

# Xarelto<sup>®</sup> (rivaroxaban) Prescriber Guide





### Patient Alert Card

A patient alert card must be provided to each patient who is prescribed Xarelto® 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.

**DOSING SCHEME**

**CONTINUOUS TREATMENT**

Xarelto® 20 mg  
once daily\*

TAKE WITH FOOD

\*In patients with moderate or severe renal impairment the recommended dose is 15 mg once daily.

Patients with renal impairment:

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 - 29 ml/min) renal impairment the recommended dose is 15 mg once daily. Use is not recommended in patients with creatinine clearance < 15 ml/min.

Duration of therapy:

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

Missed dose:

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.



## 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. This initial 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 recurrent DVT 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 only be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting.

The use of Xarelto® is not recommended in patients with creatinine clearance < 15 ml/min.

Duration of therapy:

The duration of therapy should be individualized after assessment of the treatment benefit 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. 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

**Oral Intake**

Xarelto® 15 mg and 20 mg must be taken with food. The intake of these doses with food at the same time supports the required absorption of the drug, thus ensuring a high oral bioavailability. Note: Xarelto® is also available at a 10 mg dose for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. This dose can be taken with or without food.

**Perioperative Management**

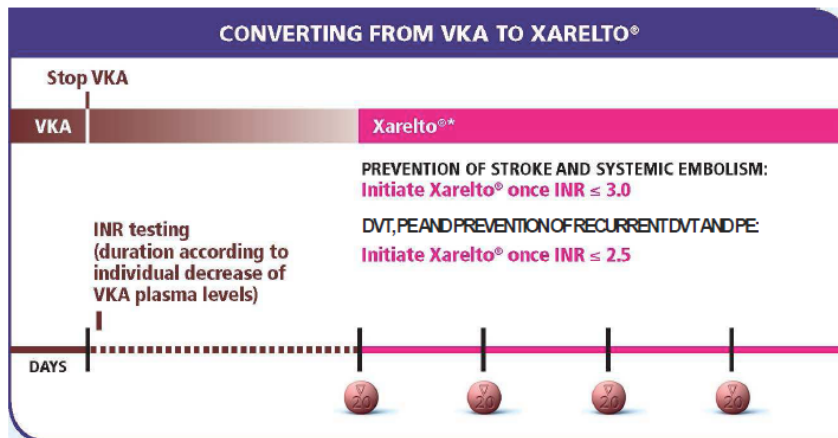
If an invasive procedure or surgical intervention is required,

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

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 intervention as soon as possible provided the clinical situation allows and adequate hemostasis has been established.

## Converting from VKA to Xarelto®



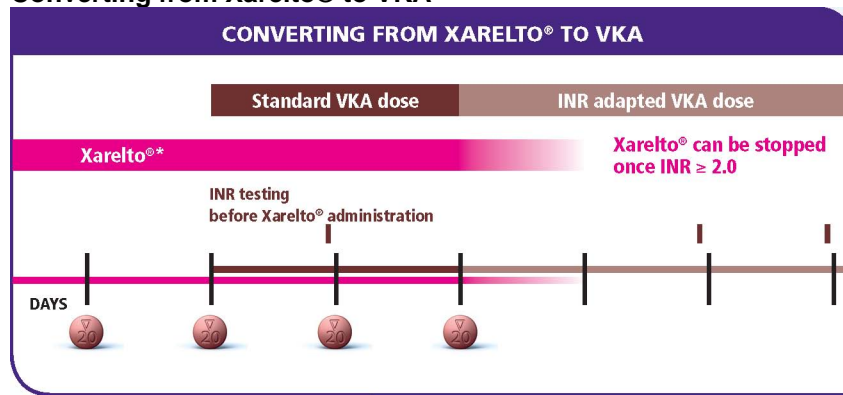
For patients treated for prevention of stroke and systemic embolism, treatment with VKA should be stopped and Xarelto® therapy should be initiated when the INR is  $\leq$ 3.0.

For patients treated for DVT, PE and prevention of recurrent DVT and PE, treatment with VKA should be stopped and Xarelto® therapy should be initiated when the INR is  $\leq$ 2.5.

\*See dosing recommendations for required daily dose

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

## Converting from Xarelto® to VKA



\*See dosing recommendations for required daily dose

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

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

INR measurement is not appropriate to measure the anticoagulant activity of Xarelto®. While patients are on both Xarelto® and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto®. Once Xarelto® is discontinued, INR values obtained at least 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: Xarelto® should be started at the time of discontinuation.
- ◆ Patients with parenteral drug on a fixed dosing scheme such as LMWH: Xarelto® should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

### Converting from Xarelto® to Parenteral Anticoagulants

The first dose of the parenteral anticoagulant should be given instead of the next Xarelto® dose at the same time.



### **Populations Potentially at Higher Risk of Bleeding**

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

Therefore Xarelto® is contraindicated in patients

- ◆ with clinically significant active bleeding
- ◆ with a lesion or condition at significant risk of major bleeding such as 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
- ◆ with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients
- ◆ receiving concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, dabigatran etexilate, apixaban etc) is not recommended except under the circumstances of switching therapy to or from Xarelto® or when UFH is given at doses necessary to maintain an open central venous or arterial catheter

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

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

- ◆ Patients with renal impairment: See “dosing recommendations” for patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 - 29 ml/min) renal impairment. Use of Xarelto® is not recommended in 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
  - Drugs affecting hemostasis such as NSAIDs, acetylsalicylic acid, or platelet aggregation inhibitors

◆ Patients with other haemorrhagic 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
- active ulcerative gastrointestinal disease
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

Xarelto® is contraindicated during pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Xarelto®.





### **Overdose**

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic 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 where knowledge of Xarelto® exposure may help to take clinical decisions, e.g., overdose and emergency surgery.

Anti-FXa assays with Xarelto®-(rivaroxaban) specific calibrators to measure anticoagulation activity are now commercially available. If clinically indicated hemostatic status can also be assessed by PT using Neoplastin as described in the SmPC.

The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalized ratio (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 except when converting from Xarelto® to VKA as described above.

## **Appropriate local safety information**

Any suspected adverse drug reactions can be reported to:

Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or at:

<http://www.medicinesauthority.gov.mt/pub/adr.doc>

Telephone Number: +356 2343 9000

Or

Alfred Gera & Sons Ltd, Triq il-Masġar, Qormi QRM 3217, MALTA, or at

[pv@alfredgera.com](mailto:pv@alfredgera.com)

Tel: +356 21446205

## **Xarelto 15 mg / 20 mg film-coated tablets**

(Refer to full SmPC before prescribing.)

**Composition:** *Active ingredient:* 15 mg / 20 mg rivaroxaban. *Excipients<sup>1</sup>:* Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate, macrogol 3350, titanium dioxide (E171), iron oxide red (E172).

**Indication:** 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  $\geq$  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. **Contraindications:** Hypersensitivity to the active substance or any of the excipients; clinically significant active bleeding; lesion or condition at significant risk of major bleeding; concomitant treatment with any other anticoagulant agent except under the circumstances of switching therapy to or from rivaroxaban or when unfractionated heparin is given at doses necessary to maintain a patent 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. *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; due to lack of data: in patients below 18 years of age, in patients with prosthetic heart valves, in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy; in patients concomitantly treated with dronedarone. *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 or with strong CYP3A4 inducers. 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. Specific dose recommendations apply for patients with moderate to severe renal impairment. 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, renal impairment, fever, peripheral oedema, decreased general strength and energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Uncommon:* thrombocytopenia, 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 (*uncommon* in prevention therapy in ACS following percutaneous intervention). *Frequency not known:* compartment syndrome or (acute) renal failure secondary to a bleeding.

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

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

**Further information available from:** Alfred Gera & Sons Limited, 10, Triq il-Masgar, Qormi QRM 3217, Malta Telephone: +356 21446205

**Version:** EU/3