Xarelto® (rivaroxaban) Prescriber Guide

First in ORAL, Direct Factor Xa Inhibition

Xarelto® rivaroxaban

Simple Protection For More Patients

Patient Alert Card

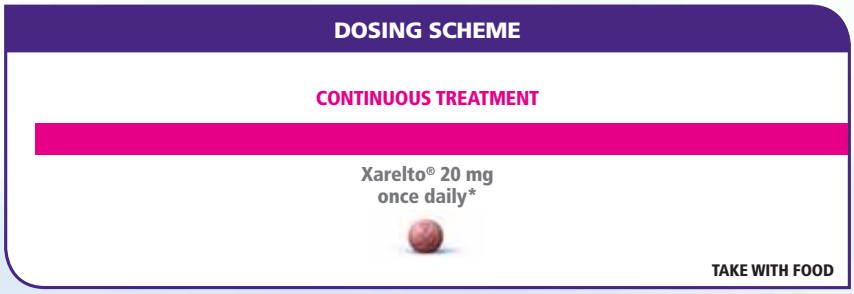
A patient alert card must be provided to each patient who is prescribed Xarelto® 15 or 20 mg, and the implications of anticoagulant treatment should be explained. Specifically, the need for compliance and signs of bleeding and when to seek medical attention should be discussed with the patient.

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.



*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:

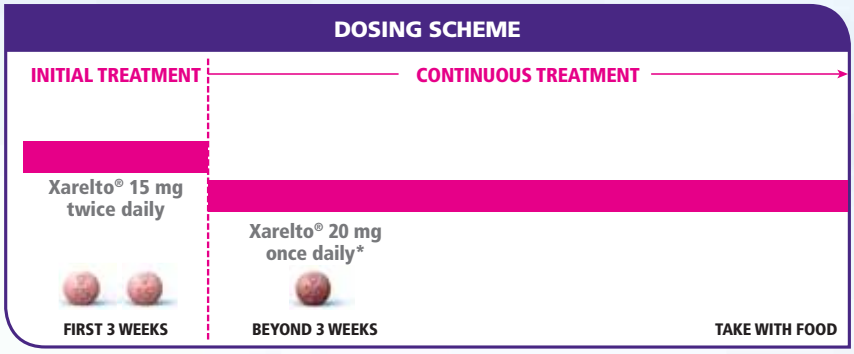
Xarelto® should be continued long term provided the benefit of stroke prevention therapy outweighs the potential risk of bleeding.

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 the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE)

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 continued treatment period.



*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 patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily. Use is not recommended in patients with creatinine clearance < 15 ml/min.

Duration of therapy:

The duration of therapy should be individualised 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 support 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 without food.

Perioperative Management

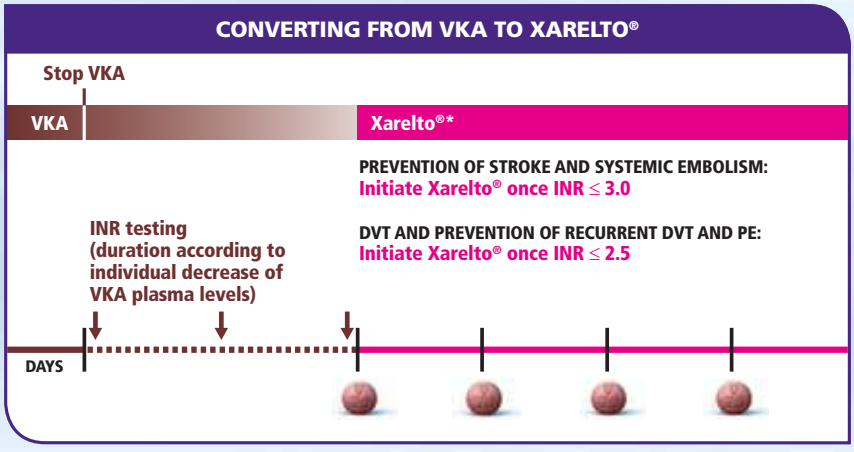
If an invasive procedure or surgical intervention is required, Xarelto® should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency 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 haemostasis 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 **≤ 3.0**.

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



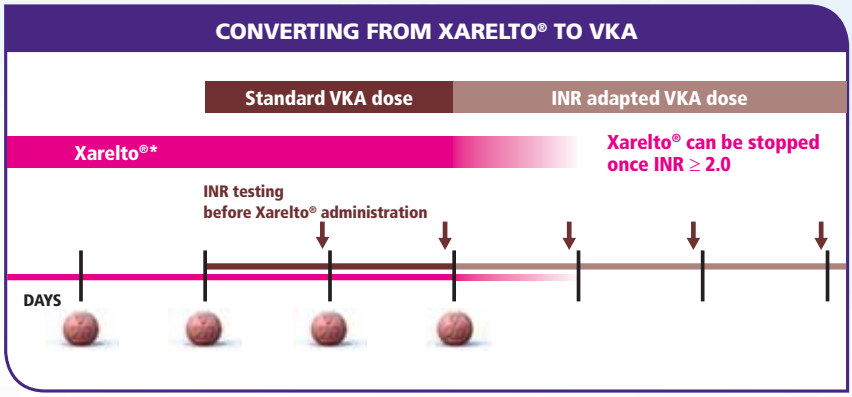
*See dosing recommendations for required daily dose

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

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 **≥ 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.



*See dosing recommendations for required daily dose

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 testing may be done reliably at least 24 hours after the last dose.

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

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications:

- **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. Xarelto® use is not recommended in patients with creatinine clearance < 15 ml/min
- **Patients with 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
- **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 haemostasis such as NSAIDs, acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents
- **Patients with other haemorragic risk factors such as**
  - Uncontrolled severe arterial hypertension
  - Active ulcerative gastrointestinal disease
  - Recent gastrointestinal ulcerations
  - Vascular retinopathy
  - Recent intracranial or intracerebral haemorrhage
  - Intraspinal or intracerebral vascular abnormalities
  - Recent brain, spinal or ophthalmological surgery
  - 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
- Haemodynamic 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 dialysable.

Coagulation Testing

Xarelto® does not require routine coagulation monitoring. The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated international normalized ratio (INR). Especially INR testing was developed for measuring VKA-effects and is therefore not appropriate 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.

If clinically indicated haemostatic status can be assessed by PT using Neoplastin as described in the SmPC.

Xarelto 15 mg / 20 mg film-coated tablets (Refer to full SmPC before prescribing.) **Composition:** *Active ingredient:* 15 mg / 20 mg rivaroxaban. Excipients: *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 ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults. **Contraindications:** Hypersensitivity to the active substance or any of the excipients; clinically significant active bleeding; 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:** *not recommended:* 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 severe renal impairment (creatinine clearance <15 ml/min); in the treatment of acute pulmonary embolism; in patients below 18 years of age or with prosthetic heart valves or in patients concomitantly treated with dronedarone due to lack of data. *Use with caution:* in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) or with renal impairment concomitantly treated with potent CYP3A4 inhibitors; in patients concomitantly treated with medicinal products affecting haemostasis or with strong CYP3A4 inducers; in patients with increased bleeding risk. In patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period. Specific dose recommendations apply for patients with moderate to severe renal impairment. Xarelto contains lactose. **Undesirable effects:** *Common:* anaemia, dizziness, headache, syncope, eye haemorrhage, tachycardia, hypotension, haematoma, epistaxis, gastrointestinal tract haemorrhage, gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, pain in extremity, urogenital tract haemorrhage, fever, peripheral oedema, decreased general strength and energy, increase in transaminases, post-procedural haemorrhage, contusion. *Uncommon:* thrombocythemia, allergic reaction, dermatitis allergic, cerebral and intracranial haemorrhage, haemoptysis, dry mouth, hepatic function abnormal, urticaria, cutaneous and subcutaneous haemorrhage, haemarthrosis, renal impairment, feeling unwell, localised oedema, wound secretion, increases in: bilirubin, blood alkaline phosphatase, LDH, lipase, amylase, GGT. *Rare:* jaundice, muscle haemorrhage, bilirubin conjugated increased. *Frequency not known:* pseudoaneurysm following percutaneous intervention, compartment syndrome or (acute) renal failure 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:** medinfo@bayerhealthcare.com **Version:** EU/1

Who to contact in the event of a suspected adverse drug reaction

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

Or

Alfred Gera & Sons Ltd, Triq il-Masġar, Qormi QRM 3217, MALTA, or at mail@alfredgera.com

Tel: +356 21446205

Bayer HealthCare

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Xarelto®
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