

**IN BRIEF**

A digest of news items about NPS RADAR, new drugs and changes to PBS listings

\* Patients discharged from public hospitals that have not yet implemented PBS prescribing may be dispensed a small supply of apixaban tablets. These are intended to cover the period between discharge and the patient seeing their GP to obtain a prescription to complete the course.

**Apixaban (Eliquis) for preventing venous thromboembolism after knee or hip replacement surgery**

From 1 January 2012, apixaban (Eliquis) can be prescribed on the Pharmaceutical Benefits Scheme (PBS) for preventing venous thromboembolism (VTE) in people undergoing total knee or total hip replacement surgery (TKR, THR).<sup>1</sup> The PBS-listed dispensed maximum quantities are 30 tablets after TKR and 60 tablets after THR.\*

**Reason for PBS listing**

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing apixaban on a cost-minimisation basis — that is, similar efficacy and cost — compared with rivaroxaban. An indirect comparison with rivaroxaban, using enoxaparin as the common comparator, was used in the PBAC submission (there are no trials comparing apixaban with rivaroxaban).<sup>1</sup>

**Apixaban is an oral anticoagulant**

Apixaban is a direct, reversible competitive inhibitor of factor Xa (activated factor X). It is from the same drug class as rivaroxaban and, along with dabigatran (a direct thrombin inhibitor),

is one of three oral anticoagulants available on the PBS for preventing VTE in people undergoing TKR or THR (Table 1).

**Apixaban reduces the incidence of venous thromboembolism**

Apixaban is approved for short-term use after elective TKR or THR. Two trials — ADVANCE-2 and ADVANCE-3 — compared the efficacy of apixaban (2.5 mg orally twice a day) with enoxaparin (40 mg subcutaneously once a day) in people undergoing TKR and THR, respectively. The primary outcome of both trials was a composite of asymptomatic and symptomatic deep vein thrombosis, non-fatal pulmonary embolism and death from all causes,<sup>†</sup> and apixaban reduced its incidence (Table 2).<sup>5,6</sup> The incidence of symptomatic VTE and death from VTE<sup>†</sup> was similar in both trials and did not differ between treatment groups. (Table 2).

**Major bleeding events for apixaban are similar to those with enoxaparin**

Major bleeding events were similar between treatment groups in both trials (Table 3).<sup>5,6</sup> People with active bleeding or at high risk of bleeding (e.g. a contraindication to anticoagulant prophylaxis, or on anticoagulant or antiplatelet therapy) were excluded from the trials.<sup>5,6</sup> Do not use apixaban in these people.<sup>2</sup>

Table 1. Oral anticoagulants available on the PBS (authority required) for preventing VTE in people undergoing TKR or THR<sup>2-4</sup>

Drug (brand)	Usual dose	Recommended duration
Apixaban (Eliquis)	2.5 mg <b>twice</b> a day	10-14 days after TKR 32-38 days after THR
Rivaroxaban (Xarelto)	10 mg once a day	14 days after TKR 35 days after THR
Dabigatran (Pradaxa)	220 mg once a day	10 days after TKR 28-35 days after THR

Table 2.  
Proportion of people who had a primary or secondary outcome in key trials<sup>†‡5,6</sup>

	Apixaban	Enoxaparin	Absolute risk difference and 95% confidence interval
<b>Knee replacement — ADVANCE-2</b>			
Primary outcome <sup>†</sup>	15.1%	24.4%	-9.3% -12.7% to -5.8% p < 0.0001
Symptomatic VTE and death from VTE <sup>‡</sup>	0.5%	0.5%	0% -0.5% to 0.5%
<b>Hip replacement — ADVANCE-3</b>			
Primary outcome <sup>†</sup>	1.4%	3.9%	-2.5% -3.5% to -1.5% p < 0.001
Symptomatic VTE and death from VTE <sup>‡</sup>	0.2%	0.4%	-0.2% -0.6% to 0.06%

<sup>†</sup> The primary outcome was a composite of adjudicated asymptomatic or symptomatic deep vein thrombosis, non-fatal pulmonary embolism and death from all causes (including VTE) that occurred during the trial or within 2 days of the last dose of study drug, whichever was longer

<sup>‡</sup> The secondary outcome — major VTE — was a composite of adjudicated symptomatic or asymptomatic proximal deep vein thrombosis, non-fatal pulmonary embolism or death from VTE during the same period

Table 3.  
Major bleeding events<sup>#</sup>

	n	Apixaban	Enoxaparin	Absolute risk difference and 95% confidence interval
Knee replacement ADVANCE-2	3009	0.6%	0.9%	-0.3% -1.0% to 0.3% p = 0.30
Hip replacement ADVANCE-3	5332	0.8%	0.7%	0.1% -0.3% to 0.6% p = 0.54

<sup>#</sup> Major bleeding events were defined as acute clinically overt bleeding accompanied by one or more of the following:

- ▶ a decrease in blood haemoglobin levels of  $\geq 20$  g/L in 24 hours
- ▶ transfusion of two or more units of packed red blood cells
- ▶ critical site bleeding (including intracranial, intraspinal, intraocular, pericardial or retroperitoneal bleeding)
- ▶ bleeding into the operated joint, requiring reoperation or intervention
- ▶ intramuscular bleeding with compartment syndrome
- ▶ fatal bleeding

There is no antidote to apixaban-induced bleeding. Stop apixaban and treat bleeding symptomatically. Arrange for hospital management if necessary. Stopping or delaying the next dose may be enough to manage minor bleeding, given that apixaban reversibly inhibits factor Xa and has a half-life of about 12 hours.<sup>2</sup>

#### **Take care combining apixaban with antiplatelet drugs or NSAIDs**

Combining apixaban with aspirin or NSAIDs may increase bleeding risk.<sup>2</sup> In the ADVANCE-3 trial, about 12% and 60% (622 and 3174 people, respectively) took at least one dose of aspirin or an NSAID.<sup>6</sup> However, there is no published information on how often these medicines were taken or on bleeding rates associated with them.

Avoid combining apixaban with other anticoagulants (e.g. heparin, rivaroxaban) or antiplatelet medicines (e.g. clopidogrel).<sup>2</sup> People taking these medicines were excluded from the trials.

#### **Do not use apixaban with strong inhibitors of CYP3A4 and/or P-glycoprotein**

Do not use apixaban with systemic azole antimycotics (e.g. ketoconazole, itraconazole), HIV-protease inhibitors (e.g. ritonavir) and other strong inhibitors of CYP3A4 and/or P-glycoprotein.<sup>2</sup> These drugs increase apixaban plasma levels and bleeding risk.

Strong inducers of CYP3A4 and P-glycoprotein (e.g. phenytoin, carbamazepine) reduce apixaban plasma levels: use with caution.<sup>2</sup>

#### **Apixaban is given twice a day**

The dose is 2.5 mg twice a day with or without food, starting 12–24 hours after surgery. The recommended duration of therapy is 10–14 days after TKR, and 32–38 days after THR.<sup>2</sup>

No dose adjustment is required for people with mild–moderate renal impairment. Use apixaban with caution if creatinine clearance (CrCl) is 15–29 mL/min: there are limited data for these people. Avoid apixaban if CrCl is < 15 mL/min: there are no data for these people.<sup>2</sup>

Use apixaban with caution in people with mild–moderate hepatic impairment (Child–Pugh class A or B). Apixaban is contraindicated in people with severe hepatic impairment (Child–Pugh class C) and in people with hepatic disease associated with a blood clotting disorder and clinically relevant bleeding risk.<sup>2</sup>

#### **REFERENCES**

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