OVERVIEW:

Rivaroxaban is an oral inhibitor of activated Factor X (Xa) with predictable pharmacokinetics

**Monitoring:** Routine laboratory monitoring is not recommended

**Pharmacokinetics:**
- The half-life of rivaroxaban among healthy individuals with normal renal function is 7 to 11 hours
- Peak anticoagulation effect with rivaroxaban is observed 2.5 - 4 hours after the dose is taken

**No proven antidote for rivaroxaban exists**
- A study in healthy volunteers suggests that nonactivated 4-factor prothrombin complex concentrate (PCC) may successfully reverse the anticoagulant effect of rivaroxaban, but this has yet to be confirmed in a rigorous clinical trial. This differs from the 3-factor PCC (low factor VII) currently available in the United States.

**Rivaroxaban cannot easily be monitored with routine coagulation assays**
- Rivaroxaban prolongs the prothrombin time (PT) and partial thromboplastin time (aPTT), but this effect is short-lived, and the effect of the drug on these assays is non-linear. Of the two tests, PT may be more sensitive to the effect of rivaroxaban than aPTT, but it is still possible that significant anticoagulant effect persists even if the PT has normalized. Therefore, the timing of last dose, rather than standard coagulation times, should be used to determine likelihood of anticoagulant effect.

INDICATION AND USAGE:

Rivaroxaban is approved by the FDA for:
- Venous thromboembolism (VTE) prophylaxis following total hip or total knee replacement surgery
- Stroke reduction in patients with non-valvular atrial fibrillation
- Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)
- Reduction of risk of recurrence of DVT and PE

DOSAGE AND ADMINISTRATION

See dosing for various indications at end of this document
CONTRAINDICATIONS

**Black Box Warning:** Discontinuing rivaroxaban places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following rivaroxaban's discontinuation in clinical trials in atrial fibrillation patients. If anticoagulation with rivaroxaban must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.

**Black Box Warning:** Epidural or spinal hematomas have occurred in patients treated with rivaroxaban who are receiving neuraxial anesthesia or undergoing spinal puncture. Consider the benefits and risks before neuraxial intervention in patients receiving or planning to begin rivaroxaban.

Rivaroxaban should NOT be used in patients:
- With CrCl < 30mL/min for DVT prophylaxis following hip/knee surgery or DVT/PE treatment and prevention
- With CrCl < 15 mL/min for stroke prevention in nonvalvular atrial fibrillation
- That are allergic to the medication
- With active pathological bleeding

Rivaroxaban should be used with caution, if at all in patients:
- With a CrCl 30-50 mL/min for DVT prophylaxis following hip/knee surgery
- Who are pregnant
- Who are taking combined P-gp and strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, lopinavir, ritonavir, indinavir, and conivaptan) which increase drug exposure and bleeding risk
- Who are taking combined P-gp and strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampin, St. John’s Wort) which decrease drug exposure and efficacy
- Who are taking other agents which might increase risk of bleeding (e.g. aspirin, clopidogrel, NSAID’s)

INTERUPTION OF RIVAROXABAN FOR SURGICAL PROCEDURES

If clinically possible, delay the surgery or intervention -
- Wait 1-2 days (CrCl ≥50 mL/min) or 3-5 days (CrCl <50 mL/min) before invasive or surgical procedures is undertaken (especially if neuraxial anesthesia is anticipated)

MITIGATION OF ACTIVE BLEEDING

Appropriate clinical support is recommended in the event of hemorrhagic complications

Consider surgical hemostasis and supportive care with blood transfusion when indicated

Rivaroxaban is primarily excreted in the urine; therefore, adequate diuresis is recommended

The use of prothrombin complex concentrates (PCC) may be considered, with limited ex and in-vivo data supporting effectiveness (Note that most research has evaluated the use of inactivated 4-factor concentrates; but presently only 3-factor concentrates are available in the United States; e.g. Profilnine®)

Factor VIIa concentrates may be considered, although usefulness in clinical treatment has not been established
PATIENT EDUCATION AND MONITORING

It is vital that patients get the same education regarding bleeding signs and symptoms to watch for as those patients taking warfarin or other anticoagulants (See rivaroxaban patient fact sheet).

For patients taking rivaroxaban long term, periodic (every 6-12 months) evaluation of renal function, bleeding risk factors, patient compliance and other influencing factors is warranted. In addition, patients should not stop the medication unless directed to do so, due to a possible increase in stroke after discontinuation.

Patients should be monitored closely when other medications are changed, especially when antiplatelet medications or those affecting the P-gp or CYP3A4 system are started or stopped.

References:

**Rivaroxaban (Xarelto®)**

**Indications & Usage:**

1. Stroke and Systemic Embolism Prophylaxis in Nonvalvular Atrial Fibrillation
2. Treatment of Deep Vein Thrombosis (DVT)
3. Treatment of Pulmonary Embolism (PE)
4. Secondary Prevention of DVT and PE
5. DVT Prophylaxis following Hip Replacement Surgery
6. DVT Prophylaxis following Knee Replacement Surgery

**Dosage and Administration:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stroke and Systemic Embolism Prophylaxis in Nonvalvular Atrial Fibrillation</td>
<td>CrCl &gt; 50 mL/min: 20 mg once daily <strong>with evening meal</strong>&lt;br&gt;CrCl 15-50 mL/min: 15 mg once daily <strong>with evening meal</strong>&lt;br&gt;CrCl &lt;15 mL/min: Avoid use</td>
</tr>
<tr>
<td>2. Treatment of DVT&lt;br&gt;3. Treatment of PE</td>
<td>CrCl ≥ 30 mL/min: 15 mg twice daily <strong>with food</strong> for first 21 days&lt;br&gt;<strong>After 21 days, transition to ↓</strong>&lt;br&gt;20 mg once daily <strong>with food</strong>, for the remainder of treatment&lt;br&gt;CrCl &lt; 30 mL/min: Avoid use</td>
</tr>
<tr>
<td>4. Secondary Prevention of DVT and PE</td>
<td>CrCl ≥ 30 mL/min: 20 mg once daily <strong>with food</strong>&lt;br&gt;CrCl &lt; 30 mL/min: Avoid use</td>
</tr>
<tr>
<td>5. DVT Prophylaxis following Hip Replacement Surgery</td>
<td>CrCl ≥ 30 mL/min: 10 mg once daily for 35 days&lt;br&gt;CrCl 30-50 mL/min: Observe and promptly evaluate any signs or symptoms of blood loss&lt;br&gt;CrCl &lt; 30 mL/min: Avoid use</td>
</tr>
<tr>
<td>6. DVT Prophylaxis following Knee Replacement Surgery</td>
<td>CrCl ≥ 30 mL/min: 10 mg once daily for 12 days&lt;br&gt;CrCl 30-50 mL/min: Observe and promptly evaluate any signs or symptoms of blood loss&lt;br&gt;CrCl &lt; 30 mL/min: Avoid use</td>
</tr>
</tbody>
</table>

*The 15 mg and 20 mg tablets should be taken with food because this increases the absorption of the drug; however the 10 mg tablet can be taken with or without food. The bioavailability of rivaroxaban is dose dependent and intake with food does not affect the AUC or Cmax at the 10mg dose.*