

rivaroxaban 10mg film-coated tablets (Xarelto®)

No. (519/08)

Bayer Schering Pharma

07 November 2008

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

In three large phase III studies in patients undergoing either total knee or total hip replacement surgery, rivaroxaban was superior to low molecular weight heparin in reducing the incidence of VTE and all cause mortality with patients while having a similar incidence of major bleeding events.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

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

Dosing information

Rivaroxaban 10mg orally once daily, starting 6 to 10 hours after surgery, provided that haemostasis has been established. For patients undergoing major hip surgery, a treatment duration of five weeks is recommended. For patients undergoing major knee surgery, a treatment duration of two weeks is recommended.

Product availability date

01 October 2008

Summary of evidence on comparative efficacy

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

Three large phase III randomised, double-blind, double-dummy studies have compared rivaroxaban with enoxaparin for the prevention of VTE after hip or knee replacement surgery.

In each study, patients were randomised to receive either rivaroxaban (10mg orally once daily, starting 6 to 8 hours after wound closure) plus placebo injections or enoxaparin (40mg subcutaneously (SC) starting 12 hours pre-operatively and restarted 6 to 8 hours after wound closure) plus placebo tablets. The duration of active study medication varied among studies: in the first study in patients undergoing total hip replacement (THR), both rivaroxaban and enoxaparin were continued for 35±4 days; in the second study, again in patients undergoing THR, rivaroxaban was continued for 35±4 days and enoxaparin for 12±2 days; and in the third study, in patients undergoing total knee replacement (TKR), both rivaroxaban and enoxaparin were continued for 12±2 days. All patients underwent mandatory bilateral venography on the day after the last dose of study medication. The primary endpoint in all studies was the composite of any deep vein thrombosis (DVT) (symptomatic or asymptomatic detected venography), non-fatal pulmonary embolism (PE), or death from any cause. The major secondary endpoint was major VTE defined as the composite of proximal DVT, non-fatal PE, or VTE-related death. All three studies were designed to test for non-inferiority which if demonstrated in the per-protocol population, resulted in a test for superiority being performed in the modified intention to treat (mITT) population (patients who had undergone surgery, taken a study drug, and undergone adequate assessment for VTE).

Rivaroxaban was superior to enoxaparin in all studies as assessed by the primary and major secondary endpoint. The key results are presented in the table below.

Table: Incidence of events for efficacy analyses in three phase III studies

	Study 1 (THR)		Study 2 (THR)		Study 3 (TKR)	
Number randomised	4,541		2,509		2,531	
Number in mITT population	3,153		1,733		1,702	
Treatment group	Riv 10mg 35±4 days (n=1595)	Eno 40mg 35±4 days (n=1558)	Riv 10mg 35±4 days (n=864)	Eno 40mg 12±2 days (n=869)	Riv 10mg 12±2 days (n=824)	Eno 40mg 12±2 days (n=878)
Primary endpoint*	18 (1.1%)	58 (3.7%)	17 (2.0%)	81 (9.3%)	79 (9.6%)	166 (19%)
Weighted absolute risk reduction (95% CI)	2.6% (1.5 to 3.7)		7.3% (5.2 to 9.4)		9.2% (5.9 to 12)	
p-value	<0.001		<0.0001		<0.001	
Relative risk reduction (95% CI)	70% (49 to 82)		79% (65 to 87)**		49% (35 to 61)	
p-value	<0.001		-		<0.001	
Components of primary endpoint: DVT	12 (0.8%)	53 (3.4%)	14 (1.6%)	71 (8.2%)	79 (9.6%)	160 (18%)
Non-fatal PE	4 (0.3%)	1 (0.1%)	1 (0.1%)	4 (0.5%)	0	4 (0.5%)
Death	4 (0.3%)	4 (0.3%)	2 (0.2%)	6 (0.7%)	0	2 (0.2%)
Secondary endpoint: Major VTE***	4/1686 (0.2%)	33/1678 (2.0%)	6/961 (0.6%)	49/962 (5.1%)	9/908 (1.0%)	24/925 (2.6%)
Weighted absolute risk reduction (95% CI)	1.7% (1.0 to 2.5)		4.5% (3.0 to 6.0%)		1.6% (0.4 to 2.8)	
p-value	<0.001		<0.0001		0.01	

THR = total hip replacement; TKR = total knee replacement; mITT= modified intention to treat; Riv = rivaroxaban; Eno = enoxaparin; CI = confidence intervals; DVT = deep vein thrombosis; PE = pulmonary embolism; VTE= venous thromboembolism

* primary endpoint was a composite of any DVT, non-fatal PE or death from any cause.

**unweighted relative risk reduction reported.

***Major VTE was a composite of proximal DVT, non-fatal PE or VTE-related death.

Summary of evidence on comparative safety

The main safety outcome, in all three studies, was the incidence of major bleeding defined as bleeding that was fatal, occurred in a critical organ (e.g. retroperitoneal, intracranial, intraocular, and intraspinal bleeding) or required re-operation or extrasurgical-site bleeding that was clinically overt and was associated with a fall in haemoglobin of ≥ 2 g/dl or that required transfusion of ≥ 2 units of whole blood or packed cells. The incidence of major bleeding across all studies was low (<0.1% to 0.6%) and did not differ significantly between rivaroxaban and enoxaparin. The incidences of on-treatment bleeding (4.8% to 6.6%) and non-major bleeding (4.3% to 6.5%) were also similar between the two treatments. No differences were reported between rivaroxaban and enoxaparin in the liver function test results. In the second study (described above), there was an excess of cardiovascular events after discontinuation of rivaroxaban; five patients (0.4%) including two cardiovascular deaths (although one occurred in a patient who had received placebo injection only) and no cardiovascular events after discontinuing enoxaparin.

Summary of clinical effectiveness issues

All three studies described above have demonstrated superior efficacy in terms of the primary endpoint with rivaroxaban compared to enoxaparin. This difference was mainly driven by a reduced rate of DVT (both symptomatic and asymptomatic) in the rivaroxaban group. In the second study described above, the relative efficacy of rivaroxaban and

enoxaparin is less clear due to the unequal treatment durations used (35±4 days for rivaroxaban and 12±2 days for enoxaparin).

Improved efficacy was achieved with no increase in the risk of major bleeding which was relatively low in both treatment groups compared to other studies. However the definition of major bleeding excluded patients with surgical site bleeding unless it led to re-operation or death. Non-major bleeding, which included surgical site bleeding, was similar in both groups. Factors such as age >75 years, extremes of weight, renal insufficiency and previous DVT are known to increase both the risk of VTE and bleeding. The number of patients included in the three studies with these risk factors was limited. The studies also excluded patients with a high risk of bleeding. This patient population is reflective of most clinical studies in this therapeutic area but it may not truly represent those treated in clinical practice.

In one of the studies, there was an excess of cardiovascular events after discontinuing rivaroxaban. The authors note that this could have been due to chance and that no trend was evident across all three studies; the numbers are too low to draw any firm conclusions. However this does raise concerns about rebound activation of coagulation and further research is warranted.

A relatively high number of patients were excluded from the efficacy analysis (6,588/9,581 (69%) randomised patients were available for mITT analysis) and this was mainly due to inadequate assessment of thromboembolism. All three studies did pre-empt that there would be non-evaluable patients and included a non-evaluable rate of 25% in the sample size calculation to account for this. However, the actual non-evaluable rate in all three studies was slightly higher than 25% (26% to 30%). Two of the studies recruited extra patients to compensate and maintain statistical power. In one study (the second described above), there was no increase in recruitment, which may have potentially limited the results. In all studies, sensitivity analyses were performed to confirm that missing data did not affect the power of the study or bias the outcome.

Like dabigatran, rivaroxaban offers the advantage of an oral preparation that does not require regular monitoring and dose adjustment or daily subcutaneous injections. When thromboprophylaxis is continued for up to five weeks this may be an advantage in the community setting. There are no direct comparative data between dabigatran and rivaroxaban so their relative efficacy and safety are unknown.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis, based on a decision tree for the acute phase of treatment and a Markov model up to five years. Rivaroxaban was compared to enoxaparin based on the clinical trial programme. Clinical trial data were used for the prophylaxis phase (up to 35 days for rivaroxaban), with longitudinal studies reported in the research literature used to estimate the rate at which asymptomatic DVTs became symptomatic, the recurrence rate for VTEs, and the incidence of post-thrombotic syndrome.

Utilities were taken from a literature search. Resource use was based on a variety of assumptions, including several taken from the economic evaluation included in the 2007 NICE Guidelines on venous thromboembolism in patients undergoing surgery.

Three ratios were presented in the comparison with enoxaparin as follows:

- In hip replacement patients, comparing 35 days of rivaroxaban with 35 days of enoxaparin: rivaroxaban was estimated to save £68 per patient and yield 0.0041 QALYs.

- In hip replacement patients where the comparator was 14 days of enoxaparin, the estimated saving was £25 per patient and the gain was 0.0194 QALYs.
- In knee replacement patients, based on 14 days of both drugs, the saving from rivaroxaban was £91 per patient and the QALY gain 0.0146 QALYs.

In each case rivaroxaban was therefore said to be dominant.

An informal indirect comparison was also provided with dabigatran and aspirin. The comparison with dabigatran suggested that the two agents offered comparable cost-effectiveness. Compared to aspirin, the submission stated cost per QALY was around £8,000 for hip replacement and dominant in knee replacement.

The results were robust across a series of sensitivity analyses; the only scenario considered where there was an important change was when long-term effects were not included. Given that there is accepted evidence that future risk is raised following symptomatic VTE, then there seems no reason to discount long-term effects in this way.

Strengths of the analysis included the range of comparators used. While the main focus was on enoxaparin, data from the Scottish Arthroplasty Study showed aspirin was the most common comparator.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In October 2002, the Scottish Intercollegiate Guidelines Network published guideline number 62, Prophylaxis of venous thromboembolism. Patients undergoing total hip or knee replacement or other elective major orthopaedic surgery should be considered for mechanical prophylaxis, aspirin, unfractionated heparin, low molecular weight heparin (LMWH) or warfarin. A consultation on a proposed review was published in 2005. Respondents agreed that some recommendations will change in the light of the new evidence and selected elements of the guideline should be reviewed.

In April 2007, the National Institute for Health and Clinical Excellence published Clinical Guideline number 46, Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. This guideline recommends mechanical prophylaxis in combination with either LMWH or fondaparinux.

Additional information: previous SMC advice

Following a full submission, SMC issued advice in November 2002: fondaparinux (Arixtra[®]) is appropriate for use in NHS Scotland. Compared with enoxaparin, fondaparinux has been shown to be associated with fewer thromboembolic events and a generally similar incidence of major bleeding. It is licensed for post-operative initiation, and this represents an advantage where regional anaesthesia and/or catheterisation are planned. It is predicted to be a cost-effective alternative to enoxaparin in a robust economic model. It may be considered for patients for whom antithrombotic therapy is appropriate, recognising that other antithrombotic agents and other approaches to prophylaxis may be more suitable in some situations.

Following a re-submission, SMC issued advice in July 2007: bemiparin (Zibor[®]) is not recommended for use within NHS Scotland for the prevention of thromboembolic events in patients undergoing orthopaedic surgery. Bemiparin was associated with a lower incidence of thromboembolic complications than unfractionated heparin and was non-inferior to another low molecular weight heparin. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Following a full submission, SMC issued advice in June 2008: dabigatran etexilate (Pradaxa[®]) is accepted for use within NHS Scotland for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. In two large phase III studies, in patients undergoing either total knee or total hip replacement surgery, dabigatran was non-inferior to low molecular weight heparin in the incidence of VTE and all cause mortality with patients having a similar incidence of major bleeding events. The two drugs have similar costs per dose but dabigatran has lower administration costs and is an oral therapy. This may facilitate longer duration of thromboprophylaxis, however the risks and benefits of this longer treatment duration need to be considered on a case-by-case basis.

Additional information: comparators

Vitamin K antagonists, LMWH, fondaparinux, mechanical compression hosiery and foot pumps. Aspirin is also used but is no longer recommended.

Cost of relevant comparators

Drug	Dose regimen	Cost per 10 days (£)	Cost per 28 to 35 days (£)
Rivaroxaban	10mg orally once daily	45	126 to 158
Fondaparinux	2.5 mg SC daily	67	186 to 233
Enoxaparin	40 mg SC daily	42	118 to 147
Dabigatran	110mg orally on day 1 then 220mg once daily	40	116 to 145
Tinzaparin	4500 IU SC daily*	36	100 to 125
Dalteparin	5000 IU SC daily	28	79 to 99
Warfarin	Orally determined by prothrombin time	<1	1 to 2
Aspirin	150mg orally once daily	<1	<1

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4/09/08. * or according to bodyweight. SC= subcutaneous.

Additional information: budget impact

The manufacturer estimated a net drug budget impact of £9k in year 1 (based on current practice being LMWH for 35 days) and £127k in year 5. However, if this were based on 13 days treatment with LMWH, as is likely to be the case with current practice in Scotland, the corresponding figures would be £22k and £307k.

There may be some savings on administration and monitoring, although it seems unlikely they would convert into realisable cash savings.

In estimating these figures, the manufacturer:

- used the Scottish Arthroplasty Project to estimate the number of operations in 2008 as being 6,916 hip replacements and 6,702 knee replacements. These were predicted to rise to 7,017 and 6,801 respectively by 2013.
- assumed 2.5% market share in year 1 rising to 35% by year 5. In turn this assumes an 85% share of the LMWH market and 15% of the aspirin market. Current prescribing seems to depend greatly on local purchasing and individual clinician preferences. This decentralised approach may make uptake somewhat slower than predicted by the manufacturer. However, the advantages of this type of medicine in terms of ease of administration by the patient may see this take a larger share of the aspirin market; as aspirin is the cheapest medicine at present this would put upward pressure on the budget impact estimate.

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.

This assessment is based on data submitted by the applicant company up to and including 10 October 2008.

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.

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

Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. New England Journal of Medicine 2008;358(26):2765-75.

Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. New England Journal of Medicine 2008;358:2776-86.

Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008;372:31-39

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