University Health System

Guidelines for Use
Rivaroxaban (Xarelto®)

FDA Approved Indications

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- For the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and for the reduction in the risk of recurrence of DVT and PE
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery
- In combination with aspirin, to reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) in patients with chronic coronary artery disease (CAD) and peripheral artery disease (PAD)

Contraindications

- Active pathologic bleeding
- Significant liver disease (Child Pugh B & C)
- Epidural/spinal anesthesia
- Hypersensitivity to rivaroxaban
- Pregnancy

Mechanism of Action

Rivaroxaban is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa. It does not require a cofactor (such as Anti-thrombin) for activity. Activation of factor X to factor Xa via the intrinsic and extrinsic pathways plays a central role in the blood coagulation cascade.

Pharmacokinetics

Half-life: 5 - 9 hours (elderly 11-13 hours)
Time to peak: 2 - 4 hours after administration
Bioavailability: Dose dependent.
10mg is 80 - 100% and not affected by food. Can be taken with or without food
20mg is 66% and increased with food. 15mg and 20mg tablets should be taken with food
Protein binding: 92-95% (not expected to be dialyzable)

Drug Interactions

Rivaroxaban is a substrate of CYP450 3A4/5, CYP2J2, and the P-gp transporters. Inhibitors and inducers of these CYP450 and P-gp may change exposure to rivaroxaban.

Table 1: Drug Interactions

Avoid use with combined strong CYP3A4 and P-gp inhibitors and inducers			
Inhibitors		**Inducers**	
Ketoconazole	Lopinavir/ritonavir	Carbamazepine	
Itraconazole	Ritonavir	Phenytoin	
Indinavir/ritonavir	Conivaptan	Rifampin	
Caution using P-gp and/or weak–moderate inhibitors of CYP3A4 in combination with rivaroxaban when CrCl is 15-50mL/min. Consider risk vs benefit and more frequent renal function assessment (every 3 months)			
Amiodarone	Azithromycin	Diltiazem	Quinidine
Dronedarone	Erythromycin	Verapamil	Ranolazine

Discontinuation of Therapy Before Surgery

Stop at least 24 hours before procedures to reduce the risk of bleeding. If deciding whether a procedure should be delayed until 24 hours post dose, weigh increase risk of bleeding against the urgency of intervention. Consider holding for 48 hours in elderly, CrCl <50 mL/min or if patient is a high bleeding risk and goal is to have minimal or no residual rivaroxaban effect. If patient will be off rivaroxaban for more than 24 hours, consider bridging with enoxaparin or heparin. Restart rivaroxaban post-op when hemostasis has been established.

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Dosage (based on indication and renal function)

1. Nonvalvular Atrial fibrillation

CrCl > 50 mL/min: 20mg orally, once daily with a full meal.
CrCl 15 – 50 mL/min: 15mg orally, once daily with a full meal. *Caution if CrCl <30 mL/min. These patients were excluded from the ROCKET AF trial[2]. Use only if potential benefit outweighs the risk and consider assessing renal function more frequently (every 3 months)
CrCl <15 mL/min or on dialysis: **Do not use**

2. Treatment of DVT and/or PE

Treatment: 15mg twice daily orally with a full meal for 21 days, then 20mg once daily orally with a full meal at approximately the same time each day for the remaining treatment period
Reduction in the risk of recurrence of DVT or PE after at least 6 months of initial treatment: 10 mg once daily with or without food.
CrCl < 30 ml/min or on dialysis : **Do not use**

3. Prophylaxis of DVT Following Hip or Knee Replacement Surgery

10mg orally, once daily with or without food. 35 days total for hip replacements, 12 days for knee replacements
CrCl 30-50 mL/min: No dose adjustment provided by the manufacturer, use with caution
CrCl < 30 mL/min or on dialysis: **Do not use**

4. Reduction of risk of major cardiovascular events in chronic CAD/PAD

2.5mg orally, twice daily with or without food in combination with aspirin 81mg once daily
CrCl < 15mL/min or on dialysis: No dose adjustments provided by manufacturer, however these patients were excluded from the COMPASS trial[3]. Use only if potential benefit outweighs risk.

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Table 2: Converting to or from Rivaroxaban to Other Anticoagulants

Drug Conversion	Action
From warfarin →rivaroxaban	Discontinue warfarin and start rivaroxaban when INR is < 3 to avoid periods of inadequate anticoagulation
From anticoagulant other than warfarin →rivaroxaban	Start rivaroxaban 0 - 2 hours before the next dose would have been due
From rivaroxaban → warfarin	(No clinical trial data available. Rivaroxaban can elevate the INR) Discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken
From rivaroxaban →anticoagulant other than warfarin (parenteral or oral)	Discontinue rivaroxaban and give the first dose of the other anticoagulant at the time the next rivaroxaban dose would have been taken

Monitoring

Routine monitoring of coagulation tests is not required. Assess renal function (Scr), liver function (LFTs), and complete blood count (CBC) at **baseline** and at least every 6-12 months thereafter to see if dose adjustment or alternative therapy is necessary. See the document titled "Direct Oral Anticoagulation Monitoring" posted to the Clinical Pathways and Guidelines page for more guidance. Though not recommended to assess effectiveness, the prothrombin time (PT), INR, and aPTT are prolonged with apixaban.

Management of Bleeding

Due to a half-life (5-9 hrs, or 11-13 hours in elderly), plasma concentration declines quickly after discontinuation. Management of bleeds should be individualized.

Table 3: Strategies for the Management of Bleeding While on Rivaroxaban

Bleed Category	Action
Minor Bleed	Hold rivaroxaban. Provide supportive measures
Life-Threatening Bleed	○ Discontinue rivaroxaban ○ Provide supportive measures (compression, surgical hemostasis, transfusions) ○ Well documented overdose: Oral charcoal (give within 1 - 2 hours of ingestion) ○ Highly protein bound- not expected to be dialyzable ○ Kcentra® 50 units/kg may be considered[4,5]. This does not reverse rivaroxaban, but is an attempt to overwhelm the effect of the drug. See the "**Oral Anticoagulation Reversal Algorithm**" on the Clinical Pathways and Guidelines page for more information.

References:

1. Rivaroxaban (Xarelto®) package insert. Janssen Pharmaceuticals, October 2018.
2. Patel MR, et al. N Engl J Med 2011;365:883-91.
3. Eikelboom JW, et al. N Engl J Med 2017;377:1319-30
4. Nutescu EA, et al. Am J Health-Syst Pharm. 2013;70:1914-29.
5. Frontera JA, et al. *Neurocrit Care.* 2016;24:6-46.

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