Prescribing Criteria for Edoxaban (Lixiana®)▼ in Stroke Prevention in (non-valvular) AF

NHS Wiltshire Clinical Commissioning Group

Edoxaban is licensed for prevention of stroke and systemic embolism in ADULT patients with non-valvular atrial fibrillation with one or more of the following risk factors:

- **Previous stroke or transient ischemic attack**
- **Age ≥75 years**
- **Diabetes mellitus, congestive heart failure or hypertension**

Edoxaban has been approved as a GREEN drug across Wiltshire

Any potential use of Edoxaban outside of NICE and/or license should be discussed with the Medicines Management Team.

NICE TA355 (published September 2015) allows Edoxaban to be used as an option in stroke prevention in AF as per the license above. **The CHADS2-VASc score can be used to assess a patient's stroke risk**.

Please use the following checklists in order to prescribe Edoxaban appropriately and safely.

*NOTE: These lists are not exhaustive and professional judgment should be used on an individual patient basis.

1. Does the patient have any of the following contra-indications * (from Summary of Product Characteristics)? *(tick any that apply)*	
	Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
	Active clinically significant bleeding
	Pregnancy & breastfeeding
	Uncontrolled severe hypertension
	Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
	Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives, oral anticoagulants except under the circumstances of switching therapy to or from Edoxaban or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.
	Hypersensitivity to Edoxaban or to any of the excipients
If any of the contra-indications apply to your patient do not prescribe Edoxaban and seek advice.	

2. Patient groups where specialist advice should be sought before prescribing * *(tick any that apply)*	
	Previous history of intracranial haemorrhage – *some AF patients especially those considered at high risk of stroke may benefit from anti-thrombotic therapy, seek the opinion of a stroke specialist.*
	Recent major extracranial bleed within the last 6 months where the cause has not been identified or treated – *seek opinion of specialist*
	Safety & efficacy of Edoxaban has not been studied in patients with mechanical heart valves, in patients during the first 3 months after implantation of a bioprosthetic heart valve, with or without atrial fibrillation, or in patients with moderate to severe mitral stenosis. Treatment with Edoxaban is therefore not recommended for these patients.
	Patient with recent history of recurrent falls who are at higher bleeding risk.

3. Assess your patient's bleeding risk. - The following risk factors can increase the risk of bleeding: The HAS-BLED score can be used to assess the bleeding risk of the patient (see reverse of 'Choosing the most suitable oral anticoagulant' document for further information)

	Previous history bleed or predisposition to bleeding (e.g. diverticulitis)		Chronic alcohol abuse- especially if associated with binge drinking.
	Congenital or acquired coagulation disorders		Uncontrolled hypertension
	Recent biopsy or major trauma		Bacterial Endocarditis
	Moderate & severe renal impairment		Acute hepatic impairment (e.g. bilirubin > 2xULN + LFTS > 3x ULN), chronic liver disease (e.g. cirrhosis)
	Low platelet count < 80 x 10^9/L or a thrombocytopenia or anaemia of undiagnosed cause		On concomitant drugs associated with an increased bleeding risk e.g. SSRIs, oral steroids, NSAIDs, clopidogrel, methotrexate or other immune-suppressant agents
	Bronchiectasis or history of pulmonary bleeding.		Vascular retinopathy

It might be worth considering co-prescription of a PPI to add gastroprotection in certain patient groups on concomitant medications which increase bleeding risk.

Dose is 60mg once daily (standard adult dose)

Renal Function – As renal function declines, drug clearance is reduced.	
Creatinine Cl (ml/min)	**Recommended dose**
Mild renal impairment (50 to ≤80ml/min)	No dose adjustment for MILD renal impairment, use std dose.
Moderate to Severe renal impairment (Cr Cl 15-50ml/min)	Reduce dose to 30mg once daily. Use is not recommended in pts with Cr Cl <15ml/min.
CrCL should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated. U&Es must be checked if there is any clinical suspicion of renal deterioration as the dose may need adjusting.	

Weight of patient
Reduce dose to 30mg daily if the patient is ≤ 60kg.

Patients being switched from warfarin
Warfarin should be stopped & then Edoxaban started once INR is ≤ 2.5, so INR monitoring is needed initially.

Other important considerations:

- A bleeding risk that would lead to a contra-indication to warfarin would also contra-indicate Edoxaban.
- Sub-optimal compliance with warfarin may not be improved by switching to Edoxaban as many of the causes of non-compliance with warfarin may also result in non-compliance with Edoxaban (e.g. alcoholism, chaotic lifestyle, wilful non-compliance). As Edoxaban has a short half-life (10-14 hours) missing a dose could be associated with an increased risk of stroke.
- Ensure that the patient is given an alert card by the pharmacy and that the patient knows to carry it around with them.
- Edoxaban is stable in monitored dosage systems (e.g. dossette) (unlike warfarin and Dabigatran).
- Edoxaban has **no antidote** and so patients with bleeds are managed with supportive care.
- For patients with swallowing difficulties or PEG tubes etc, please contact the Medicines Management Team for specific advice.

Drug Interactions (See SPC for full details, this list is not exhaustive)	
Interacting Drug	**Management**
Anti-platelets (e.g. aspirin, clopidogrel)	The SPC states that edoxaban can be co-administered with low dose aspirin (≤100mg/day). In clinical studies co-administration of aspirin, other anti-platelet agents and thienopyridines resulted in approximately a 2-fold increase in major bleeding which was a similar effect to concomitant use of these antiplatelets with warfarin. The risk of bleeding when using concomitant clopidogrel with edoxaban was less than the risk of warfarin plus clopidogrel.
NSAIDs	Chronic use of NSAIDs with edoxaban is not recommended.
P-gp inhibitors: Ketoconazole, ciclosporin, dronedarone, erythromycin	Combination thought to result in **increased** Edoxaban plasma concentrations. Reduce dose of edoxaban to 30mg daily.
P-gp inhibitors: Quinidine, verapamil, amiodarone	It is thought that the interaction with these drugs is not significant enough to warrant any dose changes.
P-gp inducers: e.g. Rifampicin, St. John's wort, Phenobarbital, Carbamazepine, or Phenytoin	Expected to result in **decreased** Edoxaban concentrations. Concomitant use with caution.
HIV Protease Inhibitors e.g. Ritonavir	Not been studied. No data.