# Xarelto® (rivaroxaban) Prescriber Guide Version 5

**Contents**

## Patient Alert Card

A patient alert card must be provided to each patient who is prescribed Xarelto®2.5, 15 or 20 mg, and the implications of anticoagulant treatment should be explained. Specifically, the need for compliance and signs of bleeding and when to seek medical attention should be discussed with the patient.

The patient alert card will inform physicians and dentists about the patient‘s anticoagulation treatment and will contain emergency contact information. The patient should be instructed to carry the patient alert card at all times and present it to every health care provider.

## Dosing Recommendations

### Dosing in patients with atrial fibrillation

The recommended dose for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation is 20 mg once daily.


***Patients with renal impairment:**

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 – 29ml/min) renal impairment the recommended dose is 15 mg once daily. Xarelto® is to be used with caution in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) and isnot recommended in patients with creatinine clearance <15 ml/min.

Xarelto® should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

**Duration of therapy:**

Xarelto® should be continued long term provided the benefit of stroke preventiontherapy outweighs the potential risk of bleeding.

**Missed dose:**

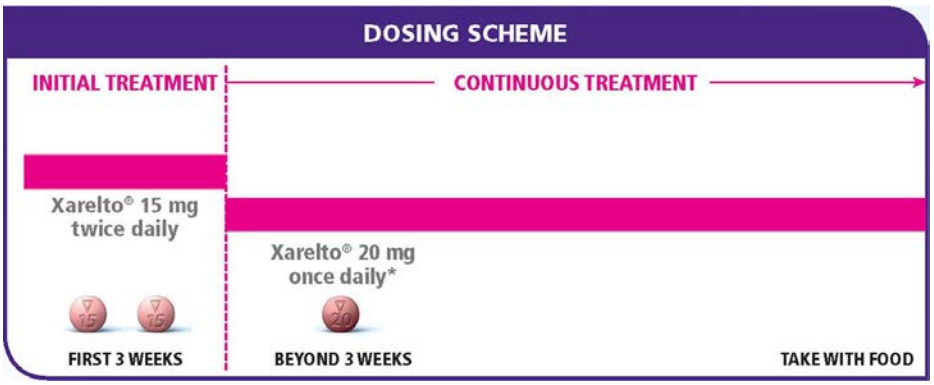
If a dose is missed the patient should take Xarelto® immediately and continue onthe following day with the once daily intake as recommended. The dose shouldnot be doubled within the same day to make up for a missed dose.

**Patients undergoing cardioversion:**

Xarelto can be initiated or continued in patients who may require cardioversion.
For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Xarelto treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation. For all patients, confirmation should be sought prior to cardioversion that the patient has taken Xarelto as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

## Dosing in treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

Patients are initially treated with 15 mg **twice daily** for the first three weeks. Thisinitial treatment is followed by 20 mg **once daily** for the continued treatment period.




***Patients with DVT/PE and renal impairment:**

Patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 - 29 ml/min) renal impairment treated for acute DVT, acute PE and prevention of recurrentDVT and PE should be treated with 15 mg twice daily for the first 3 weeks.

Thereafter, the recommended dose is 20 mg once daily.A reduction of the dose from 20 mg once daily to 15 mg once daily should beconsidered if the patient's assessed risk for bleeding outweighs the risk

forrecurrent DVT and PE. The recommendation for the use of 15 mg is based on PKmodelling and has not been studied in this clinical setting. Xarelto® is to be used with caution in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) and isnot recommended in patients with creatinine clearance <15 ml/min.

Xarelto® should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

**Duration of therapy:**

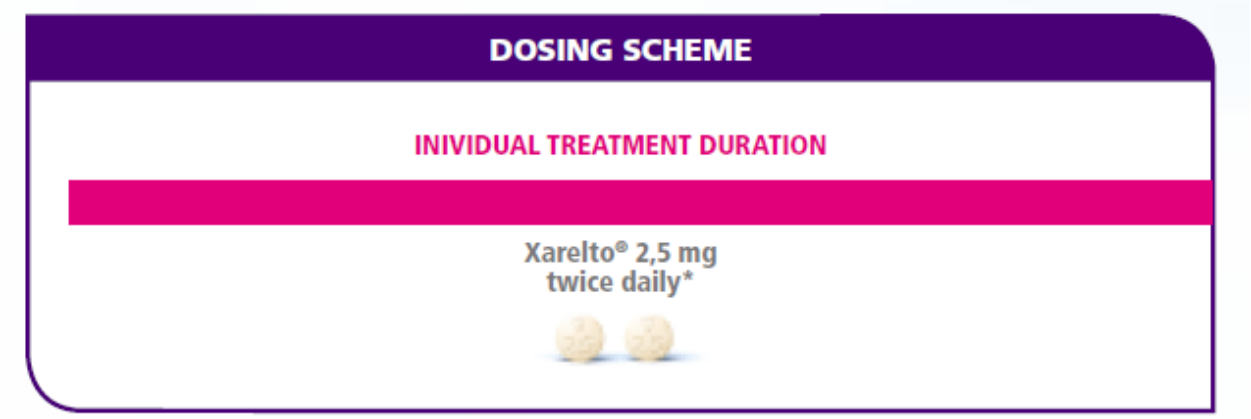
The duration of therapy should be individualized after assessment of the treatmentbenefit against the risk for bleeding.

**Missed dose:**

- **Twice daily treatment period** (15 mg bid for the first three weeks): If a dose is missed, the patient should take Xarelto® immediately to ensure intake of 30 mg Xarelto® per day.In this case two 15 mg tablets may be taken at once. Continue with the regular 15 mg twice daily intake on the following day.

- **Once daily treatment period** (beyond three weeks): If a dose is missed, the patient should take Xarelto® immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

## Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers




*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.

The recommended dose of Xarelto® is 2.5 mg twice daily, starting as soon aspossible after stabilization of the index ACS event but earliest 24 hours afterhospital admission and at the time when parenteral anticoagulation therapy wouldnormally be discontinued.

In addition to Xarelto® 2.5 mg, patients should also take a daily dose of 75-100 mg ASA or a daily dose of ASA in addition to either a daily dose of 75 mgclopidogrel or a standard daily dose of ticlopidine.Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended

### Patients with renal impairment:

No dose adjustment is required in patients with moderate renal impairment(creatinine clearance 30 - 49 ml/min). Xarelto® is to be used with caution inpatients with severe renal impairment (creatinine clearance 15 - 29 ml/min) and isnot recommended in patients with creatinine clearance <15 ml/min.

In patients with moderate renal impairment (creatinine clearance30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations Xarelto® is to be used with caution.

### Duration of therapy:

Treatment should be regularly evaluated in the individual patient weighing therisk for ischaemic events against the bleeding risks. Extension of treatment beyond12 months should be done on an individual patient basis as experience up to 24months is limited.

### Other warnings and precautions in ACS patients:

Xarelto® should be used with caution in ACS patients

- >75 years of age if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine
- with a low weight (<60 kg) if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine

Concomitant treatment of ACS with Xarelto® and antiplatelet therapy is contraindicated in patients with a prior stroke or a transient ischaemic attack (TIA).

### Missed dose:

If a dose is missed the patient should continue with the regular 2.5 mg Xarelto®dose as recommended at the next scheduled time. The dose should not bedoubled to make up for a missed dose.

## Oral Intake

Xarelto® 2.5 mg can be taken with or without food.Xarelto® 15 mg and 20 mg must be taken with food. The intake of these doseswith food at the same time supports the required absorption of the drug, thusensuring a high oral bioavailability.

Note: Xarelto® is also available at a 10 mg dose for the prevention of venousthromboembolism (VTE) in adult patients undergoing elective hip or kneereplacement surgery. This dose can be taken with or without food similar to the2.5 mg dose.

For patients who are unable to swallow whole tablets, a Xarelto® tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally. After the administration of crushed Xarelto 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

The crushed Xarelto tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Xarelto®15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding.

## Perioperative Management

If an invasive procedure or surgical intervention is required,

- Xarelto® 15/20 mg should be stopped at least 24 hours before the intervention
- Xarelto® 2.5 mg should be stopped at least 12 hours before the intervention

if possible and based on the clinical judgment of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Xarelto® should be restarted after the invasive procedure or surgical interventionas soon as possible provided the clinical situation allows and adequate hemostasishas been established.

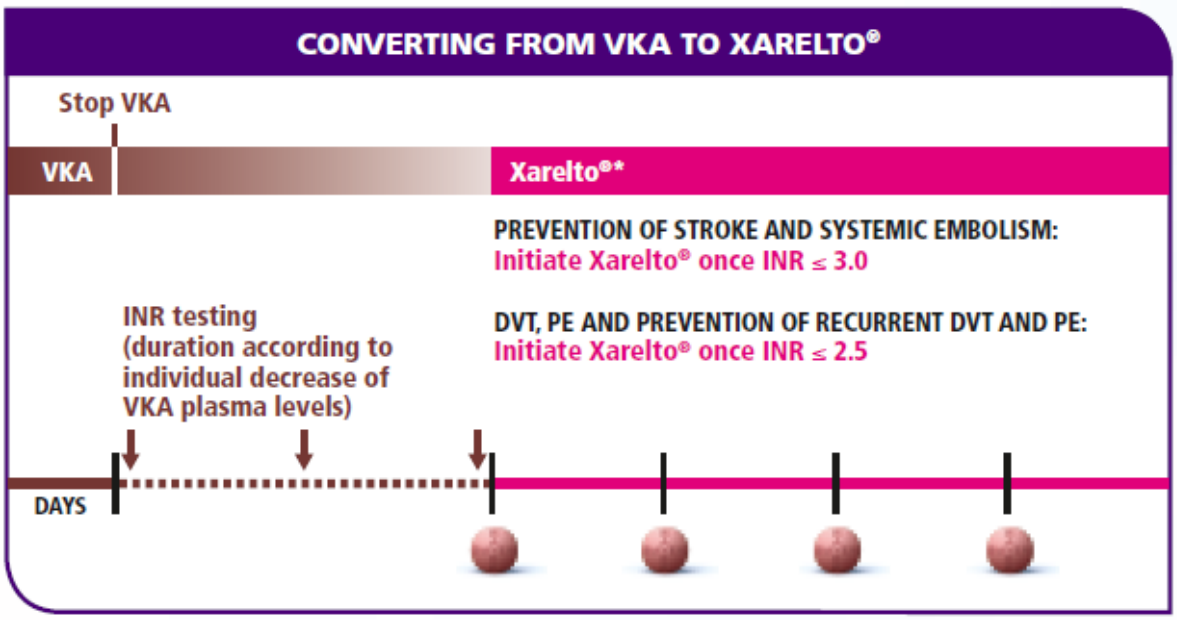
## Spinal/epidural anaesthesia or puncture

When neuraxialanaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

At least 18 hours should elapse after the last administration of rivaroxaban before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.

If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

## Converting from VKA to Xarelto®

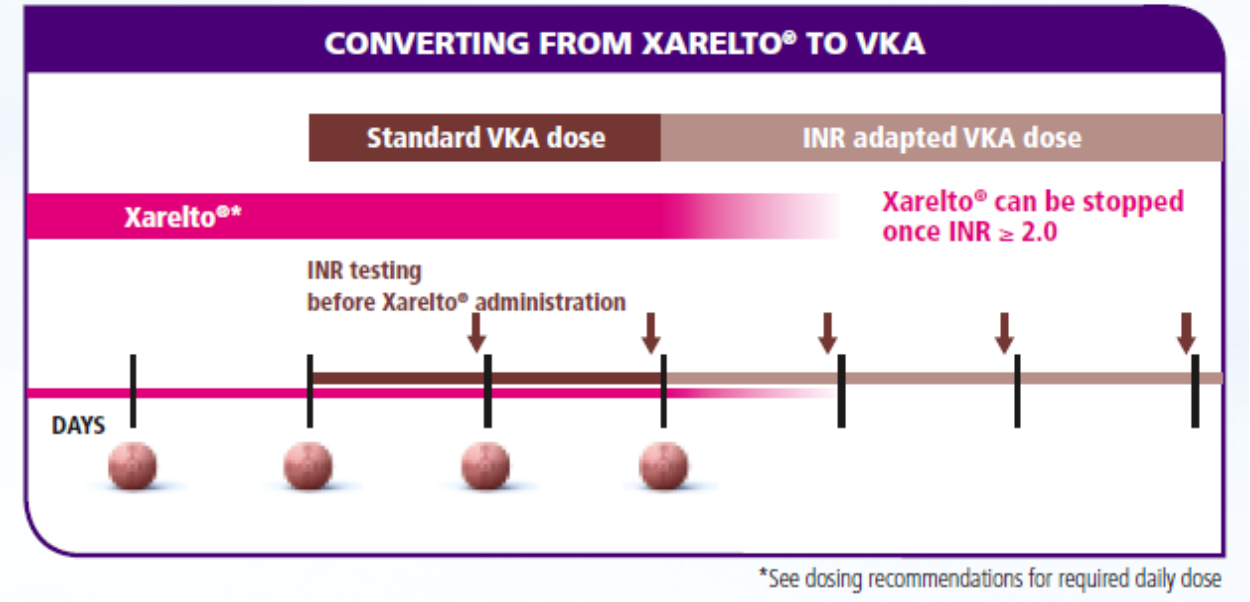



For patients treated for **prevention of stroke and systemic embolism**,treatment with VKA should be stopped and Xarelto® therapy should be initiatedwhen the **INR ≤3.0**.

For patients treated for **DVT, PE and prevention of recurrent DVT and PE**,treatment with VKA should be stopped and Xarelto® therapy should be initiatedwhen the **INR ≤2.5**.

**INR measurement is not appropriate to measure the anticoagulant activityof Xarelto®,** and therefore should not be used for this purpose. Treatment withXarelto® only does not require routine coagulation monitoring.

## Converting from Xarelto® to VKA




It is important to ensure adequate anticoagulation while minimizing the risk ofbleeding during conversion of therapy.

When converting to VKA, Xarelto® and VKA should be given overlapping until the**INR ≥2.0**. For the first two days of the conversion period, standard initial dosingof VKA should be used followed by VKA dosing guided by INR testing.

**INR measurement is not appropriate to measure the anticoagulant activityof Xarelto®.** While patients are on both Xarelto® and VKA the **INR should notbe tested earlier than 24 hours after the previous dose but prior to thenext dose of Xarelto®.** Once Xarelto® is discontinued, INR values obtained atleast 24 hours after the last dose reliably reflect the VKA dosing.

### Converting from Parenteral Anticoagulants to Xarelto®

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: StartXarelto® at the time of discontinuation.

- Patients with parenteral drug on a fixed dosing scheme such as LMWH: Discontinue parenteral drug and start Xarelto® 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

### Converting from Xarelto® to Parenteral Anticoagulants

Give the first dose of the parenteral anticoagulant at the time the next Xarelto® dose would be taken.

## Populations Potentially at Higher Risk of Bleeding

Like all anticoagulants, Xarelto® may increase the risk of bleeding.

Therefore Xarelto® is contraindicated in patients

- with active clinically significant bleeding
- with a lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms 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 malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- receiving concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc), heparin derivatives (fondaparinuxetc), oral anticoagulants (warfarin, dabigatranetexilate, apixabanetc) except under the circumstances of switching anticoagulant therapyor when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients

Several sub-groups of patients are at increased risk and should be carefullymonitored for signs and symptoms of bleeding complications.

Treatment decision in these patients should be done after assessment of treatmentbenefit against the risk for bleeding.

- Patients with renal impairment:See “dosing recommendations” forpatients with moderate (creatinine clearance 30 - 49 ml/min) or severe(15 - 29 ml/min) renal impairment. Xarelto® is to be used with caution in patients with creatinine clearance 15 - 29 ml/minand in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.Use of Xarelto® is not recommendedin patients with creatinine clearance < 15 ml/min.

- Patients concomitantly receiving other medicinal products
  - Systemic azole-antimycotics (such as ketoconazole, itraconazole,voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir):use of Xarelto® is not recommended
  - Care is to be taken in patients concomitantly receiving drugs affecting hemostasis such as NSAIDs, acetylsalicylic acid, platelet aggregation inhibitors
  - After an acute coronary syndrome 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

- Patients with other hemorrhagic risk factors
  As with other antithrombotics, Xarelto® is not recommended in patients with an increased bleeding risk such as
  - congenital or acquired bleeding disorders
  - uncontrolled severe arterial hypertension
  - other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
  - vascular retinopathy
  - bronchiectasis or history of pulmonary bleeding

## Other contraindications

Xarelto® is contraindicated during pregnancy and breast feeding. Women of child-bearing potential should avoid becoming pregnant during treatment with Xarelto®.Xarelto® is also contraindicated in case of hypersensitivity to the active substance or to any of the excipients.

## Overdose

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supra therapeutic doses of 50 mg Xarelto® and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.

**Should a bleeding complication arise in a patient receiving Xarelto®**, the next Xarelto® administration should be delayed or treatment should be discontinued as appropriate. Individualized bleeding management may include

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement
- Hemodynamic support; blood product or component transfusion
- For life-threatening bleeding that cannot be controlled with 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).However, there is currently very limited clinical experience with the use of these products in individuals receiving Xarelto®.

Due to the high plasma protein binding Xarelto® is not expected to be dialyzable.

## Coagulation Testing

Xarelto® does not require routine coagulation monitoring. However,measuring Xarelto® levels may be useful in exceptional situations whereknowledge of Xarelto® exposure may help to take clinical decisions, e.g.,overdose and emergency surgery.

Anti-FXa assays with Xarelto®-(rivaroxaban) specific calibrators to measurerivaroxaban levels are now commercially available. If clinically indicatedhemostatic status can also be assessed by PT using Neoplastin as describedin the SmPC.

The following coagulation tests are increased: Prothrombin time (PT), activatedpartial thromboplastin time (aPTT) and calculated PT international normalizedratio (INR). Since the INR was developed to assess the effects of VKAs on the PT,it is therefore not appropriate to use the INR to measure activity of Xarelto®.

Dosing or treatment decisions should not be based on results of INR exceptwhen converting from Xarelto® to VKA as described above.

▼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 to **Any suspected adverse drug reactions can be reported as follows:**

Report forms can be downloaded from www.medicinesauthority/adrportal and sent by post or email to;

**P**: ADR reporting/ 203, level 3 Rue D'Argens Gzira GZR 1368

**E**: postlicensing.medicinesauthority@gov.mt

or

E: pv@alfredgera.com

**Xarelto 10 mg / 15 mg / 20 mg film-coated tablets** (Refer to full SmPC before prescribing.)

▼ **This medicinal product is subject to additional monitoring.**

**Composition:** *Active ingredient*: 10 mg / 15 mg / 20 mg rivaroxaban. **Indications:** *10 mg:* Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. *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 deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Special populations: Patients undergoing cardioversion: Xarelto can be initiated or continued in patients who may require cardioversion. **Contraindications:** 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. *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; *not recommended due to lack of data*: in patients below 18 years of age, in patients concomitantly treated with dronedarone. 15 mg / 20 mg add*: in patients with prosthetic heart valves, 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) or with renal impairment 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; 15 mg / 20 mg add*: 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. 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. Xarelto contains lactose. **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, 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, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Uncommon*: thrombocythemia, allergic reaction, dermatitis allergic, cerebral and intracranial haemorrhage, syncope, tachycardia, dry mouth, hepatic function abnormal, urticaria, haemarthrosis, feeling unwell, increases in: bilirubin, blood alkaline

phosphatase, LDH, lipase, amylase, GGT. *Rare*: jaundice, muscle haemorrhage, localised oedema, bilirubin conjugated increased, vascular pseudoaneurysm. *Frequency not known*: compartment syndrome or (acute) renal failure secondary to a bleeding, angioedema and allergic oedema (*uncommon* in pooled phase III trials).

**Classification for supply:** Medicinal product subject to medical prescription.

**Marketing Authorisation Holder:** Bayer Pharma AG, D-13342 Berlin, Germany

**MA Number(s):** EU/1/08/472/011-21

**Further information available from:** Alfred Gera & Sons Ltd, Triq il-Masgar Qormi QRM 3217 Malta Tel: 21446205

**Date of Prepararion:** January 2015 **Version:** MT/4