Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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rivaroxaban 15 and 20mg film-coated tablets (Xarelto®) SMC No. (755/12)

Bayer PLC

13 January 2012

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

Rivaroxaban has been shown to be non-inferior to standard anticoagulant therapy including a low molecular weight heparin in combination with a vitamin K antagonist for the treatment of proximal DVT and prevention of recurrence.

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

Dosing Information

The recommended dose for the initial treatment of acute DVT 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 therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT. Experience with rivaroxaban in this indication for more than 12 months is limited.

Product availability date

19th December 2011

Summary of evidence on comparative efficacy

Rivaroxaban is 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 thrombo-embolism (VTE) in adults undergoing hip and knee surgery. The evidence to support this licence extension comes from two randomised, phase III, studies of rivaroxaban, for the treatment of acute DVT over three, six or 12 months (EINSTEIN-DVT)[1], and for continued treatment over 6 to 12 months (EINSTEIN-Extension).[1]

EINSTEIN-DVT, a phase lll, multicentre, open-label, non-inferiority study, randomised adult patients with an acute, symptomatic, objectively confirmed proximal DVT, without symptomatic pulmonary embolism (PE), to rivaroxaban (15mg twice daily for 21 days followed by 20mg once daily thereafter (n=1731)), or enoxaparin in combination with a vitamin K antagonist [VKA], (n=1718). Enoxaparin (1.0mg/kg body weight twice daily) was administered for a minimum of five days in combination with a VKA and continued until the international normalised ratio (INR) was ≥2.0 for two consecutive measurements. Warfarin or acenocoumarol were the VKAs of choice and were commenced no later than 48 hours post-randomisation. VKA doses were adjusted to maintain the INR within therapeutic range (target 2.5, range 2.0 to 3.0). Thereafter, the treatment was given for 3, 6 or 12 months depending on the investigators clinical judgement. The primary outcome was symptomatic, recurrent VTE, defined as the composite of DVT or non-fatal or fatal PE, measured in the intention to treat (ITT) population with supportive analysis in the per protocol (PP) population. Non-inferiority of rivaroxaban compared with enoxaparin/VKA would be demonstrated if the upper limit of the two-sided 95% confidence

interval (CI) for the hazard ratio (HR) was below the pre-defined non-inferiority margin of 2.0. This margin corresponds to maintenance of at least 50% of the proven efficacy of standard therapy.

The primary outcome was confirmed in 2.1% (36/1731) of patients in the rivaroxaban group and 3.0% (51/1718) of patients in the enoxaparin/VKA group, giving a hazard ratio (HR) of 0.68 (95% CI: 0.44 to 1.04) favouring rivaroxaban, and demonstrating the non-inferiority versus combined parenteral enoxaparin/oral VKA regimen in the initial treatment of DVT and prevention of recurrent VTE.

Table 1. Results of primary efficacy analysis of EINSTEIN-DVT, stratified by intended treatment duration.

		Number of patients	Composite VTE
3 months	Rivaroxaban	208	5
	LMWH/VKA	203	3
6 months	Rivaroxaban	1083	25
	LMWH/VKA	1083	29
12 months	Rivaroxaban	440	6
	LMWH/VKA	432	19
All strata	Rivaroxaban	1731	36
	LMWH/VKA	1718	51

In both the rivaroxaban and the enoxaparin/VKA groups, most primary efficacy outcome events occurred during the first month of treatment. By day 21, the primary efficacy outcome had occurred in 1.2% (21/1731) of patients in the rivaroxaban group and in 1.7% (29/1718) of patients in the standard therapy group. Net clinical benefit, a composite of the primary efficacy outcome or major bleeding, was reported in 2.9% (51/1731) of rivaroxaban patients and 4.2% (73/1718) of enoxaparin/VKA patients (HR, 0.67; 95% CI: 0.47 to 0.95; p=0.03).

EINSTEIN-Extension was a phase III, multicentre, randomised, double-blind, placebo-controlled, superiority study. It enrolled 1196 patients with an objectively-confirmed DVT or PE who had been treated for 6 to 12 months with warfarin, acenocoumarol or rivaroxaban in the EINSTEIN studies, or in routine care, and in whom there was clinical equipoise around the need for continued anticoagulation after this initial treatment. Patients were randomised to receive rivaroxaban 20mg daily (n=602) or placebo (n=594) for 6 to 12 months. The primary outcome was symptomatic, recurrent VTE, defined as the composite of DVT or non-fatal or fatal PE, measured in the ITT population with supportive analysis in the PP population.

The primary efficacy outcome was reported in 1.3% (8/602) of patients compared to 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), corresponding to a relative risk reduction of 82%, and demonstrating the superiority of rivaroxaban over placebo in the extended treatment study population. The analysis in the PP population supported the conclusion of superiority in the ITT population.

A number of secondary outcomes were measured including all-cause mortality and vascular events, both of which favoured rivaroxaban. Net clinical benefit, which was a composite of the primary efficacy outcome and major bleeding, was statistically significant in favour of the

rivaroxaban group occurring in 2.0% (12/602) of patients and in 7.1% (42/594) of patients in the placebo group (HR, 0.28; 95% CI, 0.15 to 0.53; P<0.001).

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The primary safety outcome in the EINSTEIN-DVT study was clinically relevant bleeding, defined as the composite of major bleeding and clinically relevant non-major bleeding. Major bleeding was defined as clinically overt and associated with a fall in the haemoglobin level of >20g per litre or leading to transfusion of two or more units of red cells, or if it was retroperitoneal, intracranial, occurred in a critical site, or contributed to death. Clinically relevant non-major bleeding was defined as overt bleeding not meeting the 'major bleeding' criteria but associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of study treatment, or associated with any other discomfort such as pain or impairment of activities of daily life. One patient from the rivaroxaban treatment group died from gastrointestinal bleeding and five patients from the enoxaparin/VKA treatment group also had fatal bleeding events (2 gastrointestinal, 1 thoracic and 2 intracranial bleeds). The key results of the primary safety outcomes in the EINSTEIN-DVT study, stratified by intended treatment duration, remain commercial in confidence but showed no significant differences between treatment groups.

In the EINSTEIN-DVT study, the incidence of treatment-emergent adverse events (excluding bleeding and recurrent VTE) was comparable between treatment groups and was assessed as mild to moderate. The most common events were nasopharyngitis, headache, epistaxis, and pain in extremity. No clinically relevant differences between the study groups, in terms of serious adverse events, were reported. Vascular events occurred on treatment in 0.7% (12/1718) on rivaroxaban versus 0.8% (14/1711) on comparator (p=0.55).

The primary safety outcome in the EINSTEIN-Extension study was major bleeding, which occurred in 0.7% (4/598) of patients in the rivaroxaban group and no patients in the placebo group (p=0.11). Clinically relevant non-major bleeding was predominantly mucosal bleeding. The incidence of clinically relevant non-major bleeding was higher in the rivaroxaban group at 5.4% versus 1.2% in the placebo group. Most patients (81%) who suffered from clinically significant non-fatal bleeding resumed or continued study therapy. There were no fatal bleeds. In the EINSTEIN-Extension study, the incidence of treatment-emergent adverse events, excluding bleeding and recurrent VTE, was comparable between the rivaroxaban and placebo treatment groups and, overall, was lower than in the EINSTEIN-DVT study.

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Patients who have had an episode of VTE have a risk of recurrence of approximately 30% within 8 years but this risk decreases substantially with time and may vary depending on treatment received.[2] The Scottish Intercollegiate Guidelines Network (SIGN) guideline 122 recommends that treatment with a VKA should be continued for at least 3 months after a first episode of proximal limb DVT or PE. It states that uninterrupted, long term continuation of VKA

therapy after a first episode of VTE may be appropriate in some patients and should be based on individual assessment of risk factors.

The pivotal phase lll study, EINSTEIN-DVT demonstrated that rivaroxaban was non-inferior to a combination of enoxaparin plus VKA, comparable to the current standard of care in Scotland, in the treatment of DVT and the prevention of VTE events. The EINSTEIN-Extension study demonstrated clinical superiority of rivaroxaban over placebo when treatment was extended for a further 6 or 12 months. The net clinical benefit in both studies favoured rivaroxaban. It is noted in the Summary of Product Characteristics (SPC) for rivaroxaban that experience in this indication for more than 12 months is limited.

There are some limitations to the EINSTEIN-DVT study. The design was open label, though the primary outcome was an objective health outcome adjudicated by a committee blinded to treatment allocation which may have reduced the risk of bias. The dose of enoxaparin used in the studies differed from that licensed in the UK and as the study was event-driven (enrolment could be stopped when 88 events were reached), a significant number of patients discontinued prematurely as the result of termination of the study by the investigators. The percentage of time that patients treated with VKA were maintained in the therapeutic range (2.0 to 3.0) was on average 58%. This is slightly lower than reported in the literature, and for Scottish practice according to experts consulted by SMC for this submission.

Just under half of the patients treated in the EINSTEIN-Extension study were not recruited from either of the EINSTEIN-DVT or the ongoing unpublished EINSTEIN-PE studies but from routine clinical practice. Similarly to the EINSTEIN-DVT study, a significant number of patients discontinued prematurely as the result of termination of the study by the investigators.

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 SPC advises that rivaroxaban should be stopped at least 24 hours before an invasive procedure or surgical intervention, if possible, based on the clinical judgement of the physician.

Warfarin has a narrow therapeutic margin which requires monitoring to maintain an INR within the desired therapeutic range and is associated with many drug and dietary interactions which can make therapy difficult to control. Poor control can lead to an increased risk of thrombo-embolism in patients with a low INR, or an increased risk of bleeding and associated hospitalisation in patients with an INR above the therapeutic range. Rivaroxaban requires no therapeutic monitoring which would reduce the workload of services associated with warfarin monitoring and potentially reduce the risk of poor control to the patient.

The benefit to patients of treatment with rivaroxaban was supported by positive patient-reported satisfaction measures reported in both studies which included removing the need for frequent laboratory INR monitoring and consequent dose adjustment if INR is out with the target and dietary restrictions due to interactions when taking warfarin.

Summary of comparative health economic evidence

The case submitted by the company consisted of a cost-utility analysis comparing rivaroxaban with an alternative regimen starting with a low molecular weight heparin (LMWH) followed by warfarin. Three scenarios were included, varying the duration of rivaroxaban treatment from 3 months to 6 months and 12 months.

The evaluation was carried out using a Markov model that included health states for the main events associated this condition (DVT, PE, etc.) and states for bleeding (intracranial and other) while on treatment. The model ran over the lifetime of the patient cohort (maximum time of 40 years).

The LMWH with the highest market share in Scotland was stated to be enoxaparin, and this allowed data to be used from the main clinical trial programme. The hazard ratios for VTE and bleeding observed in the EINSTEIN-DVT trial were applied to baseline event rates to estimate the claimed added benefits of rivaroxaban in terms of events avoided. Each event type was associated with a utility and, where appropriate, an added mortality risk (over and above age/sex-specific norms); these were based on reviews of previously published studies.

Costs included the medicines, their administration (for example, 92% of enoxaparin patients were assumed to self-administer with the remainder requiring community nursing or transport to a clinic) and monitoring (for example INR monitoring while on warfarin – it was assumed patients required 24 tests per year). Costs were also included for the treatment of events when they occurred.

For the 12-month treatment duration, the main result was a predicted lifetime saving of £13 and gain of 0.021 quality adjusted life years (QALYs) from using rivaroxaban rather than LMWH/warfarin. Over 6 months, the predicted results were a saving of £105 and a QALY gain of 0.021. Over 3 months treatment, the comparable figures were a saving of £143 and a QALY gain of 0.024.

Sensitivity analysis suggested hazard ratios for key events and bleeding and assumptions about monitoring costs were most important.

The base case analysis included differences in clinical event rates that had not achieved statistical significance in the clinical trial. However, the company provided additional analyses with these differences excluded showing that in the 3 month case the saving was £107, in the 6 month case the saving was £61 and in the 12 month case the net cost was £28. The QALY gain was 0 in each case. Savings were greater with short-term rivaroxaban use as the company's model assumed patients would have 9 INR tests in the first three months irrespective of treatment duration, reducing to 5 per 3-month period thereafter. There was a concern that 5 INR tests per 3-month period after the initiation of treatment may be high and 3 or 4 tests per 3 month period would be more realistic. In the case of a 6-month treatment duration, the net savings fell from £61 to £36 for 4 tests every 3 months and £11 for 3 tests every 3 months.

Feedback from SMC clinical experts suggested that a majority of patients prescribed LMWH receive dalteparin rather than enoxaparin. The company's submission stated daily costs of

£9.77 for enoxaparin and £7.06 for dalteparin, a difference of £2.71. The treatment duration was 9.6 days so this would reduce the costs of the usual care arm of the economic model by £26.02. This would reduce the savings from the levels discussed above.

In summary, the case for using rivaroxaban with a planned treatment duration of up to 12 months appeared robust but the cost-effectiveness of use for a treatment duration longer than 12 months has not been made.

Summary of patient and public involvement

A Patient Interest Group Submission was received from AntiCoagulation Europe.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 122; Prevention and management of venous thromboembolism in December 2010. The guideline states:
Patients with suspected DVT should be treated with therapeutic doses of LMWH or fondaparinux until the diagnosis has been deemed very unlikely or confirmed. In confirmed DVT the heparin or fondaparinux should be continued until the INR is at least 2.0 on a vitamin K agonist, and for at least 5 days.

- After a first episode of proximal limb deep vein thrombosis or pulmonary embolism, 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 of risk factors, including:
- After recurrent VTE, long term treatment with a VKA is recommended but the nature of the recurrence (provoked or unprovoked), the elapsed time between episodes and risk of bleeding should be considered in reaching this decision.
- The use of long term VKA should be subjected to periodic review, to include anticoagulant control, bleeding episodes and altered risk of bleeding.

Guidelines on oral anticoagulation with warfarin – fourth edition. British Journal of Haematology 2011. Treatment for acute VTE:

- Warfarin should be started along with a parenteral anticoagulant, such as unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux which should be continued for at least 5 days and until the INR is >2 for at least 24 hours, whichever is the longer.
- Patients with proximal DVT should be treated for at least 3 months.

Patients with unprovoked proximal DVT or PE should be considered for long-term anticoagulation, taking into account information that may help predict risk of recurrence and risk of bleeding in the individual patient.

Additional information: comparators

Current comparators are LMWH (bemiparin, dalteparin, enoxaparin, tinzaparin) and fondaparinux for treatment of proximal deep vein thrombosis (DVT) followed by VKA (warfarin) for prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

Cost of relevant comparators

Drug	Dose Regimen	Cost (£) duration 7-10 days of treatment*	Cost (£), duration for 12 months of treatment
Rivaroxaban	**15mg twice daily for 21 days then 20mg once daily for up to 12 months**	**N/A**	**809**
Warfarin	Orally as determined by prothrombin time	N/A	13 to 39
Bemiparin	115 units per kg every 24 hours by subcutaneous injection	31 to 44	N/A
Enoxaparin	1.5mg/kg every 24 hours by subcutaneousinjection	56 to 80	N/A
Dalteparin	15,000 units once daily (69-82kg) by subcutaneous injection	59 to 85	N/A
Fondaparinux	7.5mg every 24 hours (50-100kg) by subcutaneous injection	82 to 117	N/A
Tinzaparin	175 units/kg once daily by subcutaneous injection	83 to 118	N/A

*Costs are based on doses calculated for a 70kg adult. N/A = not applicable.
Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 14th November 2011.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 3,711 patients. Based on an estimated uptake of 10% in year 1 and 50% in year 5, the impact on the medicines budget was estimated at £175K in year 1 and £926K in year 5. The annual medicine acquisition cost used in the budget impact calculations included the following assumptions:

- 13.9% of patients will receive 91 days of treatment
- 64.9% of patients will receive 183 days of treatment
- 21.2% of patients will receive 365 days of treatment.

Medicines costs savings would be in terms of warfarin and enoxaparin. The net medicines budget impact was estimated at £136K and £719K. Note that this does not include any savings on costs of INR monitoring or nursing visits to administer enoxaparin.

References

The undernoted references were supplied with the submission.

1. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H et al. Oral rivaroxaban for symptomatic venous thromboembolism. N England Journal of Medicine 2010; 363(26):2499-2510.
2. National Institute for Health and Clinical Excellence: Single Technology Appraisal. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. Available online: www.nice.org.uk

This assessment is based on data submitted by the applicant company up to and including 12 December 2011.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

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.