrent venous thromboembolism, and did not have the disadvantages of an injected treatment followed by an oral treatment with the need for regular monitoring with blood tests.

- 4.7 The Committee considered the baseline characteristics of the EINSTEIN-DVT trial population and the results of the pre-specified subgroup analyses presented by the manufacturer. The Committee noted that rivaroxaban appeared to be more effective in people with a previous episode of deep vein thrombosis or pulmonary embolism, and that the effect of rivaroxaban varied between the subgroups allocated to the 3 different intended treatment durations. The Committee noted that the subgroup analysis by intended treatment duration suggested that rivaroxaban might be less effective than enoxaparin and warfarin in patients for whom 3 months of treatment was intended. The Committee noted the heterogeneity of the trial population in terms of underlying risk factors for deep vein thrombosis, and noted that no individually identifiable clinical group was included in only 1 treatment duration subgroup. The Committee also heard from the manufacturer that there were no specific clinical criteria or algorithms used to allocate people into the different intended treatment duration groups, and that there was no apparent biological or clinical plausibility for the differential effectiveness of rivaroxaban across the intended treatment duration subgroups. A similar view was taken by the clinical specialists, who noted that they were not aware of any clinical reasons why rivaroxaban would be less effective than LMWH and a vitamin K antagonist in people who received 3 months of treatment, while being more effective in the 6- and 12-months groups. The Committee also heard from the ERG that the lower efficacy in the patient group treated for 3 months only was based on a small number of events in both arms and the majority of events occurred in the 6- and 12-month groups. The Committee accepted that

there is insufficient evidence to demonstrate that rivaroxaban had a substantially different effectiveness across treatment durations, and was not aware of any biological reason to expect a differential effect in the first 3 months. The Committee therefore concluded that evidence of treatment effect should be based on the whole trial population of EINSTEIN-DVT.

- 4.8 The Committee questioned whether the pre-specified intended treatment duration used in the EINSTEIN-DVT trial reflects clinical practice. It noted that the clinical advisers to the ERG estimated that approximately 20% of people with deep vein thrombosis may need treatment for longer than 12 months. The Committee heard from the clinical specialists that the average duration of treatment is currently 6 months, at which time further treatment, including life-long treatment, would be considered if the person's risk of a recurrence remained high. However, the Committee noted that the summary of product characteristics for rivaroxaban states that experience with rivaroxaban in this indication for more than 12 months is limited. The manufacturer informed the Committee that there is a risk management plan agreed with the European Medicines Agency that involves the non-interventional XALIA study. The study will recruit people with a diagnosis of acute deep vein thrombosis and aims to estimate the recurrence of venous thromboembolism, incidence of major bleeding and mortality over the longer term. The Committee concluded that it may not be realistic to assume that people stop treatment once the pre-specified treatment period has ended and some people with ongoing risk factors for recurrence would need ongoing treatment, possibly for many years or lifelong.
- 4.9 The Committee discussed the results from the EINSTEIN-Ext trial. It noted that the trial inclusion criteria included people defined to be in 'clinical equipoise'. The manufacturer defined this as people for whom the decision to treat with anticoagulants was finely balanced. However, the Committee heard from the clinical specialists that in UK practice people who are to be treated for up to 12 months, as in the EINSTEIN-Ext trial, would generally not fall under this definition because they would have a strong clinical reason for further anticoagulation. It therefore agreed that the population in the EINSTEIN-DVT trial was more relevant for appraising rivaroxaban in venous thromboembolism for up to 12 months of treatment.
- 4.10 The Committee considered the adverse events reported in the EINSTEIN-DVT

and EINSTEIN-Ext trials. The Committee noted that patients treated with rivaroxaban experienced a comparable number of clinically relevant bleeding episodes to those treated with enoxaparin and a vitamin K antagonist in EINSTEIN-DVT. The Committee noted that patients treated with rivaroxaban in the extension study experienced a higher rate of clinically relevant non-major bleeding but that the comparator was placebo and not active control. The Committee concluded that treatment with rivaroxaban had an acceptable adverse event profile compared with the combination of LMWH and warfarin.

## Cost effectiveness

- 4.11 The Committee considered the cost effectiveness of rivaroxaban for up to 12 months of treatment. The Committee noted that the economic model used clinical-effectiveness data from the EINSTEIN-DVT trial and that the results were presented by treatment duration. It noted that rivaroxaban dominated treatment with enoxaparin and a vitamin K antagonist in the manufacturer's deterministic analysis, that is, rivaroxaban was less costly and more effective across all 3 treatment durations (3, 6 and 12 months). The manufacturer's model assumed a first-year INR monitoring cost of £656, and £540 in subsequent years. The Committee was mindful of the QALY increment for people treated with rivaroxaban but considered that the estimate of INR costs was too high and was not likely to reflect the actual cost in UK clinical practice. The Committee could therefore not accept the results of the manufacturer's base-case analysis as the estimate of cost effectiveness.
- 4.12 The Committee discussed the estimate of the cost of INR monitoring. The Committee acknowledged the multiple models of provision for INR monitoring across the UK and the uncertainty about the costs. It noted that estimates of INR monitoring costs varied greatly, and some community-based monitoring programmes appeared to be much cheaper than the manufacturer's estimate. The Committee considered the ERG's critique of the base-case economic model for up to 12 months of treatment. The ERG assumed a less intensive INR monitoring programme of 6 visits in the first 3 months followed by 3 visits every 3 months thereafter, and assumed different provisions for INR monitoring than did the manufacturer. The ERG's estimate of the cost of INR monitoring was £320 in the first year and £248 thereafter. It noted that the ERG estimate appeared to

be in the region of the estimated INR costs used in NICE's technology appraisal guidance on dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. The Committee heard from the clinical specialists that the population eligible for treatment with rivaroxaban is not likely to need significantly more frequent INR monitoring than people being started on anticoagulation therapy for other indications. Comments from consultees also indicated that the manufacturer's estimate of INR monitoring costs was higher than was plausible for UK practice. The Committee therefore concluded that the ERG's alternative assumptions and estimate of £320 for INR monitoring in the first year of treatment were reasonable and relevant for this appraisal.

- 4.13 The Committee considered the results of the ERG's economic evaluation of rivaroxaban treatment for up to 12 months. The ERG's estimate used clinical-effectiveness data from the whole trial population of EINSTEIN-DVT and the ERG's lower estimate for INR monitoring. The results indicated that rivaroxaban dominated therapy with LMWH and a vitamin K antagonist in the 3-month treatment duration group. The ICER for rivaroxaban was £3,200 per QALY gained for the 6-month treatment duration and £14,900 per QALY gained for the 12-month treatment duration. The Committee agreed that these cost-effectiveness results for up to 12 months of treatment using the ERG estimate for the cost of INR monitoring were more plausible than those provided by the manufacturer. The Committee concluded that treatment with rivaroxaban represented a clinical and cost-effective option in people in whom treatment for up to 12 months is indicated.
- 4.14 The Committee then discussed the manufacturer's submission for rivaroxaban in those who need long-term anticoagulation; that is, beyond 12 months of treatment. It noted that the manufacturer's economic model included a decrement in utility of 0.012 for people on warfarin only, which was taken from a small study by Marchetti et al. The Committee heard from the patient experts that warfarin has an impact on quality of life (see section 4.3). The Committee considered that although treatment with rivaroxaban could be associated with a small disutility, it was satisfied that treatment with warfarin was associated with a higher disutility than treatment with rivaroxaban, and the relative difference in disutility could be even higher than 0.012 for people who may have to take it for many years or lifelong. The Committee concluded that although it was not convinced that the utility decrement used by the manufacturer was supported by

strong evidence, it was of the opinion that the relative difference in disutility was at least as great as the value used by the manufacturer in its long-term model.

- 4.15 The Committee discussed the discontinuation rates in the economic evaluation of rivaroxaban in those who need ongoing anticoagulation. It noted that the manufacturer had used a discontinuation rate of 3.6% for every 3-month period for both treatments, which was taken from a study on long-term statin therapy. The Committee acknowledged the lack of evidence for the long-term adherence of people treated with rivaroxaban in venous thromboembolism, but noted there was no strong evidence to suggest that the people treated with rivaroxaban should have different rates of discontinuation compared with warfarin. The Committee concluded that it was satisfied that equal or near-equal discontinuation rates should be applied to both treatment arms.
- 4.16 The Committee then considered the results of the cost-effectiveness analysis of rivaroxaban for long-term anticoagulation. It noted the results from the manufacturer's long-term model which incorporated INR monitoring costs of £656 and a disutility of 0.012 applied to warfarin only, resulting in an ICER of £6,000 per QALY gained for rivaroxaban compared with enoxaparin and a vitamin K antagonist. The Committee noted that the equivalent ICER, when a less intensive INR monitoring cost of £413 was assumed, was £15,800 per QALY. The Committee also noted the ERG's exploratory analysis, which provided a range of estimates of the ICERs for ongoing anticoagulation under the scenarios outlined in 3.27. This gave ICERs ranging from £19,400 to £38,800 per QALY gained. The Committee noted that the INR monitoring costs assumed by the manufacturer were higher than are considered to be reasonable and therefore considered the ERG's analysis to be more appropriate. The Committee was satisfied that the differential disutility for warfarin compared with rivaroxaban, although uncertain, was at least 0.012 when long-term or lifelong treatment is needed. Assuming an equal discontinuation rate, a differential disutility of more than 0.012 would bring the ICER down to below £19,400 per QALY gained. The Committee also explored the scenario incorporating a discontinuation rate for rivaroxaban of just over half the warfarin discontinuation rate which, if a differential disutility of 0.012 was applied, gave an ICER of £25,100 per QALY gained. However, the Committee was not convinced that the discontinuation rate would be different, and felt that the ICER estimate of £25,100 was too high (see section 4.17). The Committee therefore concluded that £19,400 per QALY gained was a plausible estimate, and

that rivaroxaban was a cost-effective treatment option for people who need anticoagulation treatment for longer than 12 months.

- 4.17 The Committee discussed the effectiveness of rivaroxaban in people with cancer. It considered the manufacturer's mixed-treatment analyses, and found the manufacturer's secondary analysis 2 (see section 3.7) to be the most relevant because it used data from the cancer subgroup. It noted that this analysis indicated that rivaroxaban was less effective than dalteparin at preventing venous thromboembolism recurrence but induced fewer major bleeding events. It also noted that the credible intervals around these estimates were wide. The Committee acknowledged that the ERG did not find the cancer subgroup analyses to be robust and had concerns with the limited evidence and with how the mixed-treatment comparison was conducted and implemented. The Committee heard from the clinical specialists that the current standard care in treating venous thromboembolism in people with cancer is LMWH alone, which the evidence suggests provides benefits greater than warfarin. This seems to be a cancer-specific effect. The clinical specialists further stated that there is no direct trial evidence demonstrating that rivaroxaban is superior to a LMWH in people with cancer, and so would not expect the availability of rivaroxaban to change UK clinical practice in this population. The Committee heard from the patient experts that people with cancer would welcome a non-invasive treatment option such as rivaroxaban, particularly people receiving palliative care, as long as the treatment is safe and does not interact with the cancer treatment. Given the lack of clinical evidence for this group, the Committee was unable to make specific recommendations on the use of rivaroxaban in people with cancer but recognised the disadvantages of the currently available treatment, which involves regular injections, and which some people might choose to decline. The Committee concluded that rivaroxaban should not be excluded as a treatment option for preventing venous thromboembolism in people with cancer.

## 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 and the healthcare professional responsible for their care thinks that rivaroxaban is the right treatment, it should be available for use, in line with NICE's recommendations.

## 6 Recommendations for further research

- 6.1 Further research on the clinical effectiveness of rivaroxaban compared with LMWH in patients with active cancer should be conducted.

# 7 Appraisal Committee members 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

### **Professor A E Ades**

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

### **Dr Jeremy Braybrooke**

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

### **Dr Gerardine Bryant**

General Practitioner, Heartwood Medical Centre, Derbyshire

### **Dr Fiona Duncan**

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

**Mr Christopher Earl (until March 2012)**

Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

**Ms Eleanor Grey**

Lay Member

**Professor Jonathan Grigg**

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

**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 Alec Miners**

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

**Ms Pamela Rees**

Lay Member

**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 Cliff Snelling**

Lay Member

**Ms Amelia Stecher**

Associate Director of Individual Funding Requests and Clinical Effectiveness, NHS Kent and Medway

**Mr David Thomson**

Lay Member

**Mr William Turner (until May 2012)**

Consultant Urologist, Addenbrooke's Hospital

**Dr Anthony S Wierzbicki**

Consultant in Metabolic Medicine and Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

**Dr Olivia Wu**

Reader in Health Economics, University of Glasgow

## Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

- Mr Scott Harrison, Lead Pharmacist, Anticoagulation, John Radcliffe Hospital

- Dr Nigel Langford, Acute Medical Physician

## 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.

### **Kumar Perampaladas**

Technical Lead

### **Pall Jonsson**

Technical Adviser

### **Bijal Joshi**

Project Manager

## 8 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield:

- Harnan S, Rafia R, Poku E et al. Rivaroxaban for the treatment of deep vein thrombosis and secondary prevention of venous thromboembolism: A Single Technology Appraisal. ScHARR, The University of Sheffield, 2012.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist, patient or carer groups, and other consultees, had the opportunity to give their expert views.

Manufacturers or sponsors, professional or specialist, patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Bayer

Professional or specialist, and patient or carer groups:

- Anti Coagulation Europe (ACE)
- British Society for Haematology
- Lifeblood: The Thrombosis Charity
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- UK Clinical Pharmacy Association

Other consultees:

- Department of Health
- Haringey Primary Care Trust
- Northumberland Care Trust
- Welsh Government

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

- Boehringer Ingelheim
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Care Improvement Scotland
- Leo Pharma
- Medicines and Healthcare products Regulatory Agency
- National Clinical Guidelines Centre
- National Institute for Health Research Health Technology Assessment Programme
- Pfizer
- Sanofi-Aventis
- School of Health and Related Research Sheffield (SchARR)

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on rivaroxaban by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Roopen Arya, Consultant Haematologist and Director, King's Thrombosis Centre, nominated by Bayer – clinical specialist
- Dr David Bevan, Consultant Haematologist and Clinical Lead for Haemostasis and Thrombosis, nominated by Royal College of Pathologists and British Society for

#### Haematology – clinical specialist

- Ms Diane Eaton, nominated by Anticoagulation Europe – patient expert
- Mrs Annya Stephens-Boal, nominated by Lifeblood: The Thrombosis Charity – patient expert

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

- Bayer

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