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

UHS Formulary Restrictions
Rivaroxaban is approved for use with restrictions. See UHS Drug Formulary on LexiComp for more information

Contraindications
- Active pathologic bleeding
- Significant liver disease
- Concomitant therapy with CYP 3A4 inhibitors or inducers (see drug interactions below)
- Epidural/spinal anesthesia
- Active endocarditis
- 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

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Indinavir/ritonav</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Lopinavir/ritonav</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
</tr>
<tr>
<td>Conivaptan</td>
<td></td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Amiodarone</th>
<th>Azithromycin</th>
<th>Diltiazem</th>
<th>Quinidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronedarone</td>
<td>Erythromycin</td>
<td>Verapamil</td>
<td>Ranolazine</td>
</tr>
</tbody>
</table>

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.

Crystal Franco-Martinez, PharmD, BCPS
Review by members of the Anticoagulation Safety Committee April 2013
P&T Approved July 2013, Rev May 2014
Dosage (based on indication and renal function)
1. Nonvalvular Atrial fibrillation
   CrCl > 50 mL/min: 20mg orally, once daily with the evening meal
   CrCl 15 – 50 mL/min: 15mg orally, once daily with evening meal. *Caution if CrCl <30 mL/min. These patients were excluded from the ROCKET AF trial². 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 (Consider consult to Anticoagulation Clinic for dosing transition)
   CrCl > 30 mL/min: 15mg twice daily orally with food for 21 days, then 20mg once daily orally with food at approximately the same time each day for the remaining treatment period
   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 adjustment necessary, use with caution
   CrCl < 30 mL/min or on dialysis: Do not use

Table 2: Converting to or from Rivaroxaban to Other Anticoagulants

<table>
<thead>
<tr>
<th>Drug Conversion</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>From warfarin → rivaroxaban</td>
<td>Discontinue warfarin and start rivaroxaban when INR is &lt;3 to avoid periods of inadequate anticoagulation</td>
</tr>
<tr>
<td>From anticoagulant other than warfarin → rivaroxaban</td>
<td>Start rivaroxaban 0 - 2 hours before the next dose would have been due</td>
</tr>
<tr>
<td>From rivaroxaban → warfarin</td>
<td>(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</td>
</tr>
<tr>
<td>From rivaroxaban → anticoagulant other than warfarin (parenteral or oral)</td>
<td>Discontinue rivaroxaban and give the first dose of the other anticoagulant at the time the next rivaroxaban dose would have been taken</td>
</tr>
</tbody>
</table>

Monitoring
Routine coagulation monitoring is not recommended. Baseline and periodic renal function should be assessed to see if dose adjustment is necessary. PT and aPTT may be only slightly elevated at therapeutic doses and may vary greatly from one laboratory to another. The INR therapeutic target for warfarin cannot be applied to rivaroxaban.

Management of Bleeding
There is no antidote for reversing the effect of rivaroxaban. Due to a short 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

<table>
<thead>
<tr>
<th>Bleed Category</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Bleed</td>
<td>Hold rivaroxaban. Provide supportive measures</td>
</tr>
<tr>
<td>Severe or Life-Threatening Bleed</td>
<td>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 Limited animal and human data for the use of activated or non-activated prothrombin complex concentrates is available. They do not reverse rivaroxaban, but attempt to overwhelm the affect of the drug. Doses are unknown. Can consider Kcentra³ 25-50 units/kg if life threatening situation and measures above fail to control bleed</td>
</tr>
</tbody>
</table>

References:

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