

rivaroxaban 15mg and 20mg film-coated tablets (Xarelto®) SMC No. (852/13)

Bayer plc

08 February 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

rivaroxaban (Xarelto®) is accepted for use within NHS Scotland.

Indication under review: treatment of pulmonary embolism (PE), and prevention of recurrent deep vein thrombosis (DVT) and PE in adults.

Rivaroxaban was non-inferior to a regimen including a low molecular weight heparin and a vitamin K antagonist for the treatment of PE and the prevention of recurrence of DVT or PE. Duration of treatment was 3, 6 or 12 months at the discretion of the treating physician.

Experience with rivaroxaban in this indication for more than 12 months is limited therefore the cost-effectiveness of indefinite treatment has not been demonstrated.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

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

Dosing Information

The recommended dose for the initial treatment of acute PE is 15mg twice daily for the first three weeks followed by 20mg once daily for the continued treatment and prevention of recurrent DVT and PE.

Product availability date

December 2012

Summary of evidence on comparative efficacy

Rivaroxaban is a selective direct factor Xa inhibitor which interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade inhibiting thrombin formation and therefore the development of thrombi.

Rivaroxaban received initial marketing authorisation in the UK in 2008 for the prevention of venous thromboembolism (VTE) in adults undergoing hip and knee surgery and SMC accepted it for use in NHS Scotland. Subsequent licence extensions also accepted for use by SMC include; the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors; and the treatment of DVT and prevention of recurrent DVT and PE in adults. This submission relates to the most recent licence extension for the treatment of PE and the prevention of recurrent DVT and PE in adults.

Evidence to support the most recent licence extension comes from two randomised, phase III, studies of rivaroxaban for the treatment of acute PE over three, six or 12 months (EINSTEIN-PE),¹ and for continued treatment over 6 to 12 months (EINSTEIN-Extension).²

EINSTEIN-PE was a multi-centre, open-label, active-controlled, non-inferiority study, to evaluate the efficacy and safety of rivaroxaban in patients with an acute, symptomatic, objectively confirmed PE, with or without a DVT. Patients were randomised equally and stratified according to country and intended treatment duration (three, six or 12 months) to receive rivaroxaban 15mg twice daily for three weeks followed by 20mg once daily (n=2,419) or subcutaneous enoxaparin 1mg/kg of body weight twice daily and an oral vitamin K antagonist (either warfarin or acenocoumarol) within 48 hours of randomisation (n=2,413). Enoxaparin was continued for at least five days and until the international normalised ratio (INR) was 2.0 or more for two consecutive days. Vitamin K antagonist (VKA) doses were adjusted to maintain a target INR of 2.0 to 3.0. INR was measured at least once a month. The intended treatment duration was at the discretion of the treating physician: 5%, 57% and 37% of the enrolled patients were assigned to three, six and 12 months treatment respectively.

The primary efficacy outcome, measured in the intention to treat population, was symptomatic recurrent VTE, defined as a composite of fatal or nonfatal PE or DVT. Non-inferiority of rivaroxaban compared with enoxaparin and VKA would be demonstrated if the upper limit of the

two-sided 95% confidence interval (CI) for the observed hazard ratio (HR) was below the pre-defined non-inferiority margin of 2.0. A recurrent VTE was experienced by 2.1% (50/2,419) and 1.8% (44/2,413) of patients in the rivaroxaban and standard therapy groups respectively, HR 1.12 (95% CI: 0.75 to 1.68), $p=0.003$ for non-inferiority. Table 1 shows the incidence of the primary outcome stratified by intended treatment duration.

Table 1: Incidence of symptomatic recurrent VTE stratified by intended treatment duration

Intended Treatment Duration	Rivaroxaban	Enoxaparin and VKA
3 months	4.7% (6/127)	1.6% (2/122)
6 months	1.9% (27/1,387)	1.7% (24/1,387)
12 months	1.9% (17/905)	2.0% (18/904)

Patient-reported satisfaction was measured by the Anti-Clot Treatment Scale (ACTS) and the Treatment Satisfaction Questionnaire for Medicine version II (TSQM). ACTS consists of a 12 item ACTS Burdens scale and a three item ACTS Benefits scale. Mean ACTS Burdens scores were 55 versus 52 ($p<0.001$), favouring rivaroxaban. The ACTS Benefits scores were also higher in the rivaroxaban group, though the magnitude was smaller (12 versus 11, $p<0.001$). TSQM scores were significantly higher in the rivaroxaban group, supporting the ACTS results.³

EINSTEIN-Extension was a multi-centre, double-blind, superiority study. Patients were eligible for treatment if they had an objectively confirmed symptomatic DVT or PE and had been treated for six or 12 months with warfarin, acenocoumarol or rivaroxaban and there was clinical equipoise (uncertainty) regarding the need for further treatment. Patients had either completed the EINSTEIN-DVT or EINSTEIN PE studies or had been treated for six to 12 months with a VKA outwith these clinical studies. Patients were randomised equally into two groups: rivaroxaban 20mg once daily ($n=692$) or placebo ($n=594$). As with EINSTEIN-PE the treatment duration was as per treating physician choice prior to randomisation, 60% and 40% of patients were assigned an intended treatment duration of six and 12 months respectively.

The primary efficacy outcome for EINSTEIN-Extension was the same as for EINSTEIN-PE. A symptomatic recurrent VTE occurred in 1.3% (8/602) and 7.1% (42/594) of patients in the rivaroxaban and placebo groups respectively, HR 0.18 (95% CI: 0.09 to 0.39), $p<0.001$.

Summary of evidence on comparative safety

The principal safety outcome in EINSTEIN-PE was clinically relevant bleeding, defined as a composite of major and clinically relevant non-major bleeding. Bleeding was defined as major if it was clinically overt and associated with a decrease in haemoglobin level of $\geq 2\text{g/dL}$, if it led to transfusion of ≥ 2 units of red cells or if it was intracranial or retroperitoneal, occurred in another critical site, or contributed to death. Clinically relevant non-major bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with a medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug or discomfort or impairment of activities of daily life.

Clinically relevant bleeding was experienced by 10% (249/2,412) and 11% (274/2,405) of patients in the rivaroxaban and enoxaparin and VKA groups respectively. An episode of major bleeding was experienced by 1.1% (26/2,412) and 2.2% (52/2,405) of patients respectively. This was fatal in <0.1% (2/2,412) and 0.1% (3/2,405) of patients respectively.¹

Vascular events (acute coronary syndrome, ischaemic stroke, transient ischaemic attack or systemic embolism) were experienced by small numbers of patients in each group.¹

The principal safety outcome in EINSTEIN-Extension was major bleeding: this occurred in 0.7% (4/598) of patients in the rivaroxaban group and no patients in the placebo group ($p=0.11$). The incidence of major or clinically relevant non-major bleeding was 6% (36/598) and 1.2% (7/590) respectively, $p<0.001$. The incidence of clinically relevant non-major bleeding was 5.4% (32/598) in the rivaroxaban group and 1.2% (7/590) in the placebo group. The majority of clinically relevant non-major bleeding was mucosal bleeding, and most patients (81%) who suffered from clinically significant non-fatal bleeding resumed or continued study therapy. The number of vascular events was small in each treatment group.²

Summary of clinical effectiveness issues

Rivaroxaban is licensed for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults. This submission relates to the most recent licence extension for the treatment of PE and the prevention of recurrent DVT and PE in adults. Advice has previously been issued by SMC regarding the use of rivaroxaban for the treatment of DVT and the prevention of recurrent DVT and PE in adults.

SMC experts advise that the current standard treatment of non-high-risk PE is a therapeutic dose of a low molecular weight heparin (LMWH) in combination with warfarin. Both treatments should be continued for at least five days and until the INR is ≥ 2.0 , when the LMWH can be stopped. After a first episode of PE, treatment with warfarin should be continued for at least three months. Uninterrupted, long term continuation of warfarin therapy after a first episode of VTE may be appropriate in some patients.⁴

The EINSTEIN-PE study demonstrated non-inferiority of rivaroxaban to enoxaparin and a VKA for the prevention of symptomatic recurrent VTE in patients with an acute symptomatic PE. Treatment duration was three, six or 12 months at the discretion of the treating physician. EINSTEIN-Extension demonstrated superiority of rivaroxaban over placebo for patients who had initially received six or 12 months anticoagulant treatment for a DVT or PE and there was clinical equipoise regarding the continued need for anticoagulant treatment. Patients received treatment for a further six or 12 months, again at the discretion of the treating physician.

The EINSTEIN-PE study was open-label; however, the difficulties of blinding this study are acknowledged. The endpoint was adjudicated by an independent committee who were blind to the treatment allocation.

Enoxaparin was used at a dose of 1mg/kg twice daily in the EINSTEIN-PE study. This differs from the UK licensed dose of 1.5mg/kg once daily, which is used in clinical practice. The impact of this difference is unknown. Dalteparin and tinzaparin may also be used in clinical practice for this indication. There are no comparative data using these LMWHs; however, SIGN guideline

129 states that there is little evidence of differences in clinical efficacy between the preparations.⁵ Fondaparinux is also licensed for this indication but it is not recommended for use by SMC.

For patients in the “standard therapy” group of EINSTEIN-PE, the INR results were within the therapeutic range of 2.0 to 3.0 for 63% of the time. INR was above 3.0 for 16% of the time and below 2.0 for 22%. This may have biased the results in favour of rivaroxaban; however, it seems likely that these INR results are similar to those achieved in clinical practice. According to the Scottish Intercollegiate Guideline (SIGN) 129: Antithrombotics: Indication and management, the average rate of INRs within therapeutic range is 60%, even with high quality clinical support.⁵

Patients in EINSTEIN-PE were treated for three, six or 12 months at the discretion of the treating physician. Patients included in EINSTEIN-Extension had received treatment with either a VKA or rivaroxaban for six or 12 months and received a further six or 12 months treatment with rivaroxaban or placebo, again at the discretion of the treating physician. Therefore, small numbers of patients have been treated with rivaroxaban for longer than one year so long-term efficacy and safety data are limited.

In EINSTEIN-PE patients could receive pre-treatment with a LMWH, fondaparinux or heparin for up to 48 hours prior to study inclusion: 92% of patients in both treatment groups received prior treatment. The European Medicines Agency (EMA), when considering the similar situation in patients who had experienced a DVT, stated that there is little evidence to support a recommendation of the use of parenteral anticoagulants in the initial phase of acute treatment. The similar time to onset after administration is an important consideration.⁶

Einstein-Extension consisted of patients with DVT and PE. Only 38% of patients had an initial diagnosis of PE and 19% of patients had previously participated in the EINSTEIN-PE study. No sub-group data were reported, so it is unknown how generalisable the results of the Einstein-Extension study are to patients with PE.

There is no specific antidote to rivaroxaban, and since it acts at a different step in the coagulation cascade from warfarin, the standard strategies used to reverse warfarin are not appropriate. Rivaroxaban discontinuation and supportive measures are recommended as initial management of patients who bleed. This may also be an issue in patients who require emergency surgery. The summary of product characteristics advises that rivaroxaban should be stopped at least 24 hours before an invasive procedure or surgical intervention, if this is possible based on the clinical judgement of the physician. SIGN 129 suggests using four-factor prothrombin complex concentrate to reverse rivaroxaban in emergency situations, on the basis of studies in healthy individuals.⁵

SMC clinical experts suggest that rivaroxaban may be more suitable than standard therapy in patients who have poor INR control with warfarin, or in patients who find the regular INR testing inconvenient or unsuitable.

Rivaroxaban does not require the initial subcutaneous injections associated with LMWHs and the continuous monitoring associated with warfarin therapy. In the pivotal study, patient-reported satisfaction was higher in the rivaroxaban group, suggesting that patients may prefer this treatment. The reduced need for nurses to administer LMWHs may be an advantage, although many of these patients receive initial treatment as inpatients and many patients can self-administer so it is unclear how much of a benefit this would be. Fewer patients requiring INR monitoring at anticoagulant clinics may be an advantage to the service although these clinics are already very well established so it is difficult to quantify this benefit.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing rivaroxaban with enoxaparin followed by warfarin. Three scenarios were considered based on treatment durations of 3, 6 and 12 months. Patients were assumed to be aged 58 at baseline and a lifetime horizon was used in a Markov model.

Data on the relative effectiveness and safety of the treatments were taken from the main clinical study. Data on rates of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension were taken from a systematic review of the literature. Scottish population mortality rates for the relevant age and sex were applied. Utility values were taken from a variety of published sources.

Resource use included the costs of medicines, administration of medicines and treatment of adverse events (i.e. bleeding). Costs of treating events were based on assumptions about resource use, with the exception of a claimed reduction in length of stay for the index hospitalisation. In terms of savings, the assumptions about INR monitoring seemed more important and these were as follows:

- It was assumed 66% of INR monitoring happened in primary care and 34% in a hospital setting. This was based on a survey, but only 1 of the 84 organisations questioned was in Scotland.
- It was assumed the patient would require 9 INR monitoring visits in the first three months and then 5 per quarter. For 3, 6 and 12 month treatment durations, the number of INR tests would be 9, 14 and 24.

The submission presented the following results:

Patient group	Rivaroxaban		Dual LMWH/VKA		Incremental		
	Costs (£)	Quality adjusted life years (QALYs)	Costs (£)	QALY	Costs (£)	QALY	Incremental cost effectiveness ratio (ICER)
3 months	4,258	11.469	4,499	11.464	-241	0.005	Dominant (cheaper, more effective)
6 months	4,440	11.494	4,657	11.485	-217	0.009	Dominant
12 months	4,735	11.537	4,874	11.525	-139	0.012	Dominant

Notes: Costs and QALYs are quoted per patient.

This suggests the QALY gain is at most 4 quality-adjusted days over a lifetime perspective starting from age 58.

In the sensitivity analysis submitted, the only factor in one-way analysis that sent the cost per QALY over £20k was when the upper limit of the 95% confidence interval for the hazard ratio for the reduction of VTE by rivaroxaban was used.

The main issues were:

- Uncertainty around INR monitoring – the assumptions made in the base case seemed high in terms of numbers of visits, which works in favour of rivaroxaban. However, the submitting company provided additional sensitivity analysis varying these assumptions: the results for the 3 and 6 month scenarios remained dominant and the cost per QALY increased to a maximum of £12k under options tested in the 12 month treatment scenario.
- Concern that some data such as hazard ratios were used in the economic model where the 95% confidence interval showed there was no significant difference from 1. However, the submitting company provided additional analysis which demonstrated that removing these differences altered the level of incremental costs and QALYs but the overall results were still dominant.

Given the findings of the additional analyses, the economic case was demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Lifeblood: The Thrombosis Charity
- Anti Coagulation Europe (ACE)

Additional information: guidelines and protocols

SIGN has published two guidelines relevant to the indication under review: SIGN Guideline 129 Antithrombotics: indications and management (August 2012) and SIGN 122 Prevention and management of venous thromboembolism (December 2010).^{4,5} Patients with a suspected PE should be treated with therapeutic doses of heparin (low molecular weight heparin or unfractionated heparin) or fondaparinux until the diagnosis has been deemed very unlikely.⁴ Warfarin is the oral vitamin K antagonist (VKA) of choice in the UK. Despite being licensed acenocoumarol and phenindione are rarely used.⁵ Warfarin should be commenced in addition to the heparin or fondaparinux. Both treatments should be continued for at least five days and until the INR is ≥ 2.0 when the heparin or fondaparinux can be stopped.⁴ After a first episode of PE, treatment with a VKA should be continued for at least three months. Uninterrupted, long term continuation of VKA therapy after a first episode of VTE may be appropriate in some patients and can be based on individual assessment, including: an unprovoked first event, the site and severity of the first event, the presence of persistent co-morbidities, e.g. cancer, the presence of persistent antiphospholipid antibodies, male sex, bleeding risk on anticoagulant treatment and patient compliance and preference.⁴

The British Committee for Standards in Haematology published the fourth edition of guidelines on oral anticoagulation (warfarin) in 2011.⁷ Treatment of VTE with warfarin should initially also include at least five days of parenteral anticoagulation (LMWH, unfractionated heparin or fondaparinux), continuing until the INR is ≥ 2.0 . The first episode of VTE should be treated with an INR target of 2.5 and for a minimum duration of three months. Patients with unprovoked PE should be considered for long term anticoagulation, the individual patient's risk of recurrence and bleeding should be taken into account.

Additional information: comparators

Combination of a LMWH (enoxaparin, dalteparin or tinzaparin) and warfarin. Fondaparinux is licensed for the treatment of acute PE but is not recommended for use by SMC.

Cost of relevant comparators

Drug	Dose Regimen	Cost (£) for 7 to 10 days of treatment*	Cost (£) for 12 months of treatment
Rivaroxaban	15mg twice daily for 21 days then 20mg once daily for up to 12 months		809
Warfarin	Orally as determined by prothrombin time		34**
Dalteparin	15,000 units once daily	59 to 85	
Enoxaparin	1.5mg/kg every 24 hours	68 to 98	
Fondaparinux***	7.5mg every 24 hours	82 to 117	
Tinzaparin	175 units/kg once daily	83 to 118	

*Costs are based on doses calculated for a 70kg adult. **Average daily dose of warfarin is around 5mg (range 1 to 15mg).⁵ ***Not recommended for use by SMC.

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 14 November 2012.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 3,569 in year 1 rising to 3,781 in year 5, with an estimated uptake rate of 10% in year 1 and 50% in year 5. The gross impact on the medicines budget was estimated to be £200k in year 1 and £1.1m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £161k in year 1 and £855k in year 5.

Note that this does not include any savings on costs of INR monitoring or nursing visits to administer low molecular weight heparin. It should also be noted that these estimates do not assume any long-term treatment with rivaroxaban.

References

The undernoted references were supplied with the submission. The reference shaded in grey was additional to those supplied with the submission.

1. Buller HR, Prins MH, Lensin AW et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366(14):1287-97 and supplementary appendix
2. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363(26):2499-510 and supplementary appendix
3. Prins MH, Bamber L, Cano SJ et al. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic pulmonary embolism. American Society of Haematology 54th Annual Meeting. Abstract 1163. December 2012.
4. Scottish Intercollegiate Guidelines Network. SIGN 122 Prevention and management of venous thromboembolism. December 2010 www.sign.ac.uk
5. Scottish Intercollegiate Guidelines Network. SIGN Guideline 129 Antithrombotics: indications and management. August 2012 www.sign.ac.uk
6. The European Medicines Agency European Public Assessment Report. Rivaroxaban (Xarelto®). 22 September 2011, EMEA H-C-944/X/0010. www.ema.europa.eu
7. Keeling D, Baglin T, Tait C et al. Guidelines on oral anticoagulation with warfarin – fourth edition. British Journal of Haematology 2011;154:311-24

This assessment is based on data submitted by the applicant company up to and including 11 January 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.