

Drug Utilisation Review

Prescriber Drug Utilisation Reviews consider new developments in therapeutics. The information is intended to help formulary decision makers in their evidence-based assessment of new therapeutic options.

Rivaroxaban (Xarelto[®])

An orally active direct Factor Xa inhibitor

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For over 60 years, despite many inherent problems with their use, heparin and vitamin K antagonists (VKAs), such as warfarin, have been the definition of anticoagulation therapy. VKAs are effective but challenging due to their varying dose requirements between patients, and their unpredictable anticoagulant response, leading to the need for constant monitoring of coagulation by International Normalised Ratio (INR) testing and frequent dose adjustments to achieve therapeutic levels of anticoagulation.⁸ Such monitoring is inconvenient to patients and costly to the healthcare system. These limitations have prompted the development of new oral anticoagulants targeting Factor Xa or thrombin.

Venous thromboembolism (VTE) is a significant problem: it is the third most common vascular disease and pulmonary embolism (PE) is one of the leading preventable causes of death.^{9,10} There are more than 400 000 deaths from VTE annually in the European Union and around 24 000–32 000 deaths annually in the UK, which may be an underestimate.^{11,12,13}

Deep vein thrombosis (DVT) is a common problem in hospitalised patients who do not receive thromboprophylaxis. Many DVTs are asymptomatic but some can result in PE, which

EXECUTIVE SUMMARY

Many patients require anticoagulation to either prevent or treat episodes of venous thromboembolism (VTE). VTE is a common problem in post surgical patients, particularly those undergoing major orthopaedic surgery.¹ Extended prophylaxis of up to four weeks is recommended for post total hip replacement (THR) or hip fracture with daily subcutaneous injections of low molecular weight heparin or fondaparinux.² Oral vitamin K antagonists (VKAs) are associated with a number of problems, including variable dose requirements that result in the need for frequent coagulation monitoring.

Rivaroxaban is a new orally active direct inhibitor of Factor Xa that has high bioavailability, rapid onset of action and predictable pharmacology.³ This enables fixed dosing with no necessary coagulation monitoring. It is superior to enoxaparin for thromboprophylaxis in patients post THR and total knee replacement (TKR) with no increase in bleeding risk and is well tolerated by patients.^{4–6} Also, it has not been shown to adversely affect liver function.^{4–6} A recommended commencement time of 6–10 hours post surgery⁷ enables same day admission of patients undergoing elective surgery and no interference with regional anaesthesia.

can be fatal.¹⁴ The risk of VTE in medically ill patients is also significant particularly among patients admitted with stroke, heart failure or myocardial infarction.¹⁵ However, patients undergoing orthopaedic surgery are at the greatest risk, with DVT occurring in more than 40% of patients who do not receive thromboprophylaxis.¹

Prophylaxis of VTE

Prophylactic anticoagulation post orthopaedic surgery is standard practice with a minimum recommended duration of 10 days post THR or TKR.¹⁶ The risk of VTE persists for many weeks after orthopaedic surgery¹⁷ and it has been shown that extended prophylaxis for five weeks post THR surgery reduces the incidence of symptomatic and asymptomatic VTE more effectively

than short-term prophylaxis.¹⁸ New DVTs have been shown to form after the discontinuation of short-term prophylaxis¹⁹ and several meta-analyses suggest that extended thromboprophylaxis after THR leads to a reduction in symptomatic VTE without an increase in the risk of major bleeding.^{16,20–22}

These findings led to a grade 1A recommendation for extended thromboprophylaxis after THR in the American College of Chest Physicians guidelines.¹⁶ Current NICE guidelines on the prevention of DVT in patients undergoing elective orthopaedic surgery or surgery for hip fracture recommends (in addition to mechanical compression stockings) prophylaxis with a low molecular weight heparin (LMWH) such as enoxaparin (Clexane) or the indirect

Characteristic	Consequence
Rapid onset of action	No need for overlap with parenteral anticoagulant
Predictable pharmacokinetics	Simplified dosing regimens
Predictable anticoagulant response	No need for coagulation monitoring and no food or drug interactions
Rapid offset of action	Simplified management in case of a haemorrhagic event or need for an intervention, and minimises need for an antidote
Availability of a safe antidote	Provides rapid reversal in case of a haemorrhagic event or need for an intervention
No off-target effects, such as hepatotoxicity	No need for monitoring
Reasonable cost	Improved access

Table 1. Characteristics of an ideal anticoagulant²³

Factor Xa inhibitor fondaparinux (Arixtra) for four weeks after surgery where the patient has one risk factor.¹ The current commonly used treatment options for extended prophylaxis are limited. LMWH and fondaparinux preparations reduce thromboembolic events but need to be administered subcutaneously. Oral VKAs such as warfarin are less effective than LMWH at reducing the risk of DVT; they have unpredictable pharmacological effects requiring continuous monitoring, as well as numerous drug and food interactions, thus are difficult to manage.^{1,7}

The ideal characteristics of an anticoagulant are listed in Table 1. Also there is evidence to suggest that the incidence of major bleeding is higher with VKAs than with LMWH preparations when given post THR.²⁴ Low-dose aspirin is associated with an increased risk of bleeding, is less effective than VKAs, and is not recommended in current guidelines.^{1,25,26}

The limitations of current anticoagulant therapies has led to the search for new treatment modalities. Dabigatran (Pradaxa), an oral direct thrombin inhibitor, was licensed in April 2008 for the prevention of VTE following elective total hip or knee replacement. In October 2008 rivaroxaban (Xarelto), an oral direct factor Xa inhibitor, was licensed for the same indication; this review focuses on rivaroxaban.

What is rivaroxaban?

Rivaroxaban is a new, orally active, once-daily direct inhibitor of Factor Xa that is in advanced clinical development. It has completed trials for the prevention of VTE in adults undergoing elective hip or knee replacements.

How does it work?

Rivaroxaban is a direct inhibitor of Factor Xa, which has emerged as a target for new anticoagulant therapies due to its pivotal role in the coagulation pathway (Figure 1).²⁷ Factor Xa initiates the conversion of prothrombin to thrombin and binds to Factor Va on the surface of activated platelets to form prothrombinase, which amplifies the conversion of prothrombin to thrombin. In turn, thrombin promotes Factor Xa generation by binding to Factor IX bound to platelets and has a positive feedback mechanism on the intrinsic pathway. By inhibiting Factor Xa clotting times are prolonged and the formation of thrombin is reduced, hence reducing the likelihood of thrombus formation.

Factor Xa may be inhibited indirectly (by catalysing its inhibition by antithrombin such as with a LMWH or fondaparinux) or directly (by binding to its active site and preventing interaction with its substrates). Direct Factor Xa inhibitors inhibit both free Factor Xa and platelet-bound Factor

Xa, and this dual property may theoretically confer an advantage over indirect Factor Xa inhibitors such as fondaparinux.²⁸

Administration

For VTE prevention rivaroxaban is administered as a fixed once-daily dose of 10mg. For patients undergoing elective hip or knee replacement surgery rivaroxaban is commenced 6–10 hours post-operatively and given once daily thereafter. It has a high oral bioavailability of 80–100%, with maximum plasma concentrations reached 2–4 hours after administration.^{3,7,29} It has a dual mode of elimination, with two-thirds being metabolised in the liver and one-third excreted unchanged by the kidneys. The elimination half-life is 7–11 hours and there is no accumulation with repeated dosing.³ It has a predictable anticoagulant response meaning that no coagulation monitoring is required.²⁹

Efficacy – the RECORD trials

Rivaroxaban has been compared with subcutaneous enoxaparin 40mg once daily in two phase III double-blind randomised trials (RECORD 1 and 2) in patients undergoing THR and in one phase III trial (RECORD 3) in patients undergoing TKR.^{4–6}

RECORD 1 compared rivaroxaban 10mg once daily initiated 6–8 hours post surgery with enoxaparin 40mg once daily initiated on the evening before surgery and both continued for 35 days. Patients then underwent bilateral venography. The primary efficacy outcome was the composite of DVT, non-fatal PE or death from any cause.

The main secondary efficacy outcome was major VTE and the primary safety outcome was major bleeding. Rivaroxaban was significantly more effective for extended thromboprophylaxis than enoxaparin, reducing the primary efficacy endpoint from 3.7% to 1.1% (Table 2). There were no significant differences in the incidence of major or non-major bleeding events.

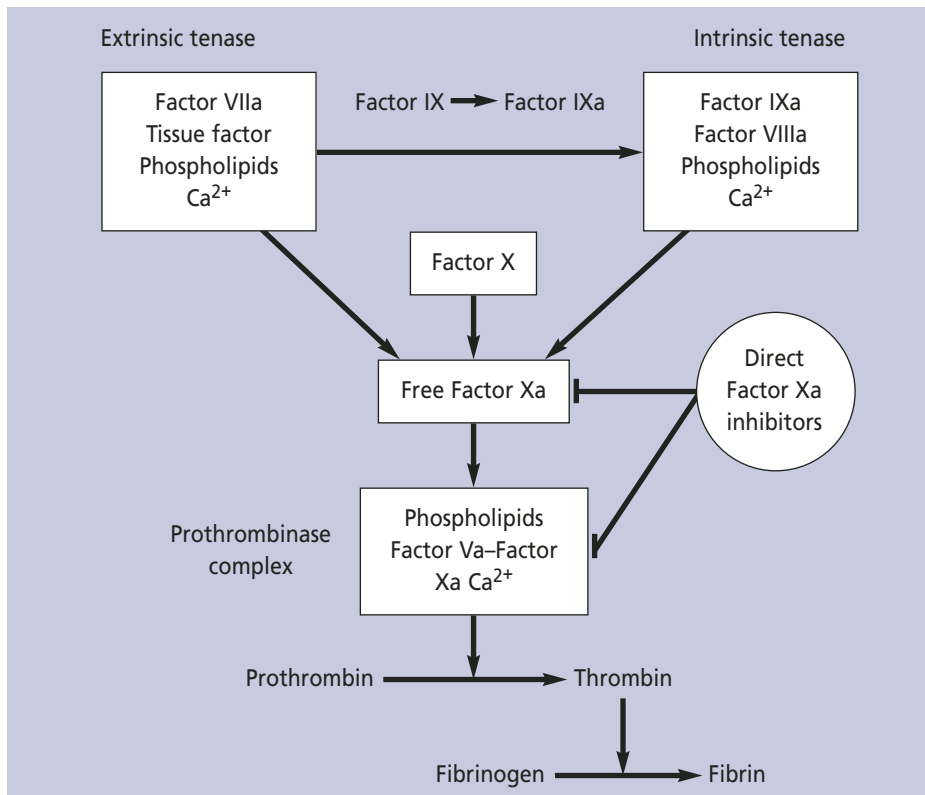


Figure 1. Simplified coagulation cascade and inhibition by Factor Xa inhibitors²⁷

RECORD 3 compared rivaroxaban 10mg daily with enoxaparin 40mg daily for 10–14 days post TKR in 2531 patients. The same endpoints were used as in RECORD 1. Rivaroxaban was superior to enoxaparin for thromboprophylaxis post TKR reducing the primary efficacy endpoint from 18.9% to 9.6%, again with a similar incidence of bleeding events.

RECORD 2 compared extended prophylaxis with rivaroxaban for 35 days to short-term prophylaxis with enoxaparin for 10–14 days. The primary efficacy outcome was the same as for RECORD 1 and results showed that extended-duration rivaroxaban treatment was significantly more effective than short-duration enoxaparin treatment, reducing the primary efficacy endpoint from 9.3% to 2.0% with comparable rates of bleeding.

Overall the RECORD trials show that oral rivaroxaban 10mg daily commenced 6–8 hours post surgery is significantly more effective than subcutaneous

enoxaparin in preventing VTE in patients undergoing elective THR or TKR.

Prophylaxis with rivaroxaban for five weeks reduced the risk of DVT, non-fatal PE and all cause mortality by 70% compared with five weeks use of enoxaparin, and by 79% compared with short-term use of enoxaparin.⁴ The relative risk reduction of major VTE post THR was 88%⁵ and post TKR was 62%.⁶

Dabigatran has a long half-life of 14–17 hours.³⁰ Studies show that dabigatran is as effective as subcutaneous enoxaparin in preventing VTE post THR and TKR with a comparable bleeding profile.^{31,32} To date, there have been no comparative trials of rivaroxaban and dabigatran.

Tolerability and safety

The RECORD trials demonstrate that rivaroxaban had a comparable safety profile to enoxaparin post-orthopaedic surgery.^{4–6} All three studies showed no significant differences between rivaroxaban and enoxaparin in the

incidence of major or other bleeding events (Table 2).

Unlike most other thromboprophylaxis studies the primary safety outcome of major bleeding in the RECORD studies excluded surgical-site bleeding unless it led to reoperation or death. As a result major bleeding rates are low but rates of non-major bleeding, which does include surgical-site bleeding, are similar in both the enoxaparin and rivaroxaban groups. In RECORD 1 there was one fatal bleed in the rivaroxaban group but this bleed occurred during surgery before the patient had received a dose of rivaroxaban. Haemorrhagic wound complications (the composite of excessive wound haematoma and reported surgical-site bleeding) occurred in similar numbers of patients in both groups. The adverse event profile of rivaroxaban was similar to enoxaparin with the most commonly reported side-effects being nausea, vomiting and constipation.^{4,6}

Due to the previous withdrawal of the oral thrombin inhibitor, ximelagatran, due to potential hepatic toxicity there were concerns about this possibility with other new oral anticoagulants.³³ In the RECORD trials there is no evidence of liver toxicity with rivaroxaban compared to enoxaparin.^{4–6} In RECORD 1 an on-treatment elevation of alanine aminotransferase level (a level more than three times the upper limit of the normal range) occurred in 2.0% of patients on rivaroxaban compared to 2.7% of patients on enoxaparin. All cases had resolved by the end of the follow-up period with the continuation of rivaroxaban. There were similar results for all the RECORD trials.

The incidence of cardiovascular events was low and similar in the RECORD 1–3 trials.^{4–6} In total (across all three trials) in the rivaroxaban group there were 12 cardiovascular events on rivaroxaban and 13 events occurred at least one day after discontinuation of the drug. In the enoxaparin group there were 16 cardiovascular events, with 8 events occurring after discontinuation.

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Trial	Operation type	N	Enoxaparin regime	Rivaroxaban regime	DVT, PE or death Events/RRR		Symptomatic VTE		Bleeding Major/ Non-major	
RECORD 1	THR	4541	40mg daily 35 days	10mg daily 35 days	3.7% vs 1.1%	70%	–	–	0.3% vs 0.1%	5.8% vs 5.8%
RECORD 2	THR	2509	40mg daily 10–14 days	10mg daily 31–39 days	9.3% vs 2.0%	79%	–	–	<0.1% vs <0.1%	6.5% vs 5.5%
RECORD 3	TKR	2531	40mg daily 10–14 days	10mg daily 10–14 days	18.9% vs 9.6%	49%	2.0% vs 0.7%	66%	0.6% vs 0.5%	4.3% vs 4.4%

Table 2. Summary of RECORD trials^{4–6}

Cost-effectiveness

There is evidence that most patients do not continue anticoagulant prophylaxis after discharge from hospital, and with hospital stays falling, even fewer patients receive even the minimum 10 days of prophylaxis recommended.^{16,34}

Oral administration of an effective drug is likely to increase the uptake of extended prophylaxis. The reduced need for coagulation monitoring, and oral administration of rivaroxaban would free-up staff time and other resources, and may offer a cost-effective alternative to commonly used treatment options.

Potential place in therapy

The licensed indication of rivaroxaban is for the prevention of VTE in adults undergoing elective hip or knee replacement surgery.

There are disadvantages with many of the commonly used treatment options. LMWHs and fondaparinux are only available as injectable preparations. This means that either patients or carers have to be taught to administer these or district/practice nurse time may be taken up with administration in the community. There is evidence that extended prophylaxis post surgery is underused post discharge because of the limitations of current therapies.³⁴

Due to the potential side-effect of heparin-induced thrombocytopenia, patients prescribed unfractionated heparin or LMWH, should receive regular monitoring of full blood counts.³⁵ Oral VKAs such as warfarin require frequent and regular blood test monitoring to ensure therapeutic levels of anticoagulation with a risk of over or under anticoagulation as INR levels fluctuate.⁸ Due to their slow and unpredictable onset of action an overlap period with LMWH is also required, which can complicate the discharge of patients.

Many patients are easily confused with the variable dose aspect of warfarin and there have been many errors relating to anticoagulation, resulting in the National Patient Safety Agency (NPSA) focus on anticoagulation and the recent safety alert that all health-care professionals should be adhering to.³⁶ This does add extra time and costs into the process of managing patients on warfarin, some of which will be avoided by the use of rivaroxaban.

Rivaroxaban seems to offer an acceptable balance of clinical effectiveness and safety. Thus, it may be a suitable choice for extended thromboprophylaxis offering easy administration and a reduced need for monitoring of coagulation. An oral preparation with a

rapid and predictable onset of action is ideal to enable smooth transfer of care from secondary to primary care.

Post-operative initiation of treatment enables same day admission of patients listed for surgery and allows for the use of regional anaesthesia.

Summary

Rivaroxaban is an orally active direct inhibitor of Factor Xa. It has a high bio-availability and achieves predictable, dose-dependant inhibition of Factor Xa. At a dose of 10mg once-daily commenced 6–10⁷ hours post-operatively it has been shown to be more effective than enoxaparin 40mg once-daily in the prevention of VTE in patients undergoing elective total hip or knee replacement surgery, reducing the risk of primary endpoints of DVT, non-fatal PE and death by 70% in patients undergoing THR, and by 49% in patients undergoing TKR. Bleeding events are comparable to enoxaparin and rivaroxaban is generally well tolerated with a similar adverse-event profile to enoxaparin.

In conclusion, rivaroxaban has demonstrated superior efficacy to enoxaparin with regard to elective total hip or knee replacement thromboprophylaxis, has a similar safety and side-effect profile and is available as an oral preparation.

References

1. National Collaborating Centre for Acute Care. Venous thromboembolism. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. April 2007 (www.nice.org.uk/nicemedia/pdf/VTEFullGuide.pdf).
2. National Institute for Health and Clinical Excellence. Venous thromboembolism. Clinical Guideline No. 46. April 2007 (www.nice.org.uk/nicemedia/pdf/CG046NICEguideline.pdf).
3. Kubitzka D, Becka M, Voith B, *et al*. Safety, pharmacodynamics and pharmacokinetics of single doses of BAY 59-7939, an oral, direct Factor Xa inhibitor. *Clin Pharmacol Ther* 2005;78:412–21.
4. Eriksson BI, Borris LC, Friedman RJ for the RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; 358:2765–75.
5. Kakkar AJ, Brenner B, Dahl OE for the RECORD2 Investigators. 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;372:31–9.
6. Lassen MR, Ageno W, Borris LC for the RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776–86.
7. Xarelto Summary of Product Characteristics. Bayer Schering Pharma. October 2008.
8. Ansell J. Long-term anticoagulation: the prospects for alternatives to warfarin. *Semin Vasc Surg* 2005;18:134–138.
9. Goldhaber SZ. Pulmonary embolism thrombolysis, a clarion call for international collaboration. *J Am Coll Cardiol* 1992;19:246–7.
10. Alikhan R, Peters F, Wilmott R, Cohen AT. Fatal pulmonary embolism in hospitalised patients: a necropsy review. *J Clin Pathol* 2004;57:1254–7.
11. Cohen AT, Agnelli G, Anderson FA, *et al*. Venous thromboembolism (VTE) in Europe: The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007;98:756–764.
12. The 5th annual congress of the European Federation of Internal Medicine. 2006; results of the VITAE (VTE Impact Assessment Group in Europe) Study.
13. Commons Health Select Committee. The prevention of venous thromboembolism in hospitalised patients. Second report of session 2004–2005. February 2005 (www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/99/99.pdf).
14. Gillespie W, Murray D, Gregg PJ, Warwick D. Risks and benefits of prophylaxis against venous thromboembolism in orthopaedic surgery. *J Bone Joint Surg Br* 2000;82-B:475–9.
15. Haas S. Venous thromboembolism in medical inpatients – the scope of the problem. *Semin Thromb Haemostasis* 2003;29(Suppl 1): 17–21.
16. Geerts WH, Pineo GF, Heit JA, *et al*. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:Suppl:338S–400S.
17. Bjonara BT, Gudmundsen TE, Dahl OE. Frequency and timing of clinical venous thromboembolism after major joint surgery. *J Bone Joint Surg Br* 2006;88B:386–91.
18. Bergqvist D, Benoni G, Bjorgell O, *et al*. Low molecular weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* 1996;335:696–700.
19. Planes A, Vochelle N, Darmon JY, *et al*. Risk of deep venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* 1996;348:224–8.
20. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001;358:9–15.
21. Hull RD, Pineo GF, Stein PD, *et al*. Extended out of hospital low molecular weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med* 2001;135:858–869.
22. O'Donnell M, Linkins LA, Kearon C, *et al*. Reduction of out-of-hospital symptomatic venous thromboembolism by extended thromboprophylaxis with low molecular weight heparin following elective hip arthroplasty: a systematic review. *Arch Intern Med* 2003; 163:1362–6.
23. Bates SM, Weitz JI. The status of new anticoagulants. *Brit J Haem* 2006;134:3–19.
24. Samama CM, Vray M, Barre J, *et al*. Extended venous thromboembolism prophylaxis after total hip replacement: a comparison of low molecular weight heparin with oral anticoagulant. *Arch Intern Med* 2002;162:2191–6.
25. Hovens MM, Snoep JD, Tamsma JT, *et al*. Aspirin in the prevention and treatment of venous thromboembolism. *J Thromb Haemost* 2006;4:1470–5.
26. Winter M, Keeling D, Sharpen F, *et al*. Procedures for the outpatient management of patients with deep venous thrombosis. *Clin Lab Haem* 2005;27:61–6.
27. Eriksson BI, Borris L, Dahl OE, *et al*. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost* 2006; 4:121–8.
28. Bates SM, Weitz JI. New anticoagulants: beyond heparin, low molecular weight heparin and warfarin. *Br J Clin Pharmacol* 2005; 144:1017–28.
29. Kubitzka D, Becka M, Wensing G, *et al*. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct factor Xa inhibitor – after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005; 61:873–80.
30. Eriksson BI, Dahl OE, Ahnfelt L, *et al*. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. *J. Thromb Haemostat* 2004; 2:1573–80.
31. Eriksson BI, Dahl OE, Rosencher N, *et al* for RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949–56.
32. Eriksson BI, Dahl OE, Rosencher N, *et al* for RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5:2178–85.
33. Eikelboom JW, Weitz JI. A replacement for warfarin: the search continues. *Circulation* 2007;116:131–3.
34. Tapson VF, Hyers TM, Waldo AL, *et al*. Antithrombotic therapy practices in US hospitals in an era of practice guidelines. *Arch Intern Med* 2005;165:1458–64.
35. The British Committee for Standards in Haematology. The management of heparin induced thrombocytopenia. *Br J Haematol* 2006;133:259–69.
36. National Patient Safety Agency. Risk assessment of anticoagulant therapy. January 2006. (www.npsa.nhs.uk/health/alerts; accessed 4.8.08).

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Xarelto® 10 mg film-coated tablets (rivaroxaban) Prescribing Information

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Xarelto® 10 mg film-coated tablets. Presentation: Light red, round, film-coated tablets containing 10 mg rivaroxaban.

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

Posology and method of administration: Dosage 10 mg rivaroxaban orally once daily with or without food; initial dose should be taken 6 to 10 hours after surgery provided haemostasis established.

Recommended treatment duration: Dependent on individual risk of patient for VTE determined by type of orthopaedic surgery: for major hip surgery 5 weeks; for major knee surgery 2 weeks. Renal & Hepatic impairment: see Warnings and precautions.

Patients above 65 years, Body weight & Gender: No dose adjustment.

Children and adolescents: Not recommended below 18 years of age. **Contraindications:** Hypersensitivity to active substance or any excipient; clinically significant active bleeding; hepatic disease associated with coagulopathy and clinically relevant bleeding risk; pregnancy and lactation.

Warnings and precautions: Treatment with rivaroxaban not recommended in patients: undergoing hip fracture surgery; receiving concomitant systemic treatment with strong CYP3A4 and P-gp inhibitors, i.e. azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole & posaconazole; fluconazole can be used with caution – see below) or HIV protease inhibitors (e.g. ritonavir); with severe renal impairment (creatinine clearance <15 ml/min); below 18 years of age. The following are at increased risk of bleeding - monitor carefully for bleeding complications after treatment initiation: patients with severe renal impairment (creatinine clearance 15 - 29 ml/min); patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; cirrhotic patients with moderate hepatic impairment (Child Pugh B) not associated with coagulopathy; patients treated concomitantly with medicinal products affecting haemostasis (e.g. NSAIDs, acetylsalicylic acid, platelet aggregation inhibitors, other antithrombotic agents) or with the moderate concurrent CYP3A4 and P-gp inhibitor fluconazole; patients with congenital or acquired

bleeding disorders; uncontrolled severe arterial hypertension; active ulcerative gastrointestinal disease; recent gastrointestinal ulcerations; vascular retinopathy; recent intracranial or intracerebral haemorrhage; intraspinal or intracerebral vascular abnormalities; recent brain, spinal or ophthalmological surgery. Strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) should be used with caution since they may reduce rivaroxaban plasma concentrations and hence efficacy. Take special care when neuraxial anaesthesia or spinal/epidural puncture is employed. Xarelto contains lactose. Interactions: see Warnings and precautions. **Pregnancy and lactation:** Contraindicated. **Effects on ability to drive and use machines:** No studies performed. Syncope and dizziness uncommon post operatively but may affect ability to drive and use machines. In these cases, patients should not drive or use machines. **Undesirable effects: Common** - increased GGT, increase in transaminases (incl. increased ALT, AST), anaemia (incl. respective laboratory parameter), nausea, post-procedural haemorrhage (incl. post-operative anaemia & wound haemorrhage) **Less frequent serious side effects** – increase in: lipase, amylase, blood bilirubin, LDH, alkaline phosphatase; tachycardia, thrombocythaemia, syncope, renal impairment (incl. increased blood creatinine/urea), any form of haemorrhage, hypersensitivity, abnormal hepatic function, hypotension. Prescribers should consult SmPC in relation to other side effects. **Legal Category:** POM. **Package Quantities/Basic NHS Costs:** 10 tablets: £45.00, 30 tablets: £135.00 and 100 tablets: £450.00 **MA Number(s):** EU/1/08/472/001-8 **Further information available from:** Bayer Schering Pharma, Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, U.K. Telephone: 01635 563000. **Date of preparation:** September 2008

® = Xarelto is a registered trademark of Bayer Schering Pharma AG.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Bayer Schering Pharma. Tel.: 01635 563500, Fax.: 01635 563703, Email: phdsguk@bayer.co.uk

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