Rationale for Initiation, Continuation and Discontinuation (RICaD)

Edoxaban ▼

For preventing stroke and systemic embolism in people with non-valvular atrial fibrillation (NICE TA 355)

This document supports the use and transfer of an agent which is classified as **AMBER**.
It is intended for completion by specialist in order to give Primary Care prescribers a clear indication of the reason for recommending an **AMBER** medication together with suggested criteria for its subsequent continuation or discontinuation. This RICaD should be provided as a supplement to the specialist's clinical letter.

Patient details		**GP details**		**Specialist details**	
Name		**GP name**	**Dr**	**Specialist name**	
NHS Number		**GP address**		**I confirm that this patient is eligible to receive edoxaban under the restrictions listed below**	
DOB				**Signature**	
Patient address				**Date**	
				Contact details	

Rationale for Choice

Relevant Diagnosis:	Non-valvular atrial fibrillation ☐
Agreed Indication(s) for inclusion in the BSSE APC Formulary:	As specified in NICE TA 355: 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. **Specialist please check appropriate box** • heart failure ☐ • high blood pressure ☐ • diabetes mellitus ☐ • prior stroke ☐ • prior transient ischaemic attack ☐ • aged 75 years or older. ☐
Reason why edoxaban has been chosen in preference to drugs without Formulary restrictions:	**Specialists please type text below and check boxes**: I can confirm that an informed discussion about the benefits and risks of edoxaban compared with warfarin has taken place with the patient. See checklist below ☐ /enclosed ☐ * (*check box as applicable) ☐ Allergic reaction/intolerance of coumarins (warfarin, phenindione, sinthrome) ☐ Patients with important and unavoidable drug interactions that favour edoxoban over warfarin ☐ Patients in whom monitoring and/or coping with variable dose regimen are difficult but who are able to comply with a fixed dose drug regime. ☐ Previous significant bleed on warfarin in patients at high risk for stroke, if bleed was associated with poor INR control in a patient who is believed to be adherent with prescribed medication. ☐ Poor INR control (e.g. more than 2 INRs >8.0 or more than 3 INRs >5.0 in 6 months) ☐ Poor Time to Therapeutic Range List TTR value: …… ☐ Patients who, following informed discussion of risks and benefits of edoxoban and warfarin, request edoxoban as their preferred choice in terms of a favourable lifestyle in comparison to warfarin
Pre-treatment test results	Specialists please complete the information in table below: | | Results | Date of test | | CrCL | | | | LFT | | | • Note: In patients with end stage renal disease (ESRD) (CrCL < 15 mL/min) or on dialysis, the use of edoxaban is not recommended. See full SPC for prescribing information at https://www.medicines.org.uk/emc/. • The patient has been informed of the need for annual (or more frequent if clinically appropriate) renal function tests in order to assess suitability for ongoing treatment. ☐ • Prior to initiating edoxaban, liver function testing should be performed.

Guidance on initiation (to be completed by the specialist)

<table>
<tr><td>Initiation dose:</td><td>
<u>Prevention of stroke and systemic embolism</u>

The recommended dose is 60 mg edoxaban once daily. Therapy with edoxaban in NVAF patients should be continued long term.
<table>
<tr><td colspan="3">Dose recommendation for patients with one or more of the following clinical factors:</td></tr>
<tr><td rowspan="3">Renal Impairment</td><td>Mild (CrCL > 50 – 80 mL/min)</td><td>60 mg once a day</td></tr>
<tr><td>Moderate or severe (CrCL 15 – 50 mL/min)</td><td>30 mg once daily</td></tr>
<tr><td>End stage renal disease (ESRD) (CrCL < 15 mL/min) or on dialysis</td><td>Not recommended</td></tr>
<tr><td rowspan="3">Hepatic Impairment</td><td>Mild to moderate - use with caution</td><td>60 mg once a day</td></tr>
<tr><td>Severe</td><td>Not recommended</td></tr>
<tr><td>Patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN</td><td>Use with caution</td></tr>
<tr><td>Low Body Weight</td><td>≤ 60 kg</td><td>30 mg once daily</td></tr>
<tr><td>P-gp Inhibitors</td><td>Ciclosporin, dronedarone, erythromycin, ketoconazole</td><td>30 mg once daily</td></tr>
</table>

Recommendation:- GP to add an end/review date on the directions and patients notes
</td></tr>
<tr><td>Specialist recommendations</td><td>Specialist to complete</td></tr>
<tr><td>Monitoring:</td><td>
• Renal function should be assessed in all patients before starting edoxaban and at least once a year or more frequently as needed in clinical situations when it is suspected that the renal function could decline or deteriorate (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products). Deterioration of renal function can significantly increase plasma concentration.
• Liver function test
</td></tr>
</table>

Suggested Criteria for Continuation or Discontinuation (to be completed by the specialist)

<table>
<tr><th colspan="2">Assessment of Efficacy</th></tr>
<tr><td>Frequency</td><td>At routine appointments but at least annually</td></tr>
<tr><td>Location</td><td>GP practice</td></tr>
<tr><td>Method</td><td>
• Renal function test
• Discussion with patient regarding compliance and any factors that may affect compliance (i.e. need for monitored dose system or swallowing difficulties)
• Reassess bleeding risk, including risk of falls, and use of medication associated with gastro-intestinal bleeding
• Review hepatic function
</td></tr>
<tr><td>Continuation Criteria</td><td>Appropriate renal & hepatic function and compliance confirmed.
CrCL 15 – 50 mL/min – patients should receive the lower dose of edoxaban 30mg once a day</td></tr>
<tr><td>Review</td><td>At least annually.</td></tr>
<tr><td>Discontinuation Criteria</td><td>
• Renal function – CrCL < 15 mL/min – discontinue
• Poor compliance
• Unacceptable bleeding risk/severe haemorrhage
• Severe hepatic impairment
• Use with interacting medication
• Discontinue prior to surgery following advice from Haematologist.
</td></tr>
<tr><td>Follow up action</td><td>Specialist to complete</td></tr>
<tr><td>Shared Care Read Code</td><td>
In the patients notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement
<table>
<tr><th>GP Prescribing System</th><th>Read Code</th><th>Description</th></tr>
<tr><td>EMIS and Vision</td><td>8BM5.00</td><td>Shared care prescribing</td></tr>
<tr><td>SystmOne</td><td>XaB58</td><td>Shared care</td></tr>
</table>
</td></tr>
<tr><td>References</td><td>

• Edoxaban SPC https://www.medicines.org.uk/emc/ (accessed 26 February 2016)
• NICE TA355 - Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation https://www.nice.org.uk/guidance/ta355

</td></tr>
</table>

Appendix : Important information from the Summary of Product Characteristics (SPC)

Special precautions	**Contraindications** • Hypersensitivity to the active substance or to any of the excipients listed. • Clinically significant active bleeding. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Lesion or condition, if 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. • Pregnancy and breast-feeding (safety and efficacy has not been established). **Cautions** Edoxaban 15 mg is not indicated as monotherapy, as it may result in decreased efficacy. It is only indicated in the process of switching from edoxaban 30 mg to VKA (Vitamin K Antagonist), together with an appropriate VKA dose. <u>Haemorrhagic risk</u> Edoxaban increases the risk of bleeding and can cause serious, potentially fatal bleeding. Edoxaban, like other anticoagulants, is recommended to be used with caution in patients with increased risk of bleeding. Edoxaban administration 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 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. Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing. A specific anticoagulant reversal agent for edoxaban is not available at the time of writing. Haemodialysis does not significantly contribute to edoxaban clearance. <u>Elderly patients</u> The co-administration of edoxaban with acetylsalicylic acid (ASA) in elderly patients should be used cautiously because of a potentially higher bleeding risk. <u>Renal impairment</u> The plasma area under the curve (AUC) for subjects with mild (CrCL > 50 - 80 mL/min), moderate (CrCL 30 - 50 mL/min) and severe (CrCL < 30 mL/min but not undergoing dialysis) renal impairment was increased by 32%, 74%, and 72%, respectively, relative to subjects with normal renal function. A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin in AF patients. In patients with end stage renal disease or on dialysis, edoxaban is not recommended. <u>Renal function in NVAF</u> • 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. • Assessment of renal function: CrCL should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated.

Hepatic impairment

- Edoxaban is not recommended in patients with severe hepatic impairment.
- Edoxaban should be used with caution in patients with mild or 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.
- Periodic hepatic monitoring is recommended for patients on edoxaban treatment beyond 1 year.

Discontinuation for surgery and other interventions

- 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.
- 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.

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).

Prosthetic heart valves and moderate to severe mitral stenosis

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. Therefore, use of edoxaban is not recommended in these patients.

Laboratory coagulation parameters

- 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.

Drug Interaction (please see SPC for more detail)

Acetylsalicylic acid (ASA)	Co-administration of ASA (100 mg or 325 mg) and edoxaban increased bleeding time relative to either medicine alone. The concomitant chronic use of high dose ASA (325 mg) with edoxaban is not recommended. Concomitant administration of higher doses than 100 mg ASA should only be performed under medical supervision.
NSAIDs	Co-administration of naproxen and edoxaban increased bleeding time relative to either medicine alone. Chronic use of NSAIDs with edoxaban is not recommended.
Thienopyridines (e.g. clopidogrel)	Concomitant use of thienopyridines (e.g. clopidogrel) monotherapy was permitted and resulted in increased clinically relevant bleeding although with a lower risk of bleeding on edoxaban compared to warfarin.
Quinidine	Plasma concentration of edoxaban possibly increased by quinidine.
Verapamil	Plasma concentration of edoxaban possibly increased by verapamil.
Ciclosporin	Increased plasma concentrations of edoxaban. Concomitant use of edoxaban with ciclosporin requires dose reduction to 30 mg once daily.
Erythromycin	Increased plasma concentrations of edoxaban. Concomitant use of edoxaban with erythromycin requires dose reduction to 30 mg once daily.
Ketoconazole	Increased plasma concentrations of edoxaban. Concomitant use of edoxaban with ketoconazole requires dose reduction to 30 mg once daily.
Dronedarone	Increased plasma concentrations of edoxaban. Concomitant use of edoxaban with dronedarone requires dose reduction to 30 mg once daily.
Anticoagulants	Increased risk of haemorrhage when edoxaban given with other anticoagulants (avoid concomitant use except when switching with other anticoagulants or using heparin to

		maintain catheter patency).
	Carbamazepine	Plasma concentration of edoxaban possibly reduced by Carbamazepine.
	Phenobarbital	Plasma concentration of edoxaban possibly reduced by Phenobarbital.
	Phenytoin	Plasma concentration of edoxaban possibly reduced by Phenytoin.
	Rifampicin	Plasma concentration of edoxaban possibly reduced by rifampicin.
	St John's Wort	Plasma concentration of edoxaban possibly reduced by St John's Wort.
Additional info:	**At the time of writing, no antidote to edoxaban had been brought to market. However PCC can be used under the advice of a haematologist.** **Tablets should be swallowed with water, with or without food. A liquid formulation is not available.** **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 patient should not take double the prescribed dose on the same day to make up for a missed dose.** **Edoxaban ▼ is a black triangle drug. All suspected adverse effects should be reported to the MHRA** **www.yellowcard.gov.uk**	

Please note the information included in this document is correct at the time of writing. The manufacturer's Summary of Product Characteristics (SPC) and the most current edition of the British National Formulary should be consulted for up to date and more detailed prescribing information.