▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the Summary of Product Characteristics (SmPC) for how to report adverse reactions

Xarelto 2.5 mg/ 10 mg / 15 mg / 20 mg film-coated tablets (rivaroxaban).

Refer to full SmPC before prescribing. **Presentation:** Film-coated tablet containing 2.5 mg / 10 mg / 15 mg / 20 mg rivaroxaban. Contains lactose. **Indications:** *2.5 mg:* Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine. Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events, co-administered with ASA. *10 mg:* Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults. *15 mg/20 mg:* Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults. Special populations: (*for 15 mg / 20 mg only*): specific dose recommendations apply for patients with moderate to severe renal impairment and in case of DVT/PE-patients only if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT/PE. 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 and undergo PCI with stent placement. **Dosage and Administration:** *ACS:* Recommended dose is 2.5 mg twice daily. Patients should also take a daily dose of 75 - 100 mg acetylsalicylic acid (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. Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited. Treatment with Xarelto should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued. *CAD/PAD:* Recommended dose is 2.5 mg twice daily. Patients taking Xarelto 2.5 mg twice daily should also take a daily dose of 75 – 100 mg ASA. Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk of thrombotic events versus the bleeding risks. In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of this treatment should be evaluated depending on the type of event or procedure and antiplatelet regimen. Safety and efficacy of Xarelto 2.5 mg twice daily in combination with ASA plus clopidogrel/ticlopidine has only been studied in patients with recent ACS. Dual antiplatelet therapy has not been studied in combination with Xarelto 2.5 mg twice daily in patients with CAD/PAD. *Renal impairment:* Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min). *Hepatic impairment:* Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. *Paediatric population:* The safety and efficacy of Xarelto in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto is not recommended for use in children below 18 years of age. *Prevention of VTE in elective hip or knee replacement surgery:* Recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established. Duration of

treatment depends on the individual risk of the patient for VTE which is determined by the type of orthopaedic surgery. For patients undergoing major hip surgery, treatment duration of 5 weeks is recommended. For major knee surgery, treatment duration of 2 weeks is recommended. *Prevention of stroke and systemic embolism:* The recommended dose is 20 mg once daily, which is also the recommended maximum dose. *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE:* 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. 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 once daily. 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 once daily, a dose of 20 mg once daily should be considered. *Renal impairment:* No dose adjustment is necessary in patients with mild renal impairment. 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. *Prevention of VTE in elective hip or knee replacement surgery:* no dose adjustment is necessary in patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min). *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* In patients with moderate or severe renal impairment, the recommended dose is reduced to 15 mg once daily. *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE:* No dose adjustment is considered necessary in moderate to severe renal impairment; although when the recommended dose is 20 mg once daily, a reduced dose of 15mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary. *Hepatic impairment:* Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C. **Contraindications:** *2.5 mg only:* Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA); concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month. *2.5 mg/ 10 mg/ 15 mg/ 20 mg:* Hypersensitivity to the active substance or any of the excipients; active clinically significant bleeding; lesion or condition if considered a significant risk for major bleeding; 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 and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C; pregnancy and breast feeding. **Warnings and Precautions:** Clinical surveillance in line with anticoagulation practice is recommended throughout treatment. Xarelto should be discontinued if severe haemorrhage occurs. Increasing age may increase haemorrhagic risk. Xarelto should be discontinued at the first appearance of a severe skin rash, or any other sign of hypersensitivity in conjunction with mucosal lesions. *Not recommended*: in patients with severe renal impairment (creatinine clearance <15 ml/min); in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- and P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; in patients with increased bleeding risk; in patients receiving concomitant treatment with strong CYP3A4 inducers unless the patient is closely observed for signs and symptoms of thrombosis; 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); *not recommended due to lack of data*: *2.5 mg*: treatment combination with antiplatelet agents other than ASA and clopidogrel/ticlopidine; *2.5 mg/ 10 mg/ 15 mg/ 20 mg:* in patients below 18 years of age, in patients concomitantly treated with dronedarone, in patients with prosthetic heart valves, *10 mg/ 15 mg/ 20 mg*: in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. *Use with caution*: in conditions with increased risk of haemorrhage; in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min); in patients with renal impairment (Xarelto 15 mg/20 mg) or with moderate renal impairment (creatinine clearance 30 - 49 ml/min) (Xarelto 2.5 mg/10 mg) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly

with medicinal products affecting haemostasis; when neuraxial anaesthesia or spinal/epidural puncture is employed. In patients at risk of ulcerative gastrointestinal disease prophylactic treatment may be considered. Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations. Contains lactose. *2.5 mg only:* Use with caution in patients ≥75 years of age or with lower body weight (<60 kg); in CAD patients with severe symptomatic heart failure. Patients on treatment with Xarelto and ASA or Xarelto and ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk. **Interactions:** Use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp. The interaction with clarithromycin, erythromycin or fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. Co-administration of Xarelto with dronedarone should be avoided. Care is to be taken if patients are treated concomitantly with any other anticoagulants. Care is to be taken if patients are treated concomitantly with NSAIDs (including ASA) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk. The possibility may exist that patients are at increased bleeding risk in case of concomitant use with SSRIs or SNRIs. Concomitant use of strong CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) should be avoided as they may lead to reduced rivaroxaban plasma concentration unless the patient is closely observed for signs and symptoms of thrombosis. Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban. **Fertility, Pregnancy and Lactation:** *Pregnancy:* Xarelto is contraindicated during pregnancy. *Breast-feeding:* Xarelto is contraindicated during breast-feeding; a decision must be made to discontinue breast-feeding or discontinue/abstain from therapy. *Fertility*: No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats, no effects were seen. **Driving and using machines:** Xarelto has minor influence on the ability to drive and use machines. Patients experiencing adverse reactions like syncope and dizziness should not drive or use machines. **Undesirable effects:** *Common*: anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, gastrointestinal tract haemorrhage, gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, increase in transaminases, pruritus, rash, ecchymosis, cutaneous and subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage (menorrhagia very common in women < 55 years treated for DVT, PE or prevention of recurrence), renal impairment, fever, peripheral oedema, decreased general strength and energy, post-procedural haemorrhage, contusion, wound secretion. *Uncommon*: thrombocytosis, thrombocytopenia, allergic reaction, dermatitis allergic, angioedema, allergic oedema, cerebral and intracranial haemorrhage, syncope, tachycardia, dry mouth, hepatic impairment, urticaria, haemarthrosis, feeling unwell, increases in: bilirubin, blood alkaline phosphate, GGT, LDH, lipase, amylase. *Rare*: jaundice, bilirubin conjugated increased, cholestasis, hepatitis (including hepatocellular injury), muscle haemorrhage, localised oedema, vascular pseudoaneurysm (*uncommon* in prevention therapy in ACS following percutaneous coronary intervention). *Very Rare:* Anaphylactic reactions including anaphylactic shock, Stevens-Johnson syndrome/ toxic epidermal necrolysis, DRESS syndrome. *Frequency not known*: compartment syndrome secondary to a bleeding, renal failure/ acute renal failure secondary to a bleeding.

Prescription only. Marketing Authorisation Holder: Bayer AG, 51368 Leverkusen, Germany. **MA numbers:** EU/1/08/472/001-024. **Further information available from:** Bayer Ltd., The Atrium, Blackthorn Road, Dublin 18. Tel: 01 2163300. **Date of Preparation:** 07/2019 **PP-XAR-IE-0243-02**