EDOXABAN (LIXIANA®)

Thrombosis Canada
Thrombose Canada

OBJECTIVE:

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

MECHANISM OF ACTION:

Edoxaban is an oral factor Xa inhibitor. By binding reversibly to the active site of factor Xa, edoxaban attenuates thrombin generation and reduces fibrin formation.

INDICATIONS:

Edoxaban 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

DOSING:

1. Edoxaban should be used with caution in patients with a creatinine clearance (CrCl) below 30 mL/min even though the FDA permits its use provided that the CrCl is over 15 mL/min. The drug should not be used in women who are pregnant or breastfeeding or in patients with severe liver disease.

2. **Prevention of stroke/systemic embolism in atrial fibrillation:** 60 mg OD. The dose is reduced to 30 mg OD in patients who meet any of the following criteria: moderate renal impairment (CrCl 30-50 mL/min), body weight of 60 kg or less, or concomitant use of potent P-glycoprotein inhibitors (such as erythromycin, cyclosporine, dronedarone, quinidine, or ketoconazole). No dose adjustment is required in patients taking amiodarone or verapamil. Although edoxaban undergoes minimal hepatic metabolism via the cytochrome P450 (CYP) system, edoxaban should not be used in conjunction with strong CYP3A4 and P-glycoprotein inducers (e.g., phenytoin, rifampicin, phenobarbital, and carbamazepine).

3. **Acute treatment of DVT or PE:** After at least 5 days of initial treatment with a parenteral anticoagulant, such as heparin, low-molecular-weight heparin (LMWH) or fondaparinux, patients can be transitioned to edoxaban 60 mg OD. The dose is reduced to 30 mg OD in patients who meet any of the following criteria: moderate renal impairment (CrCl 30-50 mL/min), body weight of 60 kg or less, or concomitant use of potent P-glycoprotein

inhibitors (such as erythromycin, cyclosporine, dronedarone, quinidine, or ketoconazole). Although edoxaban undergoes minimal hepatic metabolism via the cytochrome P450 (CYP) system, edoxaban should not be used in conjunction with strong CYP3A4 and P-glycoprotein inducers (e.g., phenytoin, rifampicin, phenobarbital, and carbamazepine).

4. **Continued prevention of recurrent DVT and PE:** Edoxaban is continued at the same dose. It is unknown whether the dose can be reduced after 6 months of treatment.

5. **Acute treatment of venous thromboembolism (VTE) in patients with cancer:** Edoxaban does not currently have a licensed indication in Canada specifically for use in this patient population but a study comparing LWMH for at least 5 days followed by edoxaban at a dose of 60 mg OD and dalteparin for the treatment of VTE in patients with active cancer showed edoxaban to be non-inferior to dalteparin for the composite primary outcome of recurrent VTE or major bleeding during 12 months after randomization. There was a statistically significant increase in major bleeding in the edoxaban group (mainly due to an increased risk of upper gastrointestinal bleeding in patients with gastrointestinal cancers). As a result, clinicians may want to exercise caution in prescribing edoxaban to patients with gastrointestinal cancer and those at increased bleeding risk.

MONITORING:

Routine laboratory monitoring is not necessary. The prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT) may be normal in patients taking edoxaban and do not provide reliable measures of its anticoagulant activity. Specific anti-factor Xa assays using edoxaban 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 edoxaban 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. Edoxaban 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 breastfeeding: Edoxaban crosses the placenta and should not be used in pregnancy. It should also be avoided in nursing mothers because it is uncertain whether edoxaban appears in the breast milk.

Renal and hepatic dysfunction: There is limited information on edoxaban in patients with CrCl < 30 mL/min and in those with hepatic impairment associated with a coagulopathy. Edoxaban should be avoided in such patients.

Drug interactions: The concomitant use of edoxaban and drugs that inhibit P-glycoprotein (P-gp) should be avoided. Patients taking strong inhibitors of P-gp are at an increased risk of bleeding. Examples of inhibitors include azole antifungals (e.g., itraconazole, ketoconazole), macrolide antibiotics (e.g., clarithyromycin, erythromycin) and HIV protease inhibitors (e.g., ritanovir).

Bleeding: There is no specific antidote for edoxaban. Approaches to the management of bleeding can be found in the Clinical Guide: NOACs/DOACs: Management of Bleeding.

Pediatrics: Edoxaban is not recommended for use in children until ongoing studies establish its pharmacokinetics, pharmacodynamics, safety, and efficacy 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
- DOACs in Obese Patients

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.