

Rivaroxaban (Xarelto) for preventing venous thromboembolism after hip or knee replacement surgery

(riv-ah-ROCKS-ah-ban)

Summary

- Rivaroxaban is an oral anticoagulant and the first direct factor Xa inhibitor.
- Rivaroxaban has only been evaluated for use in preventing deep vein thrombosis and pulmonary embolism after elective total hip or total knee replacement surgery.
- Duration of therapy is 14 days after knee replacement or 35 days after hip replacement, and no longer.
- Dose adjustment, dose titration and monitoring of prothrombin time are not required.
- There are only small differences in efficacy and safety between rivaroxaban, low molecular weight heparins, fondaparinux (Arixtra) and dabigatran (Pradaxa).
- Advise patients about the risk of bleeding.
- Rivaroxaban is contraindicated in renal impairment (creatinine clearance < 15 mL/min), moderate and severe hepatic impairment with elevated INR, or with azole antifungals or HIV-protease inhibitors. These increase blood levels of rivaroxaban and therefore bleeding risk.

PBS listing

Authority required

Preventing venous thromboembolism in patients undergoing total hip or knee replacements.

The listing provides for a dispensed maximum quantity of 40 tablets for hip-surgery patients and 15 tablets for knee-surgery patients.¹

Reason for PBS listing

The PBAC recommended a listing for preventing venous thromboembolism after total hip or knee replacement surgery, after concluding that rivaroxaban has uncertain but acceptable cost-effectiveness compared with that of enoxaparin, the drug most often used for this purpose currently. The decision was based on the RECORD1, RECORD2 and RECORD3 clinical trials along with a cost-effectiveness model incorporating data from these trials.²

The committee observed that oral rivaroxaban is more effective, but possibly less safe, than subcutaneous enoxaparin for this indication. The clinical trials reported a small absolute difference in clinical efficacy between rivaroxaban and enoxaparin.

In the pharmacoeconomic models, the incremental gains in years of life and quality-adjusted life-years were minimal. In these models, the short-term RECORD results were extrapolated to longer term outcomes using data from additional publications of long term risk of recurrent deep vein thrombosis, pulmonary embolism and post-thrombotic syndrome plus quality of life data. These extrapolated, longer-term results accounted for most of the modelled difference in effectiveness between the two drugs.²

During the same meeting the PBAC deferred its consideration of dabigatran (Pradaxa) (another new oral therapy) for a similar indication, to give the applicant an opportunity to submit a comparison with rivaroxaban.³

Place in therapy

Rivaroxaban is an oral factor Xa-inhibitor anticoagulant. It is approved for short-term use to prevent deep vein thrombosis and pulmonary embolism after elective total hip or total knee replacement surgery. Standard duration of therapy is 14 days after knee replacement or 35 days after hip replacement. Efficacy and bleeding risk do not differ greatly from those of enoxaparin, the most common therapy currently. Rivaroxaban was superior

to enoxaparin in preventing a composite of symptomatic and asymptomatic venous thromboembolism but may cause more bleeding (see Safety issues). Trials for other indications have not yet been completed.

Rivaroxaban is an oral anticoagulant

Rivaroxaban is a direct, reversible competitive antagonist of factor Xa (activated factor X) that is active when taken orally. It is the first of this new class of drugs, exhibiting a dose-dependent anticoagulant effect.⁴ Rivaroxaban and dabigatran (Pradaxa) are the first oral anticoagulants to be introduced in Australia since warfarin. Dabigatran is from a different class of drugs (direct thrombin inhibitors) and is currently only available through hospitals or by private prescription.

Rivaroxaban prevents deep vein thrombosis and pulmonary embolism after elective total hip or total knee replacement surgery

Rivaroxaban is approved for short-term use after elective total hip or total knee replacement surgery on the basis of several large clinical trials (RECORD1-3).⁵⁻⁷ There is currently no evidence for using rivaroxaban for any other surgery-related or non-surgery-related indication, pending the completion of additional clinical trials.

The key trials measured the efficacy of rivaroxaban using a composite endpoint.[†] The bulk of the recorded events were cases of venographically detected venous thromboembolism. Fewer cases of venous thromboembolism were detected in participants taking rivaroxaban than were detected in those taking enoxaparin.⁵⁻⁷ While only a fraction of venographically detected cases are clinically significant, the rate correlates with the rate of symptomatic deep vein thrombosis and pulmonary embolism.⁸

Graduated compression stockings are recommended as an adjunct to anticoagulant therapy

Guidelines recommend that surgery patients receive graduated compression/antiembolism stockings from the time of admission, to further reduce the risk of venous

thromboembolism. Patients should continue to wear their stockings after discharge until they return to their usual level of mobility.⁸

Patients using compression stockings should be shown by hospital staff how to wear them correctly. In some cases, intermittent pneumatic compression or foot impulse devices may be used as alternatives to stockings while patients are in hospital.

Participants in the RECORD trials were not permitted to use intermittent pneumatic compression devices, and use of compression stockings was not reported.⁵⁻⁷

Rivaroxaban, low molecular weight heparins, fondaparinux and dabigatran differ only slightly in effectiveness

Evidence-based guidelines from the UK National Institute for Health and Clinical Excellence (NICE) reported broadly similar efficacy for dabigatran, low molecular weight heparins, fondaparinux, or rivaroxaban after elective total hip or total knee replacements.⁸⁻¹⁰ NICE recommended that neither aspirin nor warfarin be used for this indication, because they appear to be less effective than the other agents for preventing venous thromboembolism after elective surgery.⁸

Results from the RECORD1 trial in hip surgery and the RECORD3 trial in knee surgery indicate that the benefits of rivaroxaban and enoxaparin are very similar. While rivaroxaban was superior according to the primary, composite endpoint^{6,7}, the differences in the rates of clinically significant events (symptomatic venous thromboembolism or death from any cause) were small (Table 1).

There have been no clinical trials directly comparing rivaroxaban with dabigatran or fondaparinux for venous thromboembolism prevention. The UK National Institute for Health and Clinical Excellence committee made their assessment on the basis of indirect comparisons and cost-effectiveness modelling.^{9,10}

Table 1. Incidence of symptomatic venous thromboembolism or death from all causes in key trials.¹¹

	Rivaroxaban % with events	Enoxaparin % with events
RECORD1 (hip)	0.5 (10/2209)	0.7 (15/2224)
RECORD3 (knee)	0.7 (8/1220)	2.1 (26/1239)

* Australian approval was based on data from the RECORD1-3 trials. RECORD4 used a dosing regimen of enoxaparin that is not approved in Australia, but safety data from the trial was used in some subsequent pooled analyses.

† Composite endpoint of venographically detected thromboembolism, symptomatic deep vein thrombosis or pulmonary embolism, and death from any cause.

Standard duration of therapy is 14 days after knee replacement or 35 days after hip replacement

Trials administered rivaroxaban for 14 days after knee replacement surgery or for 35 days after hip replacement surgery, durations consistent with current recommendations for other anticoagulants. A meta-analysis of hip replacement surgery data found that extending the duration of prophylaxis with heparin from 4–17 days to 27–42 days decreased the rate of symptomatic venous thromboembolism from 4.3% to 1.4% (odds ratio 0.33, 95% confidence interval 0.19 to 0.56). The meta-analysis did not demonstrate a corresponding benefit of extended prophylaxis in knee replacement surgery.¹²

Safety issues

As with other drugs used for this indication, managing the risk of bleeding is a primary concern with rivaroxaban. Bleeding risk is dose dependent and anything greater than a twofold increase in rivaroxaban exposure is considered clinically significant. Drug–drug interactions (e.g. with HIV-protease inhibitors or azole antifungals) and drug–disease interactions may increase rivaroxaban concentrations. The incidence of common adverse effects is similar to that for enoxaparin; there are insufficient data to characterise rare or long-term adverse effects.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au) [then click 'Adverse reaction to a medicine' at left] or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Average risk of serious bleeding in trials was approximately 2%

People with risk factors for bleeding constituting a contraindication for enoxaparin were excluded from trials for postsurgical prevention of venous thromboembolism. A pooled analysis of safety data for the first 2 weeks of treatment found a rate of 1.8% for major bleeds and surgical-site bleeds with rivaroxaban, compared with 1.4% with enoxaparin. Gastrointestinal haemorrhage was the only form of overt extrasurgical bleeding. There was 1 fatal bleed among 6183 people exposed to rivaroxaban across the 4 RECORD trials, and no fatal bleeds among 6200 people exposed to enoxaparin.¹¹

Rivaroxaban is contraindicated for patients with clinically significant active bleeding, spontaneous impairment of haemostasis, or lesions that may spontaneously bleed significantly (e.g. stroke within the previous 6 months). Other patients with bleeding risk factors or who may experience an increased anticoagulant effect should be counselled about the possibility of serious bleeding and to seek prompt medical attention if they exhibit signs.¹³

Combining rivaroxaban with other anticoagulants is not recommended.¹³

Take care combining with antiplatelets or NSAIDs

Aspirin, clopidogrel or NSAIDs prolong bleeding time when combined with rivaroxaban. A subset of patients receiving the combination of clopidogrel and rivaroxaban experienced a greater than additive effect.^{11,13} For the cases when a patient requiring ongoing antiplatelet therapy undergoes elective surgery, an expert should assess the risks and potential benefits of venous thromboembolism prophylaxis and select the appropriate regimen.

Renal or hepatic impairment can increase bleeding risk

Rivaroxaban is eliminated by active renal excretion and hepatic oxidation (by CYP3A4 and CYP2J2). Rivaroxaban is contraindicated in severe renal impairment (creatinine clearance < 15 mL/min) because the exposure to rivaroxaban is increased by more than twofold. Rivaroxaban is also contraindicated for people with moderate or severe hepatic insufficiency when coagulopathy is also present (i.e. abnormally elevated International Normalised Ratio [INR]).¹³

Rivaroxaban may be prescribed with caution for people with creatinine clearance of 15–29 mL/min. Renal impairment in the range 30–49 mL/min may contribute to a clinically relevant increased bleeding risk when there are other factors that increase rivaroxaban levels (e.g. drug interactions).¹³

Strong inhibitors of CYP3A4 or P-glycoprotein increase rivaroxaban levels

Rivaroxaban is contraindicated for people receiving azole antifungals (except fluconazole) or HIV-protease inhibitors. Most of these drugs are strong inhibitors of CYP3A4 and also inhibit P-glycoprotein. Less potent inhibitors or drugs inhibiting only one of these two

pathways (e.g. amiodarone, cyclosporin, clarithromycin, diltiazem, dipyridamole, erythromycin, fluconazole, tamoxifen or verapamil) are not contraindicated but may contribute to a clinically relevant increased bleeding risk when there are other factors that increase rivaroxaban levels.^{13–15}

There is no antidote to rivaroxaban-induced bleeding

Treat bleeding symptomatically and arrange hospital management if warranted. The product information lists possible emergency procoagulant treatments, but their clinical value is uncertain. Stopping or delaying the next dose may be sufficient to manage minor bleeding, given that rivaroxaban has a mean terminal elimination half-life of 5–13 hours and inhibits factor Xa reversibly.¹³

An increased risk of rare adverse events has not been ruled out

There were few serious adverse events in clinical trials. Further data are required to characterise the incidence of hepatotoxicity, renal injury, thrombotic cardiovascular events, pancreatitis or other rare or delayed adverse events.

There were rare cases of hepatic adverse events in registration trials but too few to judge if rivaroxaban was the cause. Analysis of the RECORD1–4 safety database found similar numbers of drug-related liver injury cases with rivaroxaban and enoxaparin.¹¹

There was no significant difference in the number of cardiovascular events for rivaroxaban and enoxaparin. However, too few events occurred in the RECORD trials to rule out the possibility that there is a small increase in event rate after discontinuing rivaroxaban (i.e. a rebound effect).^{11,16}

Dosing issues

The dose is 10 mg once daily, with or without food. Initiate 6–10 hours after wound closure and haemostasis. Continue rivaroxaban for 14 days after knee surgery or 35 days after hip surgery. Do not exceed the dose of 10 mg once daily or the standard duration.¹³

Dose adjustment, dose titration and monitoring of prothrombin time are not required

Rivaroxaban 10 mg once daily rapidly produces an anticoagulant effect in the correct range to prevent venous thromboembolism, without dose titration or adjustment (e.g. for body weight). Monitoring is not required. Even though prothrombin time correlates closely with inhibition of factor Xa, there are no standards to relate prothrombin times to therapeutic or adverse effects, and the INR cannot be used to characterise rivaroxaban's effect.¹³

Some patients will require a GP prescription soon after discharge

Some public hospital patients will be advised to see their GP soon after discharge for a rivaroxaban prescription to cover the remaining duration of therapy.* The average time between surgery and discharge in Australia is 9 days for hip replacements and 7 days for knee replacements.¹⁷ Hospitals that do not provide a PBS prescription on discharge may dispense a small supply of tablets to cover the period until the patient can see a GP.

Prescribers will need to take into account the number of tablets the hospital has already provided when selecting the pack size and giving instructions to the patient. As pack sizes will not always match the recommended treatment duration, there may be tablets left over.

* Patients attending public hospitals in ACT, NSW, Tasmania and some hospitals in SA that have not yet implemented PBS prescribing.

Information for patients

Advise patients and carers:

- to take 1 tablet at about the same time each day, with or without food
- that if they miss a dose, to take a tablet immediately and continue the following day with 1 tablet at the same time as usual. Do not take a double dose to make up for a forgotten tablet
- when switching from tablets dispensed by the hospital to tablets prescribed by a GP, to continue taking 1 tablet every 24 hours
- to continue to wear any compression stockings supplied by the hospital until they return to their usual level of mobility, to minimise the risk of developing venous thromboembolism
- to consult a doctor before using non-prescription medicines containing aspirin or nonsteroidal anti-inflammatory drugs. Paracetamol can be used for minor ailments
- to consult a doctor if they have any prolonged or excessive bleeding
- to consult a doctor if symptoms suggesting internal bleeding appear after leaving hospital, such as unexplained bruising, red urine or black faeces
- to tell their doctor, dentist or pharmacist they are taking rivaroxaban at each consultation.¹⁸

Discuss the Xarelto consumer medicine information (CMI) leaflet with the patient.

References

1. Australian Government Department of Health and Ageing. March 2009 PBAC outcomes: positive recommendations. <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacrec-mar09-positive> (accessed 27 April 2009).
2. Australian Government Department of Health and Ageing. Public summary document for rivaroxaban, tablet, 10 milligrams, Xarelto March 2009. <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-rivaroxaban-march09> (accessed 14 July 2009).
3. Australian Government Department of Health and Ageing. March 2009 PBAC outcomes: deferrals. <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacrec-mar09-deferrals> (accessed 27 April 2009).
4. Gulseth MP, et al. *Am J Health Syst Pharm* 2008;65:1520–9.
5. Eriksson BI, et al. *N Engl J Med* 2008;358:2765–75.
6. Kakkar AK, et al. *Lancet* 2008;372:31–9.
7. Lassen MR, et al. *N Engl J Med* 2008;358:2776–86.
8. National Institute for Health and Clinical Excellence. Venous thromboembolism. Reducing the risk in surgical inpatients. NICE clinical guideline 46. 2007. <http://www.nice.org.uk/guidance/CG46/Guidance/pdf/English> (accessed 4 May 2009).
9. National Institute for Health and Clinical Excellence. TA157 Venous thromboembolism — dabigatran: guidance. 2008. <http://www.nice.org.uk/guidance/TA157/Guidance/pdf/English> (accessed 4 May 2009).
10. National Institute for Health and Clinical Excellence. TA170 Venous thromboembolism — rivaroxaban: guidance. 2009. <http://www.nice.org.uk/guidance/TA170/Guidance/pdf/English> (accessed 4 May 2009).
11. US Food and Drug Administration and Johnson & Johnson Pharmaceutical Research & Development LLC. Briefing Information for the March 19, 2009 Cardiovascular and Renal Drugs Advisory Committee. 2009. <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm138368.htm> (accessed 22 June 2009).
12. Eikelboom JW, et al. *Lancet* 2001;358:9–15.
13. Bayer Schering Pharma. Xarelto product information. 20 November 2008.
14. Australian Medicines Handbook, 2009.
15. DuBuske LM. *Drug Saf* 2005;28:789–801.
16. US Food and Drug Administration. Transcript for the March 19, 2009 Cardiovascular and Renal Drugs Advisory Committee. 2009. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM143863.pdf> (accessed 22 June 2009).
17. Australian Government Department of Health and Ageing. National Hospital Cost Data Collection. Public Sector Estimated Cost Weights Round 10 AR-DRG v5.0. 2006. [http://www.health.gov.au/internet/main/publishing.nsf/Content/1044AF873B77B7B4CA25739E007B03BB/\\$File/Public%20Sector%20Estm.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/1044AF873B77B7B4CA25739E007B03BB/$File/Public%20Sector%20Estm.pdf) (accessed 30 June 2009).
18. Bayer Schering Pharma. Xarelto consumer medicine information. November 2008.

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