

Dabigatran (Pradaxa) for preventing venous thromboembolism after hip or knee replacement surgery

(da-BIG-a-tran)

Summary

- Dabigatran is a direct thrombin inhibitor oral anticoagulant.
- Dabigatran is approved for short-term use after hip or knee replacement surgery.
- The recommended duration of therapy is 10 days after knee replacement and 28–35 days after hip replacement.
- Dabigatran appears to have similar efficacy to that of enoxaparin 40 mg once daily after knee or hip replacement, although a clinically important difference between the two drugs cannot be completely ruled out.
- Dabigatran, rivaroxaban and fondaparinux all appear to have broadly similar efficacy although this has not been tested in head-to-head trials.
- Bleeding rates with dabigatran are similar to those with enoxaparin.
- Advise patients about the risk of bleeding.
- Dabigatran is contraindicated in hepatic impairment that is expected to have an impact on survival or in severe renal impairment (creatinine clearance < 30 mL/min).

PBS listing

Authority required

Preventing venous thromboembolism (VTE) in people undergoing total hip or total knee replacements.

The listing provides for a maximum dispensed quantity of 60 capsules for hip replacement and 20 capsules for knee replacement.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing dabigatran on a cost-minimisation basis — that is, similar efficacy and cost — compared with enoxaparin. The decision was based on 2 non-inferiority trials — 1 in people undergoing hip replacement¹ and another in people undergoing knee replacement.²

Place in therapy

Dabigatran is an oral direct thrombin inhibitor approved for short-term use to prevent deep vein thrombosis (DVT) and pulmonary embolism (PE) after hip or knee replacement surgery. The recommended duration of therapy is 10 days after knee replacement³ and 28–35 days after hip replacement.^{3,4} Dabigatran appears to be similar in efficacy to enoxaparin, a low molecular weight heparin (LMWH) that is currently the most commonly prescribed therapy. Dabigatran, rivaroxaban (an oral factor Xa-inhibitor anticoagulant) and fondaparinux appear to be similarly efficacious although this has not been tested in head-to-head trials.

Australian guidelines recommend LMWH, fondaparinux, dabigatran or rivaroxaban for thromboprophylaxis after total hip or knee replacement.⁴ These agents differ in their interactions and precautions in special populations (such as hepatic or renal impairment). These factors,

in addition to hospital availability, patient preference and patient ability to swallow oral medications after surgery, will guide the choice of drug for many people. However, dabigatran and rivaroxaban should be used more cautiously, as they are new drugs and there are insufficient data to characterise potential rare or long-term adverse effects.⁴

Dabigatran is an oral anticoagulant

The prodrug dabigatran etexilate is converted to dabigatran, a direct thrombin inhibitor, in the body.

Dabigatran is approved only for short-term use after hip or knee replacement surgery. There are trials evaluating dabigatran for the treatment of acute VTE and for stroke prevention in atrial fibrillation but these indications are not approved in Australia or overseas.^{5,6}

Dabigatran appears to have similar efficacy to that of enoxaparin 40 mg once daily after knee or hip replacement

Dabigatran 150 mg and 220 mg once daily have been compared with enoxaparin 40 mg once daily after hip or knee replacement.^{1,2} At these doses, dabigatran was no worse than enoxaparin on a primary composite endpoint of venographically detected thromboembolism*, symptomatic DVT or PE, and death from any cause (Table 1).

The margins used to test for non-inferiority in both trials were relatively large. In the trials the number of primary events in the dabigatran arm could be up to 7.7% higher than in the enoxaparin arm of the hip replacement trial and 9.2% higher than in the enoxaparin arm of the knee replacement trial before dabigatran was considered to be inferior to enoxaparin.^{1,2} However, the PBAC noted in a previous submission that a 4–5% increase in the number of primary events could be clinically important.⁷ The number of primary events for the 220 mg dabigatran dose fell within this range for both the hip replacement and the knee replacement trial. However, the trials were not designed to test whether there is a difference of this magnitude (i.e. 4–5%), so a clinically important difference cannot be completely ruled out.

* While venographically detected thromboembolism is an accepted surrogate outcome in VTE trials, not all cases are clinically significant.

Most of the primary events in the trials were venographically detected thromboemboli. A secondary endpoint, which may better reflect clinical relevant events, was major VTE (proximal DVT or non-fatal PE) or VTE-related death. There were similar numbers of symptomatic DVT, PE or VTE-related deaths in both arms of the hip and knee replacement trials (Table 1).

In another trial that tested dabigatran against the North American regimen of enoxaparin 30 mg twice daily, dabigatran was less efficacious than enoxaparin after knee replacement.⁸ However, this enoxaparin dosage is more intensive than the 40 mg once daily recommended by Australian guidelines.^{9,10}

Use graduated compression stockings as well as antithrombotic therapy

To further reduce the risk of VTE, surgery patients should wear graduated compression stockings from the time of admission until they return to their usual level of mobility.^{4,11}

Participants in the dabigatran trials were permitted to use compression stockings.^{1,2,8,12} However, information on how commonly stockings were used was not provided. Use of intermittent compression devices was not permitted.

Table 1: Proportion of people who had a primary or secondary outcome in trials of dabigatran in hip and knee replacement

	Dabigatran		Enoxaparin
	150 mg	220 mg	40 mg
Hip replacement¹ (n = 2651)*			
Primary outcome [†]	8.6%	6.0%	6.7%
Secondary outcome [‡]	4.3%	3.1%	3.9%
Knee replacement² (n = 2101)*			
Primary outcome [†]	40.5%	36.4%	37.7%
Secondary outcome [‡]	3.8%	2.6%	3.5%

* Between 23% and 30% of randomised patients did not have an evaluable venogram. Therefore, n values refer to the number of patients with an evaluable venogram, not the number initially randomised.

[†] Venographically detected or symptomatic DVT/PE or death from any cause.

[‡] Symptomatic DVT/PE or VTE-related death.

Dabigatran, rivaroxaban, low molecular weight heparins and fondaparinux 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, rivaroxaban, LMWHs and fondaparinux after hip or knee replacement.^{11,13,14} Aspirin, warfarin and unfractionated heparin are not recommended for these indications, as they appear to be less effective than the other agents for preventing VTE after elective surgery.^{4,11}

No clinical trials have directly compared dabigatran with rivaroxaban or fondaparinux for VTE prevention. NICE made their assessment on the basis of indirect comparisons and cost-effectiveness modelling.

Safety issues

Bleeding rates with dabigatran are similar to those with enoxaparin. The incidence of common adverse effects is also similar, although wound secretion is significantly more common among people taking dabigatran.³ There are insufficient data to characterise rare or long-term adverse effects.

People at high risk of bleeding were excluded from trials. Do not use dabigatran in these people (e.g. those with severe uncontrolled hypertension, thrombocytopenia or bleeding disorders), in people with severe renal impairment or in those taking strong P-glycoprotein inhibitors.^{3,10}

Combining dabigatran with other anticoagulants or antiplatelets is not recommended.³

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Rate of major bleeding is similar to that with enoxaparin

People at high risk of bleeding were excluded from trials. Major bleeding rates for both doses of dabigatran were similar to those for 40 mg enoxaparin in either hip or knee replacement surgery (Table 2).

There is no antidote to dabigatran-induced bleeding.³

Stop dabigatran and treat bleeding symptomatically. Arrange hospital management if necessary.

Take care combining with antiplatelet drugs or NSAIDs

Monitor people for signs of bleeding if they are taking dabigatran in conjunction with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).^{3,10} Combining dabigatran with other anticoagulants or antiplatelets, including clopidogrel, is not recommended.³

Trial participants were allowed to take low-dose aspirin (< 160 mg) or cyclo-oxygenase-II (COX-2) selective NSAIDs.^{1,2,12} However, there is no published information on how commonly these medicines were taken or on bleeding rates associated with their use.

Combining with P-glycoprotein inhibitors can increase bleeding risk

P-glycoprotein inhibitors may increase plasma concentrations of dabigatran and consequently increase bleeding risk. The pro-drug dabigatran etexilate (but not dabigatran) is a substrate of P-glycoprotein. Use the 150 mg dose of dabigatran if a person is taking amiodarone. Use dabigatran cautiously and monitor for signs and symptoms of bleeding if a person is taking other P-glycoprotein inhibitors (e.g. cyclosporin, clarithromycin, itraconazole, ketoconazole, ritonavir, saquinavir, tacrolimus or verapamil).³

Verapamil may increase the concentration of dabigatran if taken at the same time of day, increasing the risk of bleeding. If possible, avoid this combination. The manufacturer advises that verapamil should not be started during dabigatran therapy.³ If dabigatran is added to verapamil therapy, it must be given 2 hours before verapamil to avoid this interaction.^{3,10}

Table 2: Major bleeding rates*

	n	Dabigatran		Enoxaparin
		150mg	220mg	40mg
Hip replacement ¹	3463	1.3%	2.0%	1.6%
Knee replacement ²	1976	1.3%	1.5%	1.3%

* Major bleeding events were defined as those that resulted in: a reduction in haemoglobin levels of at least 20 g/L; transfusion of at least 2 units of blood; fatal retroperitoneal, intracranial, intraocular or intraspinal bleeding; and bleeding warranting treatment cessation or reoperation.

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

Use dabigatran and rivaroxaban (the other new oral anticoagulant) cautiously, as there is a lack of postmarketing surveillance data.⁴

People with liver disease or elevated liver enzyme levels (> 2 times the upper limit of normal) at baseline were excluded from trials of dabigatran. A drug in the same class as dabigatran, ximelagatran, was withdrawn after reports of severe liver damage.^{15,16} However, rates of elevated liver enzyme levels with dabigatran were:

- lower than that reported in people taking enoxaparin after hip replacement¹
- similar to those reported in people taking enoxaparin after knee replacement²
- similar to those reported in people taking warfarin for acute VTE or atrial fibrillation.^{5,6}

Dosing issues

Dabigatran should be taken for 10 days after knee replacement and for 28–35 days after hip replacement.

Treatment is started with a single capsule (75 mg or 110 mg) 1–4 hours after surgery. The dose is then increased to 2 capsules taken together once a day.³

Most discharged patients will be taking 220 mg dabigatran (2 × 110 mg capsules) once daily.³ However, people with moderate renal impairment (creatinine clearance 30–50 mL/min) will be taking a 150 mg dose (2 × 75 mg capsules).³

In pharmacokinetic studies, people with moderate renal impairment had an exposure to dabigatran that was almost 3 times higher than in people without renal insufficiency. This is likely to increase the risk of bleeding.³ Only about 5% of people in the

randomised trials had moderate renal impairment⁷ so it is not known whether using the 150 mg dose instead of the 220 mg dose reduces this increased bleeding risk. Until more data become available an alternative anticoagulant, such as enoxaparin, may be a better option in moderate renal impairment.

Some patients will require a prescription soon after hospital discharge

Some hospital patients will be advised to obtain a prescription from their general practitioner after discharge to cover the remaining duration of dabigatran therapy. Prescribers will need to take into account the number of capsules the hospital has already provided and the intended duration of therapy when selecting the pack size and giving instructions to the patient.

The listing provides for a maximum dispensed quantity of 60 capsules for hip replacement and 20 capsules for knee replacement.

Two pack sizes are available for people undergoing hip replacement — a 60-capsule pack and a 10-capsule pack. People undergoing hip replacement should be treated for a maximum of 35 days.⁴ The 60-capsule pack (sufficient for 30 days' treatment) should not be broken but the 10-capsule pack may be broken to allow the exact number of capsules for the remaining duration of treatment to be dispensed.

Only the 10-capsule pack is listed for people undergoing knee replacement. People undergoing knee replacement should be treated for 10 days, so they are likely to need more than 1 pack to ensure this. The pack may be broken to allow the exact number of capsules to be dispensed.

If the exact number of capsules is not dispensed there may be surplus capsules, as pack sizes will not always match the recommended treatment duration. Advise patients not to take capsules for longer than the recommended duration of treatment.

Information for patients

Advise patients and carers:

- to consult a doctor before using non-prescription medicines containing aspirin or NSAIDs. Paracetamol can be used for minor ailments
- to consult a doctor if they have any prolonged or excessive bleeding or signs of internal bleeding, such as unexplained bruising, blood in the urine or black stools
- to take 2 capsules at about the same time each day. Swallow capsules whole with water; they can be taken with or without food
- that if they miss a dose, not to take a double dose to make up for it

- not to take dabigatran supplied by the hospital and by their GP simultaneously
- to continue to wear compression stockings if recommended
- to tell their doctor, dentist or pharmacist at each consultation that they are taking dabigatran.

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

Medicine Update

An NPS *Medicine Update* leaflet on dabigatran is available for consumers. *Medicine Update* helps consumers to ask the right questions about new medicines, and helps them compare the potential benefits and harms of a new medicine with other medicines.

References

1. Eriksson BI, et al. *Lancet* 2007;370:949–56.
2. Eriksson BI, et al. *J Thromb Haemost* 2007;5:2178–85.
3. Boehringer Ingelheim Pty Limited. Pradaxa product information 11 March 2009.
4. National Health and Medical Research Council. Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals. Melbourne: NHMRC, 2009. <http://www.nhmrc.gov.au/nics/programs/vtp/prevention.htm> (accessed 11 December 2009).
5. Connolly SJ, et al. *N Engl J Med* 2009;361:1139–51.
6. Schulman S, et al. *N Engl J Med* 2009;361:2342–52.
7. Pharmaceutical Benefits Advisory Committee. Public Summary Document: Dabigatran etexilate mesilate, capsules, 75mg, 110 mg (base), Pradaxa, March 2009. Canberra: Australian Government Department of Health and Ageing, 2009. <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-dabigatran-march09> (accessed 18 January 2010).
8. Ginsberg JS, et al. *J Arthroplasty* 2009;24:1–9.
9. Therapeutic Guidelines: Cardiovascular. Version 5, 2008.
10. Australian Medicines Handbook 2010.
11. National Institute for Health and Clinical Excellence. Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. London: NICE, 2007.
12. Eriksson BI, et al. *J Thromb Haemost* 2005;3:103–11.
13. National Institute for Health and Clinical Excellence. Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. London: NICE, 2008. <http://www.nice.org.uk/guidance/TA157/Guidance/pdf/English> (accessed 11 December 2009).
14. National Institute for Health and Clinical Excellence. Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. London: NICE, 2009. <http://guidance.nice.org.uk/TA170/Guidance/pdf/English> (accessed 11 December 2009).
15. AstraZeneca International. AstraZeneca Decides to Withdraw Exanta. 2006. <http://www.astrazeneca.com/media/latest-press-releases/2006/5217?itemId=3891692> (accessed 16 December 2009).
16. Agnelli G, et al. *Thromb Res* 2009;123:488–97.

Date published: April 2010

The information contained in NPS RADAR is derived from a critical analysis of a wide range of authoritative evidence and is current at the time of publication. Any treatment decisions based on the information provided in NPS RADAR should be made in the context of the clinical circumstances of each patient.

NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes. Please refer to www.npsradar.org.au for the most recent version as well as any supplementary information.