Apixaban (Eliquis®): Guidelines for Use

**FDA Approved Indications**
- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of DVT and PE and to reduce the risk of recurrent DVT/PE following initial therapy
- For the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patient who have undergone hip or knee replacement surgery

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

**Contraindications**
- Active pathological bleeding
- Severe hypersensitivity reaction to apixaban (anaphylactic reactions)
- Severe hepatic impairment (Child-Pugh Class C)
- Epidural/spinal anesthesia

**Mechanism of Action**
- Apixaban is an orally bioavailable factor Xa inhibitor. It does not require a cofactor, such as anti-thrombin, for its antithrombotic activity. By inhibiting free and clot bound factor Xa, apixaban decreases thrombin generation and thrombus development. Apixaban also indirectly inhibits thrombin induced platelet aggregation.

**Pharmacokinetics**
- Half-life: 12 hours
- Time to peak: 3-4 hours
- Bioavailability: ~50%, (unaffected by food)
- Protein binding: ~87%
- Metabolism: hepatic, predominantly via CYP3A4

**Drug Interactions**
Apixaban is a substrate of both CYP3A4 and P-gp. Both inhibitor and inducers of CYP3A4 and P-gp may change exposure to apixaban.

**Table 1: Drug Interactions**

<table>
<thead>
<tr>
<th>Combined CYP3A4 and P-gp Strong Inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Reduce dose from 5 mg twice daily to 2.5 mg twice daily when administered with ketoconazole, itraconazole, ritonavir, or clarithromycin.</td>
</tr>
<tr>
<td>In patients already taking apixaban 2.5 mg twice daily or in patients who meet 2 of the following criteria: age ≥ 80 years, body weight ≤ 60kg or SCr &gt; 1.5 mg/dL, avoid co-administration with the above mentioned inhibitors.</td>
</tr>
<tr>
<td>Avoid use with strong dual Inducers of CYP3A4 and P-gp</td>
</tr>
<tr>
<td>rifampin, carbamazepine, phenytoin, St. John’s Wort, phenobarbital, and primidone</td>
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</table>

**Discontinuation of Therapy Before Surgery**
Apixaban should be stopped at least 48 hours prior to elective surgery or invasive procedures with a moderate to high risk of bleeding. Discontinued at least 24 hours prior to surgery or procedures with a low risk of bleeding or where the bleeding would be in a non-critical location and easily controlled. Bridging anticoagulation during the 24-48 hours after stopping apixaban and prior to the intervention is not generally required. Restart apixaban post-op as soon as adequate hemostasis has been established. If oral therapy cannot be started, consider starting a parenteral agent (heparin, or enoxaparin).
**Dosage (based on indication and renal function)**

1. **Nonvalvular atrial fibrillation**
   
   **SCr <1.5mg/dL:** 5mg by mouth twice daily unless patient has both of the following, then reduce the dose to 2.5mg by mouth twice daily: Age ≥ 80 years AND body weight ≤ 60 kg
   
   **SCr ≥1.5mg/dL:** Reduce dose to 2.5mg twice daily if age ≥ 80 years OR body weight ≤ 60 kg
   
   **ESRD requiring hemodialysis:** 5mg twice daily, reduce to 2.5mg twice daily if: Age ≥ 80 years OR body weight ≤ 60 kg.
   
   *Caution:* These patients were excluded from clinical trials. Use only if potential benefit outweighs the risk.

2. **DVT and/or PE**
   
   Treatment: 10mg by mouth twice daily for 7 days followed by 5mg by mouth twice daily for the remainder of treatment.
   
   Reduction in recurrence risk of DVT or PE: 2.5mg by mouth twice daily after at least 6 months of initial treatment.
   
   **Renal impairment:** No dose adjustments necessary, however patients with a SCr > 2.5 mg/dL or CrCl < 25 ml/min were excluded from the AMPLIFY clinical trials.

3. **Prophylaxis of VTE Following Hip or Knee Replacement Surgery**

   2.5mg by mouth twice daily, beginning 12-24 hours post-op. Continue for 35 days following hip replacement surgery and 12 days following knee replacement surgery.

   **Renal impairment:** No dose adjustments necessary, however patients with impaired renal function were excluded from the ADVANCE trials. Greater than 80% of patients in each trial had a CrCl > 60mL/min.

**Table 2: Converting to or from Apixaban to Other Anticoagulants**

<table>
<thead>
<tr>
<th>Drug Conversion</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>From warfarin → apixaban</td>
<td>Discontinue warfarin and start apixaban when the INR is &lt; 2</td>
</tr>
<tr>
<td>From anticoagulant other than warfarin → apixaban</td>
<td>Discontinue current agent and start apixaban at the time the next dose would have been taken</td>
</tr>
<tr>
<td>From apixaban → warfarin:</td>
<td>If continuous anticoagulation is necessary, discontinue apixaban and begin warfarin and a parental anticoagulant at the time the next dose of apixaban would have been administered. Discontinue the parental anticoagulant when INR is therapeutic. Note: Apixaban can elevate the INR; therefore initial INR measurements during the transition from apixaban to warfarin may not be useful in determining the appropriate warfarin dose.</td>
</tr>
<tr>
<td>From apixaban → anticoagulant other than warfarin (parenteral or oral)</td>
<td>Discontinue apixaban start the other anticoagulant at the time the next apixaban dose would have been taken</td>
</tr>
</tbody>
</table>

**Monitoring**

Routine monitoring of coagulation tests is not required. Baseline and periodic renal function should be assessed to see if dose adjustment is necessary. Though not recommended to assess effectiveness, the prothrombin time (PT), INR, and aPTT are prolonged with apixaban.

**Management of Bleeding**

There is no antidote for reversing the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose. Management of bleeds should be individualized.

**Table 3: Strategies for the Management of Bleeding while on Apixaban**

<table>
<thead>
<tr>
<th>Bleed Category</th>
<th>Action</th>
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<tbody>
<tr>
<td>Minor Bleed</td>
<td>Hold apixaban. Provide supportive measures</td>
</tr>
<tr>
<td>Severe or Life-Threatening Bleed</td>
<td>o Discontinue apixaban o Provide supportive measures (compression, surgical hemostasis, transfusions) o Well documented overdose: Oral charcoal (give if ingestion occurred within 2 to 6 hours of presentation) o Dialysis is not expected to have an impact on apixaban exposure. o Limited data for the use of clotting factor concentrates. They do not reverse apixaban, but attempt to overwhelm the effect of the drug. o Kcentra® 25-50 units/kg can be considered if life threatening situation and measures above fail to control bleed. (See Kcentra algorithm on Clinical Intranet)</td>
</tr>
</tbody>
</table>

**References:**


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Approved by P&T Committee: January 2015