A. General Information

These guidelines apply to the use of apixaban for the treatment and prevention of thromboembolic disorders.

Apixaban is a Direct Oral AntiCoagulants (DOACs), a newer class of anticoagulation medication FDA approved in adults for the treatment of venous thromboembolism (VTE), prevention of thromboembolism, and prevention of nonvalvular atrial fibrillation stroke and thromboembolism. Apixaban use in pediatric patient is not well established; however, off-label use in older children may be considered under the guidance of Hematology, Oncology, or Cardiology.

CHOP has apixaban and rivaroxaban on the formulary. Both are direct factor Xa inhibitors; which undergo hepatic metabolism (primarily CYP3A4) and renal elimination. Drug-drug interaction should be assessed with both apixaban and rivaroxaban.

Apixaban requires twice a day dosing and can be taken with or without food. Use in females with a history of heavy menstrual bleeding, apixaban has a more favorable bleeding profile compared to other DOACs. Apixaban is renally eliminated, but to a lesser extent compared to rivaroxaban. Although apixaban has been studied in patients with renal impairment, long-term safety and efficacy is not established. For patients with renal disease and creatinine clearance < 50 mL/minute/1.73 m² the preferred anticoagulant is warfarin. Warfarin has the benefit of monitoring and more experience with reversal treatment options. For patients in whom warfarin is not an option for long term therapy, apixaban may be considered on a case by case basis if renal function is stable with creatinine clearance ≥ 30 mL/minute/1.73 m².

B. Contraindications to Apixaban

Absolute contraindication:

- Acute stroke/brain ischemia or intracranial hemorrhage
- Allergy to apixaban or any components
- Incomplete spinal cord injury with suspected or known paraspinal hematoma
- Ongoing and uncontrolled bleeding
- Uncorrected coagulopathy
- Patients with cardiac valves due to an increased rate of thrombotic events as compared to warfarin.
- Patients with triple positive antiphospholipid antibody syndrome (APS) due to increased rates of thrombosis when compared with warfarin.

Discuss with Hematology/Cardiac Thrombosis:

- Patients when admitted to an intensive care setting (such as PICU, CICU, or NICU). Due to the longer half-life of the DOAC (see reversal section).
- Patients with renal disease and CrCl < 30 mL/min/1.73 m²
- Patients with any hepatic disease associated with coagulopathy (ie Child Pugh C)
CLINICAL PRACTICE GUIDELINES

Initiation and Maintenance of Apixaban

Disclaimer: These clinical practice guidelines are based upon the opinions of staff members of The Children’s Hospital of Philadelphia. Treatment should be individualized and based upon the clinical conditions of each patient.

- Patients with small and/or large bowel resection due to unknown absorption
- Patient with weight > 120 kg because there are limited clinical data available for patients at the extreme of weight.
- Patients on an interacting medication(s) such as CYP3A4 inhibitor/inducer – Contact Pharmacy (see dosing section)

C. Baseline Monitoring (To be completed prior to initiating Apixaban)

Baseline labs are to be completed to assess the patient’s coagulation and renal status:
- PT/INR
- PTT
- CBC
- Creatinine (Cr)

If the patient has abnormal coagulation studies, thrombocytopenia, the hematology team should be consulted. If the patient has an elevated Cr, the hematology and clinical pharmacy teams should be consulted for further recommendations.

D. Dosing

Initiation

In general, apixaban may be considered for adolescents and adults 50 to 120 kg for the treatment or prevention of venous thromboembolism (VTE).

NOTE:
- If patient have ongoing procedures(s) with bleed risk requiring holding of anticoagulation, then heparin or enoxaparin should be considered until the patient is more stable or closer to discharge.
- Usually administered by mouth. May be crushed and administer through gastric routes only. The dosing of apixaban is specific to the indication. Note: Patient must be 50 to 120 kg in weight. See Table 1:

<table>
<thead>
<tr>
<th>Table 1: Dosing of Apixaban for weight ≥ 50 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>Treatment of VTE (DVT, PE)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
**CLINICAL PRACTICE GUIDELINES**

Initiation and Maintenance of Apixaban

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<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Maintenance Dosing Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonvalvular atrial fibrillation</td>
<td>Maintenance: 5 mg twice daily&lt;br&gt;CrCl ≥ 30 mL/min/1.73 m²: no dosage adjustment necessary</td>
</tr>
<tr>
<td>Postoperative DVT thromboprophylaxis (Knee/Hip only)</td>
<td>Maintenance: 2.5 mg twice daily&lt;br&gt;CrCl ≥ 30 mL/min/1.73 m²: no dosage adjustment necessary</td>
</tr>
</tbody>
</table>

**Drug Interaction**

Apixaban is metabolized via cytochrome P450 (primarily CYP3A4) and renal elimination. Co-administration of apixaban with medication(s) with certain cytochrome CYP3A4 inhibition/induction is not recommended; unless benefit outweighs risk.

- **Medications with Interaction and Recommendation (Note: List is not all inclusive. Medications with similar mechanism of interaction should follow similar recommendation)**
  - Inhibitors and P-glycoprotein associated with increased apixaban serum concentration or bleeding, especially in patients with renal impairment:
    - Avoid concomitant use with: Itraconazole (inhibitor); Ketoconazole-systemic (inhibitor); Ritonavir (inhibitor)
    - Avoid concomitant use or require monitoring: Erythromycin; Fluconazole; Posaconazole; Verapamil; Voriconazole
  - Inducers and P-glycoprotein associated with decreased apixaban serum concentration:
    - Avoid concomitant use with: Carbamazepine (inducer); Fosphenytoin (inducer); Phenytoin (inducer); Rifampin (inducer)

**E. Monitoring**

- Routine monitoring of apixaban drug level is not recommended. Variable apixaban levels have been reported and does not correlate with safety or efficacy. If apixaban calibrated assay is available, the expected observed peak levels for apixaban are 16-108 ng/mL for 2.5 mg and 91–321 ng/mL for 5 mg dose. The expected trough is < 30 ng/mL.

- **Serum creatinine** should be monitored in some patients with baseline renal disease or acute kidney injury.
  - CHOP Inpatient Units: Main Hospital (Philadelphia & KOPH): weekly and may increase to monthly
  - CHOP Enterprise-wide Outpatient: once as outpatient, then every 3-6 months if needed

**F. Safety**

- **Bleeding**! The major adverse event related to apixaban, as with any anticoagulant, is bleeding. In adult trails, compared to warfarin, DOACs appear to be associated with less bleeding.
G. Apixaban Reversal

Andexanet alfa is FDA approved for the reversal of anticoagulation due to life-threatening or uncontrolled bleeding related to Xa inhibitors this includes apixaban. For majority of bleeding events the recommendation is to observe the patient.

- If urgent reversal of apixaban is needed due to serious or life-threatening bleeding, then andexanet may be considered in conjunction with Hematology consultation. If ingestion of apixaban is < 2 hours, consider activated charcoal.

  o Criteria for First dose of Andexanet (per Attending Physician in Cardiology, Critical Care, Hematology, Oncology/BMT, or Toxicology only):
    - Suspected use of apixaban in the past 18 hours hours in patients with normal renal function and acute major bleeding was defined as bleeding having one or more of the following features
      - Potentially life-threatening bleeding with signs or symptoms of hemodynamic compromise (e.g., severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained)
      - Bleeding associated with a decrease in the hemoglobin level of at least 2 g per deciliter (or a hemoglobin level of ≤8 g per deciliter if no baseline hemoglobin level was available)
      - Bleeding in a critical area or organ (e.g., retroperitoneal, intraarticular, pericardial, epidural, or intracranial bleeding or intramuscular bleeding with compartment syndrome)
  
  o Anti-Factor Xa (Lovenox) should be obtained prior to initiation of andexanet
  
  o Patient with CrCl < 30 mL/min/1.73 m² if apixaban is still in the system because may take up to 48 hours – Contact Hematology
  
  o Immediate reversal last for ≤ 2 hours after completion of the infusion is expected and may last at least 22 hours after administration. Subsequent dose(s) restricted to Hematology

- Andexanet is not FDA approved for non-bleeding patients. If patient requires urgent surgical or invasive procedure discussion with the surgical attending and Hematology is recommended. Determine if procedure can be delayed until 24 hours after rivaroxaban ingestion in patient with normal renal function or 48 hours after ingestion in patient with CrCl < 30 mL/min/1.73 m², then andexanet may be considered in conjunction with Hematology consultation.

- Prothrombin complex concentrate (Kcentra) 50 units/kg/dose (maximum 2,000 unit/dose) may be considered.

Note: There is no reported data on the use of andexanet in children < 18 years of age. Based on limited experience, the following dosing recommendations may be considered when determining risk vs. benefit of reversal of apixaban.
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Table 2. Andexanet Dosing

<table>
<thead>
<tr>
<th>Weight</th>
<th>Use of apixaban ≤ 24 hours in patients with normal renal function or up to 48 hours in patient with CrCl &lt; 30 mL/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients 12 to 30 kg</td>
<td>100 mg bolus, then 1 mg/min for up to 100-120 minutes</td>
</tr>
<tr>
<td>Patients 30 to &lt; 50 kg</td>
<td>200 mg bolus, then 2 mg/min for up to 100-120 minutes</td>
</tr>
<tr>
<td>Patients ≥ 50 kg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Last dose of Apixaban</th>
<th>Timing from last dose of Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 mg</td>
<td>400 mg bolus, then 4 mg/min for up to 100-120 minutes</td>
</tr>
<tr>
<td>&gt; 5 mg or unknown</td>
<td>800 mg bolus, then 8 mg/min for up to 100-120 minutes</td>
</tr>
</tbody>
</table>

H. Transitioning between anticoagulants

Table 3: Recommendation for transitioning between Apixaban and other anticoagulants

<table>
<thead>
<tr>
<th>Conversion</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban to new DOAC</td>
<td>Start the new DOAC 12 hours after the previous dose of apixaban</td>
</tr>
<tr>
<td>DOAC to apixaban</td>
<td>Start apixaban when the next dose of the previous DOAC is due</td>
</tr>
<tr>
<td>Continuous infusion of anticoagulation</td>
<td>Initiate apixaban at the time of discontinuation of the infusion</td>
</tr>
<tr>
<td>(i.e. bivalirudin or unfractionated heparin) to apixaban</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin to apixaban</td>
<td>Initiate apixaban 0-2 hours before the next dose of enoxaparin would have been given</td>
</tr>
<tr>
<td>Warfarin to apixaban</td>
<td>Discontinue warfarin and initiate apixaban as soon as INR falls to &lt;2</td>
</tr>
<tr>
<td>Apixaban to parenteral anticoagulation</td>
<td>Initiate parenteral anticoagulant 12 hours after last dose of apixaban</td>
</tr>
<tr>
<td>(i.e. bivalirudin, enoxaparin, or unfractionated heparin)</td>
<td></td>
</tr>
<tr>
<td>Apixaban to warfarin</td>
<td>Apixaban can elevate the INR and can complicate INR interpretation, therefore apixaban should be stopped when</td>
</tr>
<tr>
<td></td>
<td>starting warfarin and consider starting enoxaparin at the time of the next scheduled dose of apixaban until INR ≥ 2.</td>
</tr>
</tbody>
</table>

I. Apixaban reversal for elective procedures
This depends on the perceived risk of thrombosis when the patient is not anticoagulated. Some patients (recent thrombosis, recurrent thrombosis) may be considered high risk, and may need to be covered with enoxaparin or heparin as apixaban wears off. Other patients, on chronic therapy, who are more low risk, may be able to stop apixaban. Please consult the provider conducting the procedure and/or Hematology thrombosis team, as this should be individualized based upon the patient and the procedure.

- Minor procedures: hold for at least 24-48 hours prior to procedure
- Major procedure such as surgery and invasive procedures:
  - CrCl ≥ 30 mL/min/1.73 m²: hold for at least 48 hours prior to procedure.
  - Lumbar punctures may be hold for at least 24 hours depending on urgency
  - CrCl < 30 mL/min/1.73 m²: may need to hold more than 48-96 hours prior to procedure. Contact Clinical Pharmacy to determine renal function and Hematology for more information to determine risk vs. benefit.
- Emergency invasive procedure: bleeding risk is highest if time from last dose < 12 hours. See Apixaban Reversal section
- Restart after hemostasis has been established. For knee/hip replacement at least 6 to 10 hours postoperatively is recommended

J. Complications

- The attending physician of record or the attending defined responsible for outpatient management will be responsible for the diagnosis and management of any potential complications (i.e. bleeding, etc) in consultation with the division of hematology as deemed appropriate.
- Reporting of complications, including bleeding requiring transfusion, intracranial hemorrhage, and over-anticoagulation requiring reversal, into the electronic reporting system, KAPS, is highly recommended.

K. Discharge Education & Follow-Up Planning

Ordering Drug:
When writing discharge orders/instructions, appreciate that dosing is different for each indication and treatment course (initiation and maintenance). Patients may require higher dosing during initiation and then dose is decreased to maintenance dosing. See dosing section above for more information.

- Apixaban (Eliquis):
  - Starter Pack containing 74 tablets of 5 mg
  - Bottle containing 5 mg tablets
  - Bottle containing 2.5 mg tablets

Patient/Family Education:
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- Prior to discharge, all patients and their families should receive education regarding the safe use of apixaban. There are educational Patient-Family Education (PFE) on Apixaban available through via @CHOP as a patient/family pdf.
  - Apixaban

Arranging Follow-up Planning:

- All patients discharged on apixaban should have a follow-up appointment, including date and time scheduled for outpatient follow-up, at the time of discharge. In addition, the attending physician who will be responsible for outpatient management of the apixaban will be identified and documented.

Related Policy: Anticoagulation Management Program (Patient Care Manual)
- Anticoagulation Management Program (New Jersey Licensed Facilities)