

DRUG NAME: EDOXABAN (LIXIANA®)
Transfer of Care document
Treatment of acute venous thromboembolism and prevention of recurrent venous thromboembolism

INTRODUCTION – Indication and Licensing

Edoxaban is a non-vitamin K antagonist oral anticoagulant (NOAC) that works through highly selective inhibition of factor Xa. It is licensed for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE. For patients treated for venous thromboembolism (VTE) edoxaban is an attractive and cost effective treatment option. Initiation would be by secondary care only and in accordance with its licensed indication and NICE guidelines.

Due to its selective inhibition of one clotting factor, the anticoagulation effects are more predictable and as such there is no requirement for regular monitoring, unlike vitamin K antagonists (VKA) such as warfarin. Other potential advantages compared to VKAs include a standard dosing regimen and a lower likelihood of drug interactions. Disadvantages of edoxaban are its higher cost (partially offset by the reduced need for INR monitoring) and limited clinical experience of long-term use. Additional disadvantages are; there is no antidote as yet in case of life threatening bleeding, no available test for measuring residual activity before operation and no test for monitoring of patient adherence. However, in studies comparing against warfarin, less fatal bleeding was shown in comparison to warfarin in both atrial fibrillation and acute VTE and unlike warfarin has far shorter half-life and is therefore cleared quicker than warfarin, which may explain the less fatal bleeding seen in clinical trials.

PATIENT PATHWAY

Clinical Speciality / Indication	Prescribing Initiated by	Prescribing Continued by (detail when suitable for transfer to occur)	Monitored by (detail when suitable for transfer to occur IF APPROPRIATE)	Duration of treatment
Haematology/ Cardiology/ Stroke	Secondary care prescriber	Hospital after 4 weeks of initiation, where a further 4 weeks supply will be issued to patients	GP after 8 weeks	Individualised for each patients. All VTE patients will be seen by haematologist within 6 months of initiation to confirm duration of treatment

(N.B. a temporary discontinuation for surgical procedures is advised, see below for further details).

Patients are to be initiated in the first instance by a clinician in secondary care. If edoxaban is suitable, 4 weeks supply will be issued alongside the anticoagulation alert card and patient booklet.

The patient will return to anticoagulation clinic after the initial 4 weeks to ensure adequate follow up during the initiation phase providing adherence counselling addressing any patients concerns regarding therapy. If edoxaban is tolerated, then a further 4 weeks of treatment will be supplied by the hospital, after which the GP will continue the supply and monitoring. If the patient has concerns prior to commencing continuation with the GP they should contact the hospital anticoagulant team. The patient will be advised to contact their GP within 8 weeks of initiation. A NOAC initiation letter will also be forwarded to GP confirming transfer of care.

Duration of treatment will be advised initially by the anticoagulation team. A follow up within 3 to 6 months would then be carried out by a haematologist to assess the patient and extend the duration in treatment, if needed.

Long-term treatment should be reviewed at least annually by GP and an assessment made for new contraindications to ongoing anticoagulation with edoxaban (e.g. temporary discontinuation for surgery, marked decline in renal function and increased bleeding risk - see below for further advice on bleeding risk). Where new contraindications are found, treatment is to be reviewed and anticoagulation therapy withdrawn if risks are deemed to outweigh benefits. Ongoing adherence should be reviewed on a regular basis, the duration and method of adherence assessment should be determined by the GP, taking into account individual patient circumstances and factors. The GP is to re-educate the patient each time for the need to stop their edoxaban and seeing any doctor as soon as possible in case of bleeding.

ORAL DOSE AND ADMINISTRATION

Edoxaban film coated tablets are available in 2 strengths: 30mg or 60mg

Usual dose:

Dose	Renal function*		
	CrCl >50ml/min	CrCl: 15 to 50ml/min	CrCl<15ml/min
	60mg once daily	30mg once daily	Not recommended

*Cockcroft and Gault to be used – see below for formula

Dose reduction to **30mg once daily** required for:

- Body weight ≤ 60kg
- Concurrent administration of P-glycoprotein inhibitors (e.g. ciclosporin, dronedrone, erythromycin, ketoconazole).

Increased risk of bleed:

- If bleeding risk is assessed as high or patients have oesophagitis, or gastroesophageal reflux; edoxaban should be initiated cautiously for treatment of AF following discussion with a haematologist.
- Patients with an increased bleeding risk should be closely monitored clinically (looking for signs of bleeding or anaemia, more details below). Ongoing treatment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient (as CHA2DS2VASc score increases, the benefits of treatment with anticoagulation increases).
- If clinically relevant bleeding occurs, treatment should be interrupted and reviewed prior to re-initiation.

Cockcroft and Gault formula to calculate CrCl (ml/min)

$$\frac{K \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

K = 1.23 in males

K = 1.04 in females

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MONITORING

Parameter	Renal function (Creatinine clearance - CrCl) Using Cockcroft and Gault equation (see above)
Action Required	CrCl 15 to 50ml/min; dose reduction to 30mg daily. CrCL <15mls/min; contraindicated – avoid use.
Frequency of monitoring	Assess renal function prior to treatment to ensure appropriate starting dose. Then: <ul style="list-style-type: none"> • Annually (alongside Hb and liver function tests) • 6 monthly <ul style="list-style-type: none"> ○ >75years ○ Frail (defined as ≥3 of the following criteria: unintentional weight loss, self-reported exhaustion, weakness assessed by handgrip test, slow walking speed/gait apraxia, low physical activity) ○ If CrCl 30–60 ml/min • 3 monthly <ul style="list-style-type: none"> ○ If CrCl 15-29ml/min <p>More frequent renal function monitoring maybe needed as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate such as hypovolemia and dehydration.</p>
Further Action	Dose reduction may be required based on initial renal function. If renal function declines rapidly may need to temporarily withhold therapy and review prior to restarting.

Parameter	Minor bleeding (or those at high risk of bleed on treatment)
Haematological tests	Dose-dependent inhibition of Factor Xa activity was observed in humans. Routine clotting tests (PT and APTT) are not very reliable indicators of the level of edoxaban and should not be used for monitoring purposes. If measurement of an edoxaban level is required it should be with an anti-Xa assay following discussion with the haematology.
Action	If numerous episodes of minor bleeding are observed or patient at high risk of bleed discuss with haematology.

Parameter	Adherence
Target level	100%
Frequency of monitoring	Prior to initiation, likely adherence should be considered and discussed with the patient. Following initiation, adherence should be reinforced at a minimum of annually although this is left at the discretion of the physician
Action	If adherence likely to be low, consider alternative anticoagulation that can be monitored, i.e. warfarin.

Please note: Edoxaban has an inverted Black Triangle ▼ displayed in the patient information leaflet and in the summary of product characteristics (SPC). This means that it is a medicine subject to additional monitoring by regulatory authorities in the European Union (EU).

KEY ADVERSE EFFECTS & ACTIONS

Adverse effects	Symptoms/signs	Actions)
Minor Bleeding	Self-terminating minor bleeding from scratches, cuts, nosebleeds, gum bleeding etc. may be experienced. If	The degree of bleeding will dictate action. If minor bleeding is infrequent and self

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	these are frequent or patient / physician concerned - contact local haematology department for advice	terminates, patient can be reassured. If concerns are raised - liaise with haematology for advice.
Clinically significant bleeding	Bleeding that does not stop with reasonable intervention should be referred to local A&E, if in doubt contact local haematology department for advice	The degree of bleeding will dictate the action. If bleeding stops spontaneously consider omitting a dose. If concerns are raised - liaise with haematology for advice. For bleeding that does not stop with intervention, send patient to local A&E.
Gastrointestinal	Dyspepsia	Consider gastro protection in accordance with local guidance. If no further improvement, consider alternatives or referral to specialist.

This only lists the key important ADRs-For comprehensive information on cautions, contra-indications and interactions please refer to the current British National Formulary and Summary of Product Characteristics.

Important cautions: Surgery and invasive procedures

Patients on edoxaban who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require temporary discontinuation of edoxaban. If an invasive procedure or surgical intervention is required, edoxaban should be stopped at least 24hours before the intervention. See SPC for further details. If surgery cannot be delayed the case should be discussed with haematology for advice on reversal if required.

PREGNANCY AND BREAST FEEDING

The safety of edoxaban has not been established in pregnant or lactating women; as such use in these patients is to be avoided.

For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

Evidence

Edoxaban has been shown to be as effective as standard anticoagulant therapy comprising of low molecular weight heparin in combination with a vitamin K antagonist (VKA) e.g. warfarin; it has significantly lower levels of bleeding and a similar adverse effect profile.

Use of edoxaban to reduce the incidence of recurrent VTE has been studied in a large multinational, randomised control trial enrolling at least 8,000 patients with DVT and/or PE. The primary efficacy endpoint was recurrent symptomatic venous thromboembolism.

The Hokusai-VTE trial demonstrated noninferiority of edoxaban to warfarin with respect to the primary endpoint (3.2% vs 3.5% (P<0.001) edoxaban and warfarin respectively) with significantly less major and non-major bleeding (8.5% vs 10.3% (P=0.004) for edoxaban and warfarin respectively).

TRANSFER OF CARE

This document provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The transfer of care should be explained to the patient. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use.

Consultant/Anticoagulant team

1. Ensure that the patient/carer is an informed recipient of edoxaban.
2. Ensure that patients understand edoxaban treatment and monitoring (e.g. renal function) and follow up that is required (using advocacy if appropriate).
3. Ensure baseline investigations are satisfactory before commencing treatment. Give the patient an anticoagulant alert card and patient booklet.
4. Counsel the patient on the risks and benefits of treatment with edoxaban as well as importance of adherence to treatment.
5. Initiate treatment, prescribe and monitor for the first 8 weeks.
6. Send a NOAC initiation letter to the GP.
7. Clear documentation should be made as to reason for dose reduction.
8. Report any abnormal blood results to the GP where appropriate.
9. Evaluation of any reported adverse effects by GP or patient.
10. Advise GP on review, duration or discontinuation of treatment where necessary.
11. Ensure a 3 to 6 months follow up is arranged with haematologist.
12. Ensure that backup advice is available at all times.
13. Inform the patient to make a GP appointment within 8 weeks of initiation for further supplies.

General Practitioner

1. Reinforce the patient understands the nature, effect and potential side effects of edoxaban before prescribing and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the CSM, where appropriate.
5. Help in monitoring the progression of disease.
6. Prescribe and monitor the drug treatment as described and stop the drug at the specified time.
Consider

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist.
2. Ensure they have a clear understanding of their treatment (edoxaban).
3. Carry an anticoagulation card with them at all times.
4. Report any changes in disease symptoms to GP and/or specialist.

5. Alert GP and/or specialist of any changes of circumstance which could affect management of disease.
6. Administer edoxaban as prescribed and attend hospital/GP for assessment and monitoring as required.

Cost

Drug Product	Cost in primary care
Edoxaban tablets [30mg and 60mg]	£766.50 / year*

Based on *NICE 2015

Relevant contact details	
Doctor via switchboard	Dr Neil Chauhan (clinical lead for anticoagulation) via switchboard
Registrar on-call out of hours	Contact on-call haematology registrar out of hours via switchboard
Clinical Nurse Specialist/pharmacist	020 8510 4413 or 020 8510 4114 or via email huh-tr.Antico@nhs.net
Trust Homerton University Hospital NHS Foundation Medicines Information	020 8510 7000 or via email mipharmacy@homerton.nhs.uk
City and Hackney Medicines Management Team	020 3816 3224

References**With thanks to Barts Health NHS Trust,**

- Barts Health NHS Trust SCG adapted for local use.
- Büller HR, et al, Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism, New England Journal of Medicine, 2013; 369:1406-1415.
- Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism, issued August 2015, NICE technology appraisal guidance [TA354]. Available at: <https://www.nice.org.uk/guidance/ta354>, accessed 08/12/15.
- Summary of Product Characteristics, Lixiana 60mg film-coated tablets, Daiichi Sankyo, Date of revision of the text Oct 2015, accessed 20/12/15.

SCG template adopted from NELMMN and Barts Health NHS Trust (updated by JPG February 2015)