OBJECTIVE:
To provide an overview of the mechanism of action, licensed indications, dosing regimens, and side-effect profile of apixaban.

MECHANISM OF ACTION:
Apixaban is an oral factor Xa inhibitor. By binding reversibly to the active site of factor Xa, apixaban attenuates thrombin generation and reduces fibrin formation.

INDICATIONS:
Apixaban is currently licensed in Canada for:
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE.
- Prevention of DVT and PE after elective hip or knee replacement surgery.

DOsing:
1. Prevention of stroke and systemic embolism in atrial fibrillation: 5 mg BID. No dose adjustment is generally necessary in patients with mild or moderate renal impairment, or in those with CrCl 25-30 mL/min. However, a reduced dose of 2.5 mg BID is advised in patients with at least two of the following: (1) serum creatinine ≥ 133 µmol/L, (2) age ≥ 80 years, or (3) body weight ≤60 kg. Data are very limited in patients with a CrCl of 15-24 mL/min and no dosing recommendation is provided by the manufacturer. Apixaban is not recommended in patients with CrCl <15mL/min or for those undergoing dialysis.
2. Acute treatment of DVT or PE: 10 mg BID for 7 days, followed by 5 mg BID. No dose adjustment is necessary in patients with mild or moderate renal impairment (CrCl ≥ 30 mL/min). There are limited clinical data in patients with severe renal impairment (CrCl 15-29 mL/min) and apixaban should be used with caution in these patients because of a potentially higher bleeding risk. Apixaban is not recommended in patients with CrCl <15 mL/min or for those undergoing dialysis.
3. Continued prevention of recurrent DVT and PE: After at least 6 months of treatment, consideration can be given to reducing the dose to 2.5 mg PO BID for long-term prevention of recurrent VTE.
4. Thromboprophylaxis after hip/knee arthroplasty: 2.5 mg BID starting 12-24 hours after surgery and continuing for 14 or 35 days after knee or hip replacement, respectively.
**MONITORING:**

Routine laboratory monitoring is not necessary. The prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT) are often normal in patients taking apixaban and do not provide reliable measures of the anticoagulant activity. Specific anti-factor Xa assays using apixaban calibrators are available in some laboratories to determine the plasma concentration but are not validated across centres and “safe” or therapeutic levels have not been established. For more details about specific testing, see the Clinical Guide: NOACs/DOACs: Coagulation Tests.

Although routine laboratory monitoring is not required for long-term apixaban use, periodic clinical assessment is important to determine and reinforce compliance, review comorbidity and medication changes, and provide education. Furthermore, for most patients, at least yearly assessment of creatinine clearance is recommended. The creatinine should be measured more frequently in patients with an abnormal value at baseline or at risk of worsening renal function. [See Clinical Resource: Direct Oral Anticoagulant (DOAC) Follow-Up Checklist for Clinicians; Direct Oral Anticoagulation (DOAC) Monitoring Checklist for Pharmacists]

**ADVERSE EFFECTS:**

The major adverse effect of apixaban is bleeding; concomitant use of antiplatelet drugs or other anticoagulants increases the bleeding risk. Apixaban should be avoided in patients with indwelling epidural catheters or with a history of recent spinal puncture in order to reduce the risk of epidural or spinal hematomas. Drug levels can also be increased or decreased by the use of concomitant medications (see Drug interactions).

**PERI-PROCEDURAL MANAGEMENT:**


**SPECIAL CONSIDERATIONS:**

**Pregnancy and breast feeding:** Apixaban crosses the placenta and should not be used in pregnancy. It should also be avoided in nursing mothers because it is uncertain whether apixaban appears in the breast milk.

**Renal and hepatic dysfunction:** Apixaban is not recommended in patients with CrCl <15 mL/min and those undergoing dialysis. Dosing recommendations by clinical indication for patients with less severe renal dysfunction are described above under Dosing. Apixaban should be used with caution in those with mild or moderate or hepatic impairment (Child-Pugh class A or B); however, no dosing modification is recommended in these patients. Apixaban is not recommended in patients with severe hepatic impairment (Child-Pugh class C) and is contraindicated in patients with coagulopathy associated with hepatic disease.
**Drug interactions:** The concomitant use of apixaban and drugs that inhibit or induce both P-glycoprotein (P-gp) and CYP3A4 should be avoided. Patients taking strong inhibitors of both CYP3A4 and P-gp are at an increased risk of bleeding. Examples of inhibitors includeazole antifungals (e.g. itraconazole, ketoconazole, voriconazole, and posaconazole), macrolide antibiotics (e.g. clarithromycin, erythromycin) and HIV protease inhibitors (e.g. ritanovir). Alternatively, concomitant use of strong inducers (e.g. rifampin, carbamazepine, phenytoin, St. John’s Wort) can reduce apixaban levels.

**Bleeding:** An antidote for factor Xa inhibitors (Andexanet®) is currently being evaluated in clinical trials, with promising results demonstrated in both healthy volunteers and patients with acute Xa inhibitor-related bleeding events. It is not yet approved for use in Canada. Approaches to the management of bleeding can be found in the Clinical Guide: NOACs/DOACs: Management of Bleeding and the Tool: Bleed Management.

**Pediatrics:** Apixaban is not recommended for use in children until ongoing studies establish the pharmacokinetics, pharmacodynamics, safety, and efficacy of apixaban in these patients.

**Cancer-associated thrombosis:** There is not enough evidence at this time to recommend the use of apixaban or other NOACs/DOACs for first-line treatment of cancer-associated thrombosis.

**Other relevant Thrombosis Canada clinical guides, resources and tools:**

- NOACs/DOACs: Coagulation Tests
- NOACs/DOACs: Comparison and Frequently Asked Questions
- NOACs/DOACs: Management of Bleeding
- NOACs/DOACs: Peri-Operative Management
- Pediatrics: New Anticoagulants
- Stroke Prevention in Atrial Fibrillation
- Thromboprophylaxis: Orthopedic Surgery
- Clinical Resource: Direct Oral Anticoagulant (DOAC) Follow-Up Checklist for Clinicians
- Clinical Resource: Direct Oral Anticoagulant (DOAC) Monitoring Checklist for Pharmacists
- Tool: Perioperative Anticoagulant Management Algorithm
- Tool: Bleed Management

**References:**


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*Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.*