Protocol for switching to Apixaban for existing patients with non-valvular atrial fibrillation (NVAF) on Edoxaban.

This resource has been developed using currently available references to support the safe and effective switch from edoxaban to apixaban. It reflects the evidence available at the time of approval. Clinicians and healthcare professionals using this resource must refer to local guidelines, use their own clinical judgement and take responsibility for their prescribing decisions.

The Shropshire, Telford and Wrekin ICB (STW ICB) Medicines Optimisation Team has oversight only of errors occurring within its own organisation. Each organisation is responsible for any prescribing errors or omissions arising from its use of this resource and must follow its own safety-governance process.

Organisations must inform the STW ICB Medicines Optimisation Team if they become aware of any errors or required updates to this document.

Author(s) name and post	Anita Sharma - Senior Pharmacist (PCN & Place Team)
Clinical Review by	Naz Khan – STW CVRM Clinical Lead
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Adapted from the Welsh Medicines Advice Service guidance on switching to apixaban, with thanks to the Welsh Medicines Advice Service Team.[1]

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1. Introduction

There are currently four direct oral anticoagulants (DOACs) available and licensed in the UK for stroke prevention in non-valvular atrial fibrillation (NVAF); apixaban, dabigatran, edoxaban, and rivaroxaban. Apixaban and rivaroxaban are now available as a generic preparation, making them the most cost-effective DOACs. This document provides guidance on switching from edoxaban (once daily) to apixaban (twice daily).

2. Non-valvular atrial fibrillation

Non-valvular atrial fibrillation refers to atrial fibrillation in the **absence of a mechanical prosthetic heart valve or moderate-to-severe mitral stenosis** (usually of rheumatic origin), where the choice of oral anticoagulant could include either warfarin or a DOAC.

3. Comparative efficacy

Apixaban, dabigatran, edoxaban and rivaroxaban are all recommended by NICE as options for stroke prevention in eligible adults with NVAF. The choice of DOAC should reflect clinical suitability and patient preference.

4. Scope

The protocol supports prescribers and pharmacists to:

- switch patients aged 18 years and over established on edoxaban, to apixaban for stroke prevention in NVAF, where clinically appropriate as part of shared decision making.
- review the DOAC and dosing appropriateness prior to switching to ensure Apixaban is prescribed safely and only where appropriate.

This protocol covers only switching from edoxaban to apixaban for stroke prevention in NVAF. Switching from warfarin, rivaroxaban or dabigatran, or switching for another indication, is outside the scope of this protocol. Changes should only be made following consultation with the patient and as part of shared decision-making. Where there are concerns about capacity, assess and document the patient's capacity to make the specific decision. Where the patient lacks capacity, follow the Mental Capacity Act 2005 and make and document a best-interests decision, consulting any legally authorised representative and relevant family members or carers as appropriate.

5. Patients EXCLUDED from Edoxaban to Apixaban switch

5.1 Patients who must not be switched using this protocol

- The patient has capacity to make the decision and does not agree to the switch following an informed discussion; or, where the patient lacks capacity, the switch has not been established as being in their best interests in accordance with the Mental Capacity Act 2005.
- The patient is under 18 years of age.
- Edoxaban is prescribed for an indication other than stroke prevention in NVAF, or there is another indication for ongoing anticoagulation (see section 6).
- The patient cannot reliably receive apixaban twice daily despite reasonable adherence support or appropriate medicine-administration arrangements. Dementia, frailty, age, falls risk or polypharmacy alone must not be treated as an exclusion.
- The patient has a known hypersensitivity to apixaban or any of its excipients.

- Creatinine clearance calculated using Cockcroft–Gault is below 15 mL/min, or the patient is undergoing dialysis.
- The patient has a mechanical prosthetic heart valve or moderate-to-severe mitral stenosis.
- The patient has severe hepatic impairment.
- The patient has hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- The patient has confirmed antiphospholipid syndrome.
- The patient is pregnant or breastfeeding.
- The patient has active clinically significant bleeding.
- The patient has a current lesion or condition considered to present a significant risk of major bleeding.
- The patient is currently prescribed another anticoagulant in addition to edoxaban. Do not use the STW ICB routine switching protocol. Check and follow any documented specialist switching or procedural plan.
- The patient has a clinically significant interaction with apixaban that cannot be safely managed.

5.2 Patients for whom switching must be deferred pending further assessment

- Body weight (actual), full blood count, liver-function tests, urea and electrolytes or serum creatinine have not been recorded within the previous six months, or Cockcroft–Gault creatinine clearance has not been calculated. The required assessment must be completed before switching is considered.
- The patient has uncontrolled hypertension. Assess and appropriately manage the blood pressure before deciding whether to proceed with the switch.
- The patient has had a recent acute coronary syndrome or PCI or is following a current specialist antiplatelet plan.
- The patient is due to undergo cardioversion or catheter ablation. Confirm the procedural anticoagulation plan before switching.
- The patient is taking a regular NSAID, antiplatelet, SSRI, SNRI or another medicine that increases bleeding risk.
- The patient has a recent gastrointestinal ulcer, recent major bleeding, recent intracranial haemorrhage, or recent brain, spinal or ophthalmic injury or surgery, but the condition is no longer an active contraindication.
- The patient has mild or moderate hepatic impairment or abnormal liver-function results that require further assessment.
- The patient is planning pregnancy. Arrange appropriate clinical or specialist review before deciding whether to switch.
- There are unresolved concerns about frailty, cognition, polypharmacy, adherence or the patient's ability to manage twice-daily treatment.

6. Patients prescribed DOACs for multiple indications

There are several reasons why patients may be taking a DOAC either for a fixed period or for the long-term. All DOACs are licensed and approved by NICE for prevention of stroke in NVAF and for the treatment / prophylaxis of thrombosis (DVT/PE). Some DOACs are also used for thromboprophylaxis following joint replacement. This protocol is for **patients receiving a DOAC for stroke prevention in NVAF**. If a patient is on a long-term DOAC for another indication, this is outside of the scope of this protocol.

7. Switching to apixaban

- When a patient taking edoxaban for NVAF presents for a medication review, or when DOAC monitoring is due, the prescriber should consider whether switching to apixaban is clinically appropriate as part of shared decision making.
- Refer to the SmPC for apixaban for detailed information on cautions and contraindications that may need to be considered before proceeding with the switch.
- A search can be used to identify adults aged 18 years and over who are currently prescribed edoxaban for NVAF for an individual clinical review. Inclusion in the search output does not confirm suitability for switching. Before proceeding, confirm that no exclusion criterion in section 5.1 applies and that any matter identified in section 5.2 has been assessed and resolved.
- Before proceeding with the switch, complete and document a clinical review that includes:
    - confirmation of the continuing indication for anticoagulation and review of the CHA_2DS_2-VA/CHA_2DS_2-VASc and ORBIT scores
    - review of prescribed, hospital-issued, over-the-counter and herbal medicines for interactions and increased bleeding risk.
    - identification and management of modifiable bleeding-risk factors, including uncontrolled hypertension, antiplatelets, NSAIDs, SSRIs/SNRIs, harmful alcohol consumption and reversible causes of anaemia
    - A high ORBIT score should not, on its own, be a reason to withhold anticoagulation. Use the assessment to identify modifiable bleeding risks and any need for closer monitoring and discuss the findings and options with the patient as part of shared decision making
    - confirmation of pregnancy and breastfeeding status, where clinically relevant, with referral for appropriate clinical or specialist review if the person is pregnant, breastfeeding or planning pregnancy
    - confirmation that recent body weight, full blood count, liver-function tests, urea and electrolytes and serum creatinine results are available
    - calculation of creatinine clearance using the Cockcroft–Gault equation
- Use recent (within the last six months) actual body weight, full blood count, liver function tests, urea and electrolytes, and serum creatinine results. Calculate creatinine clearance using the Cockcroft–Gault equation.

- More recent results may be required depending on the patient's age, frailty, renal or hepatic function, interacting medicines or an intercurrent illness. Patients without appropriate current monitoring must have the necessary tests completed before switching.
- Determine the appropriate apixaban dose using the apixaban-specific dosing criteria in section 8.
- All consultations for changes must take place with direct patient contact. This may be via a face-to-face or telephone consultation. In addition, a leaflet should also be issued for patients suitable for the switch in a format that is clear and accessible for the patient and/or their representative. This can be found in Appendix 2.
- Patients should be advised to use up their supply of edoxaban before starting the newly prescribed apixaban to prevent any wastage.
- After the final edoxaban dose, start apixaban when the next edoxaban dose would have been due. Edoxaban and apixaban must not be taken together.
- Advise the patient that the new DOAC, apixaban, needs to be taken **twice daily.**
- Add apixaban to repeat medications and remove edoxaban from repeats.
- Ensure repeat prescriptions are authorised only until the next scheduled monitoring or review date, or in accordance with practice protocol.
- Ensure ongoing review and recall dates are recorded in line with the monitoring schedule in section 14 and current local and national guidance.
- Practices may wish to contact patients after the switch to confirm that apixaban is being taken correctly and to identify any problems. Where eligible, patients may also receive support from their community pharmacy through the NHS New Medicine Service.

8. Apixaban dosing

The standard recommended dose for stroke prevention in non-valvular atrial fibrillation (NVAF) is apixaban 5 mg twice daily. The appropriate dose must be selected using the apixaban-specific criteria below, taking account of creatinine clearance, age, body weight and serum creatinine.

Important: The apixaban dose must be determined independently using the apixaban dosing criteria and must not be based solely on the patient's current edoxaban dose.

Prescribe a reduced dose of apixaban 2.5 mg twice daily for patients with:

- ☐ severe renal impairment (creatinine clearance 15-29 mL/min)

OR

- ☐ **at least two** of the following characteristics:
  - age 80 years or over
  - weight 60 kg or less
  - serum creatinine ≥1.5 mg/dL (133 micromole/L)

Calculating renal function

Calculate creatinine clearance (CrCl) using the Cockcroft-Gault equation and actual body weight for DOAC dosing. Do not use eGFR in place of CrCl, as eGFR may overestimate renal function. Cockcroft–Gault calculators are available within GP clinical systems and on MDCalc.

NOTE: Serum creatinine ≥1.5 mg/dL (133 micromol/L) does not, by itself, require dose reduction unless the patient also meets at least one of the age or body-weight criteria.

This does not override the requirement to prescribe apixaban 2.5 mg twice daily when CrCl is 15–29 mL/min.

In patients with creatinine clearance below 15 mL/min, or in patients undergoing dialysis, there is no clinical experience; therefore, apixaban is not recommended.

Creatinine Clearance (Cockcroft-Gault Equation)

Use serum creatinine and actual body weight recorded within the previous six months, or more recently where clinically indicated. Height may be requested by some calculators to calculate BMI or provide weight-related estimates.

Calculate creatinine clearance using the Cockcroft–Gault equation and the locally approved clinical-system calculator or calculation method. At extremes of body weight, creatinine-clearance estimates may vary according to the weight used. Where different estimates cross an apixaban dosing threshold, undertake an individual clinical assessment and seek specialist advice where required.

EMIS CrCl calculator uses:

Actual body weight is used for CrCl calculation for patients taking apixaban, edoxaban or rivaroxaban. The single exception applies to obese patients taking Dabigatran, in this case the calculator uses ideal body weight. In these cases, you should record the CrCl for actual body weight in the consultation as the actual body weight was used in the clinical trials for AF with all DOACs. The calculator displays text indicating whether actual body weight or ideal body weight (IBW) has been used each time CrCl is calculated.

9. Body weight

The apixaban dose must not be adjusted solely because of high or low body weight. For stroke prevention in NVAF, prescribe apixaban 2.5 mg twice daily only where the licensed dose-reduction criteria in section 8 are met.

There is no additional licensed upper or lower body-weight cut-off for apixaban. Available evidence for DOACs is generally reassuring up to a BMI of 40 kg/m²; evidence is less robust at a BMI of 40 kg/m² or above. Treat body weight below 50 kg, body weight above 120 kg or BMI 40 kg/m² or above as prompts for an individual clinical assessment rather than as automatic exclusions or dose-adjustment criteria.

Assess the reliability of the Cockcroft–Gault creatinine-clearance estimate, bleeding and thromboembolic risks, frailty, body composition, comorbidities, interacting medicines, adherence and patient preference. Where clinically reasonable creatinine-clearance calculations fall on different sides of an apixaban dosing threshold, seek specialist pharmacy, renal or anticoagulation advice.

At a BMI of 50 kg/m² or above, seek specialist anticoagulation advice. Measurement of an appropriately calibrated apixaban level or treatment with a vitamin K antagonist may be considered following specialist review.

Extreme body weight alone must not automatically exclude a patient from apixaban, require treatment with warfarin or result in an unlicensed reduction of the apixaban dose.

10. Liver disease

Apixaban is contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk and is not recommended in severe hepatic impairment. Use apixaban with caution in mild or moderate hepatic impairment (Child–Pugh A or B), or where ALT/AST is more than twice the upper limit of normal or total bilirubin is 1.5 times the upper limit of normal or greater. No dose adjustment is required solely for mild or moderate hepatic impairment. Check liver-function tests before switching and at least annually thereafter, or more frequently where clinically indicated.

11. Drug Interactions

Please refer to the SmPC for apixaban for information on interactions. Review all prescribed, hospital-issued, over-the-counter and herbal medicines for interactions before switching. Check specifically for strong cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors or inducers, and for medicines that increase bleeding risk, including anticoagulants, antiplatelets, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors/serotonin and noradrenaline reuptake inhibitors (SSRIs/SNRIs).

12. Patient education/discussion

Refer to Appendix 1 and Appendix 2 to aid discussion with the patient

Arrange a consultation to discuss anticoagulation options and establish whether the patient is suitable for a switch to apixaban. When discussing the benefits and risks of anticoagulation, use clinical risk profiles and personal preferences to guide treatment choices.

Practical considerations include the patient's ability to take apixaban reliably twice daily and whether an enteral feeding tube is used. The apixaban SmPC describes administration of crushed tablets through a nasogastric tube. Administration through other enteral feeding tubes, including NJ, PEJ or PEG-J tubes, is off-label and requires specialist pharmacy advice and assessment in accordance with local guidance.

When discussing the anticoagulation treatment options, advise the patient of the risks and benefits of the different DOACs. Explain the need for cost-effective prescribing to make the best use of NHS resources. Explain that apixaban, dabigatran, edoxaban and rivaroxaban are all recommended options for stroke prevention in eligible adults with NVAF, and that the choice of DOAC should reflect clinical suitability and patient preference. Advise the patient about the relevant contraindications and important safety considerations for each treatment option.

Follow the guidance in the British National Formulary and MHRA advice on DOACs, particularly regarding renal impairment, reversal agents and monitoring.

If suitable to switch, advise the patient:

- apixaban must be taken **twice a day**
- to use up the supply of their existing DOAC before switching to the apixaban
- take the final edoxaban dose as agreed with the clinician. Start apixaban at the time the next edoxaban dose would normally have been due. Do not take edoxaban and apixaban together
- to ensure their DOAC alert card is updated to show apixaban and the current dose and to carry it at all times and show it to healthcare professionals.

13. Patient compliance

- Ensure the patient is aware that apixaban needs to be taken **TWICE A DAY.** If there are concerns that the patient cannot reliably take apixaban twice daily, despite appropriate adherence support or medicine-administration arrangements, the patient should not be switched using this protocol.
- Apixaban may be taken with or without food.
- There are no known issues with using apixaban in compliance devices; however, repackaging medication outside the manufacturer's original packaging involves risks and is often unlicensed. Check with a pharmacist if there is any doubt about stability.
- The community pharmacist should be informed of the change to prevent dispensing or supply errors and duplicate prescriptions.
- Apixaban tablets may be swallowed whole or crushed and mixed with water, apple juice or apple puree. Administer the crushed tablet immediately. For administration through an enteral feeding tube, follow section 12 and the apixaban SmPC.

14. Monitoring renal function and weight

- Before switching, confirm that the pre-switch monitoring requirements in sections 5.2 and 7 have been completed and documented.
- If haemoglobin or haematocrit falls without explanation, do not switch; investigate for occult bleeding and seek specialist advice.
- If renal function decreases during treatment, the apixaban dose may need to be reviewed.
    - Alternatively, if a reduced dose of apixaban has been initiated during an episode of impairment of renal function, then the dose will need to be reviewed if renal function subsequently improves
- Arrange a DOAC review approximately one month after the switch.

- At the one-month and subsequent DOAC reviews, assess adherence, bleeding or anaemia, adverse effects, symptoms of thromboembolism, medicines and interactions, modifiable bleeding risks and the patient's understanding of treatment.

- Once stable, undertake a DOAC review, full blood count, liver function tests, urea and electrolytes, creatinine clearance and body weight at least annually. Check body weight sooner where clinically indicated.

- Consider more frequent monitoring:
    - approximately every four months in people aged over 75 years or who are frail
    - where CrCl is below 60 mL/min, using CrCl divided by 10 as a guide to the monitoring interval in months
    - following an intercurrent illness that may affect renal or hepatic function
    - where interacting medicines, hepatic deterioration, significant weight change or other clinical concerns are present.

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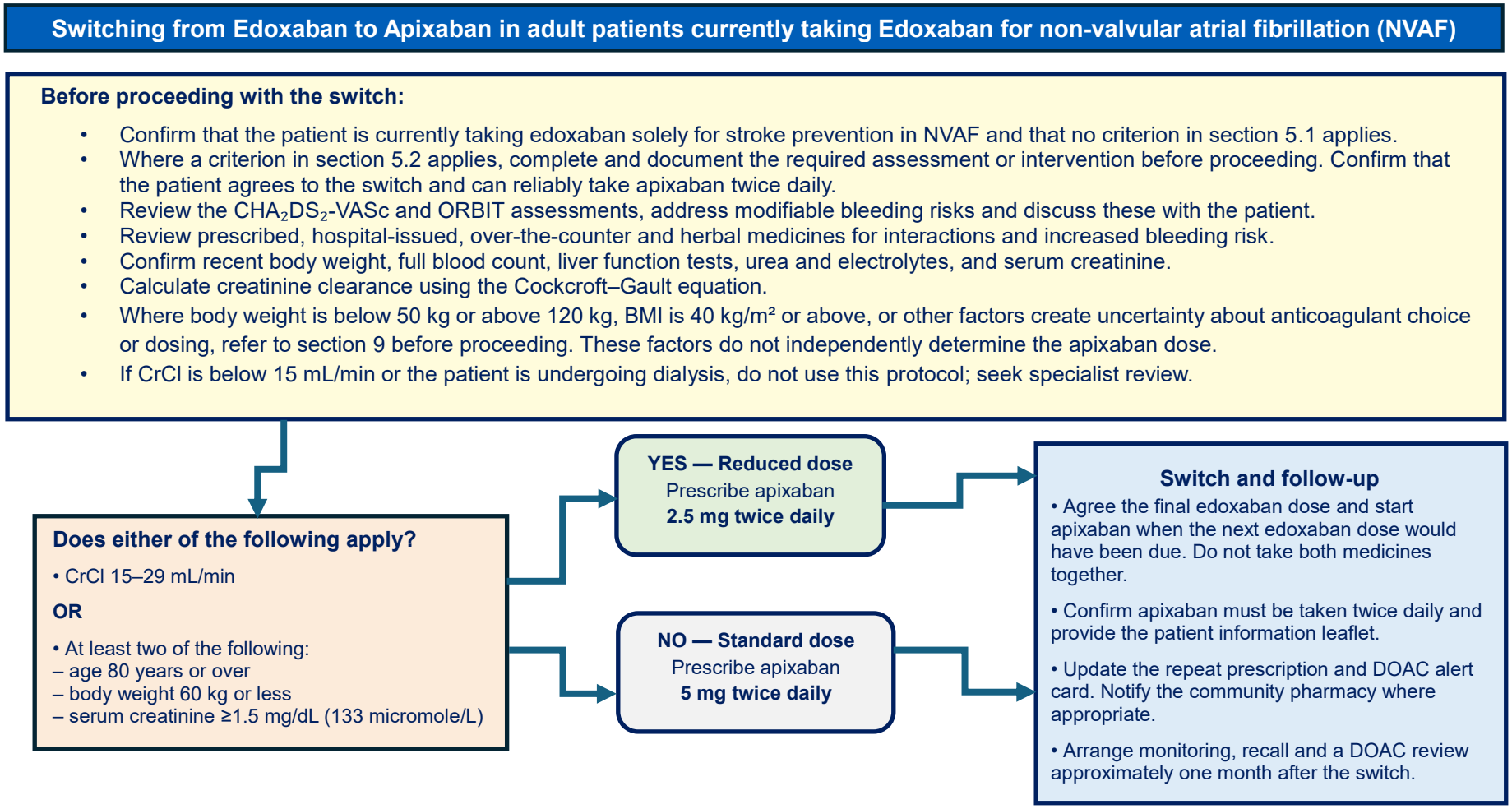
Appendix 1 – Apixaban switch algorithm

Switching from Edoxaban to Apixaban in adult patients with non-valvular AF



Appendix 2 – Patient Information Leaflet

Important Changes to your medication: Edoxaban

Switching to Apixaban - Information for patients

You have received this leaflet because you are taking a blood thinning medicine, edoxaban (Lixiana®). Apixaban is another blood thinning medicine. It is as effective as the other blood thinning medicines. Until recently only one manufacturer made apixaban. As it is no longer covered by a patent, apixaban is now available from other manufacturers. This drives the price of apixaban down, making it more cost effective for the NHS.

How will the switch happen?

Soon, you will receive prescriptions for apixaban instead of edoxaban

Your GP practice will discuss with you about switching to apixaban and provide more information. If you have any questions about this change in medicine or would like to discuss it further, please speak to your GP or practice pharmacist, or your local community pharmacist.

How to take apixaban

- Use up your current supply of edoxaban **before** starting the apixaban.
- Take the final edoxaban dose as agreed with your clinician. Take your first apixaban dose at the time your next edoxaban dose would normally have been due. Do not take edoxaban and apixaban together. Apixaban must then be taken twice daily.
- If you find the tablets hard to swallow, it may help to crush them and mix them with water, apple juice or apple puree immediately before taking them.

If you forget to take apixaban

If you miss your morning dose, take it as soon as you remember. It may be taken at the same time as your evening dose. If you miss your evening dose, take it only if you remember during the same evening. Do not take two doses the following morning. Continue taking your usual dose twice daily from the next day. If you are unsure what to do or have missed more than one dose, ask your doctor, pharmacist or nurse.

If you take too much apixaban

You may be at risk of bleeding if you take more apixaban than you have been prescribed.
Contact NHS 111 or tell your doctor, pharmacist, or nurse immediately.

Further Information

Always read the patient leaflet that comes with your medicine and remember to carry your alert card with you at all times. While taking apixaban, do not take aspirin, ibuprofen or other anti-inflammatory painkillers unless specifically advised by a doctor or pharmacist, and ask a pharmacist before starting any new medicine, herbal remedy or supplement.

Appendix 3 – Clinical Systems Resources

STW EMIS Web practices

A locally developed EMIS Web search has been built by the STW Medicines Optimisation Team to identify adult patients currently prescribed edoxaban for review under this protocol.

You will find the search at the following folder file path:

Enterprise Population reporting

STW Meds Optimisation

Enterprise > STW Meds Optimisation > Practice Level Searches > MQCF 26-27 > Project Switches

The search is a case-finding resource only. All patients identified must receive an individual clinical consultation and assessment in accordance with this protocol before any change in treatment is made. Inclusion in the search output does not confirm that a patient is suitable for switching.

Practices should use the approved STW search and should not amend the agreed search criteria without discussion with the STW Medicines Optimisation Team.

Disclaimer

This resource has been developed using currently available references to support the safe and effective switch from edoxaban to apixaban. It reflects the evidence available at the time of approval.

The accuracy of the search output depends on complete and current clinical coding and prescribing records. Clinicians using this resource must refer to local guidelines, use their own clinical judgement and take responsibility for their prescribing decision.