Prescribing EDOXABAN for stroke prevention in (non-valvular) atrial fibrillation (AF)

Note: Edoxaban is also licensed for the acute treatment and secondary prevention of venous thromboembolism (VTE) Guidance for use for this indication can be found at: Cardiovascular Disease Guidelines

Edoxaban ▼ *(Lixiana®)* is a direct oral anticoagulant (DOAC) for use for stroke prevention in (non-valvular) atrial fibrillation (SPAF). The National Institute for Health and Care Excellence (NICE) has approved the use of edoxaban as an option for SPAF, in patients with additional stroke risk factors.

In South London, edoxaban should be considered as an option, in line with its licensed indications, for stroke prevention in patients with non-valvular atrial fibrillation and a CHA_2DS_2 VASc score ≥ 2 (consider for men with CHA_2DS_2VASc score ≥ 1), except those patients in whom edoxaban is contra-indicated.

Additional resources have been developed to support implementation including:

- PAN London Position Statement for stroke prevention in AF: PAN London Position Statement on SPAF
- Screening checklist and Notification of initiation of a DOAC for SPAF. This document **must be completed and sent to the General Practitioner (GP) on initiation:** SPAF Notification of Initiation
- Transfer of prescribing responsibility to primary care for DOACs. This document **must be completed and sent to the GP when transferring the prescribing responsibility** in accordance to South London guidelines: SPAF Transfer of Care

Edoxaban should only be initiated by clinicians with expertise in managing anticoagulant therapy. The initiating clinician / organisation is responsible for ensuring patient follow up and providing a supply of edoxaban for the first three months of treatment. During this time, efforts should be made to reinforce adherence and address any adverse effects.

Transfer of prescribing responsibility to patients own GP

Following the initial 3 month period, patients may be considered for transfer back to the patient's own GP, provided the agreed transfer of care guidance is followed. If edoxaban is prescribed for unlicensed indications outside the scope of local guidance, prescribing responsibility will remain with the initiating clinician.

Contraindications (for full details – see BNF or SPC)	**Cautions** (for full details – see BNF or SPC)
• Hypersensitivity to the active substance or to any of the excipients • Clinically significant active bleeding • Any lesion or condition considered a significant risk factor for major bleeding e.g. 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 • Prosthetic heart valves requiring anticoagulant treatment or mitral stenosis - the effect of edoxaban has not been studied in this patient group • Uncontrolled severe hypertension • Severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Established renal failure (CrCl< 15 ml/min*) • Pregnancy and/ or breast feeding For contra-indications for use with other medicines see overleaf	• Conditions which carry a haemorrhagic risk e.g. bacterial endocarditis, thrombocytopenia, congenital or acquired coagulation disorders • Low body weight ≤ 60kg • Mild or moderate hepatic impairment (Child Pugh score A or B) or elevated liver enzymes > twice the upper normal limit, bilirubin >1.5x upper normal limit (these patients were excluded from trials) • Moderate to severe renal impairment (CrCl 15-49 ml/min*) • For cautions for use with other medication see overleaf

Note: BNF=British National Formulary**; SPC=**Summary of Product Characteristics

*** Estimated Glomerular Filtration Rate (eGFR) should NOT be used to guide dosing decisions. Creatinine clearance must be estimated using the Cockcroft-Gault equation calculator or refer to the South London creatinine clearance information sheet.**

Dosing

The recommended dose of edoxaban is 60mg once daily with or without food.

• Reduced dose to 30mg once daily in patients with one of the following characteristics:

- body weight ≤60 kg,
- Moderate or severe renal impairment (CrCl 15-49ml/min), or
- Concomitant treatment with ciclosporin, dronedarone, erythromycin, or ketoconazole.

For patients identified as at risk of upper GI bleeding the co-prescription of a proton pump inhibitor *(e.g. lansoprazole/omeprazole) may be considered.*

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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South East London Area Prescribing Committee. A partnership between NHS organisations in South East London: Bexley/ Bromley/ Greenwich/ Lambeth/ Lewisham & Southwark Clinical Commissioning Groups (CCGs) & GSTFT/KCH/SLAM/Oxleas NHS Foundation Trusts & Lewisham & Greenwich NHS Trust

Monitoring

International normalised ratio (INR) monitoring is not required for patients taking edoxaban. However, clinical surveillance is recommended throughout the treatment period in line with good anticoagulation practice.

- All patients prescribed edoxaban should be reviewed **at least annually** to assess benefits and risks of on-going therapy, weighing the risk for thrombotic events against bleeding risk using CHA_2DS_2VASc and HASBLED score.
- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.
- A baseline renal function test is required and consequent re-testing should take place at least annually (frequency determined by the patient's baseline renal function as guided by the initiating clinician).
- Make any other dose adjustments necessary based on bodyweight and concomitant use interacting drugs. See below.

Side effects (for full details see the BNF or SPC)

- Bleeding occurs commonly during treatment with edoxaban and patients should be monitored for signs of bleeding or anaemia. In the ENGAGE AF-TIMI 48 study, the major bleeding rate with edoxaban 2.75% per annum. Patients should be advised to seek medical advice if they experience persistent or frequent episodes of bleeding. Patients experiencing severe bleeding should seek urgent medical advice.
- Other common side effects include: nausea, rash, pruritus, abnormal liver function tests (raised bilirubin and gamma-glutamyl transferase (GGT)).

Edoxaban *is a black triangle drug - any adverse effect must be reported to the MHRA using the yellow card system and via the local incident reporting system*

Drug interactions (for full details on drug interactions – see BNF or SPC)

Drug / Drug class	Recommendation
Other anticoagulant agents (e.g. UFH or heparin derivatives, LMWHs, oral anticoagulants)	Concomitant use is contraindicated due to increased risk of bleeding, except where switching therapy to or from edoxaban or when UFH is given at doses necessary to maintain a patent catheter
Use of fibrinolytic agents for the treatment of acute ischaemic stroke	May be considered by hyper-acute stroke units if the clinician can be certain that there is no anticoagulant effect present based on laboratory testing of clotting
Aspirin and other antiplatelet agents	Increased risk of bleeding – use with caution; should be stopped if clinically appropriate (seek advice from cardiologist); if required to continue close monitoring required and gastro-protection is advised
Non-steroidal anti-inflammatory drugs (NSAIDs)	Increased risk of bleeding if used long-term. Avoid where possible; if required use at the lowest dose and for the shortest duration possible; close monitoring required and gastro-protection is advised
Any other medicinal products affecting haemostasis	May increase the risk of bleeding when used concomitantly, close monitoring required
P-glycoprotein inducers - such as St. John`s wort (Hypericum perforatum), rifampicin, phenobarbital, carbamazepine or phenytoin	Concomitant use will result in decreased edoxaban plasma concentrations. No dose adjustment to edoxaban is required, however it should be used with caution. The co-administration of edoxaban with any of these agents should only be considered under specialist haematology supervision
Systemic ketoconazole, ciclosporin, dronedarone or erythromycin	Concomitant administration increases plasma edoxaban level. **Maximum edoxaban dose of 30mg once daily when prescribed concurrently**
Protease inhibitors	Not recommended for concomitant treatment
Amiodarone, quinidine, verapamil	No dose adjustment necessary

Roles and responsibilities

Initiating clinician / organisation	Patient's own GP
• To initiate edoxaban in line with NICE and local guidance • To supply edoxaban for the first 3 months of treatment • To provide counselling to improve adherence and address any early adverse effects • To ensure the patients GP and current anticoagulant service is informed about the cessation of warfarin therapy (if previously treated with warfarin). • To transfer care to the GP in line with local transfer of care guidance	• To ensure use of edoxaban is in line with the NICE / local guidance • To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation and in line with the transfer of care guidance) • To agree to take over prescribing earlier in patients with complex medication supply issues e.g. patients using medication compliance aids (MCA) or housebound patients • To emphasise the importance of adherence to edoxaban therapy and address any patient concerns • To assess benefits and risks of on-going therapy at least annually using CHA_2DS_2Vasc / HASBLED score • To ensure monitoring of renal and hepatic function is undertaken as directed by the initiating clinician and at least annually. If results fall outside normal range then refer to contraindication, caution and dosing sections in the prescribing guidelines and/or seek specialist advice as appropriate • To monitor on-going risk of bleed and if appropriate, seek specialist advice

Additional information

1. Patients taking edoxaban should be encouraged to carry an anticoagulation card (available from initiating clinician / anticoagulation clinics) at all times or to wear a medic-alert bracelet.
2. There is no specific reversal agent should a patient experience a bleed on edoxaban. In the event of a significant bleed, the patient should be referred to accident and emergency for supportive measures.
3. Other healthcare professionals should be made aware that edoxaban is prescribed for any patients who are to undergo invasive treatments, including elective surgery and dental treatment.
4. Missed dose advice should be discussed at initiation: If a dose of edoxaban is missed, the dose should be taken immediately and then be continued the following day with the once-daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.
5. If a patient has been assessed as being appropriate for a multi-compartment compliance aid (MCA), often known as a dosette box, consideration can be given to including edoxaban tablets as they do not have any special storage requirements.

References

1. NICE TA355. Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation September 2015. . Accessed April 2016 via https://www.nice.org.uk/guidance/ta355?unlid=508859825201622363725#
2. NICE CG180: Atrial fibrillation: management. July 2014. Accessed April 2016 via: https://www.nice.org.uk/guidance/cg180/resources/atrial-fibrillation-management-35109805981381
3. SPC Lixiana. Daiichi Sankyo UK Limited. July 2015. Accessed April 2016 at http://www.medicines.org.uk/emc/medicine/30506