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

Indications

- Non-Valvular Atrial Fibrillation (NVAF)* to prevent stroke & systemic embolism
- Acute VTE treatment & prevention of recurrent VTE (for deep vein thrombosis (DVT) and pulmonary embolism (PE))
* CCS definition: AF without mechanical heart valves or without moderate/severe mitral stenosis (rheumatic and non-rheumatic)
**Cancer associated VTE (not an official indication) – data shows similar efficacy to LMWH with more bleeding

Requirements - 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

- 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

- Not recommended in hemodynamically unstable acute PE or those requiring thrombectomy or thrombolysis
- Not recommended in antiphospholipid syndrome with a history of thrombosis (especially triple positive)
- 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
- Rapid decline in anticoagulant effect after a missed dose; adherence is critical
- Limited data supporting the use in extremes of weight (under 50 kg; over 120 kg or BMI > 40)
- 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.

May offer an advantage over warfarin if:

- Difficulty stabilizing on warfarin for reasons other than poor medication adherence
- INR monitoring is problematic (e.g. poor venous access, frequent travel, remote location)
- AF: lower rate of overall bleeding including critical site bleeding and intracranial hemorrhage

Dosing Recommendations

<table>
<thead>
<tr>
<th>Stroke Prevention in Non-Valvular Atrial Fibrillation</th>
<th>CrCl&lt;30 mL/min</th>
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</thead>
<tbody>
<tr>
<td>60mg Once Daily if CrCl &gt; 50mL/min</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>30 mg Once Daily if one or more of the following:</td>
<td>CrCl&lt;30 mL/min</td>
</tr>
<tr>
<td>o CrCl 30-50mL/min</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>o Body weight ≤ 60Kg</td>
<td>CrCl&lt;30 mL/min</td>
</tr>
<tr>
<td>o Concomitant P-gp Inhibitor (excluding amiodarone or verapamil)</td>
<td></td>
</tr>
<tr>
<td>Acute DVT/PE Treatment</td>
<td>Parenteral Anticoagulant x 5-10 days, then edoxaban as per AF dosing</td>
</tr>
<tr>
<td>Hip &amp; Knee Replacement</td>
<td>Not approved</td>
</tr>
</tbody>
</table>
Avoidance of anticoagulation in patients with acute renal dysfunction

1. **References:**

**Switching Between Agents**

**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 after admission.

**From edoxaban to warfarin:**
- Start warfarin and administer edoxaban at half of the prescribed dose (either 30mg, or 15mg for those on a reduced dose for one or more of the following: CrCl 15-30mL/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.

**Anticoagulation around Invasive Procedures** (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 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, but the effect of these agents on bleeding outcomes is limited.
- Specific antidotes are not yet available in Canada.

**Pre-Procedure — If required, stop edoxaban before procedure as follows:**

<table>
<thead>
<tr>
<th>Renal function* (CrCl mL/min)</th>
<th>Last intake of drug prior to procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Bleeding Risk</strong></td>
<td></td>
</tr>
<tr>
<td>30 or more</td>
<td>at least 24 hours</td>
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<tr>
<td><strong>High Bleeding Risk</strong></td>
<td></td>
</tr>
<tr>
<td>30 or more</td>
<td>at least 48 hours</td>
</tr>
</tbody>
</table>

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

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.