Rivaroxaban (Xarelto)
for treatment of deep vein thrombosis and pulmonary embolism, and for prevention of venous thromboembolism recurrence

Key Points

An alternative to INR-adjusted warfarin with initial heparin for the treatment of symptomatic DVT (without symptomatic PE) or PE
Efficacy and safety were studied in people with acute, symptomatic proximal DVT without PE, and in people with acute symptomatic PE with or without DVT, over 3, 6 or 12 months.

Rivaroxaban is non-inferior to enoxaparin plus warfarin for preventing VTE (DVT or PE) recurrence
In trials VTE recurrence, major or clinically relevant non-major bleeding, and mortality were similar with rivaroxaban compared with enoxaparin plus either warfarin or acenocoumarol.a

For initial treatment of acute DVT or PE the dose is rivaroxaban 15 mg twice a day for the first 3 weeks then 20 mg once a day
Continue treatment for as long as the risk of VTE recurrence persists, balancing benefits and harms and patient preference.

For continuing treatment in people with a history of VTE the dose is 20 mg once a day
In trials rivaroxaban reduced recurrence of VTE in these people, but increased incidence of bleeding compared with placebo.

There is no antidote to the anticoagulant effects of rivaroxaban and no readily available and validated method of monitoring its activity in a primary care setting.
Routine coagulation monitoring is not possible but routine clinical monitoring is essential.
Advise patients to seek urgent medical attention for unexplained bruising, blood in the urine or black stools.

Bleeding risk may be higher in people with renal impairment
Very few people with renal impairment were included in trials. Do not use in people with severe renal impairment (CrCl < 30 mL/min).

PBS listing

Authority required (Streamlined)
Deep vein thrombosis.
Initial treatment or continuing treatment.
The patient must have confirmed, acute symptomatic deep vein thrombosis and must not have symptomatic pulmonary embolism.b

Authority required (Streamlined)
Pulmonary embolism.
Initial treatment or continuing treatment.
The patient must have confirmed, acute symptomatic pulmonary embolism.

Authority required (Streamlined)
Prevention of recurrent venous thromboembolism.
Continuing treatment.
The patient must have a history of venous thromboembolism.

a Acenocoumarol is not marketed in Australia.
b The diagnosis must be clinically confirmed; however, there is no requirement for prescribers to provide evidence at the time of authority application.
May be prescribed by nurse practitioners (shared care model)

Authorised nurse practitioners may prescribe this medicine when care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. See the PBS website for more information on nurse practitioner PBS prescribing.

Rivaroxaban is also PBS listed for the prevention of VTE after total hip or total knee replacement surgery [see the August 2009 NPS RADAR review ‘Rivaroxaban (Xarelto) for preventing venous thromboembolism after hip or knee surgery’].

Note that rivaroxaban is only PBS listed for primary prevention of VTE in patients who have undergone total hip or total knee surgery. The new indication is for treatment of DVT and PE and for prevention of VTE recurrence.

Rivaroxaban is TGA approved and PBS listed for stroke prevention in people with non-valvular atrial fibrillation [see the December 2012 NPS RADAR review ‘Rivaroxaban (Xarelto) for stroke prevention in non-valvular atrial fibrillation’].

What is it?

Rivaroxaban is an oral anticoagulant that acts by inhibiting factor Xa (activated factor X). Unlike warfarin it has a rapid onset of action and so does not require the use of a parenteral anticoagulant (such as enoxaparin) in the first week of treatment.

Peak concentrations are attained 2–4 hours after dosing and the drug is eliminated by hepatic (via CYP3A4- and CYP2J2-dependent, and independent, pathways) and renal pathways.

Compared with warfarin, rivaroxaban has a short half-life of 5–9 hours in young adults, and 11–13 hours in older adults due to the decline in renal function associated with ageing.

This shorter half-life makes adherence to dosing vital, as the risk of thromboembolism due to treatment failure may be greater than for warfarin if a dose is missed.

Who is it for?

Rivaroxaban is listed on the PBS for:

- treatment of people who require initial or continued treatment of confirmed acute symptomatic DVT (without symptomatic PE) or confirmed, acute symptomatic PE
- people requiring continued treatment to prevent recurrence of VTE.

The new indications do not cover use of rivaroxaban for primary prevention of DVT or PE.

Initial treatment for DVT and PE

The initial treatment of DVT with rivaroxaban was investigated in people with acute symptomatic DVT without PE (the Acute DVT Study), and the initial treatment of PE with rivaroxaban was investigated in people with acute symptomatic PE with or without DVT (the Einstein-PE Study).

In the Acute DVT Study most participants had unprovoked DVT (rivaroxaban arm 61%, enoxaparin plus warfarin or acenocoumarol arm 63%), 20% had DVT due to recent surgery or trauma and 15% had DVT due to immobilisation.

In the Einstein-PE Study, most participants had unprovoked PE (rivaroxaban arm 65%, enoxaparin plus warfarin or acenocoumarol arm 64%), 17% had PE due to recent surgery or trauma and 16% had PE due to immobilisation.

Patients could have multiple causes of PE and 25% of trial participants had symptomatic DVT as well as PE. Previous VTE was reported for 19% of trial participants in the rivaroxaban arm and 20% in the enoxaparin plus warfarin or acenocoumarol arm.

The anatomical extent of the PE was described as ‘intermediate’ for most trial participants (rivaroxaban arm 58%, enoxaparin plus warfarin or acenocoumarol arm 59%).

Treatment of people with a history of VTE

Extended treatment with rivaroxaban was investigated in people with a history of VTE (the Continued Treatment Study). Most participants in the Continued Treatment Study had an initial diagnosis of DVT (rivaroxaban arm 64% DVT, 36% PE; placebo arm 60% DVT, 40% PE). Most had unprovoked DVT or PE (rivaroxaban arm 73%, placebo arm 74%) or DVT or PE due to immobilisation (rivaroxaban arm 15%, placebo arm 13%).
When to consider switching to rivaroxaban from warfarin
Consider switching to rivaroxaban from warfarin in people:

- who are not able to maintain a consistent INR within the therapeutic range 60–70% of the time despite all correctable factors for INR fluctuation having been addressed and adherence confirmed
- who experience drug or major drug-food interactions with warfarin
- with poor venous access for INR monitoring

Do not switch to rivaroxaban in people who are non-adherent with warfarin
Because of the shorter half-life of rivaroxaban compared with warfarin, people not able to maintain a therapeutic INR with warfarin due to poor adherence are not suitable for rivaroxaban and should not be switched.

EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG?
Rivaroxaban is non-inferior to subcutaneous enoxaparin plus warfarin for preventing VTE recurrence in people with DVT (without PE) and in people with PE (with or without DVT).

In trials investigating the initial treatment of DVT (Acute DVT Study) and PE (Einstein-PE Study), incidence of ‘major or clinically relevant non-major bleeding’ was similar between patients treated with rivaroxaban and those treated with enoxaparin plus warfarin (or acenocoumarol) over 3, 6 or 12 months.

Rivaroxaban was better than placebo for preventing recurrence of VTE in the Continued Treatment Study. The people in this study had been previously treated for 6 or 12 months with rivaroxaban or warfarin (or acenocoumarol) and the benefits and harms of continued treatment were considered to be closely balanced. Treatment with rivaroxaban increased incidence of major or clinically relevant non-major bleeding, and clinically relevant non-major bleeding, compared with placebo.

AREAS OF UNCERTAINTY
The benefit of rivaroxaban for people who cannot use enoxaparin or warfarin and for people at high risk of bleeding is not known. Further studies are needed to understand the benefits and harms for people aged over 75 years and people with renal impairment.

There is also little perioperative experience and little experience of switching between rivaroxaban and other anticoagulants. There is no antidote or readily available and validated method for routine monitoring of the anticoagulant effect of rivaroxaban.

Efficacy and safety data for rivaroxaban are limited beyond 12 months. There are no head-to-head trials comparing the efficacy and safety of rivaroxaban with warfarin over extended durations of treatment in people with a history of VTE. The effect of rivaroxaban on pathology or relief of symptoms of DVT was not investigated in the key trials.

WHAT DOES NPS SAY?
Rivaroxaban can simplify treatment of DVT and PE and prevention of VTE recurrence in primary care. However, the benefits of simplified oral dosing with rivaroxaban (i.e. not having to start with heparin) as well as fewer known drug interactions must be balanced against the lack of long-term safety and efficacy data, the lack of readily available and validated monitoring techniques, and unavailability of antidotes to manage bleeding.

In trials, the benefits of rivaroxaban were evaluated in a predominantly young population with little comorbidity and, in the case of the Acute DVT Study, in the comparator group warfarin dosing and management were suboptimal. This may affect applicability of the study findings to the Australian treatment population.

Non-inferior: the effect of a new drug is not worse than that of another drug by more than a pre-specified margin.
Trial populations were relatively young with few comorbidities

The populations in the key trials may not have been representative of the Australian treatment population. It is well established that risk of VTE increases with age,9–11 as does the incidence of comorbidities such as renal impairment.

A 2008 report estimated that in Australia incidence of DVT and VTE was highest in people aged 75–79 years whereas incidence of PE was highest in people aged 70–74 and 75–79.12

The average age of participants in the rivaroxaban trials was < 60 and very few people were over 75 or had moderate or severe renal impairment.7,8,13,14

The Acute DVT Study included people with an average age of 56 who had symptomatic proximal4 DVT without symptomatic PE.7 Most (83%) weighed 50–100 kg, did not have moderate or severe renal impairment and had a median time from onset of symptoms to randomisation of 5 days.7

The Einstein-PE Study included people with an average age of 58 who had symptomatic proximal4 DVT without symptomatic PE.8 Most weighed 50–100 kg (rivaroxaban arm 84%, enoxaparin plus warfarin or acenocoumarol arm 83%) did not have moderate or severe renal impairment and had a median time from onset of symptoms to randomisation of 4 days.8

Trial participants in the Continued Treatment Study had an average age of 58, most (82%) weighed 50–100 kg and had a median time from onset of symptoms to randomisation of 204 days (rivaroxaban arm) and 206 days (placebo arm).7

In the Acute DVT Study, time in the therapeutic range for trial participants taking warfarin averaged 54% in month 1 and 66.4% in month 10, with an overall study average of 58%.7 This may be lower than the average time in the therapeutic range for Australian patients taking warfarin, who averaged 69% in a recent study.15

Time in the therapeutic range was higher in the Einstein-PE Study (overall study average 63%, 58% in month 1 and 73% in month 11) compared with that in the Acute DVT Study.8

People with distal DVT are included in the new PBS listing for treatment but were not included in the Acute DVT Study.7

Rivaroxaban data are lacking in some patient groups

Rivaroxaban has not been tested in people for whom warfarin or enoxaparin are contraindicated; however, rivaroxaban treatment is likely to be also contraindicated for these people.5,7,8

Rivaroxaban has not been tested in people under 18 years and is not recommended for use in these people.5 Rivaroxaban is contraindicated in people with severe renal impairment (CrCl < 30 mL/minute) and people with significant hepatic disease, including moderate or severe hepatic insufficiency when coagulopathy is also present (i.e. abnormally elevated INR).5 Efficacy and safety data are not available for these populations.

Do not use rivaroxaban in patients with prosthetic heart valves, due to a lack of safety and efficacy data.5 People taking warfarin for indications other than DVT were excluded from the Acute DVT Study,7 and people taking warfarin for indications other than DVT and/or PE were excluded from the Einstein-PE Study and the Continued Treatment Study.7,8

More data are needed to assess the efficacy and safety of rivaroxaban in people with active cancer.7 Only 7% of trial participants had active cancer at the time of enrolment into the Acute DVT Study.7

Where does it fit?

Rivaroxaban is a treatment option for acute symptomatic DVT and acute symptomatic PE

Rivaroxaban is a single drug option for the initial and continued treatment of both confirmed acute symptomatic DVT and PE.

Current therapy for acute symptomatic DVT and PE is with parenteral anticoagulants such as heparins, for rapid anticoagulation, overlapping the start of warfarin therapy. This dual therapy is continued until the patient’s INR is stable and within therapeutic range (2.0–3.0), after which warfarin is continued as single therapy.16

Defined as acute DVT in the popliteal vein or higher (femoral vein, common femoral vein, iliac vein, and vena cava) including clots in the deep femoral vein.

Distal or calf vein thrombosis was defined in the study as acute DVT in the three major calf veins below the popliteal vein (posterior tibial, anterior tibial, peroneal), including clots in the muscular branches to the gastrocnemius and soleal muscles, which are considered deep calf vein thrombi.

Defined as acute DVT in the popliteal vein or higher (femoral vein, common femoral vein, iliac vein, and vena cava) including clots in the deep femoral vein.
Rivaroxaban is a treatment option for prevention of recurrent VTE in people with a history of VTE
Rivaroxaban is also an option for people with a history of VTE requiring long-term anticoagulation to prevent recurrence of VTE. It is suitable both for patients in whom there is considered to be a definite benefit to treatment, and for those in whom the benefits and harms of treatment are finely balanced.

Length of treatment for patients requiring extended-duration anticoagulation is uncertain
In people requiring treatment for longer than 3 months the benefits and harms of treatment can be closely matched, and duration of treatment should be individualised depending on their risk of bleeding.\textsuperscript{17,18} Re-evaluate the risk of VTE recurrence, bleeding risk, type of anticoagulation and patient preference annually.\textsuperscript{18,19}

Continue anticoagulant treatment to prevent VTE recurrence until either:
\begin{itemize}
  \item the reduction in risk of VTE recurrence no longer outweighs the increase in bleeding risk
  \item the patient wishes to stop treatment, even if the reduction in the risk of VTE recurrence would outweigh the increase in bleeding risk.\textsuperscript{18}
\end{itemize}

Current recommendations for anticoagulant treatment durations are listed in Table 1.

How does it compare?
Rivaroxaban has no known food interactions and has fewer known drug interactions than warfarin. However, most warfarin interactions can be managed because it is possible to monitor the anticoagulation effect by INR testing. This monitoring is not possible for rivaroxaban.

The efficacy and safety of rivaroxaban for treatment of DVT, treatment of PE and for the prevention of VTE recurrence in people with a history of VTE were investigated in the Acute DVT Study, the Einstein-PE Study and the Continued Treatment Study, respectively.\textsuperscript{7,8}

Initial treatment of patients with DVT or PE
The efficacy and safety of rivaroxaban for the initial treatment of DVT and PE were compared with enoxaparin followed by dose-adjusted warfarin (or acenocoumarol)\textsuperscript{1} in individual randomised non-inferiority trials over 3, 6 or 12 months (Acute DVT Study, $n = 3499$; Einstein-PE Study $n = 4832$).\textsuperscript{7,8}

Although these were open-label trials, outcome events were confirmed by independent adjudicators who were blinded to treatment.\textsuperscript{7,8} Trial participants in the Acute DVT Study were people with acute, symptomatic, objectively confirmed proximal DVT without PE. Trial participants in the Einstein-PE Study were people with acute, symptomatic, objectively confirmed PE with or without DVT.\textsuperscript{7,8}

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\textsuperscript{1} Enoxaparin 1 mg/kg twice daily for a minimum of 5 days and until an INR $\geq 2$ for 2 consecutive days was achieved. Median duration of enoxaparin treatment was 8 days. Warfarin or acenocoumarol was started within 2 days of randomisation.

\textsuperscript{a} Surgery, immobilisation > 3 days, trauma, pregnancy or postpartum, oral contraceptive or hormone replacement therapy

\textsuperscript{b} Such as cancer (low molecular weight heparin is the preferred treatment), multiple thrombophilias and antiphospholipid syndrome

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Table 1: Current recommended duration of anticoagulation therapy\textsuperscript{17–22}

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommended duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of VTE (DVT or PE) provoked by a transient risk factor\textsuperscript{a}</td>
<td>3 months' anticoagulation\textsuperscript{17–19,21}</td>
</tr>
<tr>
<td>First episode of isolated distal DVT</td>
<td>6 weeks' to 3 months' anticoagulation.\textsuperscript{15–22} Less than 3 months' treatment may be considered appropriate in low-risk patients with first episodes of isolated distal DVT provoked by a transient risk factor, after assessment by a specialist\textsuperscript{17,22}</td>
</tr>
<tr>
<td>First unprovoked proximal DVT or PE</td>
<td>At least 3–6 months' anticoagulation.\textsuperscript{17–22} An extended duration should be considered based on patient preference and following specialist assessment of the benefits and harms. Some guidelines recommend 3 months' treatment for these patients, who are also at high risk of bleeding\textsuperscript{18}</td>
</tr>
<tr>
<td>First episode of VTE (DVT or PE) provoked by a persistent risk factor\textsuperscript{b}</td>
<td>Extended duration of treatment is recommended with specialist assessment\textsuperscript{19,21}</td>
</tr>
<tr>
<td>Recurrent unprovoked VTE (DVT or PE)</td>
<td>Extended duration of treatment is recommended, with specialist assessment\textsuperscript{19,21}</td>
</tr>
</tbody>
</table>
Prevention of recurrent VTE in patients with a history of VTE

The efficacy and safety of rivaroxaban for continued treatment of people with a history of DVT or PE was investigated in a randomised, placebo-controlled double-blind trial testing for superiority (the Continued Treatment Study, n = 1197). Participants in the Continued Treatment Study had previously been treated with rivaroxaban or warfarin (or acenocoumarol) for 6–12 months, and the investigators reported that the benefits and harms of further anticoagulation were closely matched in these people. In all three studies the intended duration of treatment was decided by the treating physician, and suspected outcomes were classified by an independent adjudication committee who were blinded to the treatment of the patient.

Initial treatment of acute symptomatic DVT — rivaroxaban is non-inferior to enoxaparin plus warfarin

In the Acute DVT Study rivaroxaban was non-inferior (pre-specified margin 2.0) to enoxaparin plus warfarin (or acenocoumarol) for preventing the recurrence of VTE (a composite outcome of recurrent symptomatic DVT or fatal or non-fatal PE) in patients with acute symptomatic DVT without PE, based on analysis of both the intention-to-treat and per protocol trial populations (Table 2). Clinical effects are unlikely to be different, and superiority was not demonstrated for rivaroxaban in the trial.

Initial treatment of acute symptomatic PE — rivaroxaban is non-inferior to enoxaparin plus warfarin

In the Einstein-PE Study rivaroxaban was non-inferior (pre-specified margin 2.0) to enoxaparin plus warfarin (or acenocoumarol) for preventing the recurrence of VTE (a composite outcome of recurrent symptomatic DVT or fatal or non-fatal PE) in patients with acute symptomatic PE with or without DVT, based on analysis of the intention-to-treat and per-protocol trial populations (Table 3). Superiority was not demonstrated for rivaroxaban in the trial. The most frequent events observed in the study were non-fatal PE (< 1% in both arms) and recurrent DVT (< 1% in both arms).

Rivaroxaban treatment of acute symptomatic DVT or PE — efficacy in patient subgroups

In both the Acute DVT Study and the Einstein-PE Study, rivaroxaban showed similar efficacy

### Table 2. Recurrence of VTE events after treatment with rivaroxaban compared with treatment with enoxaparin plus warfarin or acenocoumarol in the Acute DVT Study intention-to-treat trial populations

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n = 1731)</th>
<th>Enoxaparin plus warfarin (or acenocoumarol) (n = 1718)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE(^a)</td>
<td>36 (2.1%)</td>
<td>51 (3.0%)</td>
<td>0.68 (0.44 to 1.04)</td>
</tr>
</tbody>
</table>

\(^a\) Composite primary outcome: recurrent symptomatic DVT or fatal/non-fatal PE

\(^1\) Non-inferiority margin was 2.0

CI = confidence interval

### Table 3. Recurrence of VTE events after treatment with rivaroxaban compared with treatment with enoxaparin plus warfarin or acenocoumarol in the Einstein-PE Study intention-to-treat trial populations

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n = 2419)</th>
<th>Enoxaparin plus warfarin (or acenocoumarol) (n = 2413)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE(^m)</td>
<td>50 (2.1%)</td>
<td>44 (1.8%)</td>
<td>1.12 (0.75 to 1.68)</td>
</tr>
</tbody>
</table>

\(^m\) Composite primary outcome: recurrent symptomatic DVT or fatal/non-fatal PE

\(^n\) Non-inferiority margin was 2.0
Rivaroxaban (Xarelto)

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Patients with a history of VTE — rivaroxaban reduces the risk of recurrence

In the Continued Treatment Study, rivaroxaban used for 6–12 months was superior to placebo for preventing VTE recurrence in people where the benefits and harms of further treatment were judged to be closely matched (Table 4).7

Rivaroxaban was associated with an 82% reduction in relative risk of VTE recurrence compared with placebo. The benefits of rivaroxaban over placebo in these people were mostly seen in the prevention of recurrence of DVT (five versus 31 recurrences, respectively).7

Safety issues

As with any anticoagulant, managing the risk of bleeding is the primary concern with rivaroxaban. Determine bleeding risk before starting treatment.6

Do not use rivaroxaban in people with:

- clinically significant active bleeding (e.g. intracranial bleeding, GI bleeding)
- lesions at increased risk of clinically significant bleeding
- spontaneous impairment of haemostasis.5

Rivaroxaban may not be suitable for people at increased risk of bleeding, including those with:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative GI disease
- recent GI ulcerations
- vascular retinopathy
- recent intracranial or intracerebral haemorrhage.5

Be vigilant for haemorrhagic complications, which may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea or shock.5

The rivaroxaban safety data for treatment of DVT, treatment of PE and prevention of VTE recurrence in people with a history of VTE, from randomised trials are derived mainly from the three key studies,7,8 and data beyond 12 months are currently limited.5

Bleeding events were reported in study safety populations (all people who took the study drug) and for events that occurred during treatment or within 2 days of stopping treatment.7,8

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website (www.tga.gov.au/safety/problem.htm#medicine) or use the ‘Blue Card’ distributed three times a year with Australian Prescriber.

Table 4. Recurrence of VTE events after treatment with rivaroxaban compared with treatment with placebo in the Continued Treatment Study intention-to-treat trial populations7

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n = 602)</th>
<th>Placebo (n = 594)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE○</td>
<td>8 (1.3%)</td>
<td>42 (7.1%)°</td>
<td>0.18 (0.09 to 0.39)</td>
</tr>
</tbody>
</table>
| p Composite primary outcome: recurrent symptomatic DVT or fatal/non-fatal PE
| p Some trial participants had more than one event
Initial treatment of acute symptomatic DVT — incidence of bleeding similar to that for enoxaparin plus warfarin

In the Acute DVT Study the principal safety outcome was a composite of the first major or clinically relevant non-major bleed. Incidence of this outcome for rivaroxaban over the course of the trial was identical with that for enoxaparin plus warfarin (or acenocoumarol) (8.1% vs 8.1%) (Table 5) although it was higher for rivaroxaban during the first 4 months of treatment but lower after 6 months.

The data above refer to a composite of the first major or clinically relevant non-major bleed. The incidence of major bleeding or clinically relevant non-major bleeding identified as separate outcomes was also similar between people treated with rivaroxaban and with enoxaparin plus warfarin or acenocoumarol (Table 5).

Most reported bleeds experienced during the study (about 90%) were clinically relevant non-major bleeds. Total deaths and deaths related to bleeding were similar with rivaroxaban and enoxaparin plus warfarin (or acenocoumarol) (Table 5).

Suboptimal warfarin control in the Acute DVT Study

As average time in the therapeutic range for warfarin (or acenocoumarol) was only 58% in the Acute DVT Study, it is not known how rivaroxaban compares with warfarin in terms of safety when warfarin is optimally controlled (good warfarin control is defined as time in the therapeutic range of > 70%). The incidence of bleeding with warfarin is known to be higher when the INR is above the therapeutic range.

Bleeding was increased in people with renal impairment (see section “Bleeding risk increased in people with impaired renal function”).

### Table 5. Safety outcomes identified in the Acute DVT Study safety populations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (n = 1718)</th>
<th>Enoxaparin–warfarin (or acenocoumarol) (n = 1711)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First major or clinically relevant non-major bleed</td>
<td>139 (8.1%)</td>
<td>138 (8.1%)</td>
<td>0.97 (0.76 to 1.22)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>14 (0.8%)</td>
<td>20 (1.2%)</td>
<td>0.65 (0.33 to 1.30)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>126 (7.3%)</td>
<td>119 (7.0%)</td>
<td>0.67 (0.44 to 1.02)</td>
</tr>
<tr>
<td>Total deaths</td>
<td>38 (2.2%)</td>
<td>49 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Deaths due to PE or PE not ruled out</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Deaths due to bleeding</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* Occurring during treatment

### Table 6. Safety outcomes identified in the Einstein-PE Study safety populations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (n = 2412)</th>
<th>Enoxaparin–warfarin (or acenocoumarol) (n = 2405)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First major or clinically relevant non-major bleed</td>
<td>249 (10.3%)</td>
<td>274 (11.4%)</td>
<td>0.90 (0.76 to 1.07)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>26 (1.1%)</td>
<td>52 (2.2%)</td>
<td>0.49 (0.31 to 0.79)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>228 (9.5%)</td>
<td>235 (9.8%)</td>
<td></td>
</tr>
<tr>
<td>Total deaths</td>
<td>58 (2.4%)</td>
<td>50 (2.1%)</td>
<td>1.13 (0.77 to 1.65)</td>
</tr>
<tr>
<td>Deaths due to PE or PE not ruled out</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Deaths due to bleeding</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

* Occurring during treatment

† One patient in each group had a second recurrent event that was fatal

u Three people in the rivaroxaban group and one person in the enoxaparin–warfarin (or acenocoumarol) group died due to bleeding while no longer taking the study drug
Initial treatment of acute symptomatic PE — incidence of bleeding similar to that for enoxaparin plus warfarin

In the Einstein-PE Study the principal safety outcome was a composite of the first major or clinically relevant non-major bleed. Incidence of this outcome for rivaroxaban was similar to that for enoxaparin plus warfarin (or acenocoumarol) (10.3% vs 11.4%). The incidence of major bleeding alone was reduced with rivaroxaban compared with enoxaparin plus warfarin (or acenocoumarol) (1.1% vs 2.2%), although the incidence of fatal major bleeds, including those due to intracranial bleeds, was similar.

The incidence of non-fatal intracranial bleeds and retroperitoneal bleeds was reduced with rivaroxaban treatment compared with enoxaparin plus warfarin (or acenocoumarol) (ICH < 0.1% vs 0.4%, retroperitoneal bleeds < 0.1% vs 0.3%). However, absolute reductions were small, and use of rivaroxaban was also associated with increased incidence of GI bleeds (1.6% vs 0.7%).

Most reported bleeds experienced during the study (> 85%) were clinically relevant non-major bleeds, the incidence of which was similar between the two treatment arms (rivaroxaban arm 9.5%, enoxaparin plus warfarin [or acenocoumarol] arm 9.8%).

Total deaths and deaths related to bleeding were also similar with treatment with rivaroxaban and enoxaparin plus warfarin (or acenocoumarol) (Table 6).

Patients with a history of VTE — bleeding increased compared with placebo

Major bleeds (the principal safety outcome) were uncommon during the Continued Treatment Study. Treatment with rivaroxaban increased the incidence of clinically relevant non-major bleeds, and the composite of major or clinically relevant non-major bleeds during the study. Rivaroxaban was discontinued permanently by 19% of trial participants who experienced clinically relevant non-major bleeds (Table 7). The total number of deaths was not increased with rivaroxaban compared with placebo during the study (0.2% vs 0.3%).

No validated antidote to rivaroxaban-induced bleeding

Patients should be made aware of the lack of antidote to the effects of rivaroxaban. 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.

Contraindicated during pregnancy

Rivaroxaban is contraindicated for use in patients who are pregnant, and also in patients who are breastfeeding, due to lack of data on use in these people. Do not use rivaroxaban in women of childbearing age without effective contraception.

Contraindicated in people with severe renal impairment

Both rivaroxaban 15 mg and 20 mg are contraindicated in people with severe renal impairment (CrCl < 30 mL/min). These people were excluded from the key trials. Determine patient renal function using the Cockcroft-Gault formula before starting rivaroxaban, especially where renal impairment is suspected. Rivaroxaban is contraindicated in people on dialysis.

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**Table 7.** Safety outcomes identified in the Continued Treatment Study safety populations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (n = 598)</th>
<th>Placebo (n = 590)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First major or clinically relevant non-major bleed</td>
<td>36 (6.0%)</td>
<td>7 (1.2%)</td>
<td>5.19 (2.3 to 11.7), p &lt; 0.001</td>
</tr>
<tr>
<td>Major bleed*</td>
<td>4 (0.7%)**</td>
<td>0</td>
<td>N/A, p = 0.11</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding*</td>
<td>32 (5.4%)</td>
<td>7 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>Deaths due to PE or PE not ruled out</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* Some trial participants had more than one event
** Gastrointestinal in three subjects and menorrhagic in one

ICH: intracranial haemorrhage
Bleeding risk increased in people with impaired renal function
Sub-analysis of data from the Acute DVT Study suggests that the incidence of bleeding-related adverse events was higher in people with CrCl < 50 mL/min than in people with normal renal function (≥ 80 mL/min) (hazard ratio 3.952, 95% CI 1.637 to 9.545). 1,2,8
Bleeding risk may also be increased in patients with renal impairment taking P-glycoprotein inhibitors and weak to moderate CYP3A4 inhibitors, due to significantly increased exposure to rivaroxaban.5

Contraindicated in people with hepatic impairment
Rivaroxaban is contraindicated for people with significant hepatic disease (including moderate and severe hepatic impairment, i.e. Child–Pugh grade B or C) when coagulopathy is also present (i.e. abnormally elevated INR) leading to a clinically relevant bleeding risk.5

Avoid concomitant use of strong inhibitors of both CYP3A4 and P-glycoprotein
Rivaroxaban is contraindicated for people treated concomitantly with strong inhibitors of both CYP3A4 and P-glycoprotein, including HIV protease inhibitors (e.g. ritonavir) or systemically administeredazole antimycotics (e.g. ketoconazole, itraconazole, voriconazole, posaconazole).5
These drugs reduce rivaroxaban clearance, increase plasma concentrations and may increase risk of bleeding.5,16 Fluconazole is not contraindicated and may be co-administered.5
Strong inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John’s wort) may reduce the plasma concentration and efficacy of rivaroxaban.5,29 However, the effect of concomitant treatment with rifampicin is not clinically relevant, and concomitant use is not contraindicated.5,16 The effect of concomitant treatment with drugs that moderately inhibit either CYP3A4 or P-glycoprotein (e.g. clarithromycin, erythromycin) is also not clinically relevant and these drugs are not contraindicated.5,16 However, they could significantly increase the risk of bleeding in people with renal impairment if used with rivaroxaban.5

Caution when switching from warfarin to rivaroxaban
Stop warfarin, monitor INR and start rivaroxaban when INR is ≤ 2.5 for patients treated for DVT or PE and for prevention of recurrent VTE in people with a history of VTE.5

Switching from rivaroxaban to warfarin
Limited clinical trial data are available to guide switching people from rivaroxaban to warfarin.5 Transitioning from rivaroxaban to warfarin can place patients at risk of inadequate anticoagulation.5 Consider the expected onset time of warfarin (about 5 days) and the half-life of rivaroxaban (which depends on the patient’s renal clearance).29
Refer to the Product Information for further guidance on switching from warfarin to rivaroxaban or from rivaroxaban to warfarin.5

Dosing issues
The Australian Product Information recommends that no dose adjustment is necessary for any specific patient population, such as people with moderate renal impairment (CrCl 30–49 mL/min), extreme body weight (< 50 kg or > 120 kg) or age > 75 years.5
However, some European guidelines and Product Information recommend that certain people with moderate renal impairment should not use the 20 mg dose and should continue with the 15 mg dose.30,31 Rivaroxaban should be taken with food.5

Different doses for initial and continued treatment
The approved dose for initial treatment of confirmed acute symptomatic DVT and for treatment of acute symptomatic PE is 15 mg twice daily for 3 weeks, with 20 mg once daily approved for continuing therapy.1,2,5 The approved dose for continuing treatment for the prevention of recurrent VTE in people with a history of VTE is 20 mg once daily for the duration of required anticoagulant treatment.1,5
Prescribers are encouraged to write separate scripts for the initial and continuing treatment doses of rivaroxaban to avoid patient confusion by having two strengths at one time.28
Missed doses — initial treatment
Ensure that dosing is adhered to, because of the short half-life of rivaroxaban. During initial treatment of DVT or PE with 15 mg twice daily, if a dose is missed the patient should take the next dose immediately to ensure the intake of 30 mg total dose per day. Two tablets may be taken at once if required during twice-daily dosing. The following day the patient should continue with the regular 15 mg twice daily dosing schedule.

Missed doses — continued treatment
During continued treatment of DVT or PE, or prevention of VTE recurrence in people with a history of VTE with 20 mg once daily, if a dose is missed the patient should take the dose immediately and continue with the recommended dosing the following day. A double dose of 20 mg rivaroxaban should not be taken to make up for a missed tablet.

Information for patients
Advise patients and carers to:
- seek urgent medical attention for unexplained bruising, blood in the urine, black stools or prolonged bleeding
- tell their health professional at each consultation that they are taking rivaroxaban
- ensure adherence with the dosing regimen — adherence cannot be monitored but is crucial. Rivaroxaban has a much shorter half-life than warfarin and the risk of a blood clot may be higher if they miss a dose
- take rivaroxaban with food
- replace a missed dose as described, depending on whether rivaroxaban is being taken once or twice daily
- avoid non-prescription medicines containing NSAIDs, and antiplatelet agents such as aspirin, unless advised by their health professional
- ensure they understand the need for routine clinical monitoring, for example, to check for signs of bleeding
- avoid concomitant treatment with St John’s wort.

Discuss the rivaroxaban (Xarelto) consumer medicine information (CMI) leaflet with the patient (http://tinyurl.com/tga-cmi-rivaroxaban).

Reason for PBS listing
The PBAC recommended an Authority required (Streamlined) listing of rivaroxaban 15 mg and 20 mg tablets for the initial and continuing treatment of DVT in people without symptomatic PE, and the prevention of VTE recurrence in people with a history of VTE, on a cost-minimisation basis compared with enoxaparin and warfarin, with a cost offset for the additional INR tests associated with warfarin treatment.

This listing was extended to include the initial and continuing treatment of acute symptomatic PE on a cost-minimisation basis compared with enoxaparin 80 mg twice daily followed by INR-adjusted warfarin, at the same treatment cost.

Although some differences in bleeding outcomes were noted, the PBAC considered rivaroxaban to be non-inferior in terms of clinical effectiveness and safety compared with enoxaparin and warfarin for the prevention of recurrent VTE and fatal or non-fatal PE in patients with symptomatic proximal DVT without PE.

The PBAC also considered rivaroxaban to be non-inferior to enoxaparin and warfarin in terms of clinical effectiveness in the treatment of PE, and superior for comparative safety.
REFERENCES


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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.

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