SAFERx
SAFER USE OF HIGH RISK MEDICINES

Waitemata District Health Board
Best Care for Everyone

RIVAROXABAN - SAFE PRESCRIBING - BE BLEEDING CAREFUL

- CHECK AND MONITOR RENAL AND HEPATIC FUNCTION
- DO NOT USE DURING PREGNANCY
- ASSESS AND INFORM PATIENTS ABOUT BLEEDING RISK
- MAKE SURE PATIENTS KNOW ABOUT SAFE STORAGE AND ADMINISTRATION

Rivaroxaban is a direct oral anticoagulant indicated for the prophylaxis of venous thromboembolism (VTE) following elective hip or knee replacement surgery, for the prophylaxis of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the treatment of DVT or PE. It is also indicated for the prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF) who are considered high-risk.[1,2,8,14]

Rivaroxaban is contraindicated in patients with mechanical prosthetic valves.[9] Its use is acceptable with bioprosthetic valves, mitral valve repair or transcatheter aortic valve replacement although there is limited data.[13,14]

CHECK AND MONITOR RENAL AND HEPATIC FUNCTION

Rivaroxaban exposure is inversely correlated to a decrease in renal function. Therefore, before initiating treatment with rivaroxaban, it is important that any degree of renal impairment is accurately determined.[2]

Renal impairment

Rivaroxaban is contraindicated in patients with creatinine clearance (CrCl) less than 15 mL/min or undergoing dialysis. There is currently no data available for these patients.[2,15]

For patients with CrCl less than 30mL/min, other agents should be considered instead because the plasma levels of rivaroxaban can significantly increase, thus increasing the risk of bleeding.[2] (See Table 1 for recommended doses)

For patients with moderate renal impairment, CrCl between 30-49mL/min, rivaroxaban may be used, however dose adjustments may be required. Make sure the patient is aware that there could be an increased risk of bleeding and to seek medical care if bleeding occurs.

Table 1. Recommended doses of rivaroxaban[2]

<table>
<tr><th>Creatinine clearance and indication</th><th>VTE prevention (THJR and TKJR)*</th><th>Stroke prevention in non-valvular AF</th><th>DVT treatment; prevention of recurrent DVT and PE</th></tr>
<tr><td>>50mL/min</td><td rowspan="2">10mg daily</td><td>20mg daily</td><td rowspan="2">15mg twice daily for three weeks,
then 20mg once daily</td></tr>
<tr><td>30-49mL/ min</td><td>15mg daily</td></tr>
<tr><td>15-29mL/ min</td><td>10mg daily
(with caution)</td><td colspan="2">Contraindicated</td></tr>
<tr><td>< 15mL/min</td><td colspan="3">Contraindicated</td></tr>
</table>

*Total Hip Joint Replacement – recommended duration of treatment is 5 weeks, starting 6-10 hours after surgery

*Total Knee Joint Replacement – recommended duration of treatment is 2 weeks, starting 6-10 hours after surgery

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Hepatic impairment

For patients with moderate to severe hepatic impairment (Child-Pugh B and C, see table 2 at end of bulletin), rivaroxaban is contraindicated due to the increased bleeding risk.[2]

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Although there is no specific dose adjustment required for the elderly, increasing age may be associated with declining renal and hepatic function so rivaroxaban should be used with caution. Rivaroxaban is not recommended in those under 18 years due to a lack of available data.[2]

There is no specific dose adjustment required for differences in body weight.[2]

DO NOT USE DURING PREGNANCY

Rivaroxaban is contraindicated during pregnancy because of the risk of bleeding and the evidence that rivaroxaban crosses the placenta.[2] It is important that women of childbearing potential are aware that there is no data available about its use in pregnant women, so effective contraception should be used.

No data from breast-feeding mothers is available, so it is contraindicated during breast-feeding.[2]

ASSESS AND INFORM PATIENTS ABOUT BLEEDING RISK

As with other anticoagulants, there is a risk of bleeding, so caution is needed. Patients should be advised to inform their doctor if they experience any nose bleeds, blood in the urine or stools or cough up blood.[4] Rivaroxaban has a relatively short half-life (5-13 hours) so if patients notice any bleeding it would be advisable to delay the next administration until they have been assessed.[5]

Patients should let their dentist know they are taking an anticoagulant and inform their doctor if they need to have a dental or surgical procedure.[4] If an invasive procedure or surgical intervention is required, rivaroxaban may need to be withheld (the duration of which is dependent on individual patient factors).

Rivaroxaban should not be prescribed to patients with clinically significant active bleeding, or to those who are at significant risk of bleeding.

Examples include recent gastro-intestinal ulcer, oesophageal varices, or following recent brain, spine or ophthalmic surgery, recent intracranial haemorrhage, malignant neoplasms with high bleeding risk, or vascular aneurysm.[1] Compared with warfarin, bleeding events are considered to be similar, but evidence shows that the rate of intracerebral haemorrhage is lower with rivaroxaban but that the occurrence of gastrointestinal bleeding is higher.[3] Patients should be informed about the signs and symptoms of GI bleeding.

Routine coagulation screening tests, (INR, aPTT/PR) can be useful in an acute bleeding event but, their routine use in the ambulatory setting remains controversial. These tests do correlate with concentrations of rivaroxaban but there can be variations between tests and therefore, interpretation requires further discussion with a haematologist.[8] There is no reversal agent currently available in New Zealand, although use of prothrombin complex concentrates and FEIBA may be partially effective in overcoming the anticoagulant effect.[9]

Patients should be informed that the bleeding risk is increased when rivaroxaban is used concomitantly with other anticoagulants and there is a lack of data to support such use.[2] For patients taking concurrent antiplatelet therapy (eg clopidogrel, aspirin), there is an increased risk of bleeding.[6] Therefore caution should be used, and advice to patients to be aware of bruising or prolonged bleeding should be given. Some international guidelines recommend that unless there is a specific indication for continuing with aspirin, it is best to withhold during treatment with rivaroxaban.[5]

All NSAIDs increase the risk of bleeding so concurrent use with rivaroxaban might possibly increase this risk. Caution should be used and patients advised to watch out for bruising or prolonged bleeding.[2,6]

Medicines that can increase rivaroxaban plasma concentrations include Azole-antimycotics eg itraconazole, ketoconazole and HIV-protease inhibitors eg ritonavir.[2] Some anticonvulsants eg phenytoin, carbamazepine or St John's Wort may decrease the anticoagulant effect of rivaroxaban.[2,5] If concurrent use is unavoidable, consider switching to an alternate anticoagulant for which monitoring is available to ensure that adequate anticoagulation is maintained.[6]

MAKE SURE PATIENTS KNOW ABOUT SAFE STORAGE AND ADMINISTRATION

Emphasise to patients that rivaroxaban is an anticoagulant, and overdose or unintended use can lead to fatal haemorrhagic complications. The effect of rivaroxaban is irreversible, a specific antidote is not available in NZ and vitamin K will not affect the anticoagulant activity.[2] Due to its high degree of plasma protein binding, rivaroxaban cannot be removed by dialysis. For these reasons, it is important that rivaroxaban is kept out of reach and out of sight of children, and it must not be shared with others.

For rivaroxaban to work effectively, it should be taken at the same time each day. If a once-daily dose is missed, it should be taken immediately on the same day. If the 15mg twice-daily dose is missed, the missed tablet may be taken together with the next dose or as soon as the patient remembers (to give 30mg per day).[2] The 10mg tablets may

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be taken with or without food as absorption is not affected. However, the 15mg and 20mg tablets should be taken with food for optimal absorption.[2,5]

All strengths may be crushed and dissolve in water.

Although direct oral anticoagulants such as rivaroxaban do not require monitoring of their anticoagulant effect and interact with fewer foods and medicines compared with warfarin, adherence cannot be easily measured.[3]

Switching to rivaroxaban

If the patient is already taking warfarin or another vitamin K antagonist, it should be stopped, and rivaroxaban should only be started once the INR is below 2.5 (or 3, depending on the indication).[2,14] Refer to the data sheet for more detailed information about switching between anticoagulants.

Table 2. Child-Pugh classification

Parameter	Assign 1 point	Assign 2 points	Assign 3 points
Ascites	Absent	Slight	Moderate
Bilirubin (micromole/L)	<11	11-45	>45
Albumin (g/L)	>35	28-35	<28
Prothrombin time[#] *or* INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Grade A = total score of 5-6 (mild disease)
Grade B = total score of 7-9 (moderate disease)
Grade C = total score of 10-15 (severe disease)
[#]seconds over control

ACKNOWLEDGEMENTS

We wish to thank Dr Eileen Merriman, Consultant Haematologist and Liz Brookbanks, Pharmacist Team Leader at Waitemata District Health Board, for their valuable contribution to this bulletin.

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No: 0182-01-120, Issued March 2019; Review: March 2022