Xarelto® (rivaroxaban) Prescriber Guide

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Patient Alert Card

A patient alert card is provided to each patient who is prescribed Xarelto® with the product package. The implications of anticoagulant treatment should be explained and the importance of compliance, signs of bleeding and when to seek medical attention discussed with the patient or the caregivers.

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.

For Xarelto® 1 mg/mL granules for oral suspension for use in children, please take note of the QR-code on the respective Patient Alert Card, which leads to an educational video showing how to prepare and administer the oral suspension.

To order additional copies of the Patient Alert Cards and/or Prescriber Guides, please contact Bayer Ltd at 01 216 3300.

Prescriber Guide

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

For further information and additional details on Xarelto®, please see the Summary of Product Characteristics (SmPC)#.

The Prescriber Guide does not substitute the Xarelto® (SmPC). Before prescribing please also read the Xarelto® SmPC.

Dosing Recommendations

Stroke prevention in adult patients with non-valvular atrial fibrillation

The recommended dose for 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 (TIA) is 20 mg once daily.

ADULT DOSING SCHEME

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 next page

#Xarelto® Summary of Product Characteristics (SmPC) available on www.medicines.ie and https://www.ema.europa.eu/en/medicines/human/EPAR/xarelto

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 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.

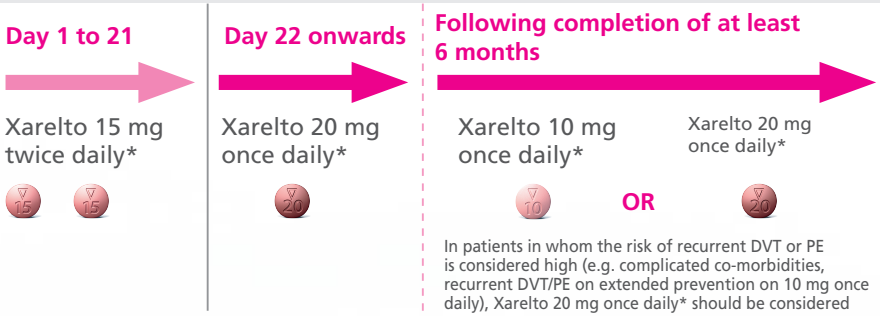
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients and treatment of VTE and prevention of recurrence in children and adolescents

Adults

Adult 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 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.

ADULT DOSING SCHEME



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

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

Children

In paediatric patients 6 months to <18 years of age, Xarelto® treatment using the most appropriate formulation should be initiated following ≥5 days of initial anticoagulation treatment with parenteral heparins. Dosing is based on body weight.

In paediatric patients from term neonates to <6 months of age, who at birth had ≥37 weeks of gestation, weigh ≥2.6 kg, and have had ≥10 days of oral feeding, Xarelto® treatment using the oral suspension formulation should be initiated following ≥5 days of initial anticoagulation treatment with parenteral heparins. Dosing is based on body weight.

For children and adolescents weighing ≥30 kg a Xarelto® tablet (15 mg for children 30-<50 kg, 20 mg for children ≥50 kg) or oral suspension once daily can be administered. The dose is determined based on body weight.

For children and adolescents with a body weight of 2.6 kg to <30.0 kg, only the oral suspension should be used. The dose and frequency of administration is determined based on body weight.

If the oral suspension is prescribed, the patient or caregiver should be advised to carefully read and follow the Instructions for Use (IFU) provided in the box of Xarelto® granules for oral suspension. The IFU shows how to prepare and take or give the Xarelto® oral suspension. There is also a QR-code on the Patient Alert Card provided with the oral suspension leading to an educational video showing how to prepare and administer the oral suspension.

It is recommended to advise the patient or caregiver which blue syringe (Liquid Dosing Device) to use to ensure that the correct volume is administered.

If the oral suspension is prescribed, the prescriber should remind the patient or caregiver of the individual weight-adjusted dose volume and frequency. Upon dispensation of the medication to the patient or caregiver, the dispensing health care provider (e.g. the pharmacist) should write the prescribed dose on the outer carton of the box.

Recommended dose for Xarelto® in paediatric patients from full-term neonates (following at least 10 days of oral feeding and weighing at least 2.6 kg) to children less than 18 years of age

Pharmaceutical form	Body weight [kg]		Regimen (1 mg rivaroxaban = 1 mL suspension)			Total daily dose (1 mg=1 mL)	Suitable Blue Syringe
	Min	Max	OD once a day	BID 2 times a day	TID 3 times a day		
Oral suspension	2.6	< 3			0.8 mg	2.4 mg	1 mL
	3	< 4			0.9 mg	2.7 mg	1 mL
	4	< 5			1.4 mg	4.2 mg	5 mL
	5	< 7			1.6 mg	4.8 mg	5 mL
	7	< 8			1.8 mg	5.4 mg	5 mL
	8	< 9			2.4 mg	7.2 mg	5 mL
	9	< 10			2.8 mg	8.4 mg	5 mL
	10	< 12			3.0 mg	9.0 mg	5 mL
	12	< 30		5 mg		10 mg	5 mL or 10 mL
Tablets or oral suspension	30	< 50	15 mg			15 mg	10 mL
	≥ 50		20 mg			20 mg	10 mL

The weight of a child should be monitored and the dose reviewed regularly, especially for children <12 kg. This is to ensure a therapeutic dose is maintained.

Use is not recommended in children <6 months of age who:
- At birth had <37 weeks of gestation, or
- Have a body weight of <2.6 kg, or
- Had <10 days of oral feeding

as dosing of Xarelto® cannot be reliably determined in these patient populations and was not studied.

Patients with renal impairment

Adults

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.

Children

No dose adjustment is required for children aged ≥1 year with mild renal impairment (glomerular filtration rate: 50 mL-80 mL/min/1.73 m^2), based on data in adults and limited data in paediatric patients.

Xarelto® is not recommended in children aged ≥1 year with moderate or severe renal impairment (glomerular filtration rate <50 mL/ min / 1.73 m^2), as no clinical data is available.

In children aged <1 year, estimation of serum creatinine instead of GFR is applied. Xarelto® is not recommended in children aged <1 year with serum creatinine results above the 97.5th percentile, as no clinical data is available (see SmPC of Granules for oral suspension section 4.2 for reference values).

Duration of therapy

Adults

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.

Children

All children, except those aged <2 years with catheter-related thrombosis

Therapy with Xarelto® should be continued for at least 3 months. Treatment can be extended up to 12 months when clinically necessary. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

Children aged <2 years with catheter-related thrombosis

Therapy with Xarelto® should be continued for at least 1 month. Treatment can be extended up to 3 months when clinically necessary. The benefit-risk of continued therapy after 1 month should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

Missed dose

Adults

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.

Children

Once daily regimen

A missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

Two times daily regimen

A missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken in the same evening.

Three times daily regimen

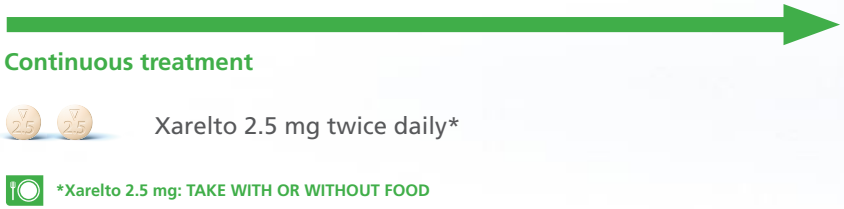
The three times daily administration schedule with approximately 8-hour intervals should be resumed at the next scheduled dose without compensating for the missed dose.

On the following day, the child should continue with the regular once, twice, or three times daily regimen.

*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

ADULT DOSING SCHEME



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

In patients after a successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD, treatment should not be started until haemostasis is achieved (see also section 5.1 of the SmPC).

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.

Co-administration with antiplatelet therapy

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.

Other warnings and precautions in CAD/PAD patients

In patients at high risk of ischaemic events with CAD/PAD, efficacy and safety of Xarelto® 2.5 mg twice daily have been investigated in combination with ASA.

In patients after recent revascularisation procedure of the lower limb due to symptomatic PAD, efficacy and safety of Xarelto® 2.5 mg twice daily have been investigated in combination with the antiplatelet agent ASA alone or ASA plus short-term clopidogrel. If required, dual antiplatelet therapy with clopidogrel should be short-term; long-term dual antiplatelet therapy should be avoided.

Patients after recent successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD were allowed to additionally receive standard dose of clopidogrel once daily for up to 6 months. (see also section 5.1 of the SmPC).

Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

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. Treatment with Xarelto® 2.5 mg should be avoided in patients with previous stroke or TIA receiving dual antiplatelet therapy.

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)

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

ADULT DOSING SCHEME

Continuous treatment

Xarelto 2.5 mg twice daily*

***Xarelto 2.5 mg: TAKE WITH OR WITHOUT FOOD**

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.

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.

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.

Co-administration with antiplatelet therapy

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.

Other warnings and precautions in ACS patients

In recent ACS patients, efficacy and safety of Xarelto® 2.5 mg twice daily have been investigated in combination with the antiplatelet agents ASA alone or ASA plus clopidogrel/ticlopidine.

Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

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 tablets can be taken with or without food.

Xarelto® 1 mg/mL granules for oral suspension, Xarelto® 15 mg and 20 mg tablets are to 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.

Adults

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.

Children

For children weighing ≥30 kg who are unable to swallow whole tablets, Xarelto® granules for oral suspension should be used. If the oral suspension is not immediately available, when doses of Xarelto® 15 mg or 20 mg are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administered orally.

The oral suspension and the crushed Xarelto® tablet may be given through nasogastric or gastric feeding tube. Gastric placement of the tube should be confirmed before administering Xarelto®. Avoid administration of Xarelto® distal to the stomach.

Perioperative Management

If an invasive procedure or surgical intervention is required, if possible and based on the clinical judgement of the physician:

- Xarelto® 10/15/20 mg tablets and Xarelto® 1mg/mL granules for oral suspension 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 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.

Indication-specific recommendations

- 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
- Treatment of VTE and prevention of VTE recurrence in children

There is no clinical experience with the use of 15 mg and 20 mg Xarelto® tablets in adults nor with the use of Xarelto® in children in these situations. To reduce the potential risk of bleeding associated with the concurrent use of Xarelto® 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 Xarelto® is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure.

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 adult patients and 26 hours in elderly patients should elapse after the last administration of Xarelto® (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next Xarelto® dose is administered. If traumatic puncture occurs, the administration of Xarelto® is to be delayed for 24 hours.

No data is available on the timing of placement or removal of a neuraxial catheter in children while on Xarelto®. Discontinue Xarelto® and consider a short acting parenteral anticoagulant.

◆ 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 Xarelto® and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Xarelto®.

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

At least 18 hours should elapse after the last administration of Xarelto® before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next Xarelto® dose is administered. If traumatic puncture occurs the administration of Xarelto® 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

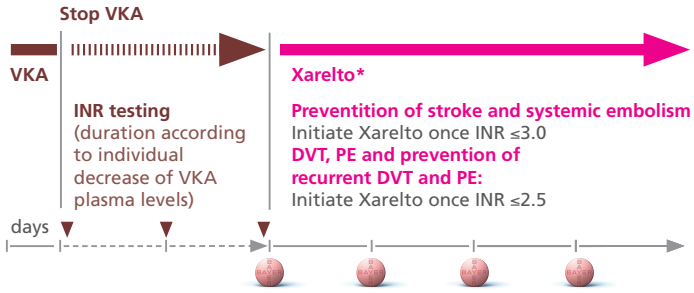
There is no clinical experience with the use of Xarelto® 2.5 mg and antiplatelet agents in these situations. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

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

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Xarelto® 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.

Converting from VKA to Xarelto®

CONVERTING FROM VKA TO XARELTO



*See dosing recommendations for required daily dose

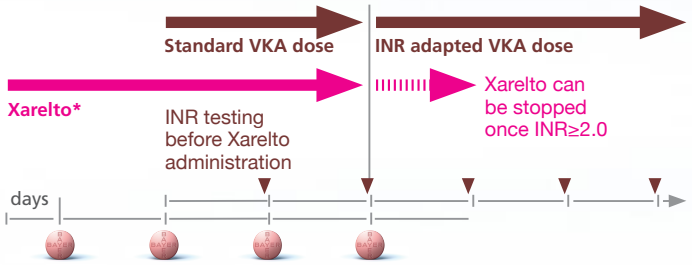
For patients treated for **prevention of stroke and systemic embolism,** treatment with VKA should be stopped and Xarelto® therapy should be initiated when the **INR ≤3.0.**

For adult patients treated for **DVT, PE and prevention of recurrent DVT** and **PE** and treatment of **VTE and prevention of recurrence** in paediatric patients, 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

CONVERTING FROM XARELTO TO VKA



*See dosing recommendations for required daily dose

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

Adults

When converting to VKA, Xarelto® and VKA should be given concurrently 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.

Children

Children who convert from Xarelto® to VKA need to continue Xarelto® for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Xarelto®. Co-administration of Xarelto® and VKA is advised to continue until the INR is ≥ 2.0. 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 clinically significant active 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.

Adults 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

Elderly population: The risk of bleeding increases with increasing age.

Several sub-groups of patients are at increased risk of bleeding 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

For adults 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, that increase rivaroxaban plasma concentrations. Use of Xarelto® is not recommended in patients with CrCl <15 mL/min.

In children aged ≥1 year no dose adjustment is required with mild renal impairment (glomerular filtration rate: 50-80 mL/min/1.73 m^2). Xarelto® is not recommended in children aged ≥1 year with moderate or severe renal impairment (glomerular filtration rate <50 mL/ min / 1.73 m^2).

Xarelto® is not recommended in children aged <1 year with serum creatinine results above 97.5th percentile, as no clinical data is available (see SmPC Granules for oral suspension section 4.2 for reference values).

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 treated with Xarelto® and antiplatelet agents 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)

Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The warnings above should be taken into account for the paediatric population.

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

* With moderate renal impairment (CrCl 30–49 mL/min) for Xarelto® 2.5 mg and 10 mg.

Patients with cancer

Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during Xarelto® therapy.

In patients with malignant neoplasms at high risk of bleeding, the use of Xarelto® is contraindicated.

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 in adults; however, no data is available at supratherapeutic doses in children. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found in children, suggesting absorption limitations for higher doses, even when taken together with food. A specific reversal agent antagonising the pharmacodynamic effect of rivaroxaban is available (refer to the Summary of Product Characteristics of andexanet alfa), however, it is not established in children. 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
- If bleeding cannot be controlled with the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa) or a specific procoagulant reversal agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa) should be considered. However, there is currently very limited clinical experience with the use of these medicinal products in adults and in children 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 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 in Adults

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 P2Y12 inhibitor (e.g. clopidogrel) PCI with stent placement in patients with impaired renal function with CrCl 30–49 mL/min[b] **Xarelto 10 mg once daily** plus a P2Y12 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**	
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.

Dosing Overview in Children and Adolescents

For dosing for the treatment of VTE and prevention of recurrence in paediatric patients, please refer to the body-weight-adjusted Xarelto dosing table on page 7.

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BID, twice daily; CAD, coronary artery disease; CrCl, creatinine clearance; DVT, deep vein thrombosis; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; INR, international normalised ratio; LMWH, low-molecular-weight heparin; NSAID, non-steroidal anti-inflammatory drug; NVAF, non-valvular atrial fibrillation; OD, once daily; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; SmPC, Summary of Product Characteristics; TID, three times daily; VKA, vitamin K antagonist; VTE, venous thromboembolism; UFH, unfractionated heparin.

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