Coventry & Warwickshire Area Prescribing Committee

Drug Positioning Statement	DPS072
Edoxaban (Lixiana® ▼) – Stroke prevention in Atrial Fibrillation	**August 2018**

VERDICT:
Edoxaban, within its licensed indications and in line with NICE TA355 is recommended as an option for the prevention of stroke in non-valvular AF and should be initiated by a specialist, tailored to the clinical situation of the patient. Follow on prescribers should receive a checklist from the initiating specialist indicating that the patient is suitable for edoxaban therapy and has received appropriate guidance form the specialist. If the checklist is not made available, follow on prescribing in primary care should not commence until the specialist has been contacted and a checklist obtained.

For Primary Care Prescribers: The committee recognises the beneficial effect of anticoagulant therapy once a diagnosis of AF has been made in primary care. In this instance, edoxaban may be initiated by a primary care prescriber where they have attended a suitable training course and can demonstrate expertise in managing anticoagulant therapy. The committee also advise that the specialist initiated drug checklist is also completed by the primary care prescriber.

Specialist Drugs Status: Specialist Advised (SA)

SUMMARY NOTES

Indication: Prevention of stroke and systemic embolism in adult patients with non-valvular 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).
Also indicated for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults[1].

Pharmacological action: Edoxaban is a highly selective, direct and reversible inhibitor of factor Xa, the serine protease located in the final common pathway of the coagulation cascade. Edoxaban inhibits free factor Xa, and prothrombinase activity. Inhibition of factor Xa in the coagulation cascade reduces thrombin generation, prolongs clotting time and reduces the risk of thrombus formation[1].

Presentation: 30 mg and 60 mg film coated tablets[1]

Dose: **Summary of posology in NVAF**

Recommended dose		60 mg once daily
Dose recommendation for patients with one or more of the following clinical factors:		
Renal Impairment	Moderate or severe (Calculated using Cockcroft-Gault Equation = CrCL 15 – 50 ml/min)	30 mg once daily
Low Body Weight	≤ 60 kg	
P-gp Inhibitors	Ciclosporin, dronedarone, erythromycin, ketoconazole	

See SPC for guidance on switching from vitamin K antagonists, NOACs and parenteral anticoagulants to edoxaban

Cost comparison[2]: Cost of 28 days treatment (N.B. these doses are for general comparison and do not imply therapeutic equivalence)

Edoxaban 30 – 60 mg daily	**£49.00**
Apixaban 2.5mg – 5 mg twice daily	£53.20
Dabigatran 110 – 150 mg twice daily	£47.60
Rivaroxaban 20 mg once daily	£50.40
Warfarin 5 mg daily	£0.61 plus monitoring costs which range widely depending on local arrangements

DRUG PROFILE

Clinical Effectiveness - full evidence and network analysis can be found in NICE TA 355[3].
The primary source of evidence was ENGAGE AF-TIMI 48, a randomised, international (46 countries, including 31 centres in the UK) double-blind, double-dummy, parallel-group, non-inferiority trial comparing edoxaban with warfarin. It included a total of 21,105 people with non-valvular atrial fibrillation and a moderate to high risk of stroke, defined as a $CHADS_2$ score of 2 or more. People were randomly assigned to treatment with low dose edoxaban (30 mg, n=7034), high dose edoxaban (60 mg, n=7035) or warfarin (n=7036).

The primary efficacy outcome was prevention of stroke or systemic embolic event in a modified Intention To Treat set which encompassed patients who underwent randomization and received at least one dose of the study drug (99.6% of the study participants) and included events occurring during the treatment period, which was defined as the period between administration of the first dose of the study drug and either 3 days after the receipt of the last dose or the end of the double-blind therapy (whichever came first).

Both edoxaban 60 mg and edoxaban 30 mg met the criteria for non-inferiority compared with warfarin. In the edoxaban 60 mg arm of the trial stroke or a systemic embolic event occurred in 182 people (1.18% per year) compared with 232 people in the warfarin arm (1.50% per year, hazard ratio [HR] 0.79, 97.5% confidence interval [CI] 0.63–0.99, p<0.001 for non-inferiority). In the lower dose arm the HR for edoxaban 30 mg was 1.07 and it too was shown to be non-inferior to warfarin; 97.5% CI, 0.87 to 1.31; P = 0.005 for non-inferiority).

As can be seen from the confidence intervals, the 60 mg dose was actually superior to warfarin in this analysis, P = 0.02 for superiority. A pre-specified superiority assessment used the whole ITT population throughout the study period; and though the HR was in favour of the 60 mg dose of edoxaban, the difference was not significant. (For the high-dose edoxaban group hazard ratio vs. warfarin, 0.87; 97.5% CI,0.73 to 1.04; P = 0.08; and for the low-dose edoxaban group hazard ratio vs. warfarin, 1.13; 97.5% CI, 0.96 to 1.34; P = 0.10)

In the principal safety analysis , compared with warfarin, edoxaban 60 mg had a significantly reduced rate of major bleeding (HR 0.80, 95% CI 0.71–0.91; p<0.001) and of several secondary bleeding endpoints including intracranial, fatal, clinically relevant non-major and life-threatening bleeds (p≤0.01 for all comparisons). Rates were even lower in the edoxaban 30 mg arm. However, major gastrointestinal bleeding occurred slightly more frequently in the edoxaban 60 mg arm than in the warfarin arm (annualised rate of 1.51% compared with 1.23%, respectively; HR 1.23 [1.02–1.50]; p=0.03). But the rate of major gastrointestinal bleeding was actually lowest with low-dose edoxaban (0.82%, HR v warfarin 0.67, p<0.001).)

The annualized rate of the primary net clinical outcome (death from any cause, stroke, systemic embolic event, or major bleeding) and indeed, all secondary net clinical outcomes was significantly lower with both edoxaban regimens than with warfarin: 8.11% with warfarin, as compared with 7.26% with high-dose edoxaban (hazard ratio, 0.89; 95% CI, 0.83 to 0.96; P = 0.003) and 6.79% with low dose-edoxaban (hazard ratio, 0.83; 95% CI, 0.77 to 0.90; P<0.001).

A network meta-analysis was conducted to estimate the relative efficacy and safety of edoxaban for treating atrial fibrillation, that included 4 trials: ENGAGE AF-TIMI 48, and 3 trials of other newer oral anticoagulants (apixaban 5 mg twice daily [ARISTOTLE]; dabigatran etexilate 150 mg twice daily or 110 mg twice daily [RE-LY]; and rivaroxaban 20 mg once daily [ROCKET-AF]). All 4 RCTs had a warfarin treatment arm. Because of significant differences in the patient characteristics and trial design between the 4 trials (for example, ARISTOTLE and RE-LY included people with a CHADS2 score of 1 or more, whereas the CHADS2 score was 2 or more in both ENGAGE AF-TIMI 48 and ROCKET-AF) only data from patients with a CHADS2 score of 2 or more from RE-LY and ARISTOTLE were used in the network meta-analyses. The results of the meta-analysis suggested that for the composite endpoint of stroke and systemic embolism, efficacy was similar for high dose edoxaban compared to other newer oral anticoagulants, but edoxaban significantly reduced major bleeding risk by 24%, 28%, and 17% compared to rivaroxaban, dabigatran etexilate 150 mg and dabigatran etexilate 110 mg, respectively. Major bleeding rates were similar between high dose edoxaban and apixaban. However, because of violation of proportional hazards assumptions both within and between trials, the NICE ERG had very little confidence in the robustness of the conclusions of the network meta-analysis (carried out by the sponsoring company.) The best they felt able to say was that the NOACs seem pretty much equivalent.

The NICE evidence committee discussed the subgroup analysis based on renal function, which used 3 categories of creatinine clearance (normal renal function, and mild or moderate impairment). It noted that the results of this analysis suggested a trend towards decreasing efficacy of edoxaban with increasing creatinine clearance. It also noted the summary of product characteristics which states that, in people with non-valvular atrial fibrillation and high creatinine clearance, edoxaban should only be used after careful evaluation of a person's thromboembolic and bleeding risk. The committee concluded that if edoxaban is used in accordance with the summary of product characteristics, there was no reason to make differential recommendations based on creatinine clearance[3].

Adverse effects: The summary of product characteristics includes the following common adverse reactions for edoxaban: bleeding, anaemia, nausea, rash, hepatobiliary disorders (increased blood bilirubin and gamma-glutamyl transferase) and abnormal liver function test.
For full details of adverse reactions and contraindications, see the summary of product characteristics[1].

Cautions[1]

- Like other anticoagulants, edoxaban is recommended to be used with caution in patients with increased risk of bleeding. Edoxaban should be discontinued if severe haemorrhage occurs.
- In the clinical studies mucosal bleedings (e.g. epistaxis, gastrointestinal, genitourinary) and anaemia were seen more frequently during long term edoxaban treatment compared with Vitamin K Antagonist 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.
- The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing.
- A specific anticoagulant reversal agent for edoxaban is not available[1]. For life-threatening bleeding that cannot be controlled with the measures such as transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of Lixiana® 30 minutes after completing the infusion. [1,3]
- Haemodialysis does not significantly contribute to edoxaban clearance.
- 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.

DRUG PROFILE cont'd

- *Anticoagulants, antiplatelets, and thrombolytics*: concomitant use of medicines affecting haemostasis may increase the risk of bleeding. These include acetylsalicylic acid (ASA), $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and chronic nonsteroidal anti-inflammatory drugs (NSAIDs).
- Edoxaban is not recommended 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, as its use has not been studied.
- Although treatment with edoxaban does not require routine monitoring, the effect on anticoagulation can be estimated by a calibrated quantitative anti-Factor Xa assay which may help to inform clinical decisions in particular situations as, e.g. overdose and emergency surgery.
- Edoxaban prolongs standard clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT) as a result of FXa inhibition. Changes observed in these clotting tests at the expected therapeutic dose are, however, small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of edoxaban[1].

Contraindications

- Clinically significant active bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Any lesion or condition that is considered to be a significant risk for major bleeding. This may include 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.
- Uncontrolled severe hypertension.
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.) except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter [1].

Elderly patients: **(≥ 65 years old):** No dose reduction is required[1].

Renal impairment: In patients with mild renal impairment (Calculated Creatinine Clearance (CrCL) using Cockcroft-Gault Equation > 50 – 80 mL/min), the recommended dose is 60 mg once daily.
In patients with moderate or severe renal impairment (CrCL 15 – 50 mL/min), the recommended dose is 30 mg once daily
In patients with end stage renal disease (ESRD) (CrCL < 15 mL/min) or on dialysis, the use of edoxaban is not recommended.
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 after a careful evaluation of the individual thromboembolic and bleeding risk. **CrCL should be monitored and calculated using Cockcroft-Gault equation at the beginning of the treatment in all patients and afterwards when clinically indicated [1].**

Hepatic impairment: In patients with severe hepatic impairment edoxaban is not recommended
Edoxaban should be used with caution in patients with mild to moderate hepatic impairment.
Patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Therefore edoxaban should be used with caution in this population. **Prior to initiating edoxaban, liver function testing should be performed[1]**. Periodic hepatic monitoring is recommended for patients treated with edoxaban beyond 1 year.

CURRENT PLACE IN THERAPY

National Institute for Health and Care Excellence (NICE)
AF: Edoxaban is recommended as an option for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation who have one or more risk factors, including:

- congestive heart failure
- hypertension
- diabetes
- prior stroke or transient ischaemic attack
- age 75 years or older

The decision about whether to start treatment with edoxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of edoxaban compared with warfarin, apixaban, dabigatran etexilate and rivaroxaban. For people considering switching from warfarin, edoxaban's potential benefits should be considered against its potential risks, taking into account the person's level of international normalised ratio (INR) control[3].

Scottish medicines Consortium (SMC)
Accepted for use within NHS Scotland for prevention of stroke and systemic embolism in adult patients with non-valvular 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).

One phase III study showed non-inferiority of edoxaban versus a vitamin K antagonist for the prevention of stroke and systemic embolism in adult patients with NVAF and a $CHADS_2$ score of ≥2. It was also associated with a significant reduction in risk of major bleeding[4].

Summary

- Edoxaban is the fourth factor Xa inhibitor.
- Edoxaban demonstrated non-inferiority to warfarin the ENGAGE-AF TIMI trial.
- The NICE TA notes a trend towards decreasing efficacy with increasing creatinine clearance for edoxaban compared to well-managed warfarin. (This may also apply to all newer oral anticoagulants, but data are needed to confirm this). The SPC therefore states that, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.
- No head-to-head studies of the NOACs have been conducted, making direct comparisons difficult. NICE has suggested through the network meta-analysis (whilst noting that the hazard ratios were not reliable) that all the newer oral anticoagulants seem to have comparable efficacy for the composite primary and bleeding outcomes.
- No NOACs are approved for use in AF patients with either mechanical valves or bioprosthetic valves.
- All the NOACs need to be adjusted in renal impairment.
- Like rivaroxaban, edoxaban is administered once daily.

References

1. Summary of product characteristics (Lixiana 60mg Film-Coated Tablets®), Date of revision of text 3/8/2018 Available from www.medicines.org.uk <Accessed 22/08/2018>
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3. National Institute for Health and Clinical Excellence. Technology appraisal guidance 355. Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. September 2015. Available at https://www.nice.org.uk/guidance/ta355 accessed 9/10/15
4. Scottish Medicines Consortium. SMC ID 1095/15 Available from: https://www.scottishmedicines.org.uk/files/advice edoxaban_Lixiana _NVAF_FINAL_October_2015_Amended_03.11.15.pdf<Accessed 22/08/18>