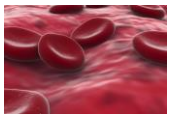

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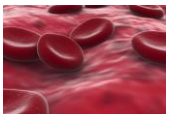


Is Edoxaban (Lixiana®) an Option for Your Patient?

Indications[1]

- ❑ Non-Valvular Atrial Fibrillation (NVAF)* to prevent stroke & systemic embolism[2]
- ❑ Acute VTE treatment & prevention of recurrent VTE [for deep vein thrombosis (DVT) and pulmonary embolism (PE)][3]

*CCS definition: AF without mechanical heart valves, rheumatic mitral stenosis, or moderate/severe non-rheumatic mitral stenosis[4]

Requirements[1] - NOTE: Edoxaban accumulates in hepatic and/or renal dysfunction

- ❑ Stable creatinine clearance (CrCl) greater than 30 mL/min
- ❑ Stable liver function [refer to Contraindications and Limitations sections below]

Contraindications[1,4]

- ❑ Mechanical heart valves
- ❑ Edoxaban, like other anticoagulants is contraindicated in patients at high risk for bleeding
- ❑ Pregnant/Breastfeeding: Safety & dosing has not been studied. Use is NOT recommended
- ❑ Significant liver disease with coagulopathy and clinically relevant bleeding risk. Patients with severe hepatic impairment have not been studied.

Potential Limitations[1]

- ❑ NVAF sub-group analysis: Less efficacy with edoxaban in preventing stroke, and lower rates of major bleeding with CrCl over 95ml/min. Thromboembolic event rates were low in this sub-group, making the data difficult to interpret.[5]
- ❑ Not recommended in hemodynamically unstable acute PE or those requiring thrombectomy or thrombolysis
- ❑ Drug Interactions: Concomitant use of strong P-gp inhibitors (cyclosporine, dronedarone, erythromycin, quinidine, ketoconazole) requires a dose reduction to 30 mg daily. AVOID Inducers (rifampin, phenytoin, carbamazepine, phenobarbital, St John's Wort) and HIV protease inhibitors as there is minimal knowledge of clinical outcomes
- ❑ Combination therapy with antiplatlets increases bleeding risk
- ❑ Rapid decline in anticoagulant effect after a missed dose; adherence is critical
- ❑ Very limited data with extremes of weight (under 50 kg; over 120 kg or BMI > 40)[6]
- ❑ Less than 18 years of age: Safety & dosing has not been established
- ❑ In acute treatment of VTE: Must be preceded by 5-10 days of parenteral anticoagulant
- ❑ Patients with ALT or AST greater than 2 x ULN or total bilirubin greater than 1.5 X ULN were excluded in clinical trials
- ❑ AF: Edoxaban 60mg daily showed a higher GI bleed rate than warfarin, although lower overall bleeding events.[2]

May offer an advantage over warfarin if:[1]

- ❑ Difficulty stabilizing on warfarin for reasons other than poor medication adherence
- ❑ INR monitoring is problematic (e.g. poor venous access, frequent travel, remote location). NOTE: Use of warfarin with point-of-care (POC) INR testing (e.g. Coaguchek XS™) may be an alternative solution
- ❑ AF: lower rate of overall bleeding including critical site bleeding and intracranial hemorrhage[2]
- ❑ Cancer associated VTE (not an official indication) – Edoxaban showed equal efficacy to LMWH with more bleeding[7]

Dosing Recommendations[1]

Stroke Prevention in Non-Valvular Atrial Fibrillation	• 60mg Once Daily if CrCl > 50mL/min*
	• 30 mg Once Daily if one or more of the following:
	  ○ CrCl 30-50mL/min
	  ○ Body weight ≤ 60Kg
	  ○ Concomitant P-gp Inhibitor (excluding amiodarone or verapamil)
		CrCl<30 mL/min Not Recommended

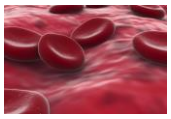
Acute DVT/PE Treatment	Parenteral Anticoagulant x 5-10 days, then edoxaban as per AF dosing	
Hip & Knee Replacement	Not approved	

*Sub-group analysis reports reduced efficacy if CrCl greater than 95mL/min, but is limited by low event rates[5]

Inform Your Patient:

- Atrial Fibrillation: Should decrease risk of stroke by 2/3 compared to no anticoagulation
- Carry information indicating they are on an anticoagulant and inform their healthcare providers, including dentists
- Adherence is essential to avoid treatment failure, take edoxaban with or without food
- Report symptoms/signs of bleeding, stroke, or DVT/PE
- Cost varies by drug plan coverage and/or provincial criteria

 Collaborative Learning on Thrombosis (CLOT) – Canadian Prairie pharmacists with an interest in thromboembolic disorders



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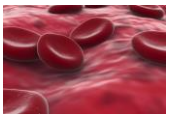

Monitoring Patients on Edoxaban

- CrCl should be determined at baseline and at least annually. Monitor more frequently if older than 75y, with renal dysfunction (CrCl <60 mL/min), or when a decline in renal function suspected
- Monitor for symptoms and signs of bleeding
- No routine coagulation testing required. NOTE: INR is not useful for monitoring. Do not target INR 2 to 3. More specialized testing should only be considered in consultation with an expert in anticoagulation.

Switching Between Agents[1]

From warfarin *to* edoxaban:

- Discontinue warfarin and start edoxaban when INR 2.5 or less.

From non-warfarin anticoagulant (oral or parenteral - e.g. LMWH, rivaroxaban, dabigatran, apixaban) **to edoxaban:**

- Start edoxaban at the time the next scheduled dose of the non-warfarin anticoagulant was to be administered.
- For unfractionated heparin infusions, stop the infusion and start edoxaban 4 hours later

From edoxaban *to* warfarin:

- Start warfarin and administer edoxaban at half the prescribed dose (either 30mg or 15mg for those on a reduced dose for one or more of the following: CrCl 15-50mL/min; ≤60Kg; use with P-gp inhibitor except amiodarone or verapamil). Once INR is 2 or greater, discontinue edoxaban. **NOTE:** Edoxaban can affect INR, therefore when starting warfarin, INR may be unreliable. If possible, checking INR just prior to next edoxaban dose may better reflect the anticoagulant effect of warfarin.

From edoxaban *to* non-warfarin anticoagulants (oral or parenteral) (e.g. LMWH, apixaban, rivaroxaban, dabigatran):

- Discontinue edoxaban and give 1st dose of non-warfarin anticoagulant at the time the next dose of edoxaban is due

Management of Bleeding Episodes with Edoxaban

- Vitamin K, protamine, tranexamic acid, plasma and/or idarucizumab will not reverse drug effects
- In the event of major hemorrhagic complications, discontinue edoxaban and refer patient for urgent assessment and locally developed management strategies
- Limited evidence demonstrates prothrombin complex concentrates (e.g. Octaplex®/Beriplex®) are able to reverse the anticoagulant effect[8], but the effect of these agents on bleeding outcomes is limited.[1]
- Specific antidotes are not yet available in Canada[9]

Anticoagulation around Invasive Procedures[10] (e.g. surgery, elective day procedures, major dental procedures)

- As with warfarin, very low risk bleed procedures (such as dental extraction) do not require withholding edoxaban
- Management plans should be made in consultation with the provider performing the procedure
- Renal and hepatic function significantly impacts clearance of edoxaban. If the recommendations below cannot be met, consultation with an expert in anticoagulation management is encouraged.
- Due to the onset/offset time of edoxaban, peri-procedural use of LMWH is not required

Pre-Procedure – If required, stop edoxaban before procedure as follows[1]:

Renal function# (CrCl mL/min)	Last intake of drug prior to procedure	
	Low Bleeding Risk	High Bleeding Risk*
30 or more	at least 24 hours	at least 48 hours

If CrCl less than 30mL/min (edoxaban not recommended), a longer duration is likely necessary

* Make a careful decision (i.e., hold longer) for patients undergoing major surgery, spinal puncture, or other regional anaesthesia in whom complete hemostasis is required. Consult specialist in these high risk patients/procedures.

For an interactive perioperative management algorithm, see Thrombosis Canada website:
http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm

Post Procedure: Resumption should not be initiated until adequate hemostasis has been achieved and clinical situation allows (usually 1 -3 days). NOTE: Full therapeutic effect occurs approximately 1-2 hours after ingestion.

References:

1. Lixiana product monograph. (Servier Canada Inc), July 26, 2017. **2.** Giugliano RP et al. N Engl J Med 2013;369:2093-2104. **3.** The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406-1415. **4.** Macle L et al. Can J Cardiol 2016;32 :1170-1185. **5.** Bohula EA et al. Circ 2016;134:24-36. **6.** Direct oral Anticoagulants in Obese Patients. Thrombosis Canada Website: http://thrombosiscanada.ca/wp-content/uploads/2018/04/DOACs-in-Obesity-2018Jan31.pdf. Accessed November 20, 2018. **7.** Raskob GE et al for the Hokusai-VTE Cancer Investigators. N Engl J Med 2018; 378 : 615-624. **8.** Zahir H, et al. Circulation 2015;131:82-90. **9.** Connolly S, et al. N Engl J Med 2016;375:1131-1141. **10.** Steffel J, et al. Eur Heart J 2018; 39:1 330-1393.