Lancashire Medicines Management Group

NHS

Prescribing Guidance for Dabigatran (Pradaxa), Rivaroxaban (Xarelto▼), Apixaban (Eliquis) and Edoxaban (Lixiana▼) in Patients with Non-Valvular AF

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VERSION CONTROL

Version Number	Date	Amendments made
Version 1.1	Nov 13	Updated contraindications and warnings for all three drugs issued by MRHA October 2013
Version 1.2	Dec 13	• Rivaroxaban dose amended from 5mg to 15mg • Apixaban renal function creatinine clearance amended from 30+ ml to >30 ml / min • Dronedarone included on the contra-indications for Dabigatran. • Box 2 page 3 extended to complete the sentence • (SEE) removed as always used in full • Guidelines put into Standard Guidelines covers • Review date amended to November 2016
Version 2.0	Mar 16	• Purpose & Scope of guidance clarified • Information on edoxaban incorporated as per NICE TA 355. • Renal section updated with information onCrCl vs eGFR. • Serious drug interactions updated as per BNF 70 • Contraindications updated as per SPC • Use of NOACs with antiplatelets considered • Prescribing information section updated • Information on dabigatran reversal incorporated • Dabigatran discontinuation information updated as per the SPC

Contents

Guidance for prescribing of Dabigatran (Pradaxa), Rivaroxaban (Xarelto▼), Apixaban (Eliquis) and Edoxaban (Lixiana▼) in Patients with Non-Valvular AF

1. **Introduction**

NICE TA 249[1], 256[2], 275[3] and 355[4] recommend dabigatran*, rivaroxaban, apixaban♦ and edoxaban respectively, as options for prevention of stroke in non-valvular Atrial Fibrillation (NVAF) if patients have one or more of the following risk factors:

- Previous stroke or TIA
- Age 75 Years or older
- Congestive heart failure
- Hypertension
- Diabetes

*For Dabigatran, NICE and SPC stipulates: heart failure of NYHA class 2 or above and age of over 65 **with** diabetes, CAD or hypertension.
♦For Apixaban, NICE and SPC stipulates: heart failure of NYHA class 2 or above

The clinician should discuss the risks and benefits of dabigatran, rivaroxaban, apixaban or edoxaban compared to warfarin or other coumarin before considering initiation or switching.

As per NICE CG 180[5] (Atrial Fibrillation Management), treatment may also be with a vitamin K antagonist such as warfarin, therefore for patients with a stable INR already on warfarin or coumarin it may be appropriate to remain on warfarin.

2. **Purpose**

This guidance has been produced to summarise and compare the Novel/Non Vitamin-K antagonist Oral AntiCoagulants (NOACs) which have been endorsed by NICE and the LMMG.

3. **Scope**

This guidance summarises and compares key prescribing considerations for the non-vitamin K antagonists when used for stroke prevention in patients with NVAF. It should be read in conjunction with the relevant Summary of Product Characteristics.

It does not:

- Provide NOAC dosing information for other (non-AF) indications
- Consider the assessment of patients with NVAF to determine if anticoagulation therapy is indicated
- Provide information on the alternative oral anticoagulant treatment options such as warfarin
- Summarise key patient counselling points

Other relevant guidance documents include:

- The Consensus statement for Oral Anticoagulant Drugs for prevention of stroke and systemic embolism
- The Anticoagulant Decision Support Tool and Patient counselling check list

These can be accessed via the guidelines section of the LMMG website

4. Guidance

4.1 NOAC Doses for Stroke Prevention in Patients with Non-Valvular AF [6,7,8&9]

Dabigatran Not suitable for a MDS	**Rivaroxaban**	**Apixaban**	**Edoxaban**
< 80yrs:150mg Twice daily * **> 80yrs:** 110mg Twice daily **Concomitant verapamil:**110mg Twice daily * **For the following patient groups the daily dose of 300mg or 220mg should be based on an assessment of the thromboembolic Vs bleeding risk** • 75-80yrs • Moderate renal impairment (CrCl 30-49ml/min) • Increased risk of bleeding e.g. gastritis, esophagitis or reflux, high has-bled	**CrCL:** **>49mL/min:** 20mg Once daily **30-49mL/min:** 15mg Once daily **15-29mL/min:** 15mg Once daily	**CrCl:** **>29ml/min:** 5mg Twice daily* **15–29ml/min:** 2.5mg Twice daily ***2.5mg twice daily if 2 of the following:** • Age >/= 80years • Weight </= 60kg • SrCr >/=1.5mg/dl (133micromol /L)	**Dose = 60mg* Once Daily** ***30mg Once daily if one or more of the following:** • CrCl 15-50ml/min • Weight ≤ 60Kg • Concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole

4.2 Use of NOACs in Renal Impairment [6,7,8&9]

The Non-Vitamin K Antagonist Oral AntiCoagulants (NOACs) dabigatran, rivaroxaban, apixaban and edoxaban are powerful anti-coagulants. Before consideration, patients must have an up to date renal function test, the results may affect treatment choice and the dose used.

CrCl>50ml/min	**All 4 NOACs may be used** Nb. Edoxaban should only be used in patients with NVAF and **high CrCl** after careful evaluation of the individual thromboembolic and bleeding risk (there is a trend towards decreasing efficacy with increasing CrCl compared to well-managed warfarin).	**See section 4.1 above for dosing information**
CrCl 30-49ml/min	**All 4 NOACs may be used** Dabigatran- dose reduction should be considered Rivaroxaban, apixiban and edoxaban- dose adjustment required	
CrCl 15-29ml/min	Dabigatran - contraindicated Rivaroxaban, apixaban and edoxaban -dose adjustment required	
CrCl <15ml/min	Dabigatran - contraindicated Rivaroxaban- use not recommended Apixiban-no clinical experience, use not recommended Edoxaban- use not recommended	

Nb. Renal function can decline while on treatment, monitor annually or more frequently in high-risk patients or when a change in renal function is suspected during treatment (e.g. hypovolaemia, dehydration)[9].

4.2.1 Use of Creatinine Clearance (CrCl) Vs eGFR [10]

- The BNF and SPCs use CrCl as the basis of dose adjustment for the NOACs. The SPCs for dabigatran and edoxaban specifically state that CrCL should be used to asses renal function.*
- CrCl and eGFR are calculated using different formulas and they are not routinely interchangeable.
- Because renal function in adults is increasingly being reported on the basis of eGFR, the BNF now provides information on dosage adjustment in terms of eGFR rather than CrCl for most drugs.
- In practice for most drugs and for most patients (over 18 years) of average build and height, the eGFR can be used to determine dosage adjustments in place of CrCl. Exceptions being for toxic drugs or drugs with a narrow therapeutic index and in patients at extremes of weight (BMI <18.5kg/m^2 and >30kg/m^2).
- Therefore, although eGFR can be used in place of CrCl to determine dose adjustments in most patients, NOAC dosing should be based on CrCl where possible (as per the BNF& SPCs). For patients at increased risk of toxicity or adverse events (e.g. because of frailty, baseline bleeding risk, extremes of body weight, drug interactions etc.), CrCl or absolute GFR should always be used.

Cockcroft-Gault Equation (Online CrCl calculators are also available. See medicines complete CrCl Calculator)

If Cr Reported in µmol/L

$$\frac{1.23 \times (140 - \text{Age [Years]}) \times \text{Weight [Kg]} \times (0.85 \text{ if female})}{\text{Serum Creatinine [µmol/L]}}$$

If Cr reported in mg/dl

$$\frac{(140 - \text{Age [Years]}) \times \text{Weight [Kg]} \times (0.85 \text{ if female})}{72 \times \text{Serum Creatinine [mg/dL]}}$$

* **The SPC for Edoxaban states** 'Renal function should be assessed in all patients by calculating the CrCL prior to initiation of treatment with Lixiana. Renal function should also be assessed when a change in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products).'
The SPC for Dabigatran States 'The method used to estimate renal function (CrCL in mL/min) during the clinical development of Pradaxa was the Cockcroft-Gault method. This method is recommended when assessing patients' CrCL prior to and during Pradaxa treatment.'

4.3 NOAC Contraindications/Use not Recommended[6,7,8,9,10&11]

Haemorrhage is a common adverse effect of all anticoagulants and all NOACs are contraindicated if there is clinically significant active bleeding. Additionally, the MHRA has clarified that contraindications relating to conditions which put patients at significant risk of bleeding and those relating to use of other anticoagulants concomitantly, apply to all NOACs and are as follows: [11]

A. **A lesion or condition, if considered a significant risk factor for major bleeding.**
This may include:
- Current or recent gastrointestinal ulceration
- Presence of malignant neoplasm 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 malformation
- Vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities

B. **Concomitant treatment with any other anticoagulant agent. For Example**: unfractionated heparin, Low Molecular Weight Heparin (such as enoxaparin or dalteparin), heparin derivatives (such as fondaparinux) or oral anticoagulants (such as warfarin). Exceptions are switching of therapy to or from the medicine, or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter

See also the MHRA Drug Safety Update New Oral Anticoagulants

DABIGATRAN CONTRAINDICATIONS

- Hypersensitivity to the active substance or excipients
- CrCl <30 mL/min
- Clinically significant active bleeding
- Lesion or condition, if considered to be a significant risk for major bleeding (See above)
- Not to be used as an anticoagulant for prosthetic heart-valve
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic: **anticoagulants, dronedarone, itraconazole, ciclosporin ketoconazole,**

Use not recommended

- Pregnancy and breastfeeding
- Concomitant **IV diclofenac, ketorolac, rifampicin, St. Johns Wort, carbamazepine, fosphenytoin, phenytoin, and tacrolimus**

RIVAROXABAN CONTRAINDICATIONS

- Hypersensitivity to the active substance or excipients
- Clinically significant active bleeding
- Lesion or condition, if considered to be a significant risk for major bleeding (See above)
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
- Pregnancy and breastfeeding

Use not recommended

- CrCl <15 mL/min
- Concomitant treatment with systemic: **anticoagulants, IV diclofenac, ketorolac, dronedarone, ketoconazole, itraconazole, posaconazole, voriconazole, atazanavir, darunavir, fosamprenavir, indinavir, saquinavir, tipranavir, lopinavir, ritonavir and cobicistat**

APIXABAN CONTRA-INDICATIONS

- Hypersensitivity to the active substance or excipients
- Clinically significant active bleeding
- Lesion or condition, if considered to be a significant risk for major bleeding (See above)
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Concomitant treatment with systemic: **anticoagulants, IV diclofenac, ketorolac, clarithromycin, telithromycin, ketoconazole, itraconazole, posaconazole voriconazole, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir & cobistat.** If treating DVT/PE also avoid: **rifampicin, St.Johns Wort & Carbamazapine**

Use not recommended

- CrCl <15 mL/min or if undergoing renal dialysis
- Pregnancy& breastfeeding

EDOXABAN CONTRAINDICATIONS

- Hypersensitivity to the active substance
- Clinically significant active bleeding
- Lesion or condition, if considered to be a significant risk for major bleeding (See above)
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Uncontrolled severe hypertension
- Pregnancy and breastfeeding
- Concomitant treatment with systemic: a**nticoagulants, chronic use of NSAIDs or acetylsalic acid**
  (Interaction with HIV protease inhibitors has not been studied, may increase edoxaban levels)

Use not recommended

- CrCl <15 mL/min or if undergoing renal dialysis

4.4 Concomitant use of NOACs and Antiplatelets[12&13]

The co-prescription of an antiplatelet agent, with a NOAC, confers an additional bleeding risk. If a patient is on an antiplatelet because of pre-existing ischeamic heart disease (or cerebral vascular disease), the antiplatelet agent should be reviewed with a view to discontinuation. As summarised by the UKMI this is a complex area because:

- Dual antiplatelet therapy reduces the risk of ischaemic cardiac events but not AF related thrombotic stroke.
- Anticoagulants reduce the risk of AF related thrombotic stroke but not of cardiac ischaemic events.
- The combination of dual-antiplatelet therapy plus anticoagulant (referred to as "triple oral antithrombotic therapy" or "triple therapy") increases the risk of bleeding events by about 2-4 times compared to anticoagulant or aspirin alone.

The optimal strategy to balance the risk of bleeding events and recurrent ischaemic events in people needing antiplatelets and anticoagulants is subject to debate because specifically designed and powered studies are not available. The choice of therapy and its duration should be individualised, based on atherothrombotic risk, cardio-embolic risk, and bleeding risk.

European guidelines advise the following:

•Patients with stable coronary artery disease (i.e. no acute ischaemic events or PCI/stent in the preceding 12 months) and concurrent AF can be managed with anticoagulation alone.
•Gastroprotection with a proton pump inhibitor should be considered in all patients on any combination of antiplatelets
•The routine use of P2Y12 inhibitors (prasugrel and ticagrelor) in combination with a NOAC is not recommended due to the increased risk of major bleeding.
•Where a NOAC is used with an antiplatelet, the lowest effective dose to reduce the risk of stroke should be considered.
•The period of dual antiplatelet therapy plus anticoagulant should be as short as possible (e.g. not exceeding 6 months for patients at low risk of bleeding or 4 weeks for patients at high risk of bleeding). This can be followed by single antiplatelet therapy plus anticoagulant for up to 12 months then lifelong anticoagulant.

Further information is available from UKMI

If there are concerns about stopping the antiplatelet then cardiology advice should be sought.

4.5 NOAC Monitoring Requirements[6789&14]

There are no specific monitoring requirements outlined in the SPCs with the exception of:
Dabigatran: Manufacture recommends that renal function should be checked at least once a year.
Edoxaban: Renal function should be checked at beginning then as clinically indicated. If treatment is beyond 1 year hepatic function should be tested periodically

However, **for all NOACs** patients at high risk of bleeding should be monitored for signs and symptoms of bleeding complications and anemia after initiation of anticoagulation. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

It is good practice to reassess anticoagulation annually or more frequently if clinically indicated. The annual check should be used as an opportunity to check adherence and reassess whether an anticoagulant/NOAC prescription is still appropriate, if the patient has any adverse effects and if any new interacting medicines have been started (e.g. over the counter medicines).

4.6 NOACs and Heart Murmurs/Valvular AF[14]

NOACs are not indicated (or licensed), for use in patients with rheumatic mitral stenosis, mechanical prosthetic heart valve or who have had a valve repair or tissue valve replacement. If a patient has a heart murmur and new AF, initiation of an anticoagulant should not be delayed whilst waiting for the cause of the murmer to be established. If valvular heart disease is later diagnosed (e.g. from an echocardiogram) the patient should be referred to cardiology who will review the medicines as appropriate.

4.7 Anticoagulant Alert Cards

All patients on NOACs should be advised to carry an anticoagulant 'alert card'. Organisations are expected to communicate local arrangements for how these are printed, distributed and obtained.

Online cards are also available for printing from the AF association: anticoagulant alert cards).

4.8 Conversion between NOACs and Warfarin[687&9]

CONVERSION from DABIGATRAN to WARFARIN Adjust the starting time of warfarin based on CrCl as follows: • **CrCl>50mL/min,** start warfarin 3 days before discontinuing dabigatran. • **CrCl 31-50mL/min,** start warfarin 2 days before discontinuing dabigatran. • **CrCl 15-30mL/min,** start warfarin 1 day before discontinuing dabigatran • **CrCl<15mL/min,** no recommendations can be made – consult with on call haematologist. Dabigatran can contribute to an elevated INR, the INR will better reflect warfarin's effect after dabigatran has been stopped for at least 2 days**.**	**CONVERSION from WARFARIN to DABIGATRAN** Discontinue warfarin and start dabigatran when the INR is below 2.0 (This usually occurs 3-5 days after discontinuing warfarin)
CONVERSION from RIVAROXABAN to WARFARIN Warfarin should be given concurrently until the INR is ≥ 2.0. (Use standard initial dosing for the first two days, after which the warfarin dose should be guided by INR testing). **NB** rivaroxaban can contribute to an elevated INR. Once rivaroxaban is discontinued INR testing may be done reliably after at least 24hrs from the last dose.	**CONVERSION from WARFARIN to RIVAROXABAN** Discontinue warfarin treatment and start rivaroxaban when INR is 3.0 or less
CONVERSION from APIXABAN to WARFARIN Continue apixaban for at 2 days after starting warfarin therapy, then check the INR. Continue co-administration of apixaban and warfarin until the INR is 2 or more	**CONVERSION from WARFARIN to APIXABAN** Discontinue warfarin and start apixaban when INR is below 2
CONVERSION from EDOXABAN to WARFARIN **For patients on a 60mg dose**, give 30mg once daily together with an appropriate dose of warfarin. **For patients on a 30mg dose,** give 15mg once daily together with an appropriate dose of warfarin. A loading dose of warfarin should not be taken. Once an INR ≥2.0 is achieved, stop edoxaban. (85% of patients should achieve this within 14 days of concomitant administration). Measure the INR at least 3 times during these 14 days of concomitant usage, (just prior to taking the daily dose of edoxaban to minimise the influence of edoxaban on the INR) .	**CONVERSION from WARFARIN to EDOXABAN** Discontinue the warfarin treatment and start edoxaban when the INR is ≤2.5

4.9 Further Drug Specific Prescribing Guidance

(To be read in conjunction with SPCs & section 4.1-4.7)

4.9.1 DABIGATRAN (Pradaxa) [6]

Missed dose: A forgotten dabigatran dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose onward, the missed dose should be omitted. No double dose should be taken to make up for missed individual doses

Special Patient Populations (See section 4.1-3 for renal dose adjustments & contraindications)

- **Patients between 75-80 years**: Treat with 150mg twice daily. A dose of 110mg twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.
- **For patients with gastritis, oesophagitis, or gastroesophageal reflux**, the dose of 110 mg capsule twice daily may be considered due to the elevated risk of major gastro-intestinal bleeding with dabigatran.
- As with warfarin, co-administration of aspirin, clopidogrel and NSAID increases risk of bleeding. (See section 4.4)
- **Patients with elevated liver enzymes > 2 upper limit of normal** were excluded in the study investigating the prevention of stroke and systemic embolism associated with atrial fibrillation. No treatment experience is available for this subpopulation of patients and therefore the use of dabigatran is not recommended in this population.
- **Pregnancy** There are limited data from the use of dabigatran in pregnant women.
- Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. The SPC states dabigatran 'should not be used during pregnancy unless clearly necessary'.
- **Breastfeeding** There are no clinical data of the effect of dabigatran on infants during breast-feeding. The SPC states breastfeeding should be discontinued during treatment.

When clinically relevant bleeding occurs: Treatment should be interrupted. Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site. Since dabigatran is excreted predominantly by the renal route adequate diuresis should be maintained.

Reversal of anticoagulant effects: Idarucizumab (Praxbind®) is a specific reversal agent for dabigatran and is indicated in patients treated with dabigatran when rapid reversal of its anticoagulant effect is needed e.g. for emergency surgery/urgent procedures or in life-treatening or uncontrolled bleeding (use is restricted to hospital). The recommended dose is 5g further information is available in the SPC

DISCONTINUATION of DABIGATRAN (If an invasive procedure or surgical intervention is required)

		Recommended timing of last dabigatran dose before surgery or invasive procedure	
Renal function (CrCl mL/min)	**Half-life (hrs)**	**Standard risk of bleeding**	**High risk or bleeding***
CrCl ≥ 80	~13	**24 hours**	**2 days**
CrCl ≥ 50 to < 80	~15	**1-2 days before**	**2-3 days**
CrCl >30 to < 50	~18	**2-3 days before (>48hrs)**	**4 days**
CrCl ≤30	Dabigatran is contraindicated if CrCl ≤30		
* Types of surgery associated with a high risk of bleeding (or in major surgery where complete haemostasis may be required) include but are not limited to; cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ. Other procedures such as spinal anaesthesia may also require complete haemostatic function. Other important determinants of bleeding risk include advancing age, co-morbidities (e.g. major cardiac, respiratory or liver disease), low body weight (< 50kg) and concomitant use of antiplatelet therapy.			

Restart as soon as possible after the invasive procedure or surgical intervention, provided the clinical situation allows and adequate haemostasis has been established.

Peak plasma concentrations are reached at 6 hours following administration in a postoperative period due to contributing factors such as anaesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. It has been demonstrated that slow and delayed absorption is usually only present on the day of surgery. On subsequent days, absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration.

4.9.2 RIVAROXABAN (Xarelto▼)[7]

Missed dose: If a dose is missed the patient should take rivaroxaban immediately and then continue the following day with once daily intake as before. No double dose should be taken to make up for a missed dose

Special Patient Populations (See 4.1-3 for renal dose adjustments & contraindications)

- **Elderly** No dose adjustment needed
- **For patients with gastritis, oesophagitis, or gastroesophageal reflux**, the lower dose of 15mg may be considered due to the elevated risk of major gastro-intestinal bleeding
- As with warfarin, co-administration of aspirin, clopidogrel and NSAID increases risk of bleeding. (See section 4.4)
- **Hepatic disease** associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C - contraindicated
- **Pregnancy** Studies in animals have shown reproductive toxicity. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and evidence that rivaroxaban crosses the placenta, rivaroxaban is contraindicated during pregnancy
- **Breastfeeding** Data from animals indicate that rivaroxaban is secreted into milk. Therefore rivaroxaban is contraindicated during breast feeding

DISCONTINUATION of RIVAROXABAN (If an invasive procedure or surgical intervention is required)

Stop at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Restart as soon as possible after the invasive procedure or surgical intervention, provided the clinical situation allows and adequate haemostasis has been established.

There is no antidote to rivaroxaban. **When clinically relevant bleeding occurs:** Treatment should be interrupted. Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.
If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). **Refer to the SPC and local hospital protocols for more information.**

4.9.3 APIXABAN (Eliquis)[8]

Missed dose If a dose is missed, the patient should take apixaban immediately and then continue with twice daily intake as before.

Special Patient Populations (See 4.1-3 for renal dose adjustments & contraindications)

- **Elderly –**See Section 4.1 dose adjustment may be required for patients >80yrs
- As with warfarin, co-administration of aspirin, clopidogrel and NSAID increases risk of bleeding. (See section 4.4)
- **Hepatic Disease** Apixaban is contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
  It is not recommended in patients with severe hepatic impairment.
  It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B).
  It should be used with caution in patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN as they were excluded from clinical trials.
- **Pregnancy** Not recommended during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
- **Breastfeeding** It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk. A risk to newborns and infants cannot be excluded.

There is no antidote to apixaban. **When clinically relevant bleeding occurs.** Discontinue treatment and investigate the source of bleeding. The initiation of appropriate treatment, e.g., surgical haemostasis or the transfusion of fresh frozen plasma should be considered. If life-threatening bleeding cannot be controlled by the above measures, administration of prothrombin complex concentrates (PCC) or recombinant factor VIIa may be considered. **Refer to the SPC and local hospital protocols for more information.**

Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery.

DISCONTINUATION of APIXABAN (If an invasive procedure or surgical intervention is required)
Stop at least 48hrs prior to elective surgery or invasive procedures with a moderate or high risk of bleeding
Discontinued at least 24hrs prior to elective surgery or invasive procedures with a low risk of bleeding including interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding against the urgency of intervention.

Restart as soon as possible after the invasive procedure or surgical intervention, provided the clinical situation allows and adequate haemostasis has been established.

4.9.4 EDOXABAN (Lixiana▼)[9]

Missed dose If a dose is missed, it should be taken immediately and then continued the following day- once daily. The patient should not take double prescribed dose on the same day to make up for a missed dose.

Special Patient Populations (See 4.1-3 for renal dose adjustments & contraindications)

- **Elderly** – No dose reduction required
- **Medicines or conditions which increase gastric emptying or moltility** have the possibility of reducing dissolution and absorption, (edoxaban is predominantly absorbed in the upper GI tract).
- As with warfarin, co-administration of aspirin, clopidogrel and NSAID increases risk of bleeding.
  The administration of a PPI can be considered. In clinical studies mucosal bleedings and anaemia were seen more frequently during long term edoxaban treatment compared with VKA treatment, therefore in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. (See also section 4.4)
- **Hepatic Disease** Edoxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. (Liver function should be checked prior to initiation).
  It is not recommended in patients with severe hepatic impairment
  It should be used with caution in patients with mild to moderate hepatic impairment (dose- 60mg once daily).
- Patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥ 1.5 x ULN were excluded in trials and so edoxaban should be used with caution in this population.
- **Pregnancy** Animal studies have shown reproductive toxicity, Due to the potential reproductive toxicity, the intrinsic risk of bleeding and evidence that edoxaban passes the placenta, it is contraindicated during pregnancy. Women of childbearing potential should avoid becoming pregnant during treatment..
- **Breastfeeding** Data from animals indicate that edoxaban is secreted into breast milk and therefore edoxaban is contraindicated during breastfeeding.

There is no specific antidote for edoxaban.
When clinically relevant bleeding occurs. Delay the next dose or discontinue as appropriate. Edoxaban has a half-life of ~10-14hrs. Management should be individualised according to severity and location of haemorrhage.
For life-threatening bleeding that cannot be controlled with measures such as transfusion or haemostasis, a 4-factor prothrombin complex concentrate at 50 IU/kg has been shown to reverse the effects of edoxaban 30mins after infusion. **Refer to the SPC and local hospital protocols for more information.**

DISCONTINUATION of EDOXABAN (If an invasive procedure or surgical intervention is required)
Stop as soon as possible and preferably at least 24 hours before the procedure.
When 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.

Restart as soon as possible after the invasive procedure or surgical intervention, provided the clinical situation allows and adequate haemostasis has been established. The time to onset of the edoxaban anticoagulant therapeutic effect is 1-2 hours.

5. Acknowledgements

NHS Somerset PCT
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;
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This guidance does not override the individual responsibility of health professionals to make decisions in exercising their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. For full prescribing information please refer to the BNF and SPC ensuring correct SPC according to dose is consulted.

6. References

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