APIXABAN (ELIQUIS®)

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 or systemic embolism in patients with non-valvular atrial fibrillation who are candidates for oral anticoagulation therapy
- Treatment of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Continued prevention of recurrent DVT and PE
- Thromboprophylaxis after elective hip or knee replacement surgery

DOsing:
- **Prevention of stroke/systemic embolism in atrial fibrillation**: 5 mg BID. No dose adjustment is necessary in patients with mild renal impairment (CrCl >50 mL/min). In patients with moderate renal impairment (CrCl 25-50 mL/min), 5 mg BID can be used but reducing the dose to 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.
- **Acute treatment of DVT or PE**: 10 mg BID for 7 days, followed by 5 mg BID.
  - Apixaban should not be used in patients with a CrCl <25mL/min, women who are pregnant or breast-feeding, patients with active cancer, or patients with severe liver disease.
- **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.
- **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 provide education. Furthermore, for most patients, at least yearly assessment of creatinine clearance is recommended.

ADVERSE EFFECTS:

A major adverse effect 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:

See the Clinical Guide: NOACs/DOACs: Peri-Operative 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: There is limited information on apixaban in patients with CrCl <25 mL/min and in those with moderate or severe hepatic impairment (Child-Pugh class B or C). Apixaban should be avoided in such patients.

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 include azole antifungals (e.g. itraconazole, ketoconazole), macrolide antibiotics (e.g. clarithromycin, erythromycin) and HIV protease inhibitors (e.g. ritanovir). Alternatively, concomitant use of strong inducers (e.g. rifampin) 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
Pediatrics: Apixaban is not recommended for use in children until ongoing studies establish the pharmacokinetics, pharmacodynamics, safety, and efficacy of apixaban in these patients. Whenever possible, pediatricians with expertise in thromboembolism should manage pediatric patients with thromboembolism. When this is not possible, a combination of a neonatologist/pediatrician and a pediatric or adult hematologist is recommended.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- NOACs/DOACs: Coagulation Tests
- NOACs/DOACs: Comparison and Frequently Asked Questions
- NOACs/DOACs: Management of Bleeding
- NOACs/DOACs: Peri-Operative Management
- Stroke Prevention in Atrial Fibrillation
- Thromboprophylaxis: Orthopedic Surgery

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.