Xarelto® (rivaroxaban) for the management of venous thromboembolism

This document has been created and fully funded by Bayer plc and is intended for UK Healthcare Professionals (HCPs) and the original recipient only. Prescribing Information and adverse event reporting for Xarelto® (rivaroxaban) is located on the last page of this document.

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search 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

1 WHAT IS THE INCIDENCE AND RISK OF VTE?

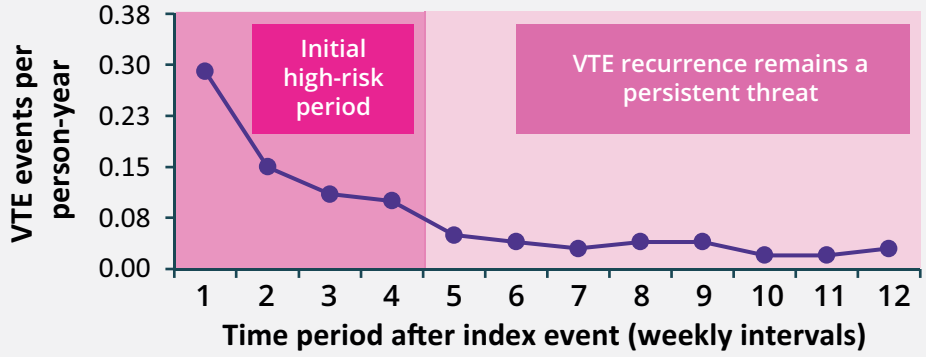
1 in 20 people will have VTE during their lifetime[1]

VTE incidence in England is 1–2 per 1000[1]

The risk of VTE is increased in certain patient populations

- **Severe renal impairment[5†§]** — 5.5 x more likely to suffer a VTE
- **Moderate renal impairment[5†‡]** — 2.5 x more likely to suffer a VTE
- **Frail Patients[4#]** — 1.3 x more likely to suffer a VTE
- **Patients with cancer[3**]** — 5-7 x more likely to suffer a VTE
- **Surgery/ major trauma/ lower limb fracture[2†]** — >10 x more likely to suffer a VTE

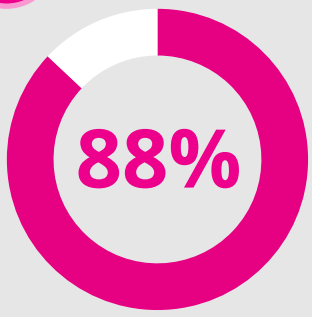
**Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during rivaroxaban therapy. In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated.



Meta-analysis of 15 trials in VTE*
n=27,237

The risk of VTE recurrence is highest in the first 3–4 weeks after the Index DVT/PE event[6]

2 WHAT IS THE EFFICACY AND SAFETY PROFILE OF XARELTO?



of acute VTE patients treated with Xarelto experienced complete or partial clot resolution (n=180)[7]

Complete resolution 41%
Partial resolution 47%
No change 12%

Predefined safety analysis of patients randomised to enoxaparin with vitamin K antagonists or Xarelto. Scans (CT-scan and Q-scan) were repeated at baseline and after 3 weeks to access clot resolution.

Recurrent VTE

2.3% Enoxaparin + VKA (n=4131)
2.1% Xarelto (n=4150)
HR: 0.89
95% CI: 0.66-1.19
p<0.001 (non-inferiority)
p=0.41 (superiority)

Xarelto had a similar efficacy outcome (symptomatic recurrent VTE, i.e. the composite of fatal or nonfatal PE or DVT) as compared to standard of care[8]

Major bleeding

1.7% Enoxaparin + VKA (n=4116)
1.0% Xarelto (n=4130)
HR: 0.54
95% CI: 0.37-0.79
p=0.002

Principal safety outcome: First major or nonmajor clinically relevant bleeding event (p = NS)
Rates of major bleeding were lower in patients treated with Xarelto as compared to standard of care[8]

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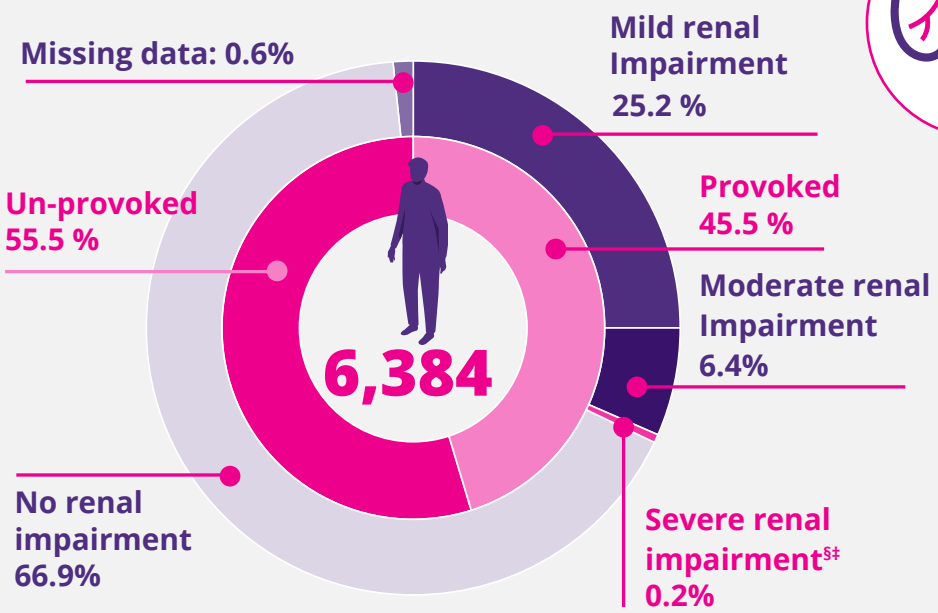
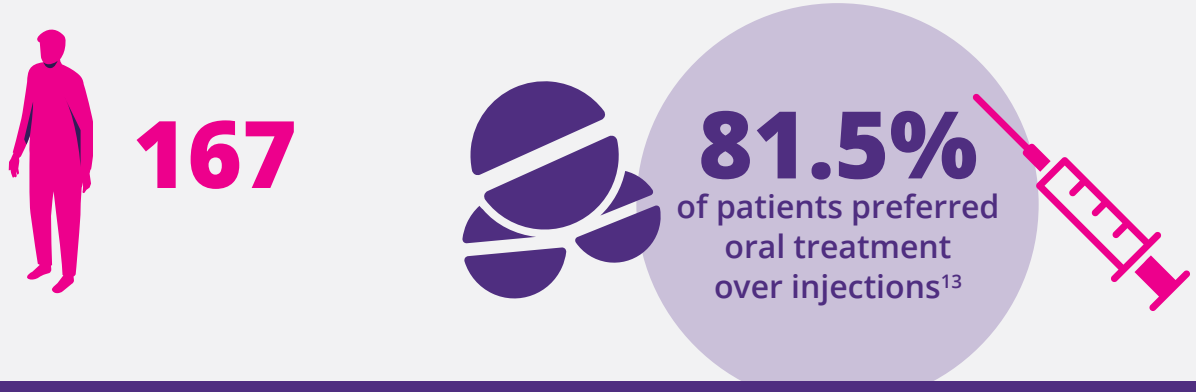
3 XARELTO HAS BEEN STUDIED IN PATIENT POPULATIONS AT INCREASED RISK OF VTE



§Use of Xarelto is not recommended in patients with creatinine clearance < 15 ml/min.
‡Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min.

Breakdown of patients in Xarelto trials (EINSTEIN DVT, PE, EINSTEIN Choice)[9,10,11]

4 PATIENTS WITH VTE SHOWED A PREFERENCE FOR ORAL ANTICOAGULANTS AS COMPARED TO INJECTIONS



National survey through a questionnaire sent by e-mail to 1936 French vascular physicians[13]

XARELTO IS RECOMMENDED BY NATIONAL AND INTERNATIONAL GUIDELINES FOR THE TREATMENT OF ACUTE VTE[14,15]

Xarelto is indicated for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults. The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE. Following completion of at least 6 months of treatment, the recommended dose is 10 mg or 20 mg.

VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; VKA, vitamin K antagonist; NS, non-significant. †Odds ratio; #Risk ratio; *trials of extended treatment and cancer patients excluded. § Use of Xarelto is not recommended in patients with creatinine clearance < 15 ml/min. ‡Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min.

1. All-Party Parliamentary Thrombosis Group. Annual Review 2019. Available at: https://thrombosisuk.org/downloads/APPTG%20Annual%20Review%202019%20100320.pdf. Accessed July 2023; 2. Anderson AA and Spencer FA. Circulation 2003;107:I9-I16; 3. Thrombosis UK, https://thrombosisuk.org/cancer-associated-thrombosis.php Accessed July 2023; 4. Folsom AR et al. The Journals of Gerontology: Series A 2007;62(1):79–82; 5. Ocak G et al. J Thromb Haemost 2013;11:627–633; 6. Adapted from Limone BL, et al Thromb Res 2013;132:420–426; 7. Van Es J et al. J Thromb Haemost. 2013;11(4):679-85; 8. Prins MH et al. Thromb J. 2013;11(1):21; 9. Buller HR et al. NEJM 2012;366:1287-97; 10. Bauersachs R et al. NEJM 2010;363:2499-510; 11. Weitz JI et al. NEJM 2017;376:1211-22; 13. Lanéelle D et al. Front Cardiovasc Med 2021; 8:675969; 14. Konstantinides et al. Eur Heart J 2020;41:543–603; 15. NICE NG158. Available at: https://www.nice.org.uk/guidance/ng158. Accessed July 2023.

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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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