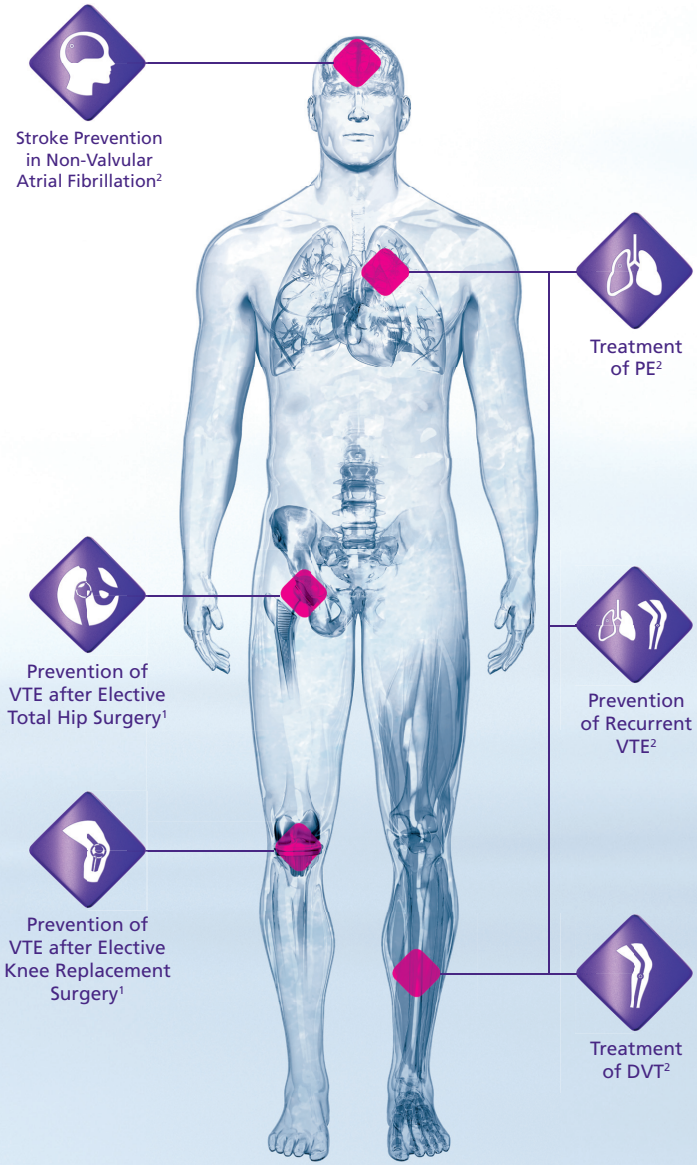
Xarelto® (rivaroxaban) Prescriber Guide



Xarelto® rivaroxaban

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PATIENT ALERT CARD

Non-VKA Oral Anticoagulants (NOACs) have emerged as an alternative for vitamin K antagonists (VKAs) e.g Warfarin for thromboembolic prevention in patients with non-valvular atrial fibrillation (AF) and for venous thromboembolism treatment.

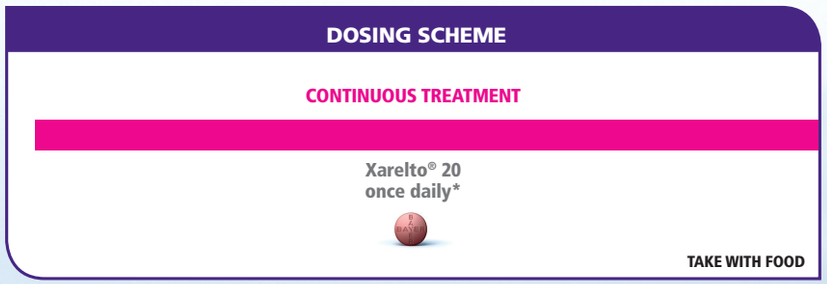
This will have an impact on many practical considerations in the daily management of these patients. Users of Warfarin have routinely been advised to carry information about their anticoagulant therapy to alert any (para) medical participant in their care. It should be equally important that those treated with NOACs carry details of this therapy.

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

DOSING RECOMMENDATIONS

Dosing in patients with non-valvular atrial fibrillation (NVAF)

Patient education on the importance of strict adherence is of utmost importance. 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) renal impairment the recommended dose is 15 mg once daily. Xarelto®15 mg should be used with caution in patients with severe (creatinine clearance 15 - 29 ml/min) renal impairment.

Duration of therapy:

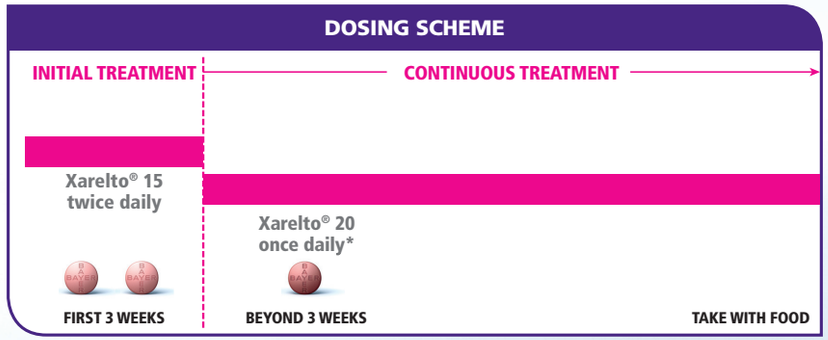
Xarelto® should be continued long term provided the benefit of stroke prevention therapy outweighs the potential risk of bleeding.

Missed dose:

If a dose is missed the patient should take Xarelto® as soon as they remember and continue on the following day, with the once daily intake as recommended. The dose should **not** be doubled within the same day (24 hourly interval) to make up for a missed dose.

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



*Patients with DVT/PE and renal impairment:

Chronic kidney disease (CKD) should be considered as an additional risk factor for stroke. But CKD also increases the bleeding risk, with a relative increase in risk for all oral anticoagulants.

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. Xarelto® 20 should be used with caution in patients with severe renal failure.

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 i.e. every 12 hours** (15 mg BD 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, two Xarelto® 15 tablets may be taken at once at the next dosing interval, and thereafter 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.

ADMINISTRATION

Xarelto® must be taken with food. The intake of Xarelto® with food at the same time supports the required absorption of the drug, thus ensuring a high oral bioavailability.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Xarelto® 15/20 should be stopped at least 24 hours before the intervention if possible and based on the clinical judgement of the doctor. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

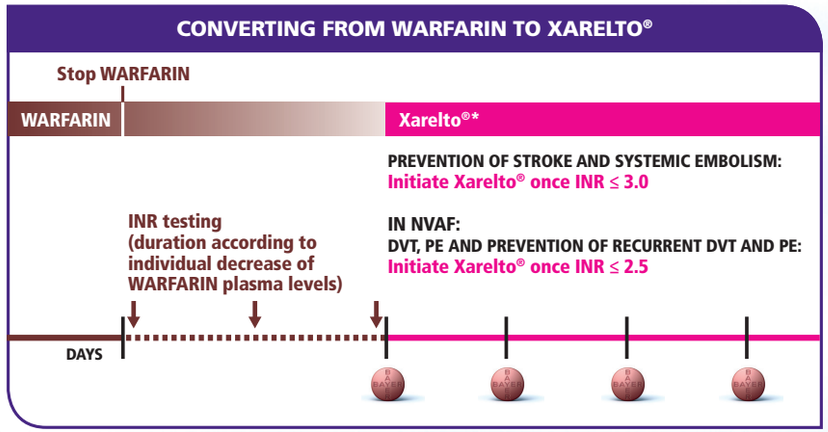
Xarelto® should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established. Any questions should be directed to the prescribing doctor. Emergency surgery - see section on how to manage bleeding pg 10.

SWITCHING BETWEEN ANTICOAGULANT REGIMENS

It is important to safeguard the continuation of anticoagulant therapy while minimising the risk for bleeding when switching between different anticoagulant therapies.

This requires insights into the pharmacokinetics and pharmacodynamics of different anticoagulation regimens, interpreted in the context of the individual patient.

CONVERTING FROM WARFARIN TO XARELTO®



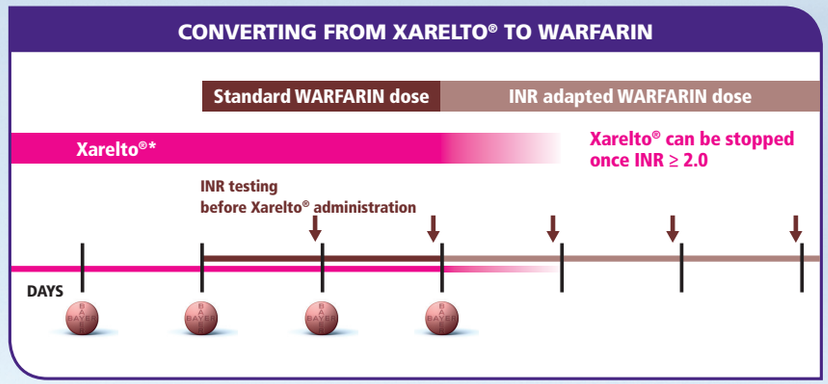
*See dosing recommendations for required daily dose

For patients treated for **prevention of stroke and systemic embolism**, **in NVAF** treatment with Warfarin should be stopped and Xarelto® therapy should be initiated when the **INR** is **≤ 3.0**.

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

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 WARFARIN



*See dosing recommendations for required daily dose

Owing to the slow onset of action of Warfarin, it may take 5–10 days before an INR in therapeutic range is obtained, with large individual variations. Therefore, Xarelto® and Warfarin should be administered concomitantly until the INR is in a range that is considered appropriate, similarly as when LMWHs are continued during Warfarin initiation.

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

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

INR measurement is not appropriate to measure the anticoagulant activity of Xarelto®. While patients are on both Xarelto® and Warfarin 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 Warfarin 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.

INDIVIDUALS AT HIGHER RISK OF BLEEDING

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

Therefore, Xarelto® is **contraindicated** in case of:

- Hypersensitivity to rivaroxaban or any excipient of the tablets

- Clinically significant active bleeding e.g. intracranial bleeding, gastrointestinal bleeding
- Known existing inherited bleeding disorders
- Hepatic disease wi**th**/with**out** coagulopathy

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
  - Care should be taken if patients are treated concomitantly with drugs affecting hemostasis such as NSAIDs, acetylsalicylic acid, platelet aggregation inhibitors
- **Patients with other haemorragic risk factors**

  As with other antithrombotics, Xarelto® should be used with caution in patients with an increased bleeding risk such as:
  - Congenital or acquired bleeding disorders
  - Uncontrolled severe arterial hypertension
  - Active ulcerative gastrointestinal disease
  - Recent gastrointestinal ulcerations
  - Vascular retinopathy
  - Recent intracranial or intracerebral haemorrhage
  - Intraspinal or intracerebral vascular abnormalities
  - Shortly after brain, spinal or ophthalmological surgery
  - Bronchiectasis or history of pulmonary bleeding

Xarelto® is contraindicated during pregnancy and breast feeding. 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.

BLEEDING COMPLICATION

There are currently no specific antidotes for the NOACs, although development for those is ongoing. However, given the relatively short plasma half life of the NOAC drugs, in the absence of bleeding a 'wait-and-see' management can be advocated in most cases.

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

Individualised bleeding management may include:

- Supportive treatment, such as local compression (where possible), 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®.
- Xarelto® is not dialysable.

COAGULATION TESTING

Xarelto® does not require routine coagulation monitoring.

However, measuring Xarelto® activity 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 rivaroxaban activity are now commercially available. If clinically indicated haemostatic status can also be assessed by PT using Neoplastin™.

The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and INR. Since the INR was developed to assess the effects of Warfarin, 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 Warfarin as described above.

REFERENCES: 1. Registered XARELTO® 10 package insert of South Africa. 2. Registered XARELTO® 15 and XARELTO® 20 package insert of South Africa.

For full prescribing information, refer to the package insert approved by the Medicines Authority (MCC).

XARELTO® 10: Each film-coated tablet contains rivaroxaban 10mg. **South Africa:** S4 Reg. No.: 42/8.2/1046; **Namibia:** NS2 10/8.2/0463. **Botswana:** S2 BOT1302278; **Zimbabwe:** PP10 Reg. 2017/10.2/5362
XARELTO® 15: Each film-coated tablet contains rivaroxaban 15 mg. **South Africa:** S4 Reg. No: 46/8.2/0111; **Namibia:** NS2 12/8.2/0006; **Botswana:** S2 BOT1302296; **Zimbabwe:** PP10 Reg. 2017/10.2/5363
XARELTO® 20: Each film-coated tablet contains rivaroxaban 20 mg. **South Africa:** S4 Reg. No: 46/8.2/0112; **Namibia:** NS2 12/8.2/0007; **Botswana** S2 BOT1302297; **Zimbabwe:** PP10 Reg. 2017/10.2/5364

PHARMACOLOGICAL CLASSIFICATION: A.8.2 Anticoagulants.

INDICATIONS: (1) Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF); (2) Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE); (3) Treatment of pulmonary embolism (PE) and for the prevention of recurrent pulmonary embolism (PE) and deep vein thrombosis (DVT); (4) Prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

CONTRA-INDICATIONS: Hypersensitivity to rivaroxaban or any excipient of the tablets. Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding). Known existing inherited bleeding disorders. Hepatic disease with or without coagulopathy. Safety and efficacy have not been established in pregnant women. Animal data show that rivaroxaban crosses the placental barrier. Therefore, the use is contra-indicated throughout pregnancy. Safety and efficacy have not been established in breastfeeding mothers. Animal data indicate that rivaroxaban is secreted into breast milk. Therefore, it may only be administered after breastfeeding is discontinued.

WARNINGS: Patients with prosthetic valves: Safety and efficacy have not been studied in patients with prosthetic heart valves; therefore, there are no data to support the use of XARELTO in this patient population. XARELTO should be used with caution in patients with an increased bleeding risk. Care should be taken if patients are treated concomitantly with medicines affecting haemostasis. Patients at risk of ulcerative gastrointestinal disease, an appropriate prophylactic treatment may be considered. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. XARELTO 15 and XARELTO 20 is to be used with caution in patients with moderate renal impairment (creatinine clearance < 50 to 30 ml/min) receiving co-medications leading to increased rivaroxaban plasma concentrations. No clinical data are available for patients with severe renal impairment (creatinine clearance < 15 ml/min). Therefore, the use of XARELTO 15 and XARELTO 20 is not recommended in these patients.

SIDE EFFECTS: Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases, as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for XARELTO 15 and XARELTO 20. Therefore, the possibility of a haemorrhage should be considered in evaluating the condition in any anticoagulated patient.

APPLICANT/HCR: Bayer (Pty) Ltd, Co. Reg. No.: 1968/011192/07, 27 Wrench Road, Isando, 1609. Tel: 011 921 5044 Fax: 011 921 5041

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