LMMG New Medicine Recommendation

Rivaroxaban (Xarelto®▼) 10mg tablets

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and <u>extended</u> prevention of recurrent DVT and PE in adults

LMMG Recommendation: Amber 0

Rivaroxaban 10mg is recommended for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and extended prevention of recurrent DVT and PE in adults.

- Suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Little or no specific monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Brief prescribing document or information sheet may be required.

Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.[1]

The prescribing information for rivaroxaban provides instructions for physicians to begin treatment with rivaroxaban 15 mg, dosed twice daily, for the first 21 days after a VTE occurrence. On day 22 through at least day 180, the daily dose decreases to 20 mg once daily. After at least 180 days (6 months), physicians can prescribe 10 mg once daily in patients at continued risk for DVT and/or PE.

When recommending or handing over care, specialists should ask primary care prescribers to take over prescribing responsibility, and should give enough information about the indication, dose, monitoring requirements, use outside product licence and any necessary dose adjustments to allow them to confidently prescribe.

Summary of supporting evidence

- In the Phase III EINSTEIN CHOICE study,[2] rivaroxaban 20 mg and 10 mg once daily were superior to acetylsalicylic acid (ASA) 100 mg once daily for the extended treatment of recurrent venous thromboembolism (VTE) with no significant differences in bleeding rates. Patients treated with rivaroxaban 20 mg and 10 mg had comparable efficacy and safety outcome rates. Both rivaroxaban groups had a favourable net clinical benefit over the ASA group with comparable results for the two rivaroxaban groups. Following completion of at least 6 months of treatment for deep vein thrombosis (DVT) or pulmonary embolism (PE), rivaroxaban 10 mg provides an additional option for extended treatment to the approved rivaroxaban 20 mg dose.
- The primary efficacy outcome of symptomatic recurrent fatal or nonfatal venous thromboembolism occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and

in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) receiving aspirin.

- Rates of major bleeding were 0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the aspirin group; the rates of clinically relevant nonmajor bleeding were 2.7%, 2.0%, and 1.8%, respectively.
- A Cochrane review on the Secondary prevention of recurrent venous thromboembolism after initial oral anticoagulation therapy in patients with *unprovoked* venous thromboembolism (2017)[3] found that the evidence is currently insufficient to permit definitive conclusions concerning the effectiveness and safety of extended thromboprophylaxis in prevention of recurrent VTE after initial oral anticoagulation therapy among participants with unprovoked VTE.
- A subset of patients with unprovoked thromboembolism in the EINSTEIN CHOICE study was included in this review however some outcome data was not made available for the analysis; the Cochrane review intends to update its findings when these become available. Cochrane concludes that additional good quality large-scale randomised controlled trials are required before firm conclusions can be reached.

Details of Review

Name of medicine (generic & brand name): Rivaroxaban (Xarelto®) 10 mg film-coated tablets

Strengths and forms: Film coated tablets available as 10mg,15mg and 20mg. This review is of the 10mg tablet only.

Dose and administration:

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with rivaroxaban 10 mg once daily, a dose of rivaroxaban 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding

BNF therapeutic class / mode of action: Chapter 2.32, Cardiovascular system, Thromboembolism, Antithrombotic drugs, factor XA inhibitors

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.[1]

Licensed indication(s):[1]

Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Proposed use:

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Course and cost: 10mg each day, 30 tablets £54.00[4]

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.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with rivaroxaban 10 mg once daily, a dose of rivaroxaban 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

	Time Period	Dosing schedule	Total daily dose
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

In the EINSTEIN CHOICE study, patients were treated with rivaroxaban for up to 12 months in addition to the 6 to 12 months anticoagulants they received before study entry.[2] A course of 10mg rivaroxaban could last 12 months in addition to initial anticoagulant treatment and this will cost an additional £648.

The maximum treatment duration for the treatment of DVT, PE and prevention of recurrence in phase III studies was 21 months.

Current standard of care/comparator therapies:

The current oral therapeutic options for extended thromboprophylaxis in adults with a first unprovoked venous thromboembolism (VTE) in order to prevent VTE recurrence after completion of an acceptable oral anticoagulant treatment period are aspirin, warfarin and the direct oral anticoagulants (DOACs).

Relevant NICE guidance:

NICE TA 261[5] Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism (Published date: 25 July 2012)

NICE TA 287[6] Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism (Published date: 26 June 2013)

NICE Clinical Guideline CG 144[7] Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (Published date: June 2012 Last updated: November 2015)

Disease Background

Venous thromboembolism (VTE) is a condition in which a blood clot forms in the deep veins of the leg or pelvis (deep vein thrombosis (DVT)), or the clot travels in the blood and blocks a blood vessel in the lungs (pulmonary embolism(PE)). People with a VTE are treated with an anticoagulant, which prevents formation of further clots. For patients with a VTE that has been caused by a certain risk factor (prolonged periods of immobility, cancer, pregnancy, oral

contraceptives, hormone replacement therapy, trauma, or blood disorder), treatment can be safely discontinued after three months. However, for patients in whom the VTE has no known cause (unprovoked), the optimal length of treatment is unknown because evidence is limited. Clinicians have to decide upon extended treatment based on benefit (i.e. prevention of VTE recurrence) versus risk (i.e. of bleeding) associated with treatment.

VTE have a high prevalence both in the community and in hospitals, and bring a considerable burden of morbidity and possible mortality.

Every year, there are approximately 10 million cases of VTE worldwide.[8]

Estimates of the number of deaths in the UK due to VTE vary. The evidence received by the House of Commons Health Committee 2004-2005 put the figures at between 24,000 and 32,000 per year.[9]

The Office for Healthcare Economics estimated in 1993 that the annual cost in the UK of treating patients who developed post-surgical DVT and PE was in the region of £204.7 to £222.8 million. The total cost (direct and indirect costs) to the UK for the management of VTE is currently estimated at approximately £640 million.[9]

Current treatment options

There is currently evidence / guidance to support the use of aspirin,[10,11] warfarin[12] and the DOACs i.e. apixaban,[13] dabigatran,[14] edoxaban[15] and rivaroxaban[5,6] for the secondary prevention of DVT and / or PE.

Summary of efficacy data in proposed use:

EINSTEIN CHOICE[1]

This was a randomized, double-blind, phase 3 study, in which 3396 patients with venous thromboembolism were assigned to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. All the study patients had completed 6 to 12 months of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation. Study drugs were administered for up to 12 months. Patients underwent assessment, either in the clinic or by telephone, at days 30, 90, 180, 270, and 360 and at 30 days after stopping the study medication. All the patients who stopped a study treatment earlier than scheduled were followed until the end of the intended treatment period. The primary efficacy outcome was symptomatic recurrent fatal or nonfatal venous thromboembolism, and the principal safety outcome was major bleeding.

Results

A total of 3365 patients were included in the intention-to-treat analyses (median treatment duration, 351 days). The primary efficacy outcome occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) receiving aspirin (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; hazard ratio for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). Rates of major bleeding were 0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the aspirin group; the rates of clinically relevant nonmajor bleeding were 2.7%, 2.0%, and 1.8%, respectively. During the 30-day follow-up after the end of the active study period, symptomatic recurrent venous thromboembolism occurred in 2 patients (0.2%) in the 20-mg rivaroxaban group, in 4 patients (0.4%) in the 10-mg rivaroxaban group, and in 6 patients (0.6%) in the aspirin group. The incidence of adverse events was similar in all three groups.

Summary

Previous studies have shown that as compared with placebo, aspirin reduced the relative risk of recurrent venous thromboembolism by 32% (2.4 percentage points),[16,17] whereas a 20-mg dose of rivaroxaban reduced the relative risk by 82% (6.8 percentage points).[18]

The findings from EINSTEIN CHOICE are consistent with these findings, showing that as compared with aspirin, both the 20-mg and 10-mg doses of rivaroxaban reduced the relative risk of recurrent venous thromboembolism by about 70% (approximately 3 percentage points).

Cochrane Review - Secondary prevention of recurrent venous thromboembolism after initial oral anticoagulation therapy in patients with unprovoked venous thromboembolism[3]

This review was conducted as currently, little evidence is available on the length and type of anticoagulation used for extended treatment for prevention of recurrent venous thromboembolism (VTE) in patients with unprovoked VTE who have completed initial oral anticoagulation therapy.

The objective of the review was to compare the efficacy and safety of available oral therapeutic options (aspirin, warfarin, DOACs) for extended thromboprophylaxis in adults with a first unprovoked VTE, to prevent VTE recurrence after completion of an acceptable initial oral anticoagulant treatment period, as defined in individual studies.

The review included randomised controlled trials in which patients with a first, symptomatic, objectively confirmed, unprovoked VTE, who had been initially treated with anticoagulants, were randomised to extended prophylaxis (vitamin K antagonists (VKAs), antiplatelet agents, or DOACs) versus no prophylaxis or placebo. Trials were also included that compared one type of extended prophylaxis versus another type of extended prophylaxis.

Results

Six studies (ASPIRE, EINSTEIN CHOICE, PADIS PE Study, WARFASA, WODIT DVT, WODIT PE) with a combined total of 3436 participants (until March 2017) met the inclusion criteria. Five studies compared extended prophylaxis versus placebo: three compared warfarin versus placebo, and two compared aspirin versus placebo. One study compared one type of extended prophylaxis (rivaroxaban) versus another type of extended prophylaxis (aspirin).

Extended prophylaxis was defined as treatment for participants with VTE who have completed at least three months and up to four years of anticoagulation therapy after initial treatment.

For extended prophylaxis versus placebo, the quality of the evidence for recurrent VTE was downgraded and all-cause mortality to moderate owing to concerns arising from risks of selection and performance bias in individual studies. For all other outcomes in this review, the quality of the evidence was downgraded to low owing to concerns arising from risk of bias for the studies stated above, combined with concerns over imprecision. For extended prophylaxis versus other extended prophylaxis, the quality of the evidence for recurrent VTE and major bleeding was downgraded to moderate owing to concerns over imprecision. Risk of bias in the individual study was low. Meta-analysis showed that extended prophylaxis was no more effective than placebo in preventing VTE-related mortality (odds ratio (OR) 0.98, 95% confidence interval (CI) 0.14 to 6.98; 1862 participants; 4 studies; P = 0.98; low-quality evidence), recurrent VTE (OR 0.63, 95%CI 0.38 to 1.03; 2043 participants; 5 studies; P = 0.07; moderate-quality evidence), major bleeding (OR 1.84, 95%CI 0.87 to 3.85; 2043 participants; 5 studies; P = 0.86; low-quality evidence), all-cause mortality (OR 1.00, 95% CI 0.63 to 1.57; 2043 participants; 5 studies; P = 0.99; moderate-quality evidence), clinically relevant non-major bleeding (OR 1.78, 95% CI 0.59 to 5.33; 1672 participants; 4 studies; P = 0.30; low-quality evidence), stroke (OR 1.15, 95% CI 0.39 to 3.46; 1224 participants; 2 studies; P = 0.80; low-quality evidence), or myocardial infarction (OR 1.00, 95% CI 0.35 to 2.87; 1495 participants; 3 studies; P = 1.00; low quality evidence).

One study showed that the novel oral anticoagulant rivaroxaban was associated with fewer recurrent VTEs than aspirin (OR 0.28, 95% CI 0.15 to 0.54; 1389 participants; P = 0.0001;

moderate-quality evidence). Data show no clear differences in the incidence of major bleeding between rivaroxaban and aspirin (OR 3.06, 95% CI 0.37 to 25.51; 1389 participants; P = 0.30; moderate-quality evidence) nor in the incidence of clinically relevant non-major bleeding (OR 0.84, 95% CI 0.37 to 1.94; 1389 participants; 1 study; P = 0.69; moderate-quality evidence).

Conclusion

The evidence is currently insufficient to permit definitive conclusions concerning the effectiveness and safety of extended thromboprophylaxis in prevention of recurrent VTE after initial oral anticoagulation therapy among participants with unprovoked VTE. Additional good quality large-scale randomised controlled trials are required before firm conclusions can be reached.

Summary of safety data

Table of Adverse events for rivaroxaban▼[3]

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto are summarised in table 3 below by system organ class (in MedDRA) and by frequency.

Table 3: All treatment-emergent adverse reactions reported in patients in phase III studies

Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)[A]		
Immune system disorders			
	Allergic reaction, dermatitis allergic		
Nervous system disorders			
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope		
Eye disorders			
Eye haemorrhage (incl. conjunctival haemorrhage)			
Cardiac disorders			
	Tachycardia		
Vascular disorders			
Hypotension, haematoma			
Respiratory, thoracic and mediastinal disorders			
Epistaxis, haemoptysis			
Gastrointestinal disorders			
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth		
Hepatobiliary disorders			
	Hepatic impairment	Jaundice	
Skin and subcutaneous tissue disorders			
Pruritus (incl. uncommon cases of generalised	Urticaria		

pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage			
Musculoskeletal and connective tissue disorders			
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
Renal and urinary disorders			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)[A]			Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions			
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]	
Investigations			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase[A], increased LDH[A], increased lipase[A], increased amylase[A], increased GGT[A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
Injury, poisoning and procedural complications			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]		Vascular pseudoaneurysm[C]	

A: observed in prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years
C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

Frequencies are defined as:
Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data)

Strengths and limitations of the evidence:

EINSTEIN CHOICE

Strengths:

- Study included 3396 patients
- The study was double blind
- Duration up to 12 months
- All the study patients had completed 6 to 12 months of anticoagulation therapy, reflective of clinical practice.

Limitations:

- Patients who required extended treatment with therapeutic doses of anticoagulant agents were excluded. Therefore, it remains unknown whether the 10-mg dose of rivaroxaban would be sufficient to prevent recurrence in such patients.
- Extended treatment was given up to 12 months in addition to initial treatment. Consequently, additional studies are needed to determine the utility of continuing treatment for longer periods.
- The study was not powered to show the noninferiority of the 10-mg dose of rivaroxaban to the established treatment regimen of 20 mg, so any conclusions with respect to this issue are speculative.
- No warfarin arm in study
- Company sponsored trial

COCHRANE REVIEW

Strengths:

- Six studies with large combined patient total
- DOACs, warfarin and placebo were considered as arms in the trials
- Independent review

Limitations:

- The quality of the evidence provided by studies included in this review ranged from low to moderate because a small number of studies with few events were included.
- This review found that trials are too few to show whether extended treatment is safe and effective in preventing further blood clots after three months' treatment.
- Further good-quality and large-scale studies are required.
- A subset of EINSTEIN choice was used in the review and not all data was available for inclusion. A fuller picture should emerge when the review is updated.

Prescribing and risk management issues:

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding. There is currently limited evidence as to the optimum duration of therapy.

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genitourinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Commissioning considerations:

Anticipated patient numbers and net budget impact

According to NHS England within its Commissioning Services that deliver High Quality VTE Prevention Guidance for Commissioners (first published May 2013)[19] the incidence of Venous Thromboembolism is 1-2 per 1,000 of the population and the risk increases with age.

In 2016, the population of Lancashire was estimated at 1,483,900[20] this equates to between approximately 1,484 and 2,968 potential VTE patients.

Associated additional costs or available discounts:

At a cost of £54 for 30 tablets, the annual cost for a single patient prescribed rivaroxaban 10mg = £648.

For 1,484 – 2,968 patients within Lancashire this would equate to an annual cost of between **£961,632 and £1,923,264.**

Alternative treatments:

Aspirin 75mg dispersible tablets have a current drug tariff price of £0.63 for 28 tablets = £8.19 / year / patient. For 1,484 – 2,968 patients within Lancashire this would equate to an annual cost of between £12,154 - £24,308

Warfarin 1mg/3mg/5mg tablets have a current drug tariff price of £0.63, £0.67 and £0.70 respectively for 28 tablets and therefore a similar impact on the overall annual drug cost as Aspirin. However, with warfarin there would be associated costs relating to drug monitoring (The cost of clinic based warfarin monitoring is around £130 per patient per year).

Productivity, service delivery, implementation:

The length of extended treatment would need to be monitored, as would adequate clinical surveillance of the patient in order to detect any occult bleeding and quantify the clinical relevance of overt bleeding.

Innovation, need, equity:

The quality of the evidence to show whether extended treatment is safe and effective in preventing further blood clots is currently limited. Optimum dosage and duration have not been determined.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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