Xarelto® (rivaroxaban) Prescriber Guide

October 2017
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

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.

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

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 15 mg twice daily for the first 3 weeks. This initial treatment is followed by 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 co-morbidities, 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 SCHEME**

<table>
<thead>
<tr>
<th>Day 1 to 21</th>
<th>Day 22 onwards</th>
<th>Following completion of at least 6 months</th>
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<tbody>
<tr>
<td>Xarelto 15 mg twice daily*</td>
<td>Xarelto 20 mg once daily*</td>
<td>Xarelto 10 mg once daily*</td>
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<td>Xarelto 20 mg once daily*</td>
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<td>Xarelto 20 mg once daily*</td>
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*Recommended dosing scheme for patients with DVT/PE and moderate or severe renal impairment see below
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 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 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

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

**DOSING SCHEME**

<table>
<thead>
<tr>
<th>Individual treatment duration</th>
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<tbody>
<tr>
<td>Xarelto 2.5 mg twice daily</td>
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<tr>
<td>Xarelto 2.5 mg: TAKE WITH OR WITHOUT FOOD</td>
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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 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® should be used with caution in ACS patients:

- If co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine
- With a low 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

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

There is no clinical experience with the use of 10/15/20 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 SPC). 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 after an ACS with elevated cardiac biomarkers

There is no clinical experience with the use of 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 SPC). 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 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 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 a continuously administered parenteral drug such as intravenous unfractionated heparin: Start Xarelto at the time of discontinuation
- 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

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

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)

◆ After an ACS, patients on treatment with Xarelto and ASA or Xarelto and ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk

Patients with other 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 (rivaroxaban) 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.
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.

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