SWITCHING BETWEEN ANTICOAGULANTS: A FOCUS ON DOAC THERAPY

An informative discussion between two healthcare professionals (HCPs), Dr Raj Mattu, Consultant Cardiologist, University Hospitals Northamptonshire and University College London and Dr Yassir Javaid, GPSI and Clinical Lead Northamptonshire ICB, focussed on non-medical switching between direct-oral anticoagulants (DOACs) for stroke prevention in non-valvular atrial fibrillation (NVAF).

Dr Raj Mattu,
University Hospitals Northamptonshire and University College London

Dr Yassir Javaid,
GPSI and Clinical Lead Northamptonshire ICB

THE NHS CVD PREVENTION AGENDA

Dr Mattu commended the NHS long-term plan which prioritises cardiovascular disease (CVD) prevention within its agenda.[1] He acknowledged that the majority of CVD management occurs in primary care, which emphasises the importance of the NHS agenda. The NHS Long Term Plan, published in 2019, outlines atrial fibrillation (AF) as a key focus within CVD prevention strategies.[1] The national 'Detect, Protect, Perfect' programme is vital in tackling AF-related strokes[2,3] and both HCPs agreed that more emphasis must be placed on all three aspects of this programme. National data from the Sentinel Stroke National Audit Programme (SSNAP) from 2021-2022 revealed that only 18.3% of patients were diagnosed with AF prior to stroke, and of these, only 67.2% of patients were prescribed anticoagulation.[4] This further highlights the importance of the 'Detect, Protect, Perfect' programme.[2,3]

There is a national programme across England to tackle the issue of AF-related strokes[1]

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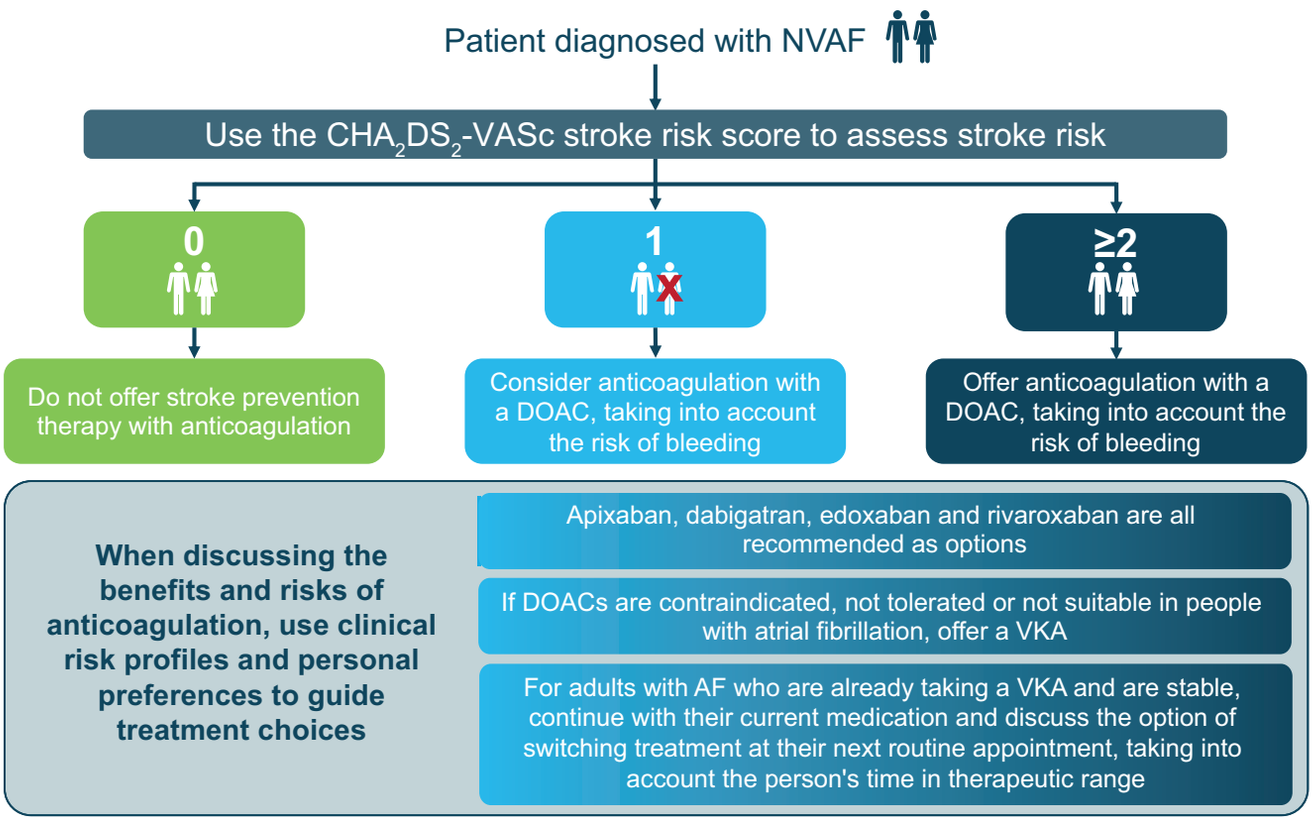
NICE GUIDANCE FOR THE USE OF ANTICOAGULANTS FOR THE MANAGEMENT OF STROKE PREVENTION IN ATRIAL FIBRILLATION

The National Institute for Health and Care Excellence (NICE) recommend all four DOACs preferentially over the use of vitamin K antagonists (VKAs) for NVAF, where clinically appropriate.[5] This recommendation was made as a result of objections raised by national leaders in NVAF, including Dr Mattu, after the publication of the draft guidance.[6,7] The initial draft of the NICE guidance for the management of AF favoured use of only twice-daily DOAC therapies, i.e. apixaban or dabigatran. This included recommendations to switch stable patients taking once-daily DOACs or warfarin to twice-daily therapies.[7] This would essentially limit patient choice and treatment-tailoring.[6] In addition, patients are more likely to adhere to once-daily medications than to twice-daily medications.[6] It has been found that ≥80% of patients with NVAF in two separate adherence studies preferred once-daily versus twice-daily therapy.[8,9] Informed decision-making with patients and patient preference is key when prescribing anticoagulation for stroke prevention in NVAF, to aid compliance[5,10] and ensure bespoke management. The national leaders urged NICE to preserve patient choice, access and shared decision-making in its recommendations for NVAF management.[6] Dr Mattu highlighted that any decision on switching between anticoagulant therapies must be undertaken by the patient and not enforced by the HCP.[5,10]

There are instances when switching between therapies may be appropriate, such as when there is a poor clinical response to treatment, adverse effects emerge or if there are adherence issues. Non-medical switching is when drug therapy is altered based on reasons other than these.[11]

NICE NG196: Anticoagulation for patients with NVAF[5]



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NHS ENGLAND COMMISSIONING RECOMMENDATIONS FOR ANTICOAGULATION IN NVAF

NHS England released a national procurement document for DOACs in January 2022, outlining commissioning recommendations for the best value treatment choices for NVAF management. The rationale behind the procurement was to allow any savings released to be utilised in diagnosing and treating further cases of CVD and AF. The document advises that the prescribing clinician should determine which DOAC is clinically appropriate for an individual patient based on the relevant NICE technology appraisal guidance.[12–16] Following the procurement process, edoxaban was highlighted as a preferred DOAC, where clinically appropriate, with the following recommendations:

- For patients initiating treatment for NVAF, NHS England advise that edoxaban should be used where clinically appropriate. Where edoxaban is contraindicated or clinically unsuitable, rivaroxaban should be considered first, followed by apixaban or dabigatran.
- For patients currently prescribed DOAC therapy for NVAF, it is advised that commissioners may consider developing local policy to review patients currently prescribed apixaban, rivaroxaban or dabigatran where clinically appropriate.[12]

CLINICAL CONSIDERATIONS AROUND DOAC TO DOAC SWITCHING

Dr Mattu stated that he is not in support of non-medical switching of patients who are on established DOAC therapy, who are stable and who are comfortable with their treatment. He pointed out that the commissioning recommendations do not give enough consideration to the latest NICE guidance on DOAC therapy which suggests all four DOACs as potential first-line agents[5] and in many areas these recommendations may be immediately converted into local policy which highlights one DOAC as the preferred first-line therapy.[17,18] He stated that where switching of therapies occur, these should be cost-effective or clinically indicated. Dr Javaid further highlighted British Medical Association (BMA) General Practice Committee guidance advising that when switching therapies, especially on the basis of cost, any prescribing decisions must be made following individualised patient assessment. General Practitioners (GPs) should always use their clinical judgement, as they ultimately remain responsible for their prescribing decisions.[19] Furthermore, switching therapies on the basis of cost-savings alone can lead to patient frustration, refusal and affect compliance.[19] Dr Javaid added that switching an individually tailored therapy that a patient has been taking through informed decision-making with no issues may erode the doctor-patient relationship. It may result in non-compliance which can be detrimental in stroke prevention in NVAF. He further added that the time and resource required for managing any drug switching would also need to be factored in. Dr Mattu agreed that the financial burden of the switching process may outweigh any potential cost-saving of making the DOAC switch.

> “I’m not in support of non-clinical switching of patients who are on established DOAC therapy, who are stable, who are comfortable with their therapy”
>
> **Dr Raj Mattu**

CLINICAL CONSIDERATIONS AROUND DOAC TO DOAC SWITCHING *continued*

Regarding non-medical switching, Dr Mattu added that it can be dangerous to assume that all drugs within a class are the same. He praised guidelines from learned societies, stating that they consider important factors such as drug interactions and dosing appropriateness when recommending drug therapies.[5,20] Dose adjustments of all DOACs are required in the presence of renal impairment. In addition to tailoring doses according to renal function, dose adjustment is required for dabigatran depending on age, for apixaban depending on age and weight, and for edoxaban depending on concomitant use of P-glycoprotein inhibitors.[21–24] The practicalities of and safety requirement for amending the dose of a DOAC is, therefore, an important consideration in all patients.

> "In scenarios where clinicians are being encouraged to switch to a less expensive drug . . . It shouldn't be a blanket decision. It needs to be done with the patients' best interests right at the heart, and . . . needs to be done with a very detailed, informed discussion with patients."
>
> **Dr Yassir Javaid**

Dr Mattu also highlighted that there is a risk of treatment duplication when switching between DOAC therapy which may increase bleeding risk and prove dangerous for the patient. Any transition must be undertaken with patient involvement.[25] The availability of a DOAC antidote is important when considering switching between DOACs. Specific reversal agents are now licensed and available for apixaban, rivaroxaban and dabigatran.[21–24]

CONSIDERATIONS AROUND PATIENT PREFERENCES

Patient preference must be factored in when switching therapies.[26] The HCPs acknowledged that younger patients with a busier lifestyle, or elderly patients with a visiting carer who supports with medication administration, may both prefer once-daily therapy. Many NVAF patients are elderly,[27] and may have swallowing difficulties.[28] Dr Mattu highlighted that tablet size is, therefore, an important consideration when prescribing DOAC therapy alongside dosing frequency.[8,9] Dr Javaid acknowledged that although the DOACs have been shown to have a favourable benefit-risk profile compared to warfarin,[29] comparisons must not be made between the DOACs as there have been no direct head-to-head clinical trials. As such, for many patients, it is difficult to suggest one drug may be superior to another.[30] Dr Mattu further added that the patient–clinician discussion on changing between DOACs should include informing the patient on the extent of efficacy and safety outcome data available for the different therapies. The HCPs recognised that real world evidence is vital in understanding benefits and risks of a drug post-marketing[31] and that there are currently differences in the wealth of real world data available between the DOACs.[32,33] Both HCPs agreed that evidence-based medicine is key, and consideration of clinical trial populations and resultant outcomes when choosing a DOAC for a specific patient is important. For example, knowledge that rivaroxaban offers proven stroke prevention, in high-risk NVAF patients with diabetes[34,35] can be considered when treating a patient with concomitant NVAF and diabetes mellitus.

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SWITCHING ANTICOAGULATION IN CLINICAL PRACTICE

The HCPs acknowledged that there may be clinical scenarios when switching between DOAC therapies is appropriate (figure 1). However, there was a general consensus that NICE guidance on shared and informed decision-making, including consideration of clinical risk profiles and patient preferences is essential when deciding on treatment choices for stroke prevention in NVAF.[5]

SWITCHING ANTICOAGULANT THERAPIES EXAMPLE SCENARIOS		

1 Clinically appropriate to switch	• Consider switching patients taking warfarin to a DOAC if they have:[5]
	  • Two international normalised ratio (INR) values higher than 5 or one INR value higher than 8 within the past six months
	  • Two INR values less than 1.5 within the past six months
	  • A time in therapeutic range (TTR) <65%
	• Drug interactions with other medications*
		

2 Consider switching, based on clinical judgement	• Patients taking warfarin with an acceptable TTR and stable should be discussed with regarding changing to a DOAC[5] • Patients who are experiencing adverse effects on their current anticoagulant and are unable to tolerate it, e.g., bleeding/ gastrointestinal upset	

Figure 1: Clinical scenarios when it may or may not be appropriate to switch between anticoagulant therapies (specialist opinion based on the clinical experience of the HCPs).
**Please refer to individual SmPCs for information on drug interactions.*

In summary, both HCPs urge caution when considering non-medical switching between DOACs. They advise that prescribers should base anticoagulant treatment decisions on national guidance, clinical factors, and patient preferences. Patients should only be switched from DOAC to DOAC based on cost alone after all necessary medical consideration and patient preference have been taken into account.

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Xarelto® (rivaroxaban) 2.5, 10, 15 and 20 mg film-coated tablets & 1mg/ml granules for oral suspension
Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 2.5mg/10mg/15mg/20mg rivaroxaban tablet & 1mg/ml granules for oral suspension. **Indication(s):** *2.5mg* Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Xarelto, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. *10mg* Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). *15mg/20mg* Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischaemic attack (SPAF). Treatment of DVT & PE, & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). *Paediatrics: 1mg/ml* – Treatment of VTE and prevention of VTE recurrence in term neonates, infants & toddlers, children, & adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment. Treatment of VTE & prevention of VTE recurrence in children & adolescents aged less than 18 years & weighing from 30 kg to 50 kg (for 15 mg) / above 50 kg (for 20 mg) after at least 5 days of initial parenteral anticoagulation treatment. **Posology & method of administration:** *2.5mg* – Oral *b.i.d.* dose; patients should also take a daily dose of 75 – 100 mg ASA or a daily dose of 75 – 100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine. Start Xarelto as soon as possible after stabilisation, including revascularisation for ACS, and should not be started until haemostasis is achieved in successful lower limb revascularisation for symptomatic PAD; at the earliest 24 hours after admission & at discontinuation of parenteral anticoagulation. If dose is missed take next dose, do not double the dose. *10mg – hip or knee replacement surgery:* Oral *o.d.* dose; initial dose taken 6 to 10 hours after surgery provided haemostasis established. *DVT & PE:* When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg *o.d.*. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xarelto 10 mg *o.d.*, a dose of Xarelto 20 mg *o.d.* should be considered. *15mg/20mg* – Take with food *SPAF:* 20 mg orally *o.d. DVT & PE:* Adults – 15 mg *b.i.d.* for 3 weeks followed by 20 mg *o.d.* for continued treatment & prevention of recurrent DVT & PE; Children & adolescents – calculate dose based on body weight: body weight <30kg refer to the SmPC for Xarelto 1mg/ml granules for oral suspension; body weight 30-50kg take 15mg *o.d.*; body weight >50kg take 20mg *o.d.*. Monitor child's weight & review regularly. Xarelto is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence. *All strengths* – Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Special populations:*** Patients undergoing cardioversion: Xarelto can be initiated or continued in patients who may require cardioversion. Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement: There is limited experience of a reduced dose of 15 mg Xarelto once daily (or 10 mg Xarelto once daily for patients with moderate renal impairment [creatinine clearance 30 – 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation & undergo PCI with stent placement. ***Renal impairment:*** mild (creatinine clearance 50-80 ml/min) – no dose adjustment; *2.5mg /10mg* – moderate (creatinine clearance 30-49 ml/min) – no dose adjustment. *15mg/20mg* – adults with moderate (creatinine clearance 30-49 ml/min) & severe (creatinine clearance 15-29ml/min) – *SPAF:* reduce dose to 15mg *o.d., DVT & PE:* 15 mg *b.i.d*. for 3 weeks, thereafter 20mg *o.d.* Consider reduction from 20mg to 15mg *o.d.* if patient's bleeding risk outweighs risk for recurrent DVT & PE; children & adolescents with moderate or severe renal impairment (glomerular filtration rate <50 mL/min/1.73 m^2) – not recommended; *All strengths* – Severe impairment: limited data indicate rivaroxaban concentrations are significantly increased, use with caution. Creatinine clearance <15 ml/min – not recommended. ***Hepatic impairment:*** Do not use in patients with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C ***Paediatrics:*** Only for treatment of VTE & prevention of VTE recurrence. **Contra-indications:** Hypersensitivity to active substance or any excipient; active clinically significant bleeding; lesion or condition considered to confer a significant risk for major bleeding (refer to SmPC); concomitant treatment with any other anticoagulants except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. Presence of malignant neoplasms at high risk of bleeding. *2.5mg* – concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or transient ischaemic attack; concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month. **Warnings & precautions (W&P):** Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. Discontinue if severe haemorrhage occurs. Increasing age may increase haemorrhagic risk. Patients with active cancer: the individual benefit of antithrombotic treatment should be weighed against the risk for bleeding. Gastrointestinal or genitourinary tract tumours have been associated with an increased risk of bleeding. Patients with CAD/PAD: after recent revascularisation procedure of the lower limb due to symptomatic PAD, if required, a dual antiplatelet therapy with clopidogrel, should be short-term, long-term dual antiplatelet therapy should be avoided. Xarelto in combination with other antiplatelets is not recommended. Xarelto should be discontinued at the first appearance of a severe skin rash, or any other sign of hypersensitivity in conjunction with mucosal lesions. 1mg/ml oral suspension - sodium benzoate may increase jaundice in newborn infants (up to 4 weeks old). *Not recommended:* in patients with an increased bleeding risk (refer to SmPC); in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- & P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; in patients with prosthetic heart valves; for patients with a history of thrombosis diagnosed with antiphospholipid syndrome; Xarelto should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR); *2.5mg* treatment in combination with antiplatelet agents other than ASA & clopidogrel/ticlopidine, patients after recent lower limb revascularisation procedures due to symptomatic PAD with a previous stroke or TIA receiving dual antiplatelet therapy; *10mg/15mg/20mg* in haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy; *1mg/1ml* in children less than 6 months of age who at birth had <37 weeks of gestation, a body weight of <2.6 kg, or had <10 days of oral feeding; in children ≥1 year old with moderate or severe renal impairment (glomerular filtration rate <50 mL/min/1.73 m^2); in children ≤1 year old with serum creatinine results >97.5th percentile. *Use with caution:* in patients treated concomitantly with medicines affecting haemostasis; when neuraxial anaesthesia or spinal/epidural puncture is employed; in patients at risk of ulcerative gastrointestinal disease (prophylactic treatment may be considered); *2.5mg* in patients ≥75 years of age or with lower body weight (<60kg); in CAD patients with severe symptomatic heart failure. Patients on treatment with Xarelto & ASA or Xarelto & ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk. *2.5mg/10mg* in patients with moderate renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; *15mg/20mg* in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; *1mg/ml* in children with cerebral vein & sinus thrombosis who have a CNS infection. *All strengths* – There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Xarelto tablets contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as clinically relevant increased rivaroxaban plasma concentrations are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving NSAIDs, ASA or platelet aggregation inhibitors due to the increased bleeding risk; use with caution in patients concomitantly receiving SSRIs/SNRIs due to a possible increased bleeding risk. Concomitant use of strong CYP3A4 inducers should be avoided unless patient is closely observed for signs & symptoms of thrombosis. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive & use machines:** syncope (uncommon) & dizziness (common) were reported. Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache (in children: very common), eye haemorrhage, hypotension, haematoma, epistaxis (in children: very common), haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting (in children: very common), increase in transaminases, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage (menorrhagia *very common* in women <55 yrs treated for DVT, PE & prevention of recurrence, common in female adolescents after menarche), renal impairment, fever (in children: very common), peripheral oedema, decreased general strength & energy, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings & Precautions – in addition:* thrombocytosis, thrombocytopenia (in children: common), Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome, anaphylactic reactions including shock, angioedema & allergic oedema, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, anticoagulant-related nephropathy or fatal outcome), syncope, tachycardia (in children: common), hepatic impairment, cholestasis & hepatitis (incl. hepatocellular injury), increases in bilirubin (in children: common), blood alkaline phosphatase & GGT, increased conjugated bilirubin, jaundice, vascular pseudoaneurysm following percutaneous vascular intervention, eosinophilic pneumonia. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** In the case of an overdose, the patient should be observed carefully for bleeding complications and other adverse reactions. A specific reversal agent is available, refer to the SmPC for andexanet alfa. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** *2.5mg* – 56 tablets: £50.40. *10mg* – 10 tablets: £18.00, 30 tablets: £54.00 & 100 tablets: £180.00. *15mg* – 14 tablets: £25.20, 28 tablets: £50.40, 42 tablets: £75.60, 100 tablets: £180.00; *20mg* – 28 tablets: £50.40, 100 tablets £180.00; Treatment Initiation pack (42 tablets of 15mg, 7 tablets of 20mg): £88.20 *1mg/ml* – 100ml bottle: £9.00, 250ml bottle: £18.00 **MA Number(s):** *Great Britain: 2.5mg* – PLGB 00010/0708. *10mg* – PLGB 00010/0705. *15/20mg* – PLGB 00010/0706, 0707, 0709. *1mg/ml* – PLGB 00010/0746. *Northern Ireland: 2.5mg* – EU/1/08/472/025-035, 041, 046-047. *10mg* – EU/1/08/472/001-010, 022, 042-045 *15mg/20mg* – EU/1/08/472/011-016, 017-021, 023-024, 036-040, 048-049. *1mg/ml* – EU/1/08/472/050-051 **Further information available from:** Bayer plc, 400 South Oak Way, Reading, RG2 6AD, U.K. Telephone: 0118 206 3000. **Date of preparation:** July 2023

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Adverse events should be reported.
Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in Google Play or Apple App Store.
Adverse events should also be reported to Bayer plc.
Tel.: 0118 206 3500, Fax.: 0118 206 3703,
Email: pvuk@bayer.com