



EDOxabAN (LIXIANA®)

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) and continued prevention of recurrent DVT and PE

DOSING:

1. Edoxaban should not be used in patients with a creatinine clearance (CrCl) below 30 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 once daily. The dose is reduced to 30 mg once daily 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 unfractionated heparin, low molecular weight heparin (LMWH) or fondaparinux, patients can be transitioned to edoxaban 60 mg once daily. The dose is reduced to 30 mg once daily 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.

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).

See also the **Clinical Guide NOACs/DOACs: Management of Bleeding** and the tool: **Bleeding Management**.

PERI-PROCEDURAL MANAGEMENT:

See the **Clinical Guide: NOACs/DOACs: Peri-Operative Management** and the tool: **Perioperative Anticoagulant Management**.

SPECIAL CONSIDERATIONS:

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 randomized study comparing therapeutic LWMH for at least 5 days followed by edoxaban at a dose of 60 mg once daily and dalteparin (200 units/kg [to a maximum of 18,000 units]

subcutaneously once daily for 30 days, then 150 units/kg once daily) 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 were fewer VTE events in the edoxaban group compared to the dalteparin group (7.9% versus 11.3%; $p=0.09$); however, the risk of major bleeding was significantly increased in the edoxaban group (6.9% vs. 4.0%, $p=0.04$) mainly due to an increased risk of upper gastrointestinal bleeding in patients with gastrointestinal cancers. In a post-hoc analysis of the 6-12 month follow-up period, the rates of recurrent VTE or major bleeding were relatively low and extended treatment with edoxaban appeared as effective and safe as dalteparin, although the number of patients with gastrointestinal cancer receiving extended treatment was relatively small and the 95% confidence interval around the relative risk estimate wide (5 events in those receiving edoxaban versus 3 in those treated with dalteparin; hazard ratio: 1.69; 95% CI, 0.40-7.10). Clinicians may want to exercise caution in prescribing edoxaban to patients with gastrointestinal cancer and those at increased bleeding risk or significant thrombocytopenia. A thorough review of the relative risks and benefits of LMWH and edoxaban, in addition to potential drug interactions and patient preference and values, is prudent prior to prescribing anticoagulant therapy in patients with newly diagnosed cancer-associated VTE.

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 $\text{CrCl} < 30 \text{ mL/min}$ and in those with hepatic impairment associated with a coagulopathy. Edoxaban should be avoided in such patients. In patients with mild to moderate hepatic dysfunction, edoxaban can be used at full doses. In patients with $\text{CrCl} 30\text{-}50 \text{ mL/min}$, edoxaban should be reduced to 30 mg once daily.

Elderly patients with AF whose bleeding risk is considered too high for standard oral anticoagulation doses: In the ELDERCARE-AF trial, elderly Japanese patients with AF who were deemed inappropriate candidates for other oral anticoagulants due to factors such as $\text{CrCl} 15\text{-}30 \text{ mL/min}$, history of bleeding, low body weight, continued NSAID or antiplatelet use were treated with a reduced dose of edoxaban 15 mg daily compared to placebo. There was a 2/3 reduction in stroke or systemic embolism (2.3% vs 6.7%; hazard ratio 0.34, 95% CI 0.19 to 0.61; $P < 0.001$ for superiority). There was increased bleeding in the edoxaban group that was not statistically significant (2.3% per year vs 0.8% per year; $P=0.09$). Other secondary endpoints were similar to ENGAGE AF-TIMI. For elderly or frail patients, low dose edoxaban may be an approach for patients with AF who are not receiving standard dose oral anticoagulants.

Atrial fibrillation patients receiving P2Y₁₂ inhibitors for recent percutaneous coronary intervention (PCI) for either chronic or acute coronary syndrome (ACS): The ENTRUST-AF PCI trial showed that in patients with atrial fibrillation who underwent PCI edoxaban plus clopidogrel 75 mg daily for 12 months was non-inferior to the combination of vitamin K antagonist and clopidogrel 75 mg daily with acetylsalicylic acid (ASA) 100 mg once daily for 1- 12 months with

respect to major or clinically relevant non-major bleeding, with similar numbers of ischemic events without significant differences in ischemic events.

Atrial fibrillation ablation: Based on the results of the multinational randomized ELIMINATE-AF trial, uninterrupted edoxaban therapy represents an alternative to uninterrupted VKA therapy in patients undergoing AF ablation.

Drug interactions: Patients taking strong inhibitors of P-gp are at an increased risk of bleeding. Examples of inhibitors include cyclosporin, dronedarone, erythromycin, ketoconazole and quinine. If concomitant use of edoxaban and a strong P-gp inhibitor is necessary, edoxaban should be decreased to 30 mg once daily.

Combined strong inducers of P-gp and CYP3A4 should be avoided. Examples of strong inducers are phenytoin, carbamazepine, rifampicin and phenobarbital.

Low dose ASA (<100mg) may be co-administered with edoxaban if bleeding risk is assessed before co-administration. Indications for concomitant use of ASA and edoxaban are sparse and the combination should be considered carefully.

Chronic use of NSAIDs is not recommended due to increased risk of bleeding. Short term use may be possible with caution.

Thienopyridines (clopidogrel) and SSRIs may increase the risk of bleeding due to reported effects on platelets, use cautiously with edoxaban.

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:

- Cancer and Thrombosis
- 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
- Direct Oral Anticoagulants in Obese Patients

- Clinical Resource: Direct Oral Anticoagulation (DOAC) Follow up Checklist for Clinicians
- Clinical Resource: Direct Oral Anticoagulation (DOAC) Follow up Checklist for Pharmacists
- Tool: Bleed Management
- Tool: Perioperative Anticoagulant Management

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