

## 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 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 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), severe renal impairment (CrCl 15-29 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), severe renal impairment (CrCl 15-29 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: [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. Drug levels can also be increased or decreased by the use of concomitant medications (see Drug Interactions).

See also the **Clinical Guide [DOACs: Management of Bleeding](#)** and the tool: [Bleeding Management](#).

## Peri-procedural Management:

See the **Clinical Guide: [DOACs: Peri-Operative Management](#)** and the tool: [Perioperative Anticoagulant Management](#).

## Special Considerations:

**Acute treatment of venous thromboembolism (VTE) in patients with cancer:** A randomized study comparing therapeutic LWMH for at least 5 days followed by edoxaban at a dose of 60 mg (with aforementioned dose reduction criteria) 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 CrCl < 15 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 moderate renal impairment CrCl 30-50 mL/min and severe renal impairment 15-29 mL/min, edoxaban should be reduced to 30 mg once daily.

**Bioprosthetic valves:** The ENGAGE AF-TIMI 48 Trial excluded patients with mechanical valves or moderate-severe mitral stenosis, but did not exclude bioprosthetic valves, so there was an opportunity for an analysis on this high-risk subgroup. There were 191 (0.9%) patients enrolled in the trial who had a bioprosthetic valve implantation. Rates of stroke and systemic embolic events were similar for high and low dose edoxaban versus warfarin. This subgroup analysis suggests that edoxaban may be a safe alternative to warfarin in patients with atrial fibrillation and bioprosthetic valves.

**Transcatheter Aortic Valve Implantation (TAVI):** The ENVISAGE-TAVI AF trial (n=1426) randomized patients with atrial fibrillation after successful TAVI to either edoxaban 60 mg once daily (30mg once daily with aforementioned dose reduction criteria) or a vitamin K antagonist (VKA; dose adjusted to INR of 2.0 to 3.0, or 1.6 to 2.6 for patients from Japan). Edoxaban was non-inferior to a VKA with respect to the primary outcome (composite of all-cause mortality, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis or major bleeding); 17.3 events per 100 person-years versus 16.5; respectively, hazard ratio, 1.05; 95% CI, 0.85 to 1.31. However, edoxaban was associated with a higher incidence of major bleeding than a VKA; 9.7 events per 100 person-years versus 7.0; respectively, hazard ratio, 1.40; 95% CI, 1.03 to 1.91. The increased bleeding was mainly due to major gastrointestinal bleeding (56 events versus 27; hazard ratio, 2.03; 95% CI, 1.28 to 3.22). Edoxaban may be a reasonable alternative to VKAs after TAVI in patients with an indication for oral anticoagulant therapy, but if the patient has risk factors for gastrointestinal bleeding, a VKA might be preferable.

**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 CrCl 15-30 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 P2Y<sub>12</sub> 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. Patients can be initiated or maintained on edoxaban while being cardioverted.

**Atrial fibrillation and stable coronary artery disease:** The EPIC-CAD trial randomized 1,040 patients with atrial fibrillation and stable coronary artery disease to either edoxaban monotherapy or edoxaban plus a single antiplatelet agent. At 12 months, patients in the monotherapy group had a significantly lower risk of the primary composite endpoint, which included death from any cause, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, and major or clinically relevant nonmajor bleeding (HR, 0.44; 95% CI, 0.30–0.65;  $P<0.001$ ). This benefit was primarily driven by a reduction in bleeding events. The cumulative incidence of major ischemic events was similar between the two groups. These findings suggest that edoxaban monotherapy may be a safer alternative to dual therapy in this population.

**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.

Strong inducers of P-gp 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:** Andexanet alfa (Ondexxya®) is indicated for adult patients treated with FXa inhibitors rivaroxaban or apixaban when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Approaches to the management of bleeding can be found in the **Clinical Guide: [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](#)
- [DOACs in Patients with Obesity](#)
- [DOACs: Coagulation Tests](#)

- [DOACs: Comparison and Frequently Asked Questions](#)
- [DOACs: Management of Bleeding](#)
- [DOACs: Peri-Operative Management](#)
- [Stroke Prevention in Atrial Fibrillation](#)
- [Thromboprophylaxis: Orthopedic Surgery](#)
- 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 Algorithm](#)

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