NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Rivaroxaban for the treatment of pulmonary embolism and prevention of recurrent 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.

Key issues for consideration

Clinical effectiveness

- The clinical effectiveness data comes from EINSTIEN PE. In this trial 57% of people were treated for 6 months. Does this reflect current practice? What proportion of people would be expected to receive a lifelong treatment?
- In EINSTEIN PE
  - the average age was 58 years
  - the low molecular weight heparin used was enoxaparin (dose: 1.0 mg/kg twice daily until anticoagulation was established) which differs from the dose covered by the European and UK marketing authorisation for enoxaparin
  - the time in therapeutic range for people in the low molecular weight heparin with vitamin K antagonist arm was 62.7%.

How generalisable is this trial to UK clinical practice?

- In EINSTEIN-PE approximately 5% of people had cancer. These people received low molecular weight heparin with a vitamin K antagonist however the standard treatment in UK clinical practice for people with cancer who have pulmonary embolism is low molecular weight heparin without a vitamin K antagonist. No indirect comparison was presented for rivaroxaban to low molecular weight heparin. In NICE technology appraisal guidance 261, which appraised rivaroxaban for the prevention of deep vein thrombosis and the prevention of recurrent venous thromboembolism there was a similar lack of evidence for this group. The Committee were unable to make 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. Is the evidence presented for the cancer subgroup in the current submission sufficient to make a recommendation for the use of rivaroxaban for pulmonary embolism in people with cancer?
- The ERG noted that the population of EINSTEIN-PE did not include all people with pulmonary embolism. The trial had excluded not only people who were contraindicated to rivaroxaban but also people who had severe renal failure, who may still be eligible for rivaroxaban. Is the trial population representative of the treatment population in general?

Cost effectiveness

- The summary of product characteristics does not specify the longest length of time a person could receive rivaroxaban. The longest treatment duration in EINSTEIN-PE was 12 months. Economic analyses are presented for a 3-6-, 12 months and lifelong treatments. Would some people be expected receive a lifelong treatment with rivoraxaban?
- The manufacturer assumed the weighted average cost (taking into account setting) of a first international normalised ratio (INR) monitoring visit of £26.26 and £24.88 for a subsequent visit. In NICE technology

appraisal 261 the manufacturer's estimated weighted average cost of a first INR monitoring visit was £33.77 and for a subsequent visit £26.23. In NICE technology appraisal 261 the Committee considered that the ERG's estimate that people would have 6 visits in the first 3 months and 3 in subsequent quarters with a first year cost of £320 for INR monitoring to be reasonable. Are the costs of INR monitoring visits presented in the current submission for rivaroxaban for pulmonary embolism representative of what would be expected in clinical practice?

- What is the standard number of days a person would receive low molecular weight heparin in clinical practice?
- The ERG noted that the manufacturer had not included the costs of stopping a bleed in their base case, and presented a scenario where the costs of treating bleeds with prothrombin complex concentrate or activated recombinant factor VII (rFVIIa) were taken into account. How would bleeds experienced while taking low molecular weight heparin, vitamin K antagonists or rivaroxaban be managed?
- The manufacturers reported that 94.2% of patients in EINSTEIN-PE showed compliance to rivaroxaban treatment of at least 80%. Will a similar level of compliance be expected in UK clinical practice? Would compliance be expected to remain the same over time?
- The hazard ratio for bleeding for rivaroxaban compared with low molecular weight heparin with a vitamin K antagonist was more favourable towards rivaroxaban in EINSTEIN-PE (0.493) than EINSTEIN-DVT (0.63). EINSTEIN-DVT was one of the key trials supporting the clinical effectiveness of rivaroxaban in the manufacturer's submission for NICE technology appraisal 261. Does the Committee consider this relevant?

1 Background: clinical need and practice

1.1 Venous thromboembolism (VTE) is a condition in which a blood clot (thrombus) forms in a vein, most commonly in the deep veins of the

legs or pelvis. This is known as deep vein thrombosis, or DVT. The thrombus can dislodge and travel in the blood (embolise), particularly to the arteries in the lung. This is known as pulmonary embolism (PE). The term venous thromboembolism includes both DVT and PE. The PE can be provoked such as following trauma, or resulting from a transient risk factor such as surgery. Alternatively the pulmonary embolism can be unprovoked when there is no known cause or it occurs spontaneously. The clinical course of PE may be complicated by recurrent episodes of DVT or PE. Unprovoked PE has a higher risk of recurrence than provoked PE.

1.2 The annual incidence of VTE is approximately 2 per 1000 people. Risk factors associated with venous thromboembolism include: thrombophilia, history of deep vein thrombosis, age over 60 years, surgery, obesity, prolonged travel, acute medical illness, immobility and cancer. The annual incidence of diagnosed PE in the UK has been reported as 7-8 per 10,000 people. The risk varies substantially with age; for people under 40 years the annual incidence of venous thromboembolism is 1 in 10,000, whereas for people over 80 years the incidence rises to 1 in 100. People who have had an episode of VTE have a risk of recurrence within 8 years of approximately 30%. However, the risk of recurrence decreases substantially with time and may vary according to the treatment received. The manufacturer estimates that there would be approximately 38,600 incident cases of adults with acute PE in 2013 in England and Wales, of which around 34,000 (90%) would be the patients' first PE. The manufacturer expects the incident population to increase over time because of population growth and an aging population.

1.3 PE can cause sudden death. Those who survive can occasionally require intensive care and recovery can take several weeks or

months. If a person with a PE experiences a subsequent DVT there is a risk of developing post-thrombotic syndrome, a chronic disorder that may include symptoms such as pain, heaviness, swelling , cramps, itching or tingling, increased skin pigmentation and ulceration in the affected limb. Other complications include chronic thromboembolic pulmonary hypertension (CTEPH).

1.4 NICE has published guidance on the management of venous thromboembolic diseases (NICE clinical guideline 144, venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing). This guideline recommends that people with confirmed pulmonary embolism should be offered a choice of low molecular weight heparin (LMWH) or fondaparinux, taking into account co-morbidities, contraindications and drug costs. The following exceptions apply: people with an increased risk of bleeding for whom treatment with unfractionated heparin may be considered; people with severe renal impairment or renal failure (estimated glomerular filtration rate [eGFR] less than 30 ml/min/1.73 m^2) who should be offered unfractionated heparin or LMWH (both with appropriate dose adjustments); people who have a PE and are haemodynamically unstable (which may indicate a massive embolism blocking a pulmonary artery) who should be offered unfractionated heparin and for whom thrombolytic therapy should be considered. In addition to heparin, people with PE should also be offered a vitamin K antagonist such as warfarin within 24 hours of diagnosis. The guideline recommends that treatment with LMWH, unfractionated heparin or fondaparinux should be started as soon as possible and continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer. The guidelines state that a patient should continue to take a vitamin K antagonist for 3 months at

which point the risks and benefits of continuing with a vitamin K antagonist should be assessed. People with active cancer who experience a PE do not take vitamin K antagonists and continue with LMWH for 6 months, at which point the risks and benefits of continuing treatment are assessed.

1.5 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. NICE clinical guideline 144 did not make recommendations on which setting initial heparin treatment should take place, but the manufacturer suggested that a minority of patients with a PE may receive their initial anticoagulation either completely or partially at home. 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 and training is self-injection), or who have poor dexterity. These considerations are of particular importance for people with cancer who require longer term treatment with LMWH. 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 order 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 with warfarin therefore needs an

infrastructure for blood sampling, testing, monitoring and dose adjustment.

2 The technology

2.1 Rivaroxaban (Xarelto, Bayer) is an anticoagulant that acts by direct inhibition of factor Xa. The licence for rivaroxaban includes the following therapeutic indication: treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults. The marketing authorisation was granted in two stages. In July 2012, NICE issued guidance recommending rivaroxaban as an option for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism (technology appraisal 261). At this time, the marketing authorisation only covered the DVT indication. On 18th October 2012 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for rivaroxaban to include treatment of pulmonary embolism (PE). The manufacturer stated that on 20th November 2012 that rivaroxaban was approved by the European Commission for the new indication.

2.2 The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE. The duration of treatment recommended in the summary of product characteristics (SPC) 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, trauma or immobilisation and longer treatment is recommended for people with permanent risk factors or idiopathic (unprovoked) DVT or PE. The SPC further states that experience

with rivaroxaban in this indication for more than 12 months is limited. A reduced dosage of 15 mg twice daily followed by 15 mg once daily can be considered in people with moderate (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/min) renal impairment if the person's assessed risk for bleeding outweighs the risk for recurrent DVT or PE.

2.3 The SPC lists the following adverse reactions for rivaroxaban: anaemia, dizziness headache, fainting, bleeding events, tachycardia (rapid heartbeat), low blood pressure, haematoma, stomach pain, dyspepsia (heartburn), nausea, constipation, diarrhoea, vomiting, pruritus (itching), rash, bruising, pain in the extremities, fever, swelling, especially of the ankles and feet. For full details of adverse reactions and contraindications, see the SPC.

2.4 The list price of rivaroxaban is £2.10 per tablet for both the 15 mg and 20 mg strengths (excluding VAT; 'British National Formulary' [BNF] edition 64). The average length of a course of treatment is 3 to 12 months according to assessment of individual risk-benefits. The drug costs (excluding VAT) would be £235.86, £427.61 or £811.13 for 3, 6 or 12 months of treatment respectively. Costs may vary in different settings because of negotiated procurement discounts.

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 of acute symptomatic pulmonary embolism with or without symptomatic deep vein thrombosis and the prevention of recurrent venous thromboembolism.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with pulmonary embolism	No difference. However, rivaroxaban is not recommended in all categories of patients with PE, according to its SPC

The ERG noted that the licence indication for the treatment of DVT and PE is restricted to adults and that the scope issued by NICE and the decision problem does not make a distinction between children and adults.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Rivaroxaban	
Comparators	Initial treatment with a low molecular weight heparin (such as enoxaparin, tinzaparin and dalteparin) or fondaparinux with continued therapy as follows: vitamin K antagonist (such as warfarin, acenocoumarol and phenindione) low molecular weight heparin for people for whom a vitamin K antagonist is not considered an appropriate treatment	As stated, but without fondaparinux

The manufacturer stated that there is a lack of evidence specific to fondaparinux for PE which can be generalised to UK clinical practice which means it may not be 'best practice'. The manufacturer also stated that it appears to be very seldom used and that they did not consider it to be an appropriate comparator. The ERG highlighted that its clinical adviser had advised that fondaparinux is rarely used in practice.

The ERG stated that unfractionated heparin is specified as a comparator in the scope, in subgroups of patients with severe renal failure, increased risk of

bleeding, PE and haemodynamic instability. It noted that the decision problem does not include these subgroups of patients as the draft SPC states that rivaroxaban is not suitable for these subgroups of patients.

The ERG noted that the scope requires consideration of continued therapy with LMWH for people for whom a vitamin K antagonist is not considered appropriate. The ERG commented that the manufacturer interprets this to mean patients with active cancer. It noted that for the populations for whom warfarin is contraindicated, rivaroxaban would also not be suitable, but suggested that there may be other groups who would not receive vitamin K antagonists but for whom rivaroxaban would be suitable such as intravenous drug users or people with poor venous access for blood sampling.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	The outcome measures to be considered include: -Mortality -Venous thromboembolism recurrence -Complications of pulmonary embolism such as pulmonary hypertension and heart failure -Complications following deep vein thrombosis, including post thrombotic syndrome -Adverse events of treatment (including clinically relevant bleeding) -Health-related quality of life	-Mortality -Venous thromboembolism recurrence -Pulmonary hypertension -Cardiac failure -Post thrombotic syndrome -Clinically relevant bleeding (major / non-major /all) -Adverse events of treatment -Treatment satisfaction

The ERG commented that the outcomes specified in the decision problem generally match the final scope issued by NICE and that there do not appear to be any clinically relevant outcomes omitted.

The ERG noted the manufacturer's comment that health-related quality of life was not measured in the EINSTEIN programme trials that had assessed rivaroxaban for VTE.

The ERG highlighted the additional outcomes reported in the manufacturer's submission (but not specified in the decision problem). These include: net clinical benefit; INR target range with LMWH/ vitamin K antagonist; and healthcare resource utilisation (duration in hospital).

	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. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	

The ERG noted that a cost-minimisation analysis rather than a cost utility analysis was conducted for the cancer subgroup.

4 Clinical-effectiveness evidence

4.1 The manufacturer carried out a systematic review of randomised controlled trials of rivaroxaban for patients with symptomatic PE looking for studies in which data on pulmonary embolism could be separated from data on deep vein thrombosis. They identified 1 relevant randomised control trial, (EINSTEIN-PE), an international, event-driven, open-label assessor-blind, non-inferiority study. The study included 4832 people in the intention to treat population. In EINSTEIN-PE people could be treated for 3, 6 or 12 months. Treatment duration was determined prior to randomisation by a study investigator and was based on the risk profile of the patient

and local preferences. The participants were randomised to either rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily for the intended treatment duration or to enoxaparin (a LMWH) 1.0 mg/kg twice daily until anticoagulation was established plus a vitamin K antagonist (either warfarin or acenocoumarol), which was dose adjusted to maintain the INR within a therapeutic range of 2.0 to 3.0 with a target of 2.5. The enoxaparin was administered for at least 5 days and was discontinued when the INR was greater than 2.0 on 2 consecutive measurements at least 24 hours apart. There was an advised overlap with the vitamin K antagonist of 4 to 5 days. Participants were followed up for their intended treatment duration followed by a 30- day observation period. The manufacturer noted that there was a difference in the dose of enoxaparin used in the trial and the dose covered by the European and UK licence which is 1.5 mg/kg once daily, for at least 5 days and until adequate oral anticoagulation is established. However, the manufacturer commented that the time in therapeutic range using the trial dose of enoxaparin/vitamin K antagonist (62.7%) was consistent with what would be achieved in a UK setting using the licensed dose of enoxaparin.

4.2 Einstein-PE excluded people with a creatinine clearance of less than 30 ml/min and people for whom rivaroxaban was not suitable or who were contraindicated to enoxaparin, warfarin or acenocoumarol.

4.3 The primary efficacy outcome for EINSTEIN-PE was symptomatic recurrent VTE, which is a composite endpoint comprising recurrent DVT or PE. This includes both fatal and non-fatal PE including unexplained death for which a PE could not be ruled out. The primary safety outcome was clinically relevant bleeding, that is major bleeding and clinically relevant non-major bleeding.

4.4 The analysis of the primary efficacy outcome in EINSTEIN-PE was carried out on an intention- to -treat basis (rivaroxaban n = 2419; enoxaparin/vitamin K antagonist [LMWH/VKA] n = 2413). Additionally, a supportive analysis of the primary efficacy outcome was carried out based on the per protocol population, which consisted of all randomised patients without any major deviation from the protocol (rivaroxaban n = 2224; LMWH/VKA n = 2238). The safety analysis was based on the safety population, which consisted of all patients who had received at least one dose of the study drug (rivaroxaban n = 2412; LMWH/VKA n = 2405).

4.5 In the intention- to treat- population the mean age was 58 and approximately 53% were male. Around 25% of people in both treatment arms had a concurrent DVT. The PE was unprovoked in 65% of people receiving rivaroxaban and 64% of people receiving LMWH/VKA. Approximately 5% of people in both treatment arms had active cancer and 19 % and 20% of people in the rivaroxaban and LMWH/VKA treatment arms respectively had experienced a previous VTE. Out of the whole study population, 5.2% were allocated to receive 3 months of treatment, 57.2% allocated to 6 months of treatment and 16.0% allocated 12 months of treatment. The median time from onset of symptoms to randomisation was 4 days. The EINSTEIN-PE study was designed to allow a limited amount of treatment before randomisation. A similar proportion in the rivaroxaban arm (92.5%) and the LMWH/VKA arm (92.1%) received pre-randomisation anticoagulation (p=0.62, post hoc binomial test); among those who received pre-randomisation anticoagulation ,62.5% of people received anticoagulation for 1 day, the maximum duration permitted was 48 hours. A total of 555 (11.5%) patients discontinued treatment, the number of people who discontinued was similar in both treatment groups (p=0.07).

4.6 The primary objective of EINSTEIN-PE was to assess whether rivaroxaban was non-inferior to LMWH/VKA for the combined endpoint of symptomatic recurrent VTE. In the intention to treat population, rivaroxaban met the non-inferiority criteria using a non-inferiority margin of 2.0. Symptomatic recurrent VTE events occurred in 50 (2.1%) people in the rivaroxaban arm compared to 44 (1.8%) people in the LMWH/VKA arm (hazard ratio [HR] 1.12; 95% confidence interval [CI] 0.75 to 1.68) which was not statistically significantly different.

[redacted]

Table 1 Results of primary efficacy analysis reported in manufacturer's submission (modified from ERG table 2 page 27)

Treatment group (n)	Primary efficacy outcome	Death (PE)	Death (PE cannot be excluded)	Symptomatic PE and DVT	Symptomatic recurrent PE only	Symptomatic recurrent DVT only
Rivaroxaban (2419)	50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH/VKA (2413)	44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LMWH, low molecular weight heparin; VKA, vitamin K antagonist; PE, pulmonary embolism; DVT, deep vein thrombosis.

4.7 The 3 subgroups of interest in the final scope issued by NICE were underlying risk of bleeding, provoked or unprovoked VTE and presence of active cancer.

[redacted]

4.8 The manufacturer highlighted that in the comparator arm of the trial, people with cancer had received LMWH/VKA, whereas standard care for these people is LMWH alone. The manufacturer also highlighted that there were no head to head trials comparing rivaroxaban to long-term treatment with LMWH for people with PE who also have cancer. The manufacturer searched the Cochrane library and found a systematic review of long-term treatment of VTE in people with cancer (published in 2011). The manufacturer stated that this study had been cited in its submission to NICE for technology appraisal 261 (rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism, published July 2012), in which it had carried out an indirect comparison for the cancer subgroup. The manufacturer stated that the ERG for technology appraisal 261 had identified limitations with this analysis, including heterogeneity across the included studies and that the Appraisal Committee had acknowledged that the ERG did not find the cancer subgroup analysis to be robust. Given the Appraisal Committee's consideration of the indirect comparison carried out for technology appraisal 261, the manufacturer did not consider it appropriate to conduct a network meta-analysis to estimate the relative effectiveness of rivaroxaban verses LMWH in people with cancer.

4.9 Results from the safety analysis indicated that there was no difference between rivaroxaban and LMWH/VKA in clinically relevant bleeding which was experienced by 249 (10.3%) and 274 (11.4%) of people in each treatment arm respectively (HR 0.90, 95% CI 0.76 to 1.07). The proportion of people who experienced major bleeding was lower with rivaroxaban (1.1%) than LMWH/VKA (2.2%), (HR 0.49, 95% CI 0.31 to 0.79). During the intended treatment period there was a similar number of deaths in the rivaroxaban arm (58 deaths) and LMWH/VKA arm (50 deaths), (HR

1.13, 95% CI 0.77 to 1.65).

[redacted]

◊ Table 2: bleeding outcomes from the EINSTEIN-PE trial (Manufacturer's submission page 74)

	Rivaroxaban	LMWH/ VKA	Hazard ratio
	N (%)		(95% CI, p-value)
Safety population	2412	2405	
Primary safety outcome (clinically relevant bleeding)	249 (10.3)	274 (11.4)	0.90 (0.76-1.07, P=0.23)
Major bleeding	26 (1.1)	52 (2.2)	0.49 (0.31-0.79, P=0.003)
Fatal	2 (<0.1)	3 (0.1)	NR
Non-fatal into a critical site	7 (0.3)	26 (1.1)	NR
Associated with a fall in haemoglobin of ≥2g/dl or transfusion of ≥2 units of blood	17 (0.7)	26 (1.1)	NR
Clinically relevant non-major bleeding	228 (9.5)	235 (9.8)	NR

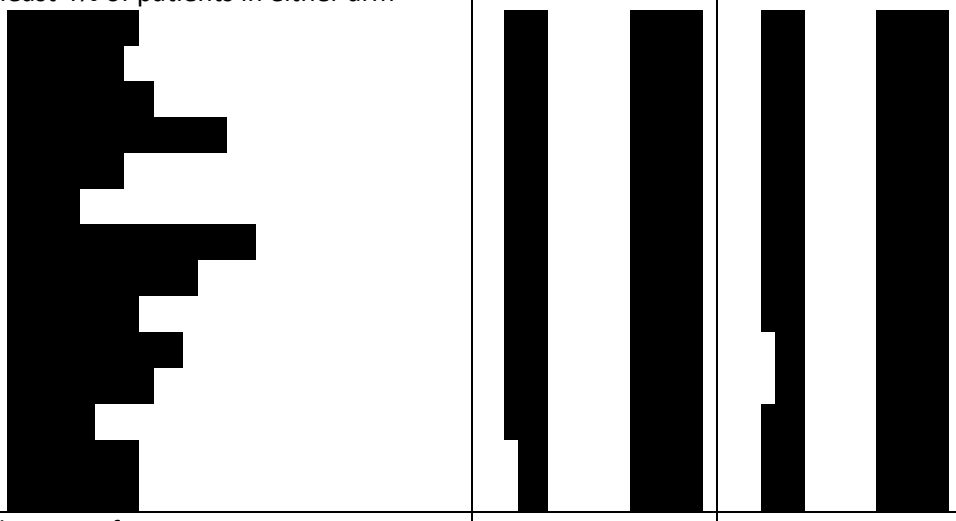
Abbreviations: LMWH, low molecular weight heparin; VKA vitamin K antagonist; NR, not reported; CI, confidence interval

4.10 Treatment-emergent adverse events (other than bleeding and recurrent VTE) were similar between the treatment arms [redacted]. Approximately 5% of people in the rivaroxaban arm and 4% in the LMWH/VKA arm discontinued treatment because of an adverse event.

[redacted]

◊ Table 3 summary of adverse events in EINSTEIN -PE (Manufacturer's response to clarification page 23)

	Rivaroxaban		Enoxaparin/VKA		P-value
Adverse events (AEs)					
Any	1941	(80.5)	1903	(79.1)	0.29
Serious event	476	(19.7)	470	(19.5)	0.86
Resulting in permanent discontinuation of study drug	123	(5.1)	99	(4.1)	0.10
Leading to or prolonging hospitalisation	475	(19.7)	430	(17.9)	0.82
Treatment-emergent AEs experienced in at least 4% of patients in either arm					
Other AEs of interest					
Acute coronary event	15	(0.6)	21	(0.9)	
Cerebrovascular event	12	(0.5)	13	(0.5)	
Systemic embolism	5	(0.2)	3	(0.1)	
Alanine aminotransferase level of more than three times the upper limit of the normal range and a bilirubin level of more than twice the upper limit of the normal range	5	(0.2)	4	(0.2)	



◊ Abbreviations: AE, adverse event; VKA, vitamin K antagonist

◊

4.11 Health-related quality of life was not measured in EINSTEIN-PE. The manufacturer described 2 measures of treatment satisfaction that had been measured in EINSTEIN-PE; the Anti Clot Treatment Scale (ACTS) and the Treatment Satisfaction Questionnaire

(TSQM). Treatment satisfaction was not used to derive any of the utilities used in the economic analysis.

4.12 The ERG considered that overall the manufacturer's submission provided an unbiased estimate of the treatment effect. The ERG commented that it was based on a well conducted systematic review of clinical effectiveness, which identified 1 RCT of reasonable quality with low risk of bias. The ERG noted that, owing to the different methods of administration for rivaroxaban and LMWH/VKA, patients and trial investigators in EINSTEIN-PE were not blinded to their treatment allocation. However, the ERG acknowledged that suspected cases of symptomatic recurrent VTE, bleeding, vascular events and cause of death had to be assessed by a central independent adjudication committee who were blinded to treatment allocation. The ERG commented that the lack of patient blinding may have affected the more subjective outcomes such as treatment satisfaction or pain-related adverse events.

[redacted]

4.13 The ERG considered whether EINSTEIN-PE was generalisable to the population who would receive rivaroxaban in UK clinical practice. They noted that the patient population in the trial may not be fully representative of the treatment population in general. In particular it stated that patients with severe renal impairment (a creatinine clearance of 15-29 ml/min) were excluded from the trial. The ERG stated that the SPC specifies that rivaroxaban can be used with caution in these patients and recommends use of the standard dose (unless the risk of bleeding outweighs the risk for recurrent VTE, in which case a lower dosage of 15 mg once daily is recommended after the first 3 weeks of treatment). The ERG stated that as these patients are at higher risk of bleeding and were

excluded from the trial, it is possible that the trial may have underestimated the rate of bleeding that may be seen in clinical practice with rivaroxaban.

4.14 The ERG also noted that the trial only assessed outcomes up to a 12 month treatment period. Therefore the effectiveness and safety of long-term treatment with rivaroxaban is unknown. The ERG stated that its clinical adviser had commented that the risk of recurrent VTE is cumulative over time, and therefore rates of future symptomatic recurrent VTE events could be higher than those found in the trial as it only measured these within a limited post treatment follow-up period.

4.15 The ERG noted that the manufacturer had used intended treatment duration as a proxy for both underlying risk of bleeding and provoked/unprovoked PE. However the ERG's clinical adviser commented that there are no robust markers for determining length of treatment in advance which suggests that pre-specified treatment durations may not be a good proxy for other variables.

4.16 The ERG noted that EINSTEIN -PE included a small number of patients with active cancer, and that in the standard care arm of the trial, these people received LMWH with a vitamin K antagonist, despite vitamin K antagonists not being recommended for people with cancer. The ERG stated that people with active cancer are standardly treated with LMWH only following a PE. The ERG considered that the outcomes could, in theory have been worse in the active cancer group than those seen for other patients due to increased bleeding risk. The ERG noted that the manufacturer's subgroup analyses did not find a significantly higher risk of clinically relevant bleeding in patients with active cancer in the LMWH/VKA arm. The ERG considered that this may be because of the low

numbers (109 [4.6%] people in this treatment arm had active cancer).

[redacted] However, the ERG felt that this result should be treated with caution, as the 95% confidence intervals around the hazard ratio for the patients with active cancer presented by the manufacturer were wide, indicating that there is uncertainty around where the true effect lies.

[redacted] It highlighted that only 2 of the 114 people in the rivaroxaban arm and 3 of the 109 people in the LMWH/VKA arm with active cancer at baseline experienced a symptomatic recurrent VTE.

5 Comments from other consultees

5.1 Clinical specialists commented that people with a PE are generally treated with immediate parenteral anticoagulation, most commonly with a LMWH delivered by subcutaneous injection and with an oral vitamin K antagonist such as warfarin. The LMWH is continued for at least five days or until the patient's INR is within the therapeutic range for 24 hours, at which point it is withdrawn. The duration of continued treatment with a vitamin K antagonist is dependent on a person's individual risk of recurrent VTE. Some people, such as people with moderate to severe renal impairment, may receive unfractionated heparin instead of LMWH; some people may receive fondaparinux instead of LMWH. People presenting with a PE and haemodynamic instability receive thrombolysis (or embolectomy if thrombolysis is contraindicated) prior to receiving a vitamin K antagonist. A proportion of people will remain on heparins because vitamin K antagonists are either contra-indicated, less effective, for

example in people with cancer or because repeat blood sampling for INR monitoring is difficult because of poor venous access.

5.2 The clinical specialists highlighted that the current treatment with low molecular weight heparin or unfractionated heparin with vitamin K antagonists is known to be effective, has a relatively low side effect profile (other than bleeding) and is well known to practitioners. Furthermore, the effects of vitamin K antagonists are measured using routine laboratory tests, there are established antidotes, to reverse bleeding and can be used by people with renal failure, unlike rivaroxaban. However, the disadvantages, particularly with vitamin K antagonists are the requirement for monitoring of INR and dose adjustments; vitamin K antagonists have many drug and food interactions making INR difficult to stabilise. Monitoring can be inconvenient and costly to patients.

5.3 The clinical specialists highlighted that taking a fixed dose oral drug such as rivaroxaban rather than two overlapping medications would make the patient pathway simpler and would avoid LMWH injections which may be preferable to some patients. However, haemodynamic stability would need to be assessed before commencing treatment with rivaroxaban. Rivaroxaban does not require monitoring, but that the lack of regular monitoring limits patients' contact with healthcare professionals and opportunities to discuss management of their condition. There may be instances when an urgent assessment of the degree of anticoagulation with rivaroxaban such as for people requiring surgery, but there is no routine test for rivaroxaban. Should a bleed occur there is no established antidote for rivaroxaban, although it has a relatively short half-life. A disadvantage of a short half-life means missed doses may lead to insufficient anticoagulation and as patients would not be monitored to the same extent as with warfarin

treatment the importance of adherence would need to be emphasised. Clinical specialists highlighted that besides the bleeding adverse events common to all anticoagulants, rivaroxaban also was associated with additional side effects such as nausea, diarrhoea and dizziness.

5.4 Patient experts highlighted the symptoms of a PE which include chest pain, shortness of breath, anxiety, coughing up blood and feeling light headed and dizzy. They commented that people who recover from a PE may be impaired in their day to day lives and need a significant period of time to recover and resume normal activities; some people will need on going additional support and care. The risk of recurrence of a VTE can increase after the first episode and this is of considerable concern to many people.

5.5 The patient experts stated that standard treatment was subcutaneous injections with LMWH or unfractionated heparins followed by a vitamin K antagonist. Heparin is administered by injection which can cause pain, bruising and anxiety for some people. Treatment with warfarin requires patients to monitor and adjust the dose in order to be in the appropriate therapeutic range and to allow medical procedures such as dental work to be carried out. The monitoring requirements of warfarin are inconvenient, as it has an impact on managing day-to-day activities such as schooling, work and travel. It can cause anxiety and is a constant reminder that they have a chronic health condition rather than allowing people to return to the normality of their pre-event lives. Some people find it difficult to stabilise their INR on warfarin and cannot stay within the recommended range, despite having regular testing. Warfarin is contraindicated to many other drugs and can be a challenging treatment for patients with co-morbidities.

5.6 The patient experts noted that advantages of rivaroxaban are that people take one drug rather than two; it is administered orally and avoids the inconvenience and anxiety associated with monitoring and dose adjustment with warfarin. However, as rivaroxaban has a short half-life patients will need to be advised on the importance of regular and timely dosing and the importance of drug compliance. The patient experts commented that all anticoagulants are associated with a risk of bleeding and suggested that research had been carried out relating to using a pro-thrombin concentrate as an antidote.

6 Cost-effectiveness evidence

6.1 Summaries of the manufacturer's base case, the ERGs corrections to errors in the model and the ERG's exploratory analysis are given in sections 6.1 to 6.3. Subsequent sections give further detail of how the analyses were carried out and how the cost effectiveness estimates were derived. The manufacturer presented 4 deterministic base cases for people receiving treatment for 3-, 6- and 12 months or a lifelong treatment. For a treatment of 3-, 6- or 12 months rivaroxaban dominated LMWH/VKA treatment (that is rivaroxaban was associated with higher QALYs but lower costs). For a lifelong treatment, the ICER for rivaroxaban compared with LMWH/VKA was £13,252 per QALY gained. In the equivalent probabilistic base cases for treatments of 3-, 6- and 12 months, rivaroxaban also dominated LMWH/VKA. For a lifelong treatment the probabilistic ICER for rivaroxaban compared LMWH/VKA was £13,918 per QALY gained. For further details of the results of the manufacturers base case analyses, see table 4.

Table 4: Manufacturer's deterministic base case results

	Rivaroxaban	Dual LMWH / VKA therapy
Patients appropriate for 3 months of anticoagulation		
Technology acquisition cost	216.74	0
Other costs	4294.59	4907.14
Total costs	4511.33	4907.14
Difference in total costs	-395.80	
LYG	14.571	14.546
LYG difference	+0.025	
QALYs	11.940	11.912
QALY difference	+0.027	
ICER	Dominant	Dominated
Patients appropriate for 6 months of anticoagulation		
Technology acquisition cost	392.52	0
Other costs	4153.16	4758.89
Total costs	4545.68	4758.89
Difference in total costs	-213.21	
LYG	14.630	14.622
LYG difference	+0.008	
QALYs	11.992	11.979
QALY difference	+0.013	
ICER	Dominant	Dominated
Patients appropriate for 12 months of anticoagulation		
Technology acquisition cost	727.71	0
Other costs	4153.77	5014.60
Total costs	4881.48	5014.60
Difference in total costs	-133.13	
LYG	14.679	14.668
LYG difference	+0.011	
QALYs	12.032	12.012
QALY difference	+0.019	
ICER	Dominant	Dominated
Patients appropriate for lifelong anticoagulation		
Technology acquisition cost	5969.36	0
Other costs	4898.46	9493.09
Total costs	10867.82	9493.09
Difference in total costs	+1374.73	
LYG	15.333	15.303
LYG difference	+0.03	
QALYs	12.479	12.375
QALY difference	+0.104	
ICER	13252	

Abbreviations: LMWH, low molecular weight heparin; VKA, vitamin K antagonist; LYG, life years gained; QALY, quality adjusted life years; ICER, incremental cost effectiveness ratio

6.2 The ERG amended errors in the manufacturer's model (see section 6.28), which affected the lifelong treatment analysis and re-ran the manufacturer's deterministic base case. For the ERG's 'amended base case' for the lifelong treatment, the ICER for rivaroxaban compared with LMWH/VKA was £7,072 per QALY gained. For the ERG's 'amended probabilistic base case' for lifelong treatment, the ICER for rivaroxaban compared with LMWH/VKA was £7,019 per QALY gained.

6.3 The ERG's corrections to the manufacturer's model were included in all of the scenarios analysed by the ERG. For the majority of scenarios, rivaroxaban continued to dominate LMWH/VKA or the ICER for rivaroxaban compared with LMWH/VKA remained below £20,000 per QALY gained. Exceptions included a scenario in which anticoagulation reversal drug costs were included alongside a higher hazard of major bleed with rivaroxaban. In this scenario, the ICER for rivaroxaban compared with LMWH/VKA for a12 month treatment duration increased to £23,364 per QALY gained and to £44,046 for a lifelong treatment duration. A multiway scenario that included various INR monitoring changes, an increased hazard of recurrent VTE with rivaroxaban after 12 months and a shorter mean LMWH treatment increased the ICER for rivaroxaban compared with LMWH/VKAfor the lifelong treatment duration analysis to £35,909 per QALY gained. The ERGs scenario analyses are described in full in sections 6.29 to 6.37.

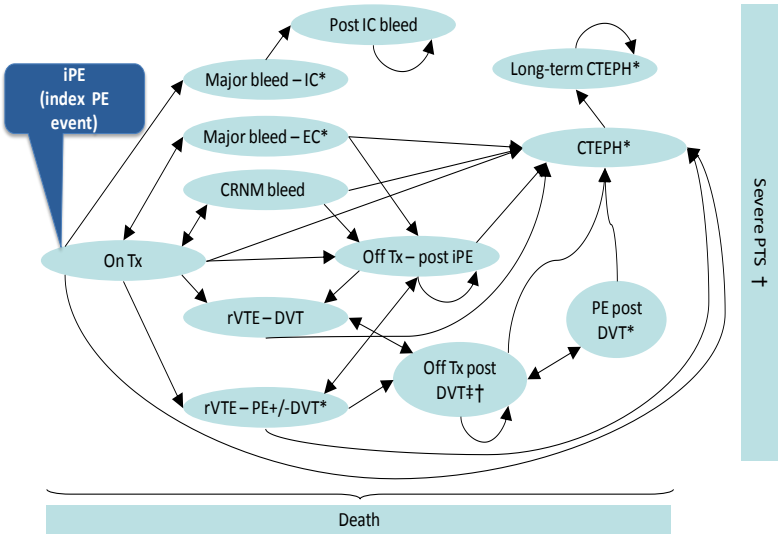
6.4 The manufacturer carried out a systematic review for economic evaluations of any pharmaceutical for the treatment and secondary prevention of VTE in people with suspected PE or DVT. Seven

studies were identified. However, none of the economic evaluations had assessed rivaroxaban and the manufacturer stated that none were relevant to the decision problem.

6.5 The manufacturer constructed a Markov model to evaluate the consequences of a 3-, 6-, 12-month and life-long treatment with rivaroxaban for the prevention of recurrent VTE in people who experience an acute PE. The results for each anticipated treatment duration were presented separately. The time horizon in the model was 40 years. The cycle length used in the model was 3 months. In order to reflect the change in the risk patients experience over time, different risks were applied in cycle 1 (months 0-3), 2 (months 3-6), 3 and 4 (months 6-12) and 5 onwards (12 months onwards). The evaluation was undertaken from an NHS and Personal Social Services Perspective and costs and utilities were discounted at 3.5% per year after the first year. A separate cost-minimisation analysis comparing rivaroxaban with LMWH only was undertaken to inform the appraisal of the potential value of rivaroxaban in reducing the monitoring burden for patients with PE and active cancer.

6.6 For people initially treated for 3, 6 or 12 months there were 13 health states including death (See Figure 1 below). In the lifelong treatment model there was an additional state. People entered the model after their index PE to an on treatment state ('On Tx') where they received 3, 6, 12 month or lifelong treatment with rivaroxaban or LMWH/VKA. They then either stay on treatment; experience a recurrent VTE (PE or DVT); experience an adverse event (clinically relevant non-major bleed; major intracranial bleed; major extracranial bleed); move to an off treatment health state or enter a long term complication state (e.g. CTEPH) or die.

Figure 1: Schematic of manufacturer's model



Notes: *Additional mortality; ‡ A proportion of patients with rPE also experience a symptomatic DVT (PTS risk); † At risk of PTS: cost applied to % patients in this state

Abbreviations: **On Tx**: On treatment; **Off Tx**: Off treatment; **rVTE**: recurrent VTE event; **DVT**: Deep vein thrombosis; **PE**: Pulmonary embolism; **PTS**: Post Thrombotic syndrome; **CTEPH**: Chronic thromboembolic pulmonary hypertension; **IC**: intracranial; **EC**: extracranial; **CRNM**: clinically relevant nonmajor

6.7 People in some health states had a greater risk of dying. These included the major intracranial or extracranial bleed health states ('Major bleed -IC, Major bleed -EC); Health states in which people had experienced a recurrent PE (rVTE-PE+/- DVT, PE post DVT) and the CTEPH health states (CTEPH, Long-term CTEPH). The general underlying mortality risk was estimated from a cohort life table based on the Office of National Statistics 2008-2010 interim tables for England and Wales combined. Yearly mortality was calculated according to baseline patient characteristics from the EINSTEIN-PE. Mortality associated with model events was derived through systematic review.

6.8 People in some health states stopped or switched treatments. People who had a recurrent PE or DVT were assumed to be treated for 6 months with LMWH/VKA. People who experienced a clinically relevant non major bleeds were assumed to temporarily discontinue treatment for one month during the cycle in which the

bleeding event took place. People experiencing a major extracranial bleed were assumed to discontinue treatment for 3 months. After that time they could stay off treatment, return to treatment or enter the CTEPH state. People who had an intracranial bleed discontinued treatment completely.

6.9 All patients who experienced a DVT after their index PE were at risk of post thrombotic syndrome. The incidence of post thrombotic syndrome was calculated outside of the model and the consequences were applied as costs and health related quality of life payoffs to patients in the 'off treatment post DVT' state and people who had a PE post DVT would return to the 'Off Tx post DVT state' in order to still be exposed to the risk of post thrombotic syndrome conferred by their DVT history. For people receiving lifelong treatment the risk of post thrombotic syndrome was applied in the 'On treatment post-DVT' state.

6.10 The modelled cohort was adults with an acute PE who matched the licensed indication, the EINSTEIN-PE trial population and the stated decision problem. Data from EINSTEIN-PE was used to inform the clinical effectiveness of treatments and to derive the transition probabilities used in the model; this was supplemented with data from the manufacturer's systematic reviews.

6.11 Health related quality of life was not measured in EINSTEIN-PE, the manufacturer therefore performed a systematic review to find evidence on utility associated with venous thromboembolism, including events such as PE, DVTs, bleeding, CTEPH and post thrombotic syndrome in patient populations with index PE, DVT or VTE generally. The manufacturer assigned a baseline utility value of 0.825 to all patients with PE entering the model. Clinically relevant non major bleeds were not associated with a utility

decrement. The decrease in utility was temporary following certain events. People who had a recurrent VTE were assumed to have a reduction in health related quality of life for 1 month. People who had a major extracranial bleed had a utility reduction lasting 1 month. People who had a major intracranial bleed had a permanent utility decrement of 0.33 in the intracranial bleed state and 0.71 when they moved to the post intracranial bleed state.

Table 5: Utility values assumed in the manufacturer's cost-effectiveness analyses (table 43, pg 160 manufacturer's submission)

Model state	Point estimate	Sensitivity analyses Lower	Upper	Notes	Source
Population norm	0.825	0.819	0.831		Kind 1998157
Disutility due to warfarin therapy	0.012	0.016	0.006		Marchetti, 2001104
Post IC bleed	0.71	0.70	0.72		Rivero-Arias 2010158
CTEPH	0.56	0.53	0.59		Meads 2008155
Adjustments to utility norm due to modelled events					
DVT	0.84	0.64	0.98		Locadia 2004154
PE	0.63	0.36	0.86		Locadia 2004154
EC bleed	0.65	0.49	0.86	GI bleed was the disease state valued	Locadia 2004154
IC bleed	0.33	0.14	0.53	Haemorrhagic stroke was the disease state valued	Locadia 2004154
PTS	0.93	0.76	1.00	Serious PTS was the disease state valued	Lenert 1997153

Abbreviations: IC, intracranial; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; PE, pulmonary embolism; EC, extracranial.

6.12 The manufacturer estimated the resource use associated with hospital admission and outpatient costs for the index event, recurrent events and complications; the monitoring of the patients' disease, treatment management and INR monitoring (for vitamin K antagonist treatment). The manufacturer took into account that EINSTEIN PE had shown that people receiving rivaroxaban stayed

for a mean of 0.5 days fewer in hospital than those people treated with LMWH/VKA. The manufacturer assumed that people would take a LMWH for [redacted] based on the mean duration of treatment with enoxaparin in EINSTEIN -PE. The resource usage assumptions are summarised below in table 6.

Table 6: Summary of resource usage assumptions (see table 47, pg. 180 manufacturers submission for sensitivity ranges and rationales)

Resource item	Point estimate
Acute treatment	
Number of days of acute treatment (i.e. LMWH) required by a PE patient	[redacted]
Proportion of patients who self-inject LMWH	92%
Proportion of remaining patients who require nurse assistance at home	80%
INR monitoring whilst on LMWH/VKA	
Visits in first 3 months	9
Visits each 3 months thereafter	5
Recurrent VTEs: proportion treated as outpatients rather than inpatients	
Recurrent DVT patients	69%
Incident PE patients	17%
Other	
Proportion of patients requiring NHS-funded transportation	8.55%
Proportion of CTEPH patients who require PEA	68.4%

Abbreviations: LMWH, low molecular weight heparin; VKA, vitamin K antagonist; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

6.13 Unit costs in the model were taken wherever possible from the NHS National Schedule of Resource Costs, The Personal Social Services Research Unit (PSSRU) and the British National Formulary (BNF) 64 (The NHS reference costs used in the model are listed in table 49, page 186 manufacturer's submission). The drug acquisition cost for rivaroxaban used in the model was £2.10 per tablet (both the 15 mg and 20 mg doses). This meant that for the first 15 days the daily cost was £4.20, and subsequently the

daily cost was £2.10. The manufacturer stated that the daily maintenance cost of warfarin is usually between 3 and 9 mg and in their model they assumed people taking warfarin would take one 5 mg tablet and one 1 mg tablet per day. The BNF 64 specifies that 28 tablets of 1 mg warfarin costs £0.86 and 28 tablets of 5 mg warfarin costs and £0.92. The manufacturer assumed that the LMWH people would receive would be enoxaparin which has a daily cost of £9.77 for a person weighing 80 kg (the daily costs of the other LMWH, dalteparin sodium and tinzaparin sodium are £8.47 and £11.85 respectively). The average cost of a first INR monitoring visit was assumed to be £26.26 and £24.88 for a subsequent visit.

6.14 The manufacturer performed 123 deterministic sensitivity analyses for each of the 4 durations of treatment. However, the manufacturer did not present the full set of results in its submission, but instead presented tornado diagrams for the 15 most sensitive parameters for the 3, 6 and 12-month treatment durations. As rivaroxaban dominated LMWH/VKA for the 3-, 6- and 12 month treatment durations (see section 6.1), the manufacturer presented the tornado plots using the net monetary benefit (NMB; [change in QALY * £20,000]- change in cost). In all of the deterministic sensitivity analyses performed for these treatment durations, the NMB was positive indicating that they were cost effective at a willingness to pay of £20,000.

6.15 The sensitivity analysis of lifelong treatment was presented using ICERs. The base case ICER was £13,252 per QALY gained. Cost effectiveness was most sensitive to changes around the frequency of INR-monitoring visits, where the ICER increased from £13,252 per QALY gained to d £27,914 per QALY gained if people have 3 rather than 5 visits in each quarter after the first.

6.16 The manufacturer also carried out probabilistic sensitivity which showed that there were 99.9%, 95.9% and 93.7% probability for the 3-, 6-, and 12 month treatment groups that the base case ICER was lower than £20,000 per QALY gained. For lifelong anticoagulation therapy, the probabilistic sensitivity showed that there was a 59.1% probability that the base case ICER was lower than £20,000 per QALY gained.

6.17 The manufacturer conducted one scenario analysis, where the time horizon was reduced from 40 years to 5 years. For the 3-, 6- and 12-month treatment durations rivaroxaban remained dominant to LMWH/VKA with a 5 year time horizon. For the lifelong treatment duration, reducing the time horizon to 5 years decreased the ICER of rivaroxaban compared with LMWH/VKA to £12,282 per QALY.

6.18 The manufacturer produced a cost minimisation analysis to compare rivaroxaban with LMWH (dalteparin) for people with cancer. Over this period rivaroxaban was associated with a cost saving of £903.

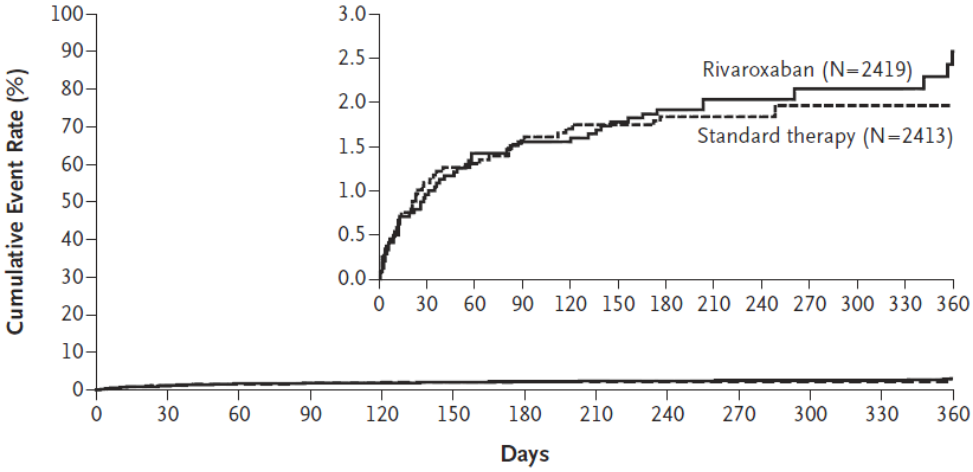
6.19 The ERG considered the structure adopted for the economic model to be reasonable, consistent with current clinical understanding of PE and to be consistent with the previous economic evaluations of treatments for venous thromboembolism in the submission for NICE technology appraisal 261. It stated that the cost effectiveness analysis generally met the requirements of the NICE reference case, with the exception of the active cancer subgroup in which a cost-minimisation analysis was performed.

6.20 The ERG considered that the parameters used in the model were generally appropriate. It stated that the population used in the model, drawn from EINSTEIN-PE is broadly representative of the PE population in the UK. However it noted that the trial did not

include people for whom rivaroxaban is contraindicated or people with severe renal impairment who may still be eligible for rivaroxaban. The ERG also highlighted that the base case analyses used a population with a mean age of 58 years that is lower than the mean age of some other PE and DVT patient populations described in the literature.

6.21 The ERG noted that the manufacturer had applied treatment effects based on the whole trial population in its model and considered this to be appropriate. The ERG highlighted that the lifelong treatment effect of rivaroxaban beyond 12 months is highly uncertain as the trial was only one year long. The ERG stated that the manufacturer's Kaplan Meier plot of cumulative VTE rates suggested a worsening of the relative hazard of recurrent VTE while on rivaroxaban compared with LMWH/VKA towards the end of the 12 month treatment period (see Figure 2 below). The ERG commented that it is plausible that the hazard of recurrent VTE might worsen further if treatments are compared in the longer term, particularly if adherence to rivaroxaban (which does not require the regular monitoring of vitamin K antagonists) declines. The ERG noted that the long term adherence to rivaroxaban may be far lower than the 80% plus observed in the majority of patients in EINSTEIN -PE.

Figure 2: Kaplan-Meier cumulative event rate of recurrent venous thromboembolism in EINSTEIN-PE (manufacturer's submission page 71).



No. at Risk													
Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Standard therapy	2413	2316	2295	2273	2155	2146	2050	835	787	772	746	722	675

6.22 The ERG noted that health related quality of life was not measured in EINSTEIN-PE, and that the manufacturer had used utilities identified through a systematic review. The ERG noted that some of the sources of utility values identified and used by the manufacturer, were small studies or did not use the EQ-5D instrument that is specified in NICE's reference case.

6.23 The ERG considered the utility value of 0.33 for an intracranial bleed based on Locadia (2004) which the manufacturer had applied for 3 months in the intracranial bleed state model to be low. The ERG identified a prospective, longitudinal study by Pickard et al (2004) that suggested a utility value of 0.31 immediately after an intracranial bleed (stroke), increasing to 0.55 after 1 month and to 0.61 by 3 months. The ERG stated that as rivaroxaban is associated with fewer intracranial bleeds than LMWH/VKA a mid-value of 0.55 for the intracranial bleed health state utility value would be a more conservative assumption.

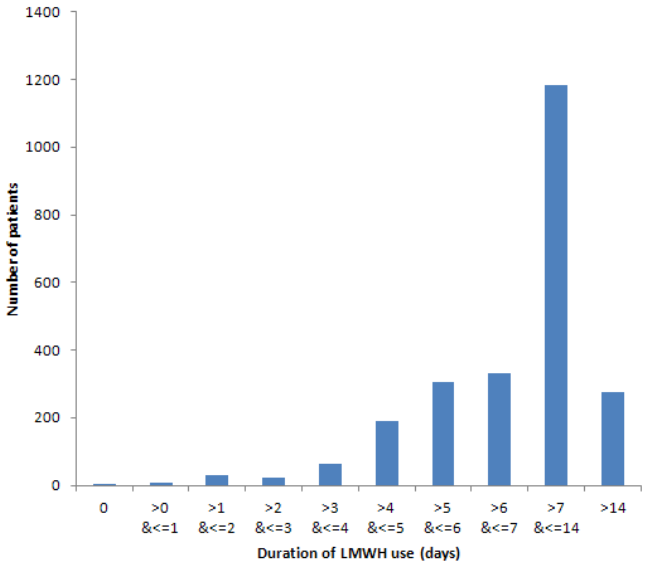
6.24 The ERG also questioned the manufacturer's choice of utility values for post thrombotic syndrome. The manufacturer had chosen a utility value of 0.93 based on Lenert (1997); however the ERG stated that Locadia, (2004), which the manufacturer had used to obtain utility values for some of the health states in its model, gave a utility value of 0.86 for post thrombotic syndrome. The ERG stated that as patients taking rivaroxaban are more likely to experience post thrombotic syndrome, that the manufacturer's choice of utility value for post thrombotic syndrome was not a conservative assumption.

6.25 The ERG noted that the manufacturer had assumed 9 INR monitoring visits in the first quarter for people receiving LMWH/VKA and 5 in each subsequent quarter, and that this was consistent with what was presented by the manufacturer for NICE technology appraisal 261. The ERG considered 9 initial INR visits to be reasonable but estimated that the subsequent visit frequency would be 3-4 per quarter, rather than 5. The ERG highlighted that in NICE technology appraisal 261, the Committee had concluded that a less intensive INR monitoring programme of 6 visits in the first 3 months followed by 3 visits every 3 months thereafter was reasonable and relevant (when a DVT was the index thromboembolism). The ERG noted that the manufacturer assumed that the INR monitoring took place in a primary care setting in 66% of cases and in secondary care in 34% of cases. The ERG stated that its clinical adviser said generally most vitamin K antagonist monitoring is done in secondary care. The ERG's clinical adviser commented that if INR monitoring is done in primary care that the monitoring would predominantly be performed by a nurse.

6.26 The ERG considered the manufacturer's estimate of treatment duration with LMWH, that is, people would receive LMWH for

[redacted]. The ERG noted that the manufacturer's estimation was based on the average length of treatment with LMWH in the LMWH/ VKA arm of EINSTEIN PE. The manufacturer had used categorical data and used the midpoint of each category to derive the mean estimate. People who received up to 7 days of treatment were distributed between 8 categories, whereas there was 1 category for people who had received from 7 to 14 days of LMWH and 1 category for people who had received over 14 days of LMWH (see figure 3 below). The ERG noted that the between 7 to 14 or fewer days category contained the most people, but the manufacturer had not provided a breakdown of the treatment lengths in this category and that the manufacturer had used a midpoint of [redacted]. The ERG stated that this midpoint was [redacted] the treatment durations with LMWH recommended by the Scottish Intercollegiate Guidelines Network (which is 6-10 days), and that the midpoint used for both this category and the more than14 day category affected the estimate of average treatment duration.

Figure 3: histogram of duration of LMWH use in the LMWH/VKA arm of EINSTEIN PE



6.27 The ERG was satisfied that the unit costs used in the economic model were relevant and had been obtained using suitable methods. However, it noted that the costs of reversing the effects of rivaroxaban and warfarin in the case of major bleeding or elective surgery had not been included and that these may be significant. The ERG stated that vitamin K, fresh frozen plasma and prothrombin complex concentrate (PCC) are used to reverse bleeding events on warfarin but there is no specific antidote for rivaroxaban. The ERG commented that either activated recombinant factorVII (rFVIIa) or PCC may be considered for the management of severe and life-threatening bleeding in patients on rivaroxaban. The ERG's clinical adviser considered that the reversal of bleeding on warfarin is likely to require less PCC than rivaroxaban, and that rFVIIa may be more effective for reversing rivaroxaban than PCC. The ERG estimated that the cost of treating a patient weighing 70 kg with rFVIIa is £19,303. The ERG also estimated that the cost of treating a bleed while receiving rivaroxaban with PCC would be £1,680 and the maximum cost for treating a bleed on warfarin with PCC concentrate would be £1,260.

6.28 The ERG noted two model input errors that it amended for its exploratory analyses, but noted that these errors did not have a substantive impact on the model outcome. The ERG noted that all transition probabilities were treatment-specific in the lifelong model but that there appeared to be a further error in the model as after 36 months the probability of recurrent VTE and bleeding events were the same for rivaroxaban and LMWH/VKA. The ERG stated that the probabilities of these events after 36 months were not explicitly stated in the manufacturer's submission. The ERG believed this to be an unintended model wiring error, and corrected the model so that the treatment effect of rivaroxaban past

36 months was applied to the LMWH/VKA transition probabilities. Following this amendment, the ICER for rivaroxaban compared with LMWH/VKA in the lifelong treatment analysis was reduced from £13,252 per QALY gained to £7,072 per QALY gained. For all of the subsequent analyses, the ERG incorporated this correction and referred to this as the "amended base case".

6.29 The ERG conducted the following exploratory scenario analyses:

- reduction in assumed frequency of INR monitoring visits
- reduction in mean LMWH treatment length
- reduction in the efficacy of rivaroxaban after 12 months in the lifelong treatment analysis in preventing recurrent VTE
- higher hazard of major bleed on rivaroxaban in the lifelong treatment analysis
- higher utility values for the intracranial bleed state
- higher mean age of model population
- costs of emergency anticoagulant reversal taken into account in all cases of major bleeding
- multiple assumption scenario

6.30 The ERG found that rivaroxaban becomes relatively less cost-effective compared with LMWH/VKA when fewer INR monitoring visits are assumed for people treated with LMWH/VKA as this reduced the incremental costs associated with LMWH/VKA. The ERG reduced the frequency of INR monitoring visits from 9 visits in the first quarter and 5 visits in each subsequent quarter as assumed in the manufacturer's base case to 6 visits in the first

quarter and 3 in each subsequent. The ICER for rivaroxaban compared with LMWH/VKA increased from £7,072 to £17,857 per QALY gained in the lifelong treatment duration analysis, the ICER was £3,542 per QALY gained for the 12 -month treatment duration analysis whereas rivaroxaban had dominated LMWH/VKA in this analysis in the manufacturer's base case. Rivaroxaban continued to dominate LMWH/VKA in the 6 month treatment analysis. The ERG did not present the effect of a reduced INR monitoring frequency scenario on the 3 month treatment analysis. For the lifelong treatment duration analysis, the ERG assessed a further scenario of 6 visits in the first quarter and 2 in each subsequent quarter. This assumption increased the ICER for rivaroxaban compared with LMWH/VKA from £7,072 to £22,912 per QALY gained.

6.31 Assuming a shorter treatment duration with LMWH from [redacted] days in the base case to either 9, 8 or 6 days was found to have a minimal cost saving effect in the 6 month treatment duration analysis, Rivaroxaban continued to dominate LMWH/VKA regardless of the treatment duration with LMWH. The ERG did not present the effect of assuming the shorter treatment duration with LMWH on the 3 month, 12 month or lifelong treatment duration analyses.

6.32 The ERG performed scenario analyses which assessed varying efficacy and safety effects of rivaroxaban. The hazard ratio for recurrent VTE for rivaroxaban compared with LMWH/VKA was 1.123 for the entirety of the lifelong treatment base case. The ERG assessed two scenarios where the hazard ratio was increased to either 1.5 or 2.0 after 12 months (that is rivaroxaban assumed to be increasingly less effective relative to LMWH/VKA). Assuming a hazard ratio of 1.5 for VTE after 12 months for the population in the lifelong treatment analysis increased the ICER for rivaroxaban

compared with LMWH/VKA increased from £7,072 to £9,043 per QALY gained. When a hazard ratio of 2.0 was assumed, the ICER for rivaroxaban compared with LMWH/VKA increased from £7,072 to £14,090 per QALY gained.

6.33 In the manufacturer's base case analyses, the hazard ratio for major bleed of rivaroxaban compared with LMWH/VKA was 0.493. The ERG assessed two scenarios in the lifelong treatment duration analysis where the hazard ratio for major bleeds was increased. In the first scenario, the ERG used a hazard ratio for major bleeds of 0.65. This was taken from the EINSTEIN-DVT trial (one of the key trials supporting the clinical effectiveness of rivaroxaban in the manufacturer's submission for NICE technology appraisal 261) which compared rivaroxaban with LMWH/VKA in preventing recurrent VTE in people who had experienced a DVT. In this scenario the ICER for rivaroxaban compared with LMWH/VKA increased from £7,072 to £10,070 per QALY gained for the lifelong treatment duration. In the second scenario, the ERG used a hazard ratio for major bleeds of 0.79 which was the upper limit of the 95% confidence interval surrounding the hazard ratio for a major bleed seen in EINSTEIN-PE. Applying this hazard ratio the ICER for rivaroxaban compared with LMWH/VKA increased from £7,072 to £14,177 per QALY gained for the lifelong treatment duration.

6.34 Assuming a higher utility value in the intracranial bleed state from 0.33 in the base case to 0.55 based on utility values presented in Pickard et al (2004) did not appreciably change the total QALYs and the model outcomes were hardly altered: for 6 and 12 month treatment durations rivaroxaban remained dominant; in the lifelong treatment analysis the ICER increased from £7,072 to £7,098 per QALY gained. The effect of assuming a higher utility value in the

intracranial bleed state on the 3 month treatment analysis was not presented by the ERG.

6.35 Assuming a higher mean age of the model population from 58 years in the base case to 65 years did not have a large effect on the cost effectiveness estimates: rivaroxaban remains dominant at 6 and 12 month treatment durations; for a lifelong treatment duration the ICER increased from £7,072 to £7,911 per QALY gained. The effect of assuming a higher mean age of the model population on the 3 month treatment analysis was not presented by the ERG.

6.36 The ERG assessed 3 scenarios where the costs of emergency anticoagulant reversal were taken into account. The first scenario assumed that all people received PCC in all cases of major bleeding. The second scenario assumed that people who had a bleed while taking LMWH/VKA received PCC while those taking rivaroxaban received rFVIIa. The third scenario assumed the same as the second scenario in terms of treatments received to reverse major bleeding but also assumed risk of a major bleed with rivaroxaban to be more similar to the risk experienced on LMWH/VKA (HR 0.65 from EINSTEIN-DVT) and the frequency of INR monitoring for people receiving LMWH/VKA to be 6 in the first quarter and 3 in each subsequent quarter. The first scenario had a modest effect on the base case analyses for the 12 month and lifelong treatment durations: rivaroxaban remains dominant in the 12 month treatment analysis and the ICER decreases from £7,072 to £6,868 per QALY gained in the lifelong treatment analysis. The second scenario resulted in an ICER for rivaroxaban compared with LMWH/VKA of £2,328 per QALY gained for the 12 month treatment duration ,and increased the ICER from £7,072 to £19,642 per QALY gained for a lifelong treatment duration. In the third

scenario the ICER for increased for the 12 month treatment cohort to £23, 364 per QALY gained and to £44,046 per QALY gained for a lifelong treatment.

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

6.38 The ERG re-ran the manufacturer's probabilistic base case for the lifelong treatment duration following its corrections to the model (see section 6.28). The amended probabilistic base case ICER for rivaroxaban compared with LMWH/VKA was £7,019 per QALY gained. The ERG also re-ran the probabilistic sensitivity analysis with amendments to the following parameters: INR monitoring frequency (6 in first quarter, varying between 8 and 5; 3 thereafter, varying between 4 and 2); and a hazard ratio of recurrent VTE after 12 months treatment of 1.5 (95% CI 1.1 to 1.19) applied to the rivaroxaban arm. The ICER for rivaroxaban compared with LMWH/VKA associated with the mean costs and QALYs from this probabilistic sensitivity analysis was £22,787 per QALY gained.

6.39 The ERG noted that the manufacturer had presented a cost minimisation analysis of rivaroxaban compared with LMWH. However, the ERG considered the analysis to be speculative because, as acknowledged by the manufacturer, there were few data and no robust analyses to support the assumed equivalence of rivaroxaban and dalteparin in the treatment of PE.

7 Equalities issues

7.1 During consultation on the scope for this appraisal one consultee suggested that special consideration should be given to people who cannot take warfarin. However, as people who cannot take warfarin are not a protected group, this was not considered an equalities issue. The manufacturer, patient and professional groups and the ERG did not identify any equalities issues.

8 Innovation

The manufacturer suggested several health-related benefits from rivaroxaban that offer the NHS a 'step-change' in the management of patients with pulmonary embolism such as that rivaroxaban is an oral fixed dose agent with minimal food and drug interactions, which does not require monitoring and does not require "bridging" therapy with LMWH injections and that rivaroxaban has the potential for earlier hospital discharge than other treatments.

9 Authors

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Appendix A: Supporting evidence [Any additional supporting information should be included here]

Related NICE guidance

Published

- Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. NICE clinical guideline 144 (2012). Available from http://guidance.nice.org.uk/CG144

- 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

- Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. NICE technology appraisal guidance 261 (2012) Available from http://guidance.nice.org.uk/TA261

- 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

- There is a NICE pathway on venous thromboembolism, which is available from http://pathways.nice.org.uk/pathways/venous-thromboembolism

Appendix B: Clinical efficacy section of the draft European public assessment report [if not yet published]

[To be added as a confidential appendix.]