NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Pre-meeting briefing

Rivaroxaban for the treatment of deep vein thrombosis and secondary prevention of venous thromboembolism

This premeeting briefing is a summary of the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

The manufacturer was asked to provide:

- **Additional data on patient-specific efficacy and safety by treatment duration**
- **Additional data on patients with deep vein thrombosis only for results reported in the EINSTEIN-Ext trial**
- **An exploratory cost-effectiveness analysis for the subgroup of patients with active cancer**
- **Details of the methodology used in the meta-analysis for the mixed treatment comparison**

Key issues for consideration

Clinical effectiveness

- The time in therapeutic range (TTR) reported in the EINSTEIN-DVT trial was 57.7% across all centres and 59.7% in western European centres. Does the Committee feel this to be reflective of current UK practice?
- The dose of low molecular weight heparin (LMWH) used in the EINSTEIN trials (1 mg/kg twice daily) does not reflect UK clinical practice (1.5 mg/kg once daily). Does the Committee consider this affects the measure of clinical efficacy of rivaroxaban compared with LMWH?
- The Evidence Review Group (ERG) noted that several groups of patients are not included in the EINSTEIN trials, and evidence of rivaroxaban use in these groups has not been presented. These groups include those with bleeding risk, renal impairment and high blood pressure, liver impairment, and non-proximal deep vein thrombosis. What is the Committee's view on the generalisability of the EINSTEIN trials to a UK setting and their relevance to clinical practice?
- The EINSTEIN-DVT trial did not treat patients beyond 12 months and the manufacturer has assumed a treatment duration of 3, 6 and 12 months in the economic evaluation. Does the Committee consider this reflects the expected duration of rivaroxaban treatment for the patient population in question?
- The ERG's clinical advisers estimated that approximately 20% of patients need ongoing anticoagulation. The ERG also noted that the population in the EINSTEIN-Ext trial is poorly defined and it is unclear whether it includes these patients. Does the Committee agree with this view?
- The EINSTEIN-DVT trial provided no data on longer-term treatment with rivaroxaban, and data from the EINSTEIN-Ext trial provided data for rivaroxaban compared with placebo, rather than an active treatment. What

is the Committee's view on the clinical evidence provided for this group of patients?

- The ERG noted that patients for whom vitamin K antagonist (VKA) is not appropriate and unfractionated heparin is indicated were not represented in the EINSTEIN trials. In addition, the comparison of rivaroxaban with LMWH in people for whom VKA is not appropriate is based on a subgroup of patients with cancer. The ERG believes that patients with cancer may not be representative of all patients for whom VKA is not appropriate, such as people with renal failure and liver impairment. What is the Committee's view on the generalisability of the clinical evidence in these patient groups?
- The ERG noted that rivaroxaban appears to be less effective in certain groups of patients, including those for whom 3 months of treatment is clinically indicated. What is the Committee's view on the statistical significance of this finding. Are there any clinically relevant reasons for this?
- The manufacturer conducted a network meta-analysis to estimate the treatment effect of rivaroxaban compared with LMWH in a subgroup of patients with active cancer. The ERG had concerns about the validity of the results from the network meta-analysis because of the high levels of heterogeneity and the way the analysis was implemented. Does the Committee agree with the ERG's concerns and what weight does the Committee give to the network meta-analysis undertaken?

Cost effectiveness

- The manufacturer reported that that rivaroxaban provided more quality-adjusted life years (QALYs) at a lower cost (dominant) in patients treated for 3, 6, and 12 months compared with LMWH/VKA in the base-case. The ERG undertook probabilistic sensitivity analysis that incorporated corrections to the manufacturer's base case and found that rivaroxaban was not dominant for people treated for 3 months, i.e. less costly but also less effective (ICER of £11,792 per QALY yielded; incremental cost saving

of £182 and 0.02 QALYs lost). Rivaroxaban remained dominant in probabilistic sensitivity analysis for patients treated for 6 and 12 months. Does the Committee find the ERG's corrected model based on treatment duration and probabilistic sensitivity analysis or the manufacturer's deterministic analysis more plausible?

- The ERG conducted a scenario analysis that allowed the proportion of venous thromboembolism that are pulmonary embolisms to differ between arms. What is the Committee's view on the assumptions underlying the exploratory analysis and does it consider the assumptions plausible?
- The ERG noted that the cost effectiveness of rivaroxaban is sensitive to assumptions in INR monitoring (including cost and frequency of visits) and setting of care. What is the Committee's view on this and their applicability to UK clinical practice?
- The ERG noted that the manufacturer did not present an economic analysis for patients treated beyond 12 months. Does the Committee find this reasonable?
- The manufacturer also presented a cost-minimisation analysis for a subgroup of patients with active cancer for the comparison of rivaroxaban with LMWH (dalteparin). Does the Committee consider the cost-minimisation analysis to be appropriate?

1 Background: clinical need and practice

1.1 The term venous thromboembolism is used to describe deep vein thrombosis and pulmonary embolism. Deep vein thrombosis is the formation of a thrombus in a deep vein which usually occurs in the lower limbs. If dislodged, thrombi from a deep vein thrombosis can circulate to the lungs causing a pulmonary embolism, which can cause sudden death. Patients who survive a pulmonary embolism can expect weeks or months of recovery. The recovery can be further complicated with recurrent deep vein thrombosis, the development of post-thrombotic syndrome, a rare condition known as chronic thromboembolic pulmonary hypertension, and a chronic disorder that comprises a cluster of symptoms that include pain, heaviness, swelling, cramps, itching, increased skin pigmentation and ulceration in the affected limb. Venous thromboembolism can substantially affect people's quality of life and impose a large burden on the healthcare system.

1.2 The annual incidence of deep vein thrombosis in the general population is estimated to be between 48 and 182 per 100,000 and that of venous thromboembolismabout 1 per 2000. These figures vary substantially with age – for people younger than 40 the annual incidence of venous thromboembolism is 1 in 10,000; for people older than 80 the incidence rises to 1 in 100. The risk of recurrence is high and people with a previous episode of venous thromboembolism have a 30% chance of recurrence within 8 years (although the risk depends on the type of treatment received and decreases substantially with time). The manufacturer estimates that there will be 46,300 incident cases of adult acute deep vein thrombosis in 2012 in England and Wales, of which around 38,600 will be first deep vein thromboses. This rises to a projected 49,100 incident cases in 2016 as a result of growth and ageing in the

population. All but a very small proportion of people – those with hepatic impairment or very severe renal impairment (creatinine clearance less than 15 ml/min) – would be potentially eligible for treatment with interventions considered in this assessment.

1.3 There is no current NICE guidance on the management of venous thromboembolism. In 2010 NICE published 'Venous thromboembolism: reducing the risk' (NICE clinical guideline 92), which gives advice on reducing the risk of venous thromboembolism in patients admitted to hospital. Treatments for venous thromboembolism include starting the patient on a LMWH (such as enoxaparin, which is commonly used in the UK), unfractionated heparin or fondaparinux sodium. This treatment is then overlapped with an oral VKA, such as warfarin, until the latter is effective and the correct dose is achieved. This is assessed by a blood test reported as the international normalised ratio (INR). The target INR range for venous thromboembolism is between 2.0 and 3.0. Major fluctuations in INR can cause bleeding so patients are monitored frequently and the dose of warfarin adjusted as needed. Clinical opinion on the optimal duration of warfarin treatment varies. UK and international guidelines recommend at least 3 months of anticoagulation, but this may be extended indefinitely depending on risk factors and prior medical history. NICE is currently developing a technology appraisal on dabigatran etexilate for the treatment of acute venous thromboembolic events and a clinical guideline on managing venous thromboembolic diseases and the role of thrombophilia testing.

1.4 Anticoagulation services in the UK may be based in a number of settings, including secondary care, secondary care satellite clinics, primary care (GP-, nurse- and community pharmacy led) or a combination of these depending on the stage of care and local

commissioning arrangements. It is common for the condition to be managed routinely on an outpatient basis because LMWHs are administered by subcutaneous injection; these injections can pose problems for patients who experience needle phobia, who need assistance with LMWH administration (that is, a daily visit from a healthcare professional or education for injection training), or who have poor dexterity. Warfarin is widely used in clinical practice and is associated with a number of well reported limitations including: a narrow therapeutic index with a fine balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage; a response that is substantially influenced by genetic polymorphisms, diet, concomitant medications (which may be of particular concern in older adults with comorbidities); and the need for dose adjustment using frequent, inconvenient and costly INR monitoring. The frequency of monitoring depends on individual patient characteristics; management using warfarin therefore needs an infrastructure for blood sampling, testing, monitoring and dose adjustment.

2 The technology

2.1 Rivaroxaban (Xarelto, Bayer) is indicated for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism following an acute deep vein thrombosis in adults. For the initial treatment of acute deep vein thrombosis, the recommended dose 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: short-term (3 months) for transient risk factors such as surgery and trauma; longer duration

for permanent risk factors or idiopathic deep vein thrombosis. A reduced dose of 15 mg twice daily for 21 days followed by 15 mg once daily should be used in patients with renal impairment (creatinine clearance less than 50 ml/min). There are limited data for rivaroxaban use beyond 12 months in all groups.

2.3 The summary of product characteristics lists the following adverse reactions for rivaroxaban: anaemia, bleeding events, dizziness, headache, syncope, eye haemorrhage and gastrointestinal tract haemorrhage. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The anticipated list price of rivaroxaban is £2.10 per tablet. The acquisition cost may be reduced by negotiated discount agreements between the manufacturer and appropriate NHS budget holders. The cost of rivaroxaban would be £235.86 for 3 months, £427.61 for 6 months and £811.13 for 12 months.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment and secondary prevention of venous thromboembolism.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with confirmed symptomatic deep vein thrombosis	Adults with an acute deep vein thrombosis Rationale: to match wording of licensed indication.

3.2 The ERG highlighted that patients recruited into the EINSTEIN trials did not fully reflect the population with deep vein thrombosis

because a number of important patient groups were excluded from EINSTEIN-DVT and EINSTEIN-Ext, most notably patients with bleeding risk, impaired kidney function, liver impairment and high blood pressure.

3.3 The ERG also noted that EINSTEIN-Ext included patients with both deep vein thrombosis and pulmonary embolism index events (pulmonary embolism is outside NICE scope but included in the composite endpoint venous thromboembolism recurrence) and the criteria used to determine 'clinical equipoise' were not adequately defined. However, the ERG's clinical advisers acknowledged that deep vein thrombosis and pulmonary embolism are manifestations of the same underlying condition.

3.4 The ERG also noted that the EINSTEIN trials did not include patients for whom VKA is not appropriate, other than patients with cancer.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention	Rivaroxaban	Rivaroxaban
Comparators	Initial treatment with unfractionated heparin or a LMWH (such as enoxaparin) with continued therapy as follows: • vitamin K antagonist (such as warfarin) • unfractionated heparin or LMWH for people for whom a vitamin K antagonist is not considered an appropriate treatment • No preventive therapy	Initial treatment with LMWH with continued vitamin A antagonist therapy for the remainder of 3,6 or 12 months, followed by no active therapy Vitamin K antagonist is not considered an appropriate treatment in patients with cancer, and in this subgroup, the use of LMWH will be evaluated. Rationale: Guidelines consistently recommend treatment with vitamin K antagonist (or LMWH in patients with cancer) for at least 3 months after initial stabilisation with LMWH. 'No therapy' is not a recommended option. Treatment and prevention are recognised as being at alternative ends of a continuum of care. Unfractionated heparin is generally recommended over LMWH only if there is severe renal impairment (creatinine clearance less than 30 ml/min). Such patients were excluded from the principle phase III trials of rivaroxaban and the use of rivaroxaban in such patients is cautioned against in the draft summary of product characteristics.

3.5 The ERG and its clinical advisers considered the comparator (enoxaparin) used by the manufacturer to be appropriate, despite the dose used in the EINSTEIN trials (1 mg/kg twice daily) not being in line with UK clinical practice (1.5 mg/kg once daily). Using the twice-daily dose may have been unfavourable to rivaroxaban.

3.6 The ERG noted that the comparator 'no preventive' treatment was intended to be interpreted as an ongoing treatment option comparator, and is partially addressed by EINSTEIN-Ext. However, the ERG concluded that, based on the presented available evidence, it cannot be determined that rivaroxaban is the optimal choice for long-term treatment because no direct comparison was made with other LMWH treatments.

3.7 In the population for which VKA is not recommended, the comparators listed in the scope were unfractionated heparin and LMWH. The ERG noted that evidence was not presented for comparisons with unfractionated heparin in this population. The ERG also noted that the comparison with LMHW was undertaken in a group of people with cancer, and that the population comprises other high risk patients, such as people with renal failure and liver impairment. These groups were excluded from the EINSTEIN trials so evidence for the use of rivaroxaban compared with LMWH is limited.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	Mortality Recurrent venous thromboembolism Complications following deep vein thrombosis including post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension Adverse reactions to treatment including bleeding events Health-related quality of life	As final scope

3.8 The ERG noted the absence of health-related quality of life data derived from a validated, preference based measure, but noted utility values taken from literature reviews to be satisfactory.

3.9

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that: • the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY) • the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences between the technologies being compared. Costs will be compared from an NHS and personal social services perspective.	As final scope. A lifetime horizon will be used. A cost-minimisation approach to the economic analysis was considered more appropriate and has been used in the submission. This is because both trials considered in the submission looked for, and demonstrated non-inferiority of clinical outcomes between rivaroxaban and LMWH/vitamin K antagonist.
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to: • underlying risk of recurrent venous thromboembolism, including the presence of active cancer • underlying risk of bleeding (for example people older than 60 years)	Additional analyses will be presented for patients with active cancer. Results will be presented that reflect the duration of treatment received and the characteristics of the population for whom such a duration is appropriate. The evaluation will account for individualised risks. Rationale: risk of bleeding, risk of recurrent venous thromboembolism and age are among various patient-specific characteristics that influence duration of anticoagulation.

3.10 The manufacturer assumed a maximum treatment duration of 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 clinical advisers estimated that 20% of people with deep vein thrombosis would have long-term treatment because recurrence of venous thromboembolism would indicate ongoing risk.

3.11 The ERG noted that there could be differential impacts on mortality, costs and quality of life for deep vein thrombosis and pulmonary embolism, and composite endpoints are valid only if there is no reason to believe that these two events behave differently in response to treatment.

3.12 The manufacturer noted that risk of bleeding, risk of recurrent venous thromboembolism and age are patient-specific characteristics that influence duration of anticoagulation, and so presenting results stratified by duration of treatment received (3, 6 or 12 months) was appropriate.

4 Clinical-effectiveness evidence

4.1 The manufacturer carried out a search of the literature to identify placebo- or active-controlled comparative studies investigating the treatment of acute, symptomatic deep vein thrombosis. The key clinical evidence for this submission came from two pivotal multicentre phase III trials (EINSTEIN-DVT and EINSTEIN-Ext).

4.2 EINSTEIN-DVT is an open-label non-inferior study that compared rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for 3, 6 or 12 months) with enoxaparin overlapped with VKA (warfarin or acenocoumarol) in patients with acute symptomatic deep vein thrombosis without any symptoms of pulmonary embolism, and for the prevention of recurrent venous thromboembolism. The intended duration of treatment was either 3,

6 or 12 months and was pre-determined by the treating physician based on individual patient risk factors. A total of 1731 patients were randomised to rivaroxaban and 1718 were randomised to enoxaparin/VKA.

4.3 EINSTEIN-Ext is a randomised double-blind placebo-controlled superiority study that compared rivaroxaban (20 mg once daily; n = 602) with placebo once daily (n = 594) in people with objectively confirmed symptomatic deep vein thrombosis or pulmonary embolism that had been treated for 6 or 12 months with VKA (warfarin or acenocoumarol) or rivaroxaban up to the moment of randomization.. Among the intention-to-treat population in EINSTEIN-Ext, 53% had participated in EINSTEIN-DVT and 27.8% had previously used rivaroxaban. About 60% of patients entering EINSTEIN-Ext were assigned to 6 months rather than 12 months of randomised treatment. For more details see tables 11 and 13, pages 36–43 of the manufacturer's submission.

4.4 Patients with creatinine clearance less than 30 ml/min, clinically significant liver disease, high blood pressure (systolic above 180 mmHg or diastolic above 110), active bleeding or high risk of bleeding were excluded from both EINSTEIN-DVT and EINSTEIN-Ext.

4.5 The primary efficacy outcome for EINSTEIN-DVT and EINSTEIN-Ext was symptomatic recurrent venous thromboembolism, which is a composite endpoint comprising deep vein thrombosis or pulmonary embolism. This includes both fatal and non-fatal pulmonary embolism. For details of the criteria used to define the composite endpoints, see table 15, page 45 of the manufacturer's submission.

4.6 The primary safety outcomes were clinically relevant bleeding for EINSTEIN-DVT (major bleeding and other clinically relevant non-major bleeding) and major bleeding for EINSTEIN-Ext. Results are for the intention-to-treat populations, except where indicated.

4.7 Results for EINSTEIN-DVT are reported on pages 55–61 of the manufacturer's submission, and summarised in table 1, below. The primary efficacy endpoint occurred in 2.1% of patients in the rivaroxaban group compared with 3.0% of patients in the enoxaparin/VKA group (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.44 to 1.04, p<0.001 for non-inferiority and p=0.0764 for superiority). For both treatment arms, most confirmed cases of venous thromboembolism occurred within the first month of treatment and before the end of the treatment initiation stage (day 21). Venous thromboembolism recurred in 21 patients (1.2%) treated with rivaroxaban and 29 patients treated with enoxaparin /VKA (1.7%). Recurrent deep vein thrombosis occurred less frequently in patients treated with rivaroxaban than with enoxaparin/VKA (14 compared with 28) and pulmonary embolism events (fatal and non-fatal) were similar across both treatment groups (24 compared with 24).

4.8 Rivaroxaban was at least as effective as to enoxaparin/VKA in regard to the safety outcomes clinically relevant bleeding (HR 0.97, 95% CI 0.76 to 1.22, p = 0.77) and all-cause mortality (HR 0.67, 95% CI 0.44 to 1.02, p = 0.06). Net clinical benefit, defined as a composite of symptomatic recurrent venous thromboembolism and major bleeding, favoured rivaroxaban over enoxaparin/VKA (51 compared with 73, HR 0.67, 95% CI 0.47 to 0.95, p = 0.03).

4.9 The manufacturer reported a time in therapeutic range for the comparator enoxaparin/VKA of 57.7% across all centres and 59.7%

in western European centres. The manufacturer highlighted that guidelines recommend a time in therapeutic range of at least 60% and noted there was no interaction observed in EINSTEIN-DVT between time in therapeutic range and treatment effect. For details see page 88 of the manufacturer's submission.

4.10 A range of pre-specified subgroups were reported by the manufacturer, including age, intended treatment duration, previous episodes of deep vein thrombosis or pulmonary embolism, parenteral anticoagulation before randomisation, and active cancer. Although the results of the subgroup analyses were complicated by uncertainty about the point estimates for venous thromboembolism recurrence, a general point estimate trend towards increasing efficacy of rivaroxaban was reported for age and for patients who had a previous episode of venous thromboembolism. See figure 8 on page 56 of the manufacturer's submission for details of the results for the pre-specified subgroups for the primary efficacy outcome. Also see table 11, page 42 of the manufacturer's submission, for baseline characteristics of patients in both studies.

Table 1 Summary of EINSTEIN-DVT results (taken from page 50 of ERG report, see also tables 18 and 29 of manufacturer's submission)

Trial name	**Einstein-DVT**		
Group	**Rivaroxaban n (%)**	**Enoxaparin /VKA n (%)**	**Hazard ratio (95% CI, p value)**
Primary outcome venous thromboembolism recurrence			
Intention-to-treat population	36 (2.1)	51 (3.0)	0.68 (0.44 to 1.04, p < 0.001)
Per protocol population	NR	NR	[redacted]
Secondary outcomes (intention-to-treat population)			
Fatal pulmonary embolism	1 (0.1)	0 (0)	NR
Pulmonary embolism cannot be ruled out	3 (0.2)	6 (0.3)	NR

Trial name	**Einstein-DVT**		
Group	**Rivaroxaban n (%)**	**Enoxaparin /VKA n (%)**	**Hazard ratio (95% CI, p value)**
Non-fatal pulmonary embolism	20 (1.2)	18 (1.0)	NR
Recurrent deep vein thrombosis plus pulmonary embolism	1 (0.1)	0 (0)	NR
Recurrent deep vein thrombosis	14 (0.8)	28 (1.6)	NR
Safety outcomes			
First major or clinically relevant non-major bleeding during treatment	139 (8.1)	138 (8.1)	0.97 (0.76 to 1.22, p = 0.77)
Major bleeding	14 (0.8)	20 (1.2)	0.65 (0.33 to 1.30, p = 0.21)
Clinically relevant non-major bleeding	126 (7.3)	119 (7.0)	NR
Vascular events On treatment Off treatment (30-day follow-up)	 12 (0.7) 1 (< 0.01)	 14 (0.8) 4 (0.2)	 0.79 (0.36 to 1.71, p = 0.55)
All cause mortality	38 (2.2)	49 (2.9)	0.67 (0.44 to 1.02, p = 0.06)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Any adverse event on treatment	1078 (62.7)	1080 (63.1)	NR
[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse events	201 (12.0)	233 (13.6)	NR
Serious, drug-related adverse reactions	[redacted]	[redacted]	NR
Cause of death			
Pulmonary embolism confirmed or not ruled out	4 (0.2)	6 (0.3)	NR
Bleeding	2 (0.1)	5 (0.3)	NR
Cancer	25 (1.4)	20 (1.2)	NR
Cardiovascular disease	2 (0.1)	4 (0.2)	NR
Other	6 (0.3)	14 (0.8)	NR
Quality of life/patient satisfaction			
ACTS burden (mean)	55.2	52.6 (p < 0.0001)	NR

Trial name	**Einstein-DVT**		
Group	**Rivaroxaban n (%)**	**Enoxaparin /VKA n (%)**	**Hazard ratio (95% CI, p value)**
ACTS benefits (mean)	11.7	11.5 (p = 0.006)	
Treatment satisfaction questionnaire	NR, states 'consistently higher'	NR	NR
Other outcomes			
[redacted]	[redacted]	[redacted]	NR
Adherence [redacted]	[redacted]	[redacted]	NR
Time in target range	NA	57.7%	NA
Abbreviations: ACTS, Anti-Clot Treatment Scale; CI, confidence interval; n, number of patients; NA, not applicable; NR, not reported.			

4.11 Results for EINSTEIN-Ext are reported in table 2, below. Patients taking rivaroxaban experienced fewer recurrences of venous thromboembolism (1.3%) than patients taking placebo (7.1%) in extended treatment and this result was statistically significant (HR 0.18, 95% CI 0.09 to 0.39, p < 0.0001). The differences in the Kaplan–Meier cumulative event probability rate favoured rivaroxaban, with a difference of 6.04% at 6 months and 6.65% at 12 months. In the extension study, net clinical benefit favoured treatment with rivaroxaban over placebo (12 patients compared with 42 patients, HR 0.28, 95% CI 0.15 to 0.53, p < 0.001). The number of clinically relevant non-major bleeding events was significantly higher in the rivaroxaban arm than in the placebo arm (32 patients compared with 7 patients, p < 0.001) and a higher

number of major bleeding events were reported in patients treated with rivaroxaban (4 patients compared with 0 patients), although this does not reach statistical significance. Patients on rivaroxaban experienced significantly fewer cases of the composite endpoint all-cause mortality and venous thromboembolism recurrence (secondary outcome 1) than patients randomised to enoxaparin/VKA (8 compared with 43, HR 0.18, 95% CI 0.09 to 0.38, p < 0.001).

Table 2 Summary of EINSTEIN-Ext results (taken from page 69 of ERG report, data on page 59 of manufacturer's submission and clarification letter)

Trial name	**Einstein-Ext**			**Einstein-Ext; deep vein thrombosis patients only**		
Group	Rivaroxaban, n (%)	Placebo, n (%)	Hazard ratio (95% CI, p value)	Rivaroxaban, n (%)	Placebo, n (%)	Hazard ratio (95% CI, p value)
Intention-to-treat population: Safety population: Per protocol population:	602 598 550	594 590 554	NA	[redacted]	[redacted]	[redacted]
Primary outcome: Venous thromboembolism recurrence Intention-to-treat population: Per protocol population:	8 (1.3) NR	42 (7.1) NR	0.18 (0.09 to 0.39, p < 0.0001) [redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes						
Fatal pulmonary embolism	0	1	NR	[redacted]	[redacted]	[redacted]
Pulmonary embolism cannot be ruled out	1	0	NR	[redacted]	[redacted]	[redacted]

Trial name	**Einstein-Ext**			**Einstein-Ext; deep vein thrombosis patients only**		
Group	Rivaroxaban n, (%)	Placebo n, (%)	Hazard ratio (95% CI, p value)	Rivaroxaban n, (%)	Placebo n, (%)	Hazard ratio (95% CI, p value)
Non-fatal pulmonary embolism	2	13	NR	[redacted]	[redacted]	[redacted]
Recurrent deep vein thrombosis	5	31	NR	[redacted]	[redacted]	[redacted]
Adverse events (safety population)						
Clinically relevant bleeding (major or clinically relevant non-major bleeding)	NA	NA	5.19 (2.3 to 11.7, p = 0.001)	[redacted]	[redacted]	[redacted]
Major bleeding	4 (0.7)	0 (0)	p = 0.11	[redacted]	[redacted]	[redacted]
Clinically relevant non-major bleeding	32 (5.4)	7 (1.2)	p < 0.001	[redacted]	[redacted]	
Vascular events						
On treatment	3 (0.5)	4 (0.7)	0.74 (0.17 to 3.3, p = 0.69)	[redacted]	[redacted]	
Off treatment (30-day follow-up)	2 (0.3)	0 (0.0)		[redacted]	[redacted]	
All cause mortality	1 (0.2)	2 (0.3)	NR	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Any adverse event on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related adverse reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious, drug-related adverse reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quality of life/patient satisfaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CI, confidence interval; n, number of patients.						

4.12 EINSTEIN-DVT included presence of active cancer as a pre-specified baseline covariate. To facilitate a comparison of the relative effects of rivaroxaban, dual enoxaparin/VKA therapy and long-term LMWH therapy for patients with cancer, a mixed treatment comparison was undertaken by the manufacturer. The manufacturer reported the relative effectiveness for rivaroxaban compared with dual enoxaparin/VKA, long-term LMWH compared with enoxaparin/VKA and rivaroxaban compared with long-term LMWH. For the indirect analysis, the manufacturer prepared two separate analyses. The primary analysis used data reported in the Akl et al (2011)[1] review and from the whole EINSTEIN-DVT trial. The secondary analysis 2 used data from a trial by Lee et al (2003)[2] evaluating the LMWH dalteparin for the prevention of recurrent venous thromboembolism in patients with cancer and the data from the cancer subgroup of EINSTEIN-DVT only (rather than the whole EINSTEIN-DVT trial).

4.13 Results from the primary analysis indicate that for patients with active cancer the venous thromboembolism recurrence hazard ratio for rivaroxaban compared with long-term LMWH was 1.44 (95% CI 0.07 to 31.4). The manufacturer noted that indirect comparison had wide margins of uncertainty for the efficacy and safety of rivaroxaban and long-term LMWH. The manufacturer also noted that a test for interaction showed that the presence of active cancer has [redacted] The manufacturer noted that there were minimal differences in the results of the mixed treatment comparison between the primary and

[1] Akl EA, Vasireddi SR, et al. Anticoagulation for patients with cancer and central venous catheters. Cochrane Database Syst Rev 201;(4):CD006468

[2] Lee AY, Levine MN, et al. Low-molecular weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349(2):146-153

secondary analysis (see tables 24–28, pages 74–77 of the manufacturer's submission).

4.14 The reported incidence of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension were low in both EINSTEIN-DVT and EINSTEIN-Ext. Results for safety outcomes are reported in table 18, page 62 of the manufacturer's submission.

4.15 The manufacturer reported adverse events from EINSTEIN-DVT and EINSTEIN-Ext that were experienced in at least 4% of any treatment group (table 29, page 81 of manufacturer's submission). The most common adverse events across both EINSTEIN trials were headache, pain in extremity, nasopharyngitis and epistaxis. The manufacturer noted that 24% of patients exposed to at least one dose of rivaroxaban reported adverse events thought to be related to the treatment. In patients treated for venous thromboembolism recurrence, bleeding events occurred in approximately 22.7% of patients and anaemia in approximately 1.8% of patients.

4.16 Health-related quality of life outcomes were not collected in EINSTEIN-DVT or EINSTEIN-Ext (see page 64 of the manufacturer's submission). Instead, a patient-reported treatment satisfaction scale, called the 'anti-clot treatment scale' (ACTS), and a treatment satisfaction questionnaire (known as TSQM) were used EINSTEIN-DVT. ACTS consists of two scales: ACTS Burdens which covers 12 items, and ACTS Benefits which covers 3 items. It is collected at pre-specified interval across the duration of the trial and higher scores indicate higher satisfaction. TSQM is an 11-item instrument with four subscales: effectiveness, side-effects, convenience and global satisfaction. Patients reported higher satisfaction with rivaroxaban than with enoxaparin/VKA (mean

ACTS Burden score 55.2 compared with 52.6, $p < 0.0001$). Patients on rivaroxaban reported higher scores for TSQM across all subscales.

4.17 The European Public Assessment Report (EPAR) noted that the majority of patients (73% in the rivaroxaban arm) were treated with an LMWH before a diagnostic procedure and before randomisation, but concluded there is little evidence to support a general recommendation for the use of a parenteral anticoagulant in the initial phase of acute treatment.

4.18 The EPAR also noted that patients recruited into EINSTEIN-Ext had varied risk profiles, and this could affect the primary efficacy outcome. It also noted that EINSTEIN-Ext did not compare the efficacy of rivaroxaban with VKA (which could be an alternative), but concluded that the low event rates observed in rivaroxaban arm would be expected in patients otherwise treated with VKA.

4.19 The EPAR highlighted the lack of data for treatment beyond 1 year. This needs to be appropriately addressed and is a consideration in the product information/risk management plan.

Evidence Review Group comments

4.20 Overall, the ERG considered the clinical effectiveness presented by the manufacturer broadly relevant to the decision problem but raised a number of concerns about the manufacturer's submission:

- The ERG noted the population recruited into the EINSTEIN trials excluded a number of important groups relevant to the decision problem. These include patients with: bleeding risk, 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 at high risk of bleeding (with the exception of patients with cancer). This group was specifically mentioned in the NICE scope as a potential subgroup analysis.

- The ERG raised concerns about the population and interpretation of 'clinical equipoise' in EINSTEIN-Ext and the inclusion criteria used to assess clinical benefit. It is unclear to the ERG (who estimate that 20% of patients with deep vein thrombosis need long-term anticoagulation) which patients would have been included in the EINSTEIN-Ext trial.
- The ERG's clinical advisers highlighted that intended treatment duration could extend beyond 12 months depending on patient risk factors, and noted that approximately 20% of the deep vein thrombosis population would currently proceed to long-term (ongoing) treatment mainly because of recurrence of venous thromboembolism. The ERG noted that the manufacturer did not provide an analysis beyond 12 months and an assumption based on current UK practice would have been appropriate.
- The ERG raised concerns about the robustness of the mixed treatment comparison. The ERG noted that the included trials lacked heterogeneity, the studies varied in length of follow-up, and choice and dosage of LMWH varied across studies.
- The ERG highlighted that international guidelines recommend LMWH treatment only, which was not the comparator in EINSTEIN-DVT. The ERG was concerned that the use of LMWH/VKA as a comparator could favour the comparison with rivaroxaban because patients are expected to fare worse on LMWH/VKA.
- The ERG highlighted that, although bleeding events were similar across intended treatment duration groups in EINSTEIN-DVT,

subgroup analyses and interaction tests revealed significant differences in efficacy across intended treatment duration when considered separately (3, 6, 12 months) for the outcome venous thromboembolism recurrence [redacted]

- The ERG noted that for clinically relevant bleeding the safety profile of rivaroxaban was significantly worse than for placebo in EINSTEIN-Ext (HR 5.19, 95% CI 2.3 to 11.7), despite rivaroxaban being superior to placebo for prevention of venous thromboembolism recurrence. For patients with only a deep vein thrombosis index event compared with all patients in the trial, [redacted]
- The ERG noted that health-related quality of life was not measured using a validated, preference-based measure in line with the NICE reference case.
- The ERG also noted that anticoagulation with rivaroxaban could increase access to treatment for patients from some religious denominations (because warfarin is made of porcine heparin) and for patients with poor dexterity or needle phobia. The ERG also noted that reversal of rivaroxaban is a potential issue because this has not yet been standardised.
- The ERG and its clinical advisers considered whether rivaroxaban and LMWH/VKA could have differential effects on pulmonary embolisms and deep vein thromboses, because pulmonary embolism is more serious than deep vein thrombosis. The ERG concluded that no significant differences were observed in the presented data but noted that this could be attributed to the small number of total events observed.

Additional submitted analyses

4.21 The ERG asked the manufacturer for clarification and an interaction test on the subgroup analyses of intended treatment duration, and noted that there are significant differences across treatment durations at the p = 0.1 significance level (table 3, below). The ERG highlighted rivaroxaban increased the probability of venous thromboembolism recurrence in patients treated for 3 months. However, the ERG acknowledged that these endpoints were not powered and the total numbers of events were small.

4.22 The manufacturer also submitted analyses for the subgroup of patients with active cancer but no analysis for risk of bleeding. The manufacturer noted that it would have been unethical to include groups for whom this treatment was contraindicated and that the risk:benefit of anticoagulation in regard to bleeding was taken into account at the time of randomisation because patients were allocated to treatment duration based on risk of bleeding. The ERG noted that certain subgroups of patients with bleeding risk were excluded (in line with the manufacturer's protocol).

Table 3 Additional interaction test statistics for the primary analysis of time to venous thromboembolism recurrence of table 1, page 8, manufacturer's clarification (reproduced table 11 of ERG report)

	Hazard ratio (95% CI)	Tests for interaction	
		Wald	Gail-Simon
Previous episode of deep vein thrombosis/pulmonary embolism		[redacted]	[redacted]
Yes	[redacted]		
No	[redacted]		
Intended duration of anticoagulation		[redacted]	[redacted]
3 months	[redacted]		
6 months	[redacted]		

12 months	[redacted]	[redacted]		
Age group			[redacted]	[redacted]
Younger than 65 years	[redacted]	[redacted]		
65-75 years	[redacted]	[redacted]		
Older than75 years	[redacted]	[redacted]		
Renal function: creatinine clearance			[redacted]	[redacted]
80 ml/min or more	[redacted]	[redacted]		
50 to less than 80 ml/min	[redacted]	[redacted]		
Less than 50 ml/min	[redacted]	[redacted]		
Missing	[redacted]	[redacted]		

4.23 For the EINSTEIN-Ext trial, the ERG requested trial results for patients with deep vein thrombosis only (excluding patients with initial diagnosis of pulmonary embolism, who would not be included in the proposed licensed indication). [redacted]

4.24 The ERG asked the manufacturer to submit additional analysis for the network meta-analysis used in the 'patients with active cancer' subgroup. The ERG expressed concern with how the network meta-analysis was implemented, especially the lack of clarity on study characteristics, the accuracy of the data to estimate treatment effects, the lack of consideration for other LMWH treatments (that is, enoxaparin and tinzaparin) and the chosen distribution for the between-study standard deviations. A revised analysis by the ERG showed that rivaroxaban is less effective than LMWH at preventing venous thromboembolism recurrence (HR 1.32, 95% CI 0.06 to 32.3) but induces fewer major bleeding events (odds ratio 0.24, 95% CI 0.00 to 9.44). The ERG felt the secondary analysis 2 was more appropriate because it is based on the cancer subgroup alone and felt the primary analysis (based on the whole

EINSTEIN-DVT trial, which showed no significance for the presence of active cancer) was inappropriate. The ERG concluded the mixed treatrment comparison did not provide good estimates of the uncertainty associated with the true treatment effect, but felt the point estimate to be reasonable.

4.25 The ERG revised the manufacturer's analysis to take into account a more plausible – and smaller – distribution of between-study standard deviations (as opposed to the use of extreme values used by the manufacturer) and found rivaroxaban to be less effective than LMWH at preventing venous thromboembolism recurrence, but to induce fewer major bleeding events. The ERG concluded that any reliance on the results of the network meta-analyses may lead to inaccurate estimates of mean ICERs because they are based on inflated expected values.

5 Comments from other consultees

5.1 Clinical specialists noted that the current standard treatment is immediate therapy with a LMWH followed by a VKA until optimal INR is achieved. VKA is usually continued for 3 months before long-term anticoagulation is considered. Clinical specialists expect the diagnosis of deep vein thrombosis and pulmonary embolism to be made in hospital (where treatment will be initiated) and continued prescription to be in primary care.

5.2 The clinical specialists noted that deep vein thrombosis in the lower limbs can cause the patient severe pain and pulmonary embolism needs intensive nursing and monitoring. Patients taking warfarin need to make lifestyle modifications and undergo routine INR monitoring. The clinical specialists also noted that some patients are unable to tolerate warfarin.

5.3 The clinical specialists stated that the advantages of rivaroxaban are its oral formulation, no requirement for monitoring (therefore a reduced need for support services), no transition from one anticoagulant to another, and it can be given immediately after a diagnosis of deep vein thrombosis. They also noted that rivaroxaban is likely to benefit patients who have had a venous thromboembolism before, who are classified to be medium or high risk, who are needle phobic or who want to resume normal patterns of daily life without having to find time to attend clinics. Disadvantages include short half-life, inability to determine treatment failure or poor adherence and lack of a specific antidote for direct reversal in case of haemorrhagic complications.

5.4 Patients highlighted rivaroxaban's ease of use, its potential to improve quality of life and that it is associated with fewer contraindications (that is, no dietary restrictions or drug interactions).

5.5 Northumberland Care Trust noted that it would cost about £200 a year to treat a patient with warfarin. This is lower than the £656 estimated by the manufacturer (based on revised model) and £320 estimated by the ERG. The cost of INR monitoring for a patient with venous thromboembolism is not known.

6 Cost-effectiveness evidence

Manufacturer's submission

6.1 The manufacturer's submission states that a Markov-based model was used for the economic evaluation of rivaroxaban within its licensed indication for the treatment of deep vein thrombosis and prevention of recurrence of venous thromboembolism. Two analyses were presented: a primary analysis comparing

rivaroxaban with LMWH/VKA over 3, 6 and 12 months; and a cost-minimisation analysis for patients with active cancer, which used dalteparin as the comparator.

6.2 The Markov model comprised 11 health and treatment states and patients entered the model following a diagnosis of deep vein thrombosis. The model relied on the whole trial population of EINSTEIN-DVT to derive baseline risk events, treatment effects, probabilities for bleeding events and discontinuation rates. 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 (British national formulary, NHS Reference Costs 2010-11 and PSSRU 2010) and generally reflected UK clinical practice. The model did not include monitoring for patients treated with rivaroxaban or LMWH. It assumed nine visits in the first 3 months, followed by five visits thereafter (every 3 months) for patients treated with a VKA. It also assumed that 66% of visits for INR monitoring would take place in primary care and 34% in secondary care. For more details see pages 105–117 of the manufacturer's submission.

6.3 The manufacturer did not collect utility data during the EINSTEIN trials and instead assigned a baseline utility value of 0.825 to all patients with deep vein thrombosis entering the model, which was taken from the EQ-5D survey by Kind et al ([1998]) and adjusted with disutility values for deep vein thrombosis, pulmonary embolism, extracranial (EC) bleed, intracranial (IC) bleed and post-thrombotic syndrome (see table 46, page 134 of the manufacturer's submission).

6.4 For primary care, the manufacturer assumed INR monitoring would be delivered equally by a GP and a nurse (50/50 split). The

secondary care cost of INR monitoring was assumed to be £47.19. See table 51 and page 150 of the manufacturer's submission for more details.

6.5 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 demonstrated a greater discounted life expectancy and quality-adjusted life expectancy than LMWH/VKA across all treatment durations. Treatment with rivaroxaban was shown to be cost saving compared with LMWH/VKA across all treatment durations (a cost-saving of £162.85 at 3 months; £124.22 at 6 months and £32.80 at 12 months). See table 46, pages 132–135 of the manufacturer's submission and table 4, below.

Table 4 Summary of lifetime costs by category of resource (adapted from table 75 of manufacturer's submission, page 196)

Cost category	Rivaroxaban arm	LMWH/VKA arm	Increment	ICER
3 months of treatment				
Drug cost	221.69	98.91	122.77	
Monitoring cost	0.00	245.00	-245.00	
Event cost	687.88	697.89	-10.00	
Bleeds cost	52.53	77.83	-25.30	
PTS/CTEPH	173.14	178.46	-5.32	
Total	1,135.24	1,298.09	-162.85	Rivaroxaban dominates
QALY	13.348	13.325	0.023	
6 months of treatment				
Drug cost	397.14	104.70	292.44	
Monitoring cost	0.00	367.21	-367.21	
Event cost	679.87	691.79	-11.92	
Bleeds cost	68.97	100.27	-31.31	
PTS/CTEPH	172.23	178.45	-6.22	
Total	1,318.20	1,442.42	-124.22	Rivaroxaban dominates

QALY	13.365	13.345	0.020	
12 months of treatment				
Drug cost	737.13	115.90	621.23	
Monitoring cost	0.00	604.03	-604.03	
Event cost	660.64	673.81	-13.17	
Bleeds cost	75.58	105.66	-30.08	
PTS/CTEPH	169.73	176.48	-6.75	
Total	1,643.08	1,675.88	-32.80	Rivaroxaban dominates
QALY	13.377	13.356	0.020	

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; LMWH, low-molecular weight heparin; PTS, post thrombotic syndrome; QALY, quality-adjusted life year.

Definitions: Dominates means the treatment is less costly and more effective than the comparator.

6.6 The manufacturer conducted subgroup analysis evaluating the benefits of rivaroxaban in patients with active cancer. Because patients with cancer are closely monitored and need frequent clinic visits and because there are no significant differences between rivaroxaban and the chosen comparator dalteparin, which has a UK marketing authorisation for treatment of venous thromboembolism recurrence in patients with cancer, the manufacturer opted for a cost-minimisation analysis. Patients with cancer were assumed to be treated for 6 months. At 6 months, rivaroxaban is associated with cost savings of £904 (dalteparin £8.47 per day for 1 month and £7.06 per day for 5 months; £2.10 per day for rivaroxaban). Importantly, INR monitoring was not included in the model because it was assumed that patients with cancer would have a more predictable pharmacokinetic profile.

6.7 The manufacturer undertook a series of one-way and multivariate deterministic sensitivity analyses to test the robustness of the results by varying most of the parameters used in the economic evaluation, based on upper and lower 95% confidence intervals,

interquartile ranges and 30% variation of unit costs. The manufacturer also conducted probabilistic sensitivity analysis through repeated sampling with varied probabilities for recurrent venous thromboembolism, bleeding events and other clinical events and resource factors. The results indicated that the cost effectiveness of rivaroxaban was largely insensitive to variations in the assumptions in most parameters. There was a 94 to 98.9% probability of rivaroxaban being cost effective if the maximum acceptable ICER was £20,000 per QALY gained for all treatment durations, with the treatment duration of 3 months producing the most cost savings and increased incremental QALYs. The probability of rivaroxaban being the dominant treatment option (that is, less costly and more effective than LMWH/VKA) was 97.1% in patients needing 3 months of anticoagulation, 83.9% in those needing 6 months and 53% in those needing 12 months.

6.8 The manufacturer noted that the main factors influencing the cost effectiveness of rivaroxaban were the reduction of venous thromboembolism recurrence in the whole population for rivaroxaban compared with LMWH/VKA (HR 0.68, 95% CI 0.44 to 1.04). Patients treated with rivaroxaban do not need routine INR monitoring or LMWH therapy, which consume additional resources (drug cost, nurse visit and education).

6.9 The manufacturer noted that the key limitations in the economic model relate to the fact that it was not possible use health state utilities elicited using the EQ-5D, the dependency on point estimates derived from a non-inferiority trial design (EINSTEIN-DVT) and the uncertainty in the credible intervals for the indirect comparison of rivaroxaban and long-term LMWH therapy.

ERG critique and exploratory analyses

6.10 The ERG noted that the subgroup for underlying risk of bleeding was not presented. The ERG did not request such an analysis because of equity and accessibility issues and because patients with bleeding risk were excluded from the EINSTEIN trials.

6.11 The ERG raised a number of concerns about the manufacturer's model. First, the ERG pointed out that point estimates for probabilities and treatment effects should be based on intended treatment duration and not the whole trial population of EINSTEIN-DVT, because there is clinical evidence to support differential effectiveness across treatment durations. The manufacturer provided the ICERs, which are presented in table 5, below.

Table 5 Summary of results based on patient-specific data (not whole trial population); treatment and time horizons for 3, 6 and 12 months

Duration specific	Cost category	Rivaroxaban arm	LMWH/VKA arm	Increment	ICER
3 months of treatment					
	Drug cost	[redacted]	[redacted]	[redacted]	
	QALY	[redacted]	[redacted]	[redacted]	[redacted]
6 months of treatment					
	Drug cost	[redacted]	[redacted]	[redacted]	
	QALY	[redacted]	[redacted]	[redacted]	[redacted]
12 months of treatment					
	Drug cost	[redacted]	[redacted]	[redacted]	
	QALY	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LMWH, low molecular weight heparin; QALY, quality adjusted life year

Definitions: Dominates means the treatment is less costly and more effective than the comparator.

6.12 The ERG questioned whether separate probabilities for the treatment effects of rivaroxaban and the comparator would be more appropriate than the assumption of proportional hazards made by the manufacturer. [redacted]

Furthermore, the ERG questioned whether assuming a constant ratio of deep vein thrombosis and pulmonary embolism independent of treatment was plausible, and modelled a scenario in which a different split was assumed (see tables 27 and 36 of the ERG report).

6.13 Finally, the ERG noted that monitoring is an important parameter for the ICER, and varied the assumptions on INR monitoring to be less intensive. The ERG explored a scenario in which patients require six visits for the first 3 months (instead of nine), three visits thereafter (instead of five). The ERG assumed that the same proporation of patients were managed in primary and secondary care as in the manufacturer's submission but assumed that among visits that happen in primary care, 25% were with a GP and 75% with a nurse (instead of the 50/50 split assumed by manufacturer). The annual monitoring cost estimated by the ERG for this scenario is £320 (compared with the estimate of £656 from the manufacturer). These figures were higher than reported by a primary care trust (£200/year) and those noted in NICE clinical guideline 92. The ERG also noted that the cost reported by the primary care trust is based on atrial fibrillation and monitoring costs in venous thromboembolism patients may be different.

6.14 The ERG undertook exploratory analyses based on additional data submitted by the manufacturer and took into account the above described areas of uncertainty. The results are presented in table 6, below.

Table 6 Summary of ERG exploratory analysis by treatment duration (tables 37, 43 and 49 of ERG report)

		Incremental cost	Incremental QALY	Cost per QALY gained or *yielded*
3 months				
1	Manufacturer base case (rivaroxaban compared with LMWH/VKA)	-£180	-0.02	*£11,787 per QALY yielded*
2	1 + errors corrected	-£182	-0.02	*£11,792 per QALY yielded*
3	2 + with INR monitoring costs altered	-£86	-0.01	*£6358 per QALY yielded*
4	2+ with constant pulmonary embolism:deep vein thrombosis relaxed	-£170	-0.03	*£5031 per QALY yielded*
5	2+ with INR monitoring costs and constant pulmonary embolism:deep vein thrombosis relaxed	-£75	-0.04	*£2123 per QALY yielded*
6 months				
1	Manufacturer base case (rivaroxaban compared with LMWH/VKA)	-£101	0.01	Dominant
2	1 + errors corrected	-£104	0.01	Dominant
3	2 + with INR monitoring costs altered	£71	0.01	£8341 per QALY gained
4	2+ with constant pulmonary embolism:deep vein thrombosis relaxed	-£91	-0.00	*£26,343 per QALY yielded*
5	2+ with INR monitoring costs and constant pulmonary embolism:deep vein thrombosis relaxed	£84	-0.00	Dominated
12 months				
1	Manufacturer base case (rivaroxaban compared with LMWH/VKA)	-£13	0.04	Dominant
2	1 + errors corrected	-£10	0.04	Dominant
3	2 + with INR monitoring costs altered	£307	0.04	£8089 per QALY gained
4	2+ with constant pulmonary embolism:deep	-£3	0.03	Dominant

	vein thrombosis relaxed			
5	2+ with INR monitoring costs and constant pulmonary embolism:deep vein thrombosis relaxed	£309	0.03	£12,183 per QALY gained
Abbreviations: LMWH, low molecular weight heparin; QALY, quality-adjusted life year.				

6.15 The ERG asked the manufacturer to conduct an exploratory cost-effectiveness analysis comparing rivaroxaban with LMWH in the subgroup of patients with active cancer. The results of the exploratory analysis are presented below (table 7). The analysis indicates that rivaroxaban is less costly and provides marginally more QALYs than dalteparin (LMWH).

Table 7 Exploratory cost-effectiveness analysis in the subgroup of patients with active cancer submitted by the manufacturer based on 6-month treatment duration (table 21 of clarification letter)

Time horizon		Rivaroxaban arm	LMWH/VKA arm	Increment	ICER
6 months					
	Drug cost	[redacted]	[redacted]	[redacted]	
	QALY	[redacted]	[redacted]	[redacted]	[redacted]
1 year					
	Drug cost	[redacted]	[redacted]	[redacted]	
	QALY	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime					
	Drug cost	1,117.13	4.6799	-1,085.38	Rivaroxaban Dominates
	QALY	2,202.52	4.6786	0.0013	
Abbreviations: ICER, incremental cost effectiveness ratio; LMWH, low molecular weight heparin; QALY, quality-adjusted life year.					

6.16 However, the ERG cited a number of concerns with the parameter estimates adopted in the exploratory analysis (assumed large between-study deviations, treatment effect calculated from medians rather than means – rivaroxaban showed no gains in QALYs when means were used for treatment effect, data on risk of events after 6 months were not specific to patients with cancer, baseline utility assumed and impact on quality of life assumed to be same for patients with cancer and those without cancer) and concluded that the results of this exploratory analysis were not robust.

6.17 The ERG conducted three exploratory analyses using the mean HR or odds ratio and assuming different between study variability. Results are presented for the deterministic analysis in table 8. However, the ERG believes these results to be exploratory rather than definitive due to the following caveats: a series of assumptions were made to estimate the baseline risk of events; the treatment effect was taken from the mixed treatment comparison but there was a considerable uncertainty; data not specific to cancer patients was used once treatment ceased; uncertainties about the utility estimates.

Table 8: Summary of ERG exploratory analyses in cancer patients

		Incremental cost (£)	**Incremental QALY**	**Cost per QALY gained (£)**	**Cost per QALY yielded (£)**
1	Manufacturer base case	-£1,085	0.00135	Rivaroxaban Dominates	
2	As 1, but erros corrected	-£1,272	0.00129	Rivaroxaban Dominates	
3	As 2 using mean HR assuming U (0,5)	-£1,141	-0.03272		34,865 per QALY yielded
4	As 2 using mean HR	-£1,202	-0.01594		75,408 per QALY

	assuming U (0,2)				yielded
5	As 2 using mean HR assuming U (0,6)	-£1,253	-0.00319		392,242 per QALY yielded
* When evaluating cost per QALY lost, values greater than the assumed threshold are deemed cost-effective, with values under the threshold indicating that a treatment would not be cost-effective					

6.18 Overall, the ERG noted that the savings in costs (and gains in QALYs) with rivaroxaban were small (costs £38–£218, QALYs 0.0015–0.0458). Rivaroxaban remained dominant in the probabilistic sensitivity analysis at 6 and 12 months, but not at 3 months (for which it provided fewer QALYs at a lower cost, cost per QALY yielded £11,787).

6.19 The ERG believed the results presented by the manufacturer to be plausible but noted that large uncertainties remain in the data and assumptions, which could affect the ICER. The ERG noted that the model is sensitive to changes in assumptions to the extent that results can change from dominant to dominated and from cost effective to not cost effective.

6.20 The ERG explored only two assumptions (INR monitoring and relaxing constant deep vein thrombosis and pulmonary embolism ratio, table 6) and highlighted that additional scenarios could not be modelled because of lack of data but could affect the ICER. The ERG acknowledged there is uncertainty surrounding the cost of INR monitoring for patients treated for venous thromboembolism with a VKA because values ranged from £200 in atrial fibrillation patients to £656 for venous thromboembolism patients, which is reported by the manufacturer. An analysis of patients treated beyond 12 months was not presented and the ERG raised

concerns about why rivaroxaban was not considered for the treatment of subsequent recurrence.

6.21 The manufacturer also submitted revised probabilistic sensitivity analysis estimates based on effectiveness data specific to treatment duration. These showed that if the maximum acceptable ICER was £20,000 per QALY gained, rivaroxaban had a 58.4% probability of being cost effective for a 3-month duration of treatment, 85% for 6 months and 95.4% for 12 months. They also showed that rivaroxaban was dominant (that is, more QALYs and lower cost) in 48.5% of cases for 3-month durations, 68.7% for 6 months and 48.8% for 12 months.

6.22 Taken together, the ERG considered that the manufacturer's approach to the economic evaluation was acceptable. The ERG noted that the EINSTEIN-DVT trial was well designed in that patients were allocated according to intended treatment duration before randomisation and the modelling assumptions used in the model were generally plausible. However, the ERG noted areas of uncertainty and weaknesses, including: the trial not being powered to detect outcomes stratified by intended treatment duration; data with unfractionated heparin as a comparator were not available; some patient populations were missing; patients with cancer received treatment not recommended in international guidelines; health-related quality of life was not measured using a preference-based measure; the mixed treatment comparison relied on heterogeneous evidence; and the ERG felt that the manufacturer was likely to have underestimated the uncertainty in the decision problem.

7 Equalities issues

7.1 The ERG highlighted that rivaroxaban could increase access to treatment for people from some religious denominations (because warfarin is made from porcine heparin) and for people who have needle phobia or other problems with injection.

8 Innovation

8.1 The manufacturer noted that rivaroxaban offers a step change in the management of deep vein thrombosis (oral administration and no requirement for routine INR monitoring).

9 Authors

Kumar Perampaladas (Technical Lead), Dr Pall Jonsson (Technical Adviser), with input from the Lead Team (Dr Louise Longworth and Dr Anne McCune).

Appendix A: Supporting evidence

Related NICE guidance

Published

- Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline 92 (2010). Available from http://guidance.nice.org.uk/CG92

- Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults. NICE technology appraisal guidance 245 (2012). Available from http://guidance.nice.org.uk/TA245

- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. NICE technology appraisal guidance 170 (2009). Available from http://guidance.nice.org.uk/TA170

- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal guidance 157 (2008). Available from http://guidance.nice.org.uk/TA157

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. NICE clinical guideline. Publication expected June 2012.
- Dabigatran etexilate for the treatment of acute venous thromboembolic events. NICE technology appraisal. Publication date to be confirmed.

Appendix B: Clinical efficacy section of the draft European public assessment report

[To be added as a confidential appendix.]