Xarelto® (rivaroxaban) Prescriber Guide

December 2019

Version MT 9

Contents

Prescriber Guide

The Prescriber Guide provides recommendations for the use of 'Xarelto' in order to minimise the risk of bleeding during treatment with 'Xarelto'.

The Prescriber Guide does not substitute the 'Xarelto' Summary of Product Characteristics (SmPC).*

[*optional: https://www.ema.europa.eu/en/medicines/human/EPAR/xarelto]

Patient Alert Card

A patient alert card must be provided to each patient who is prescribed 'Xarelto' 2.5 mg, 10 mg, 15 mg or 20 mg and is provided with the product package. The implications of anticoagulant treatment should be explained. Specifically, the need for compliance, 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 healthcare provider.

Dosing Recommendations

Stroke prevention in adult patients with non-valvular atrial fibrillation

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

DOSING SCHEMES

Continuous treatment

'Xarelto' 20 mg once daily*

Take with food

*Recommended dosing scheme for patients with atrial fibrillation and moderate or severe renal impairment see below

Patients with renal impairment

In patients with moderate (creatinine clearance [CrCl] 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment the recommended dose is 15 mg once daily. 'Xarelto' is to be used with caution in patients with severe renal impairment (CrCl 15–29 ml/min) and is not recommended in patients with CrCl <15 ml/min.

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

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.

Patients with non-valvular atrial fibrillation undergoing PCI 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.

Patients undergoing cardioversion

'Xarelto' can be initiated or continued in patients who may require cardioversion.

For transoesophageal 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.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients

Patients are initially treated with 'Xarelto' 15 mg **twice daily** for the first 3 weeks. This initial treatment is followed by 'Xarelto' 20 mg **once daily** for the continued treatment period. 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 'Xarelto' 20 mg **once daily** should be considered.

'Xarelto' 10 mg is **not** recommended for the initial 6 months' treatment of DVT or PE

DOSING SCHEMES

Day 1 to 21

Xarelto 15 mg twice daily*

Day 22 onwards

Xarelto 20 mg once daily*

Following completion of at least 6 months

Xarelto 10 mg once daily*

OR

Xarelto 20 mg once daily*

In patients in whom the risk of recurrent DVT or PE is considered high (e.g. complicated comorbidities, recurrent DVT/PE on extended prevention on 10 mg once daily), Xarelto 20 mg once daily* should be considered

'Xarelto' 10 mg: TAKE WITH OR WITHOUT FOOD - 'Xarelto' 15/20 mg: MUST BE TAKEN WITH FOOD

*Recommended dosing scheme for patients with DVT/PE and moderate or severe renal impairment see next page

Patients with renal impairment

Patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment treated for acute DVT, acute PE and prevention of recurrent DVT and PE should be treated with 'Xarelto' 15 mg twice daily for the first 3 weeks.

Thereafter, the recommended dose is 'Xarelto' 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk of bleeding outweighs the risk of recurrent DVT and PE. The recommendation for the use of 15 mg is based on pharmacokinetic (PK) modelling and has not been studied in this clinical setting. 'Xarelto' is to be used with caution in patients with severe renal impairment (CrCl 15–29 ml/min) and is not recommended in patients with CrCl <15 ml/min. When the recommended dose is 10 mg once daily, (after ≥6 months of therapy) no dose adjustment from the recommended dose is necessary.

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

Duration of therapy

Short duration of therapy (≥3 months) should be considered in patients with DVT/PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT/PE not related to major transient risk factors, unprovoked DVT/PE, or a history of recurrent DVT/PE.

Missed dose

Twice-daily treatment period (15 mg twice daily for the first 3 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 3 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

*With moderate renal impairment (CrCl 30-49 ml/min) for 'Xarelto' 10 mg

Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events

DOSING SCHEMES

Continuous treatment

'Xarelto' 2.5 mg twice daily*

'Xarelto' 2.5 mg: TAKE WITH OR WITHOUT FOOD

Patients taking 'Xarelto' 2.5 mg twice daily should also take a daily dose of 75–100 mg acetylsalicylic acid (ASA).

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 (see below).

Dual antiplatelet therapy has not been studied in combination with 'Xarelto' 2.5 mg twice daily in patients with CAD and/or PAD.

Patients with renal impairment

No dose adjustment is required in patients with moderate renal impairment (CrCl 30–49 ml/min). Xarelto is to be used with caution in patients with severe renal impairment (CrCl 15–29 ml/min) and is not recommended in patients with CrCl <15 ml/min.

In patients with moderate renal impairment (CrCl 30–49 ml/min) concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations, Xarelto is to be used with caution.

Duration of therapy

Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks.

Other warnings and precautions in CAD/PAD patients

In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of 'Xarelto' 2.5 mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen.

Concomitant treatment of CAD/PAD with 'Xarelto' 2.5 mg twice daily and ASA is contraindicated in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month.

'Xarelto' co-administered with ASA should be used with caution in CAD/PAD patients:

- ≥ 75 years of age. The benefit-risk of the treatment should be individually assessed on a regular basis
- With a lower weight (<60 kg)
- In CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with 'Xarelto'. (See section 5.1 of the SmPC for further clarification)

'Xarelto' 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 be doubled to make up for a missed dose.

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

The recommended dose of 'Xarelto' is 2.5 mg twice daily, starting as soon as possible after stabilisation of the index ACS event but at the earliest 24 hours after hospital admission and at the time when parenteral anticoagulation therapy would normally be discontinued.

In addition to 'Xarelto' 2.5 mg, 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 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 (CrCl 30–49 ml/min). 'Xarelto' is to be used with caution in patients with severe renal impairment (CrCl 15–29 ml/min) and is not recommended in patients with CrCl <15 ml/min.

In patients with moderate renal impairment (CrCl 30–49 ml/min) concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations, 'Xarelto' is to be used with caution.

Duration of therapy

Treatment should be regularly evaluated in the individual patient, weighing the risk of 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.

Other warnings and precautions in ACS patients

'Xarelto', co-administered with ASA or with ASA plus clopidogrel or ticlopidine, should be used with caution in ACS patients:

- ≥75 years of age. The benefit risk of the treatment should be individually assessed on a regular basis
- With a lower weight (<60 kg)

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 be doubled to make up for a missed dose.

Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

The recommended dose is 10 mg 'Xarelto' 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

The duration of treatment depends on the individual risk of the patient for venous thromboembolism, which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended
- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended

Missed dose

If a dose is missed the patient should take 'Xarelto' immediately and then continue the following day with once-daily intake as before.

Oral Intake

'Xarelto' 2.5 mg and 10 mg can be taken with or without food.

'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.

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' 10/15/20 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 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.

Spinal/Epidural Anaesthesia or Puncture

When neuraxial anaesthesia (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.

For indication-specific recommendations, please refer to the sections below:

- Prevention of stroke and systemic embolism in adult patients with NVAF
- Treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients

There is no clinical experience with the use of 15 mg and 20 mg 'Xarelto' in these situations. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

For the removal of an epidural catheter and based on the general pharmacokinetic characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients, should elapse after the last administration of rivaroxaban (see section 5.2 of the SmPC). 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.

- Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban.

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2 of the SmPC).

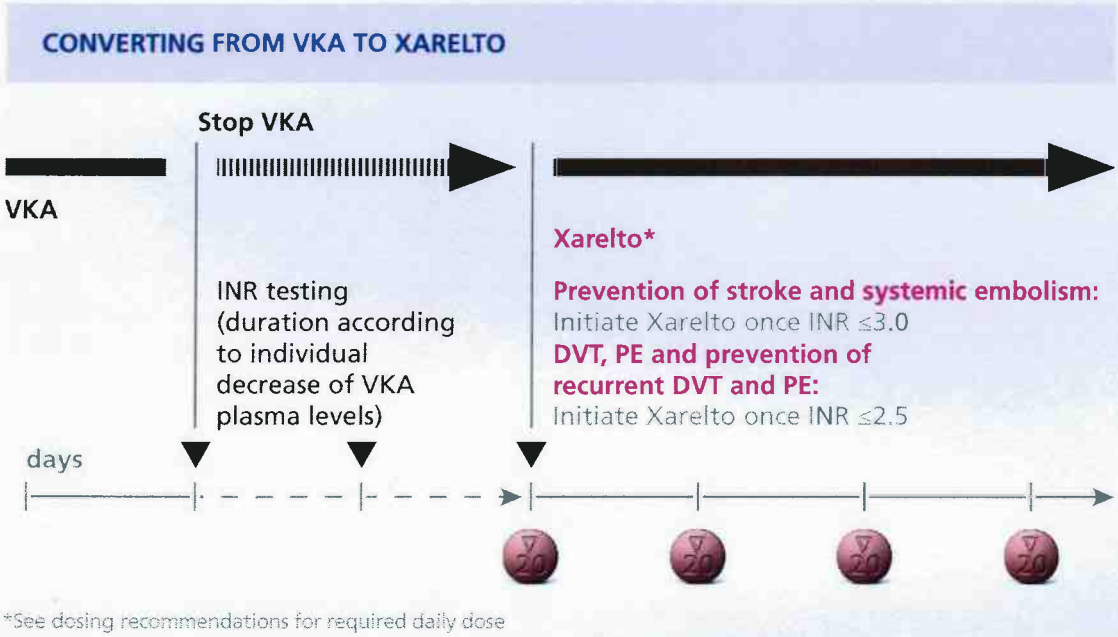
At least 18 hours should elapse after the last administration of rivaroxaban before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered. If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

- Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events
- Prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers

There is no clinical experience with the use of 'Xarelto' 2.5 mg with ASA alone or with ASA plus clopidogrel or ticlopidine in these situations. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban.

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2 of the SmPC). However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

Converting from VKA to Xarelto®

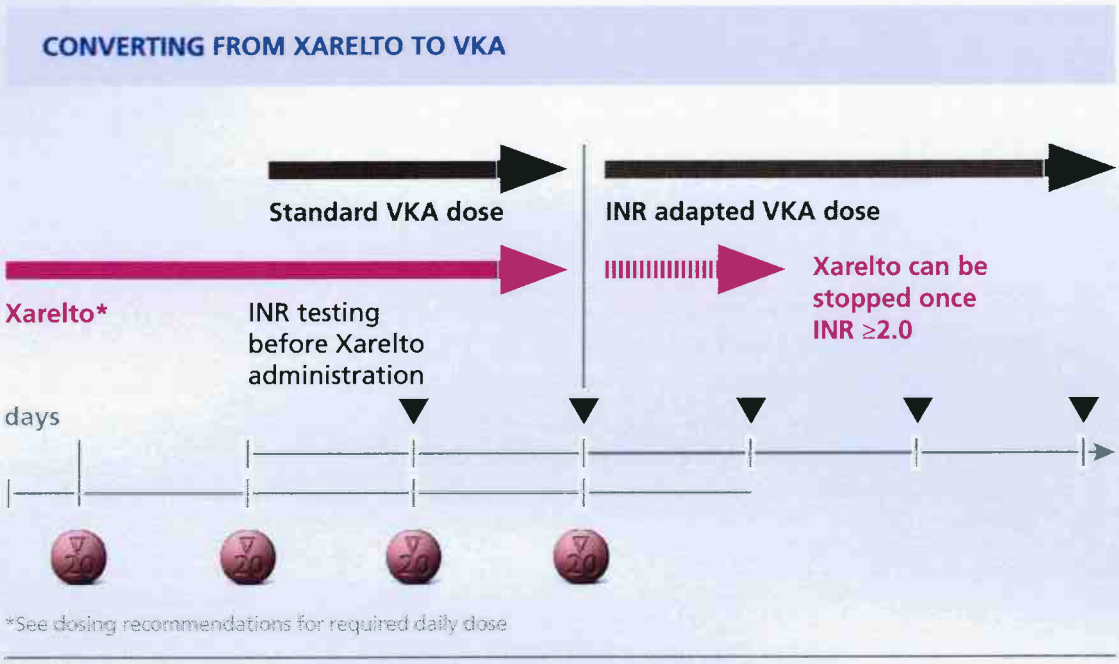


For patients treated for **prevention of stroke and systemic embolism**, treatment with VKA should be stopped and 'Xarelto' therapy should be initiated when the **INR ≤3.0**.

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 ≤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 VKA



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

When converting to VKA, Xarelto and VKA should be given overlapping until the INR **≥2.0.** For the first 2 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 anticoagulantactivity 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 a parenteral drug on a fixed dosing scheme such as low-molecular-weight heparin (LMWH): Discontinue parenteral drug and start 'Xarelto' 0 to 2 hours before the time of the next scheduled administration of the parenteral drug
- Patients with a continuously administered parenteral drug such as intravenous unfractionated heparin: Start 'Xarelto' at the time of discontinuation

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), LMWHs (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching anticoagulant therapy or 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.

The risk of bleeding increases with increasing age.

Several subgroups 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 carried out after assessment of treatment benefit against the risk for bleeding.

Patients with renal impairment

See dosing recommendations for patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment. 'Xarelto' is to be used with caution in patients with CrCl 15–29 ml/min and in patients with renal impairment* concomitantly receiving other medicinal products, which increase rivaroxaban plasma concentrations. Use of 'Xarelto' is not recommended in patients with CrCl <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 haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), ASA, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
- ACS patients and CAD/PAD patients: Patients on treatment with 'Xarelto' and ASA or with 'Xarelto' and ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
- The interaction with erythromycin, clarithromycin or fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients (for patients with renal impairment see further above)

*With moderate renal impairment (CrCl 30–49 ml/min) for 'Xarelto' 2.5 mg and 10 mg

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
- 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 breastfeeding. 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 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. Individualised 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 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. 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-specific calibrators to measure rivaroxaban levels are now commercially available. If clinically indicated haemostatic status can also be assessed by prothrombin time (PT) using Neoplastin as described in the SmPC.

The following coagulation tests are increased: PT, activated partial thromboplastin time (aPTT) and calculated PT 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.

Dosing Overview

INDICATION[1]	DOSING[1]	SPECIAL POPULATIONS[1]
Stroke prevention in adult patients with non-valvular atrial fibrillation[a]	'Xarelto' 20 mg once daily	In patients with impaired renal function with CrCl 15–49 ml/min[b] **'Xarelto' 15 mg once daily** PCI with stent placement For a maximum of 12 months **'Xarelto' 15 mg once daily** plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel) PCI with stent placement in patients with impaired renal function with creatinine clearance 30–49 ml/min[b] **'Xarelto' 10 mg once daily** plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel)
Treatment of **DVT** and **PE**[c], and prevention of recurrent DVT and PE in adult patients	Treatment and prevention of recurrence, day 1–21 **'Xarelto' 15 mg twice daily** Prevention of recurrence from day 22 onwards **'Xarelto' 20 mg once daily** Extended prevention of recurrence, from month 7 onwards **'Xarelto' 10 mg once daily** Extended prevention of recurrence, from month 7 onwards **'Xarelto' 20 mg once daily** in patients at high risk of recurrent DVT or PE, such as those: with complicated comorbidities who have developed recurrent DVT or PE on extended prevention with 'Xarelto' 10 mg	In patients with impaired renal function with CrCl 15–49ml/min[b] Treatment and prevention of recurrence, day 1–21 **'Xarelto' 15 mg twice daily** Thereafter **'Xarelto' 15mg once daily** instead of 'Xarelto' 20mg once daily if patient's assessed risk for bleeding outweighs risk for recurrence When the recommended dose is 'Xarelto' 10 mg once daily, no dose adjustment is necessary
Prevention of VTE in adults undergoing elective **hip or knee replacement surgery**	**'Xarelto' 10 mg once daily**	

INDICATION[1]	DOSING[1]	SPECIAL POPULATIONS[1]
Prevention of atherothrombotic events in adult patients with **CAD** or **symptomatic PAD** at high risk of ischaemic events	**'Xarelto' 2.5 mg twice daily in combination with acetylsalicylic acid** 75–100 mg/day	
Prevention of atherothrombotic events in adult patients after an **ACS** with elevated cardiac biomarkers	**'Xarelto' 2.5 mg twice daily in combination with standard antiplatelet therapy** (acetylsalicylic acid 75–100 mg/day alone or acetylsalicylic acid 75–100mg/day plus clopidogrel 75 mg/day or a standard dose of ticlopidine)	

'Xarelto' 15 mg and 20 mg must be taken with food[1]

For patients who are unable to swallow whole tablets, 'Xarelto' tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally.

[a]With one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

[b]Use with caution in patients with creatinine clearance 15–29 ml/min and in patients with renal impairment when concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration.

[c]Not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.

Reference: 1. Xarelto (rivaroxaban). Summary of Product Characteristics, as approved by the European Commission.

Abbreviated Summary of Product Characteristics

▼ 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: Alfred Gera and Sons Ltd. Tel 21446205, Date of Preparation:** 07/2019

▼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.
Suspected adverse reactions and medication errors should be reported.
Report forms can be downloaded from:
www.medicinesauthority.gov.mt/adrportal
and sent to:
E: postlicensing.medicinesauthority@gov.mt or
E: pv@alfredgera.com

Please note that details of the marketing authorisation for rivaroxaban as noted in this document, including the approved indications, may differ from those in your country. Therefore you should always be guided by your local Prescribing Information.

MA-XAR-MT0003 December 2019

Xarelto® rivaroxaban