Edoxaban
for the treatment and prevention of venous thromboembolism (DVT or PE) or stroke prevention in non-valvular AF

Traffic light classification- Amber 2 specialist initiation / recommendation
Information sheet for Primary Care Prescribers

Relevant Licensed Indications
Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). Treatment of deep vein thrombosis (DVT), and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Therapeutic Summary
Most patients with venous thromboembolic disease are anticoagulated with a Low Molecular Weight Heparin (LMWH) whilst the diagnosis is established and then proceed to anticoagulation with warfarin (a vitamin K antagonist) or a direct oral anticoagulant (DOAC).

DOACs may be more suitable for patients with allergy to warfarin, extremely unstable warfarin control, compliance problems with warfarin, intravenous drug users (e.g. may have poor veins for INR sampling or there may be concerns over adherence with INR monitoring). anticoagulation in malignancy:-
- Newly diagnosed patients with active malignancy should not be warfarinised until their treatment plan is agreed as warfarin control is often very unstable in these patients. In this patient group LMWH’s are first line, a DOAC or warfarin should only be used if LMWH’s are contraindicated
- Patients with chronic malignant conditions e.g. Prostate cancer may be suitable for warfarin, but treatment should be reviewed by the specialist team if liver metastases are present. DOACs should only be considered if warfarin is contraindicated

Medicines Initiation
DVT/PE: Edoxaban will be initiated in secondary care on the advice of a specialist only. The hospital will provide the first 28 days treatment. The GP will be asked to provide any further supplies. Patients with a new diagnosis of DVT/PE should be treated with at least 5 days of parenteral anticoagulant (e.g. enoxaparin) prior to switching to oral edoxaban. See appendix 1 for advice on safe switching to edoxaban
AF: Edoxaban may be initiated in primary or secondary care on the advice of a specialist. If the patient is already on another anticoagulant see appendix 1 for advice on safe switching to edoxaban

Dosage and route of administration
The usual treatment dose is 60mg once daily.
- In patients weighing ≤60kg or with moderate to severe renal impairment (creatinine clearance 15 - 49 ml/min) the recommended dose is 30mg once daily
- In patients concomitantly taking edoxaban and the following P-gp inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole, the recommended dose is 30 mg once daily

N.B. Patients who develop acute renal failure should discontinue edoxaban. Creatinine clearance must be calculated (see here for calculator), eGFR is NOT considered a suitable alternative.
**Duration of treatment**

DVT/PE: The duration of treatment will depend on the indication for edoxaban and individual patient factors. The usual duration of therapy for DVT or PE is 3 to 6 months, though some patients warrant long-term anticoagulation. For patients with DVT secondary to intravenous drug injection it is usual to treat with edoxaban or LMWH for a shortened duration of 3 months. The intended duration of therapy will be advised by secondary care on discharge. It is acceptable for the GP to stop therapy once the treatment course has been completed without re-referral to secondary care.

AF: Following an assessment of risk of anticoagulation as detailed in the Nottinghamshire Atrial Fibrillation (Non-valvular): prescriber decision support on anticoagulation treatment is likely to be required long term. A periodic assessment of risks and benefits is advised as per national guidelines

**Relevant Contraindications**

- Creatinine clearance less than 15ml/min
- Clinically significant active bleeding
- Acute bacterial endocarditis (risk of haemorrhagic transformation of cerebral emboli)
- Active major bleeding and conditions with a high risk of uncontrolled haemorrhage, including recent haemorrhagic stroke.
- Active gastric or duodenal ulceration
- Uncontrolled severe hypertension.
- Allergy to edoxaban or any of the tablet excipients
- Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
- Severe hepatic impairment
- Pregnancy and breast feeding. Women of child-bearing potential should avoid becoming pregnant during treatment with edoxaban (animal studies have shown reproductive toxicity and that the medicines is secreted in breast milk)
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin, low molecular weight heparins (e.g. enoxaparin), heparin derivatives (e.g. fondaparinux), oral anticoagulants (e.g. warfarin, dabigatran etexilate, apixaban) except under the circumstances of switching therapy to or from edoxaban.

**Precautions**

- Increased potential risk for bleeding
- As for any patient receiving anticoagulant therapy, in the event of any trauma (especially to the head), referral to the Emergency Department (ED) should be considered.
- PE patients who:
  I. Are haemodynamically unstable
  II. May receive thrombolysis
  III. May require pulmonary embolectomy
  The safety and efficacy of edoxaban has not been established in these situations.
- mild to moderate hepatic impairment
- elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN
- A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance (e.g. >90ml/min) after a careful evaluation of the individual thromboembolic and bleeding risk.
Adverse Effects
Common side effects reported include anaemia, eye haemorrhage, epistaxis, gastrointestinal haemorrhage, dyspepsia, nausea, pruritus, rash, bruising, urogenital tract haemorrhage, increase in liver transaminases GGT and bilirubin, post procedural haemorrhage

Haemorrhage
- Refer patient immediately to the Emergency Department (ED) if serious bleeding occurs e.g. GI bleeding, epistaxis lasting more than 1 hr
- Refer patient immediately to the Emergency Department (ED) for investigation if there is any unexplained fall in haemoglobin or blood pressure
- In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito-urinary) and anaemia were seen more frequently during long term edoxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.¹

Invasive procedures and surgical intervention:
If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, edoxaban should be stopped as soon as possible and preferably at least 24 hours before the procedure. Contact haematology to discuss if need to assess edoxaban effect.
In deciding whether a procedure should be delayed until 24 hours after the last dose of edoxaban, the increased risk of bleeding should be weighed against the urgency of the intervention. Edoxaban should be restarted after the surgical or other procedures as soon as adequate haemostasis has been established, noting that the time to onset of the edoxaban anticoagulant therapeutic effect is 1 – 2 hours. If oral medicinal products cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant and then switch to oral once daily edoxaban.

Reversal or overdose:
There is no specific reversal agent and as yet there is very little clinical evidence or experience in humans on the reversal of Edoxaban. Contact haematology for advice if required

Clinically relevant medicine interactions and their management
- Edoxaban is metabolised by P-gp and should be used with caution in combination with inhibitors or inducers of these (e.g. erythromycin, rifampicin).
- Concomitant use of edoxaban with P-gp inhibitors cyclosporin, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once daily. Concomitant use of edoxaban with quinidine, verapamil, or amiodarone does not require dose reduction based on clinical data.
- Agents which affect haemostasis (e.g. NSAIDS, antiplatelets, prasugrel, clopidogrel, GPIIb/IIIa receptor antagonists, vitamin K antagonists, heparin) should be reviewed and consideration given to their discontinuation prior to edoxaban therapy. If the combination cannot be avoided, edoxaban should be used with careful monitoring.
- HIV Protease inhibitors (e.g. Ritonavir) – Not been studied by manufacturer. Avoid concomitant use with all protease inhibitors
- Rifampicin – plasma concentration of edoxaban decreased by rifampicin. The concomitant use of edoxaban with other strong P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced edoxaban plasma concentrations¹. Consider use of an alternative drug to avoid this interaction.⁶ If this is not possible, contact specialist for advice.
Monitoring requirements
Clinical trials have demonstrated that the therapeutic anticoagulation effect of edoxaban does not require routine monitoring. As such regular INR tests are not required. Unlike warfarin, a prothrombin time may not be sensitive to the anticoagulant effect of edoxaban. Likewise an INR will not demonstrate the level of anticoagulation.

As approximately a third of the active drug is eliminated by the renal route, it is prudent to monitor the renal function of a patient taking edoxaban. The following regimen is in line with NICE guidance on Chronic Kidney Disease and based on consensus clinician opinion. Should the individual patient be deemed at a greater risk of developing renal dysfunction, more frequent monitoring may be warranted:

<table>
<thead>
<tr>
<th>Baseline tests to be done by secondary care</th>
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<tbody>
<tr>
<td>U + Es (Creatinine clearance)</td>
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<tr>
<td>Full blood count</td>
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<tr>
<td>Coagulation screen</td>
</tr>
<tr>
<td>Liver function tests</td>
</tr>
<tr>
<td>✓</td>
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<tr>
<td>✓</td>
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<td>✓</td>
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</table>

Follow up monitoring tests to be done by primary care

<table>
<thead>
<tr>
<th>U + Es (Creatinine clearance)</th>
<th>Full blood count</th>
<th>Coagulation screen</th>
<th>Liver function tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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Renal function monitoring frequency

<table>
<thead>
<tr>
<th>Creatine Clearance of patient</th>
<th>Frequency of renal function monitoring</th>
</tr>
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<tbody>
<tr>
<td>&gt;60ml/min</td>
<td>Annually</td>
</tr>
<tr>
<td>30 - 60ml/min</td>
<td>Six Monthly</td>
</tr>
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</table>

The exact frequency should depend on the clinical situation. The frequency of testing will need to be increased if there is rapid progression, or during intercurrent illness and perioperatively in all patients with CKD.

* see Haemorrhage section above

Creatinine clearance must be used for calculating renal function for this agent; due to the risks associated with a patient taking an inappropriate dosage (eGFR is NOT a suitable alternative). The patient’s Creatinine Clearance should be calculated using the Cockroft & Gault equation (see below or click here for calculator):

\[
(140 - \text{age}) \times \text{weight (kg)} \times 1.04 \text{ (female) or } 1.23 \text{ (male)} \times \text{serum creatinine (micromol/l)}
\]
Criteria for review and discontinuation of the medicine

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td>Refer patient immediately to ED if serious bleeding occurs eg GI bleeding, epistaxis lasting more than 1 hr</td>
</tr>
<tr>
<td>Excessive bruising (eg. bruises larger than a palm or purpura on the palate)</td>
<td>Seek immediate haematologist advice</td>
</tr>
<tr>
<td>Any acute illness that MAY effect renal function</td>
<td>Measure U+Es and calculate creatinine clearance. Reduce dose or withhold treatment if required. Consider seeking advice regarding restarting treatment from the local anticoagulation service</td>
</tr>
<tr>
<td>Significant reduction in renal function or weight</td>
<td>Reduce dose to 30mg once daily if calculated Creatinine Clearance &lt; 50ml/min (see above for calculation). If renal function continues to worsen discuss with haematologist.</td>
</tr>
<tr>
<td>If creatinine clearance falls to below 15ml/min</td>
<td>Stop edoxaban, assess for bleeding and seek advice as to whether specific assays are indicated / alternative anticoagulation required</td>
</tr>
</tbody>
</table>

Information given to patients (secondary care)
Patients should be counselled on the risks and benefits of their treatment where appropriate. The patient should be told the indication for edoxaban, intended duration and advised of what side effects to look out for.

Cost and availability
Edoxaban is available in 15mg, 30mg and 60mg tablets. 15mg tablets are only licensed for switchin between edoxaban and warfarin, and therefore should not be used for any other circumstance. Continuing treatment of 60mg once daily costs £756 per patient per annum.

References
1. Lixiana 60mg tablets Summary of Product Characteristics. Last updated on 01/07/2015
3. NICE technology appraisal guidance [TA354] Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism August 2015

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Contact details
NUH Anticoagulation service: Helpline - (0115) 9194413
SFH Anticoagulation service: King’s Mill Hospital - (01623) 672224 Newark Hospital - (01636) 685751
Appendix 1: How to switch patients:

Switching should only be carried out in secondary care by the anticoagulation service.

<table>
<thead>
<tr>
<th>Vitamin K antagonists (VKA) to edoxaban</th>
<th>Stop VKA and commence edoxaban when INR≤ 2.5</th>
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<tbody>
<tr>
<td>Oral anticoagulants other than VKA</td>
<td>Discontinue dabigatran, rivaroxaban or apixaban and start edoxaban at the time of the next dose of the oral anticoagulant</td>
</tr>
<tr>
<td>• dabigatran</td>
<td></td>
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<tr>
<td>• rivaroxaban</td>
<td></td>
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<tr>
<td>• apixaban</td>
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<tr>
<td>Edoxaban to VKA</td>
<td>If patient is taking edoxaban 60mg once daily: Decrease dose to 30mg once daily and begin maintenance warfarin therapy (do not use loading doses) Once an INR ≥ 2.0 is achieved, edoxaban should be discontinued, and continue to titrate warfarin accordingly</td>
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<td></td>
<td>If patient is taking edoxaban 30mg once daily (due to renal function, weight or interacting medicine): Decrease dose to 15mg once daily and begin maintenance warfarin therapy (do not use loading doses) Once an INR ≥ 2.0 is achieved, edoxaban should be discontinued, and continue to titrate warfarin accordingly Edoxaban can elevate the INR</td>
</tr>
<tr>
<td>Parenteral anticoagulants to edoxaban</td>
<td>Subcutaneous LMWH or fondaparinux: Discontinue subcutaneous anticoagulant and start edoxaban at the time of the next scheduled subcutaneous anticoagulant dose. Intravenous unfractionated heparin infusion: Discontinue the infusion and start edoxaban 4 hours later.</td>
</tr>
<tr>
<td>Edoxaban to parenteral anticoagulants</td>
<td>Discontinue edoxaban and give first dose of parenteral anticoagulant at the time the next edoxaban dose would be taken</td>
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