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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 indicated for the prophylaxis of venous thromboembolism (VTE) following elective hip or knee replacement surgery, and for the prophylaxis of recurrent deep vein thrombosis (DVT) and recurrent pulmonary embolism (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]

There is currently no data to support rivaroxaban in patients with prosthetic valves.[2,3]

CHECK AND MONITOR RENAL AND HEPATIC FUNCTION

Before initiating treatment with rivaroxaban, renal and hepatic function must be checked. Rivaroxaban is contraindicated in patients with severe renal impairment (creatinine clearance (CrCl) less than 15mL/min) and for those with moderate to severe hepatic impairment. There is currently no data available for these patients.[2]

Renal impairment

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

Rivaroxaban can be used for patients with moderate renal impairment (CrCl 30-49mL/min),[2] however dose adjustments may be required. Make sure such patients are aware there might be an increased risk of bleeding, and to seek medical care if bleeding occurs.

The dose of rivaroxaban should be adjusted to accommodate for degree of renal impairment. See Table 1 for dose recommendations as per condition and renal function.

Table 1. Recommended doses of rivaroxaban[2]

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

* 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

Hepatic impairment

For patients with moderate to severe hepatic impairment (Child-Pugh** B and C), rivaroxaban is contraindicated due to an increased bleeding risk.[2]

**see Table 2 for explanation

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]

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RIVAROXABAN

DO NOT USE DURING PREGNANCY

Rivaroxaban is considered pregnancy category C, so should not be used. 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. Rivaroxaban is considered to be contraindicated during pregnancy because of the risk of bleeding and the evidence that rivaroxaban crosses the placenta.[2]

Likewise, there is no information about the use of rivaroxaban in nursing mothers. There is however evidence that it is secreted into breast milk, so it is considered to be contraindicated during breastfeeding.[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 bleeding occurs it would be advisable to delay further doses[5] until they have been assessed.

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 risk of bleeding. Examples include recent gastro-intestinal ulcer, oesophageal varices, or following recent brain, spinal or ophthalmic surgery. Compared with warfarin, bleeding events are considered to be similar, but there is some evidence to suggest that the rate of intracerebral haemorrhage may be lower with rivaroxaban but with a higher rate of gastrointestinal bleeding.[3]

Coagulation tests (APTT/PR) are not a reliable measure of anticoagulant effect in patients who are taking rivaroxaban. If a patient is bleeding, and measurement of the anticoagulant effect is considered necessary, discuss further with a haematologist. They may recommend an anti-Xa level or measurement of plasma rivaroxaban concentration which are generally more informative.

Patients should be informed that the bleeding risk is increased when rivaroxaban is used concomitantly with other anticoagulants, and that there is a lack of data to support such combinations.[2] For patients taking antiplatelet therapy (eg clopidogrel, aspirin), a careful risk-benefit assessment should be performed to determine bleeding risk versus thrombosis risk.[2] 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]

There is some evidence to suggest there can be an increased bleeding time if rivaroxaban is co-administered with **naproxen**. Although many patients in clinical trials were taking NSAIDs, and experienced a similar bleeding time to those without NSAIDs, special care is advised if anticoagulated patients are treated with this combination.[2]

Medicines that can increase rivaroxaban plasma concentrations include itraconazole and ritonavir, however fluconazole may be co-administered.[2] Some anticonvulsants (eg phenytoin, carbamazepine) and St John's Wort may decrease the anticoagulant effect of rivaroxaban. If concurrent use is unavoidable, monitor closely for symptoms of thrombosis.[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 vitamin K has no affect on anticoagulant activity.[2] Rivaroxaban cannot be removed by dialysis due to its high degree of plasma protein binding. 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.

Patients should be aware that if they become breathless or notice any unexplained swelling or signs of allergy, they should seek medical attention immediately.[2]

For rivaroxaban to work effectively, it must be taken every day, preferably at the same time each day, and for the recommended duration of time. If a dose is missed and it is the same day, it should be taken.

For optimal absorption, the 15mg and 20mg tablets should be taken with food.[2,5]

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There are benefits with novel oral anticoagulants such as rivaroxaban. Compared with warfarin they do not require monitoring, and interact with few foods and medicines, however, 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] Refer to the data sheet for more detailed information about switching between anticoagulants.

Note: INR is only validated for vitamin K antagonists (eg warfarin) and cannot be used for novel oral anticoagulants such as rivaroxaban.[2]

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**Child-Pugh classification

Adequate hepatic function is necessary to metabolise many medicines effectively. Assessing hepatic function is not always straightforward because there is no single test that reliably measures this. The Child-Pugh classification incorporates several parameters and the resulting grades can be used as an indicator of how well medicines are metabolised.[6]

Depending on hepatic clearance and the therapeutic index of the medication, dose adjustments or avoidance may be required in grade B and C chronic liver disease, as is the case for rivaroxaban.

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

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