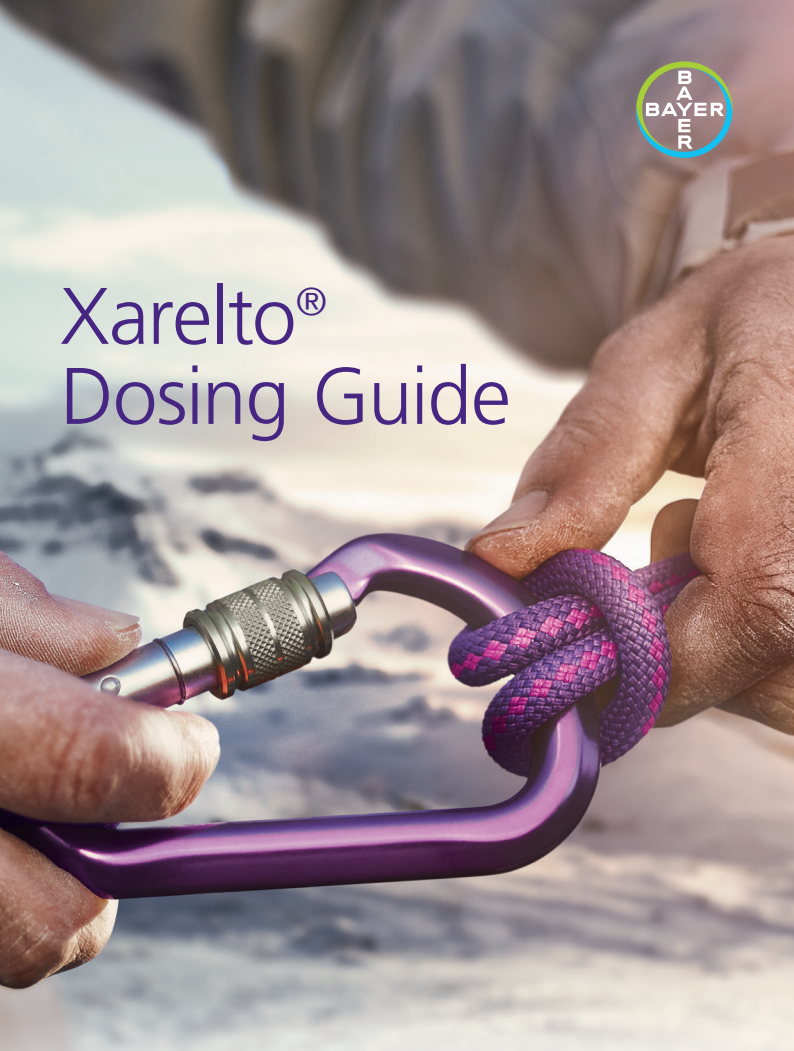


Xarelto® Dosing Guide

Tailored Protection for Your Cardio-Vascular Patients[1]

NEW APPROVED INDICATIONS

PP-XAR-ALL-0156-1

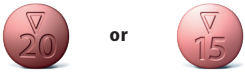
Xarelto® rivaroxaban

Xarelto®. Tailored Dosing Regimens for Your Cardio-Vascular Patients[1]

Stroke Prevention

Prevention of stroke and systemic embolism[1]

In adults with non-valvular atrial fibrillation (NVAF) with one or more risk factors[a]

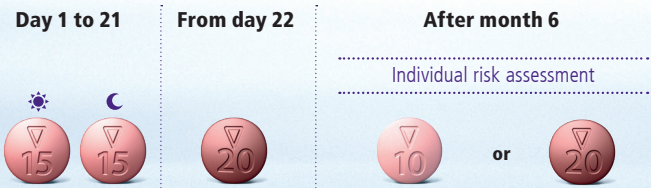


20 mg OD
CrCl ≥50 ml/min

15 mg OD
CrCl 15–49 ml/min[b]

Venous Protection

Treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT), and prevention of recurrent PE/DVT (in adults)[c,1]



15 mg BID[b]

20 mg OD[b,d]

10 mg OD[b]

20 mg OD[b,d,e]

Prevention of venous thromboembolism (VTE)[1]

In adults undergoing:

- Elective hip replacement surgery
- Elective knee replacement surgery

10 mg OD[b]

Xarelto 15 mg and 20 mg should be taken with food
Xarelto 10 mg can be taken with or without food

[a]Such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack. [b]Not recommended in patients with CrCl <15 ml/min; use with caution in patients with CrCl 15–29 ml/min and in patients with CrCl 30–49 ml/min 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. [d]In patients with CrCl 15–49 ml/min a reduction of the dose from 20 mg OD to 15 mg OD should be considered if the patient's assessed risk of bleeding outweighs the risk of recurrent PE/DVT. The recommendation for the use of 15 mg OD is based on pharmacokinetic modelling and has not been studied in this clinical setting. [e]If high risk of VTE recurrence (complicated comorbidities and/or recurrent PE/DVT on extended prevention) while on Xarelto 10 mg once daily.

Prescribed for More than 42 Million Patients Worldwide[a,2]

Vascular Protection

Prevention of atherothrombotic events[1]

In adults with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events

Aspirin
low dose OD[b]

Xarelto vascular dose
2.5 mg BID[c]

Secondary prevention after acute coronary syndrome (ACS)[1]

In combination with antiplatelet therapy[d] in adults with elevated cardiac biomarkers[e]

Antiplatelet therapy[d]

Xarelto vascular dose
2.5 mg BID[c]

NEW – INDICATED FOR **CAD** OR **SYMPTOMATIC PAD**

Xarelto® 2.5 mg can be taken with or without food

[a]Calculations based on IQVIA MIDAS Database: Quarterly Sales Q1 2018. [b]75–100 mg OD. [c]Not recommended in patients with CrCl <15 ml/min; use with caution in patients with CrCl 15–29 ml/min and in patients with CrCl 30–49 ml/min concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration. [d]ASA alone or ASA plus clopidogrel or ticlopidine. Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended. [e]Troponin-I/T; creatine kinase-muscle and brain isoenzyme (CK-MB).

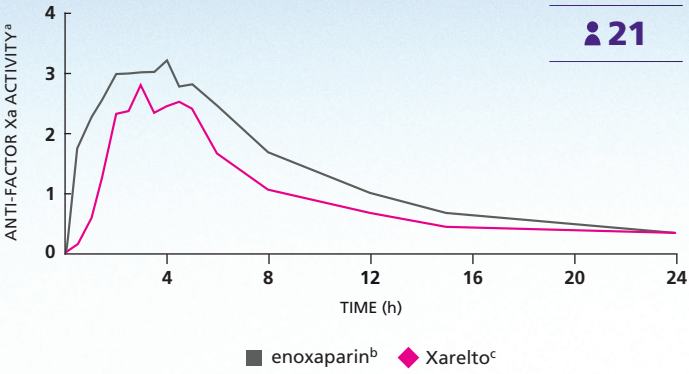
Mode of Action[1,3]

Xarelto® is a fast-acting, oral, direct factor Xa inhibitor that provides protection for your patients, with simple dosing[1]

Characteristics	
Administration	Oral
Bioavailability	80–100%[1] 15 mg and 20 mg to be taken with food[1] 2.5 mg and 10 mg independent of food intake[1]
Half-life	5–9 h in young adults[1] 11–13 h in elderly[1]
Time to peak plasma concentration	2–4 h[1]
Renal excretion as unchanged drug	~33%[1]

Fast onset of action[3]

- Xarelto works as fast as enoxaparin, with no injections required[3]



Graph adapted from Kubitza D., *et al.* 2013.[3]

[a]Change from baseline (ng/ml enoxaparin). [b]Enoxaparin 40 mg. [c]Xarelto 10 mg.

Non-Valvular Atrial Fibrillation[1]

Indication[1]

- Prevention of stroke and systemic embolism in adults with NVAF with one or more risk factors
- Risk factors include: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or TIA

Treatment[1]

Simple dosing, with a dose reduction only for patients with renal impairment

Adults with NVAF

Normal renal function CrCl ≥50 ml/min	 **20 mg OD**
Impaired renal function CrCl 15–49 ml/min	 **15 mg OD[a]**
CrCl <15 ml/min	**Not recommended**

Important notes[1]

- Xarelto® provides early protection and treatment should be continued long term, provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding
- Xarelto is not recommended for patients with prosthetic heart valves

Xarelto 15 mg and 20 mg should be taken with food

[a]Use with caution in patients with CrCl 15–29 ml/min and in patients with CrCl 30–49 ml/min concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration.

Special Populations

Cardioversion

Recommendations based on X-VeRT[1,4]

Reassuring safety in anticoagulated NVAF patients undergoing cardioversion, comparable to VKA

Adults with NVAF undergoing cardioversion[a]

	≥4 h before cardioversion	≥4 wk after cardioversion
TEE-guided cardioversion[b,1,4]	 **20 mg OD[c]**	 **20 mg OD[c]** Evaluate long-term anticoagulation[5]
	≥3 wk before cardioversion in adherent patients	**≥4 wk after cardioversion**
Non-TEE-guided cardioversion[d,1,4]	 **20 mg OD[c]**	 **20 mg OD[c]** Evaluate long-term anticoagulation[5]

Ablation

Recommendations based on VENTURE-AF[6]

Uninterrupted Xarelto® showed comparable efficacy and safety to uninterrupted VKA in anticoagulated NVAF patients undergoing ablation[6]

Adults with NVAF undergoing catheter ablation[e]

	1–7 days before ablation[f]	≥8 wk after ablation
TEE/ICE: no intracardiac thrombus	 **20 mg OD[c]**	 **20 mg OD[c]** Evaluate long-term anticoagulation[5]
	≥3 wk before ablation[f]	**≥8 wk after ablation**
No TEE/ICE	 **20 mg OD[c]**	 **20 mg OD[c]** Evaluate long-term anticoagulation[5]

Xarelto 20 mg should be taken with food

[a]For all patients, confirmation should be sought prior to cardioversion that the patient has taken Xarelto as prescribed. [b]TEE-guided (OAC-naïve/untreated or experienced patients) OR adherent patients pretreated with OAC for ≥3 weeks. [c]For dosing recommendations in patients with renal impairment please refer to pages 2 and 5. [d]Patients inadequately treated with OAC and no TEE planned. [e]Patients with CrCl >50 ml/min only (patients with CrCl ≤50 ml/min have not been studied). [f]Uninterrupted anticoagulation in combination with heparin during ablation.

Special Populations

PCI

Recommendations based on PIONEER AF-PCI[1,7]

Adults with NVAF undergoing PCI with stenting[a]

	Up to 12 months	After 12 months
Normal renal function CrCl ≥50 ml/min	 **15 mg OD** Plus a $P2Y_{12}$ inhibitor	 **20 mg OD[b]** Lifelong Xarelto monotherapy[5]
Impaired renal function[c] CrCl 30–49 ml/min	 **10 mg OD** Plus a $P2Y_{12}$ inhibitor	 **15 mg OD[b]** Lifelong Xarelto monotherapy[5]

Xarelto® 15 mg and 20 mg should be taken with food
Xarelto 10 mg can be taken with or without food

[a]Data on efficacy in PCI population are limited. No data are available for such patients with a history of stroke/TIA. [b]For dosing recommendations in patients with renal impairment please refer to pages 2 and 5. [c]Use with caution when patient is concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration. Patients with CrCl <30 ml/min have not been studied.

Pulmonary Embolism and Deep Vein Thrombosis[1,8,9]

Indication[1]

- Treatment of PE/DVT and prevention of recurrent PE and DVT in adults

Treatment[1,8,9]

Simplified dosing that demonstrated clot regression within 21 days and enduring protection[1,8,9]

Adults

	Day 1 to 21	From Day 22	After month 6
Normal renal function CrCl ≥50 ml/min	 **15 mg BID** From PE or DVT diagnosis	 **20 mg OD**	 **10 mg OD or** **If high risk of VTE recurrence:** · Complicated comorbidities · Recurrent PE/DVT on extended prevention[a]  **20 mg OD**
Impaired renal function CrCl 15–49 ml/min	**15 mg BID[b]**	**20 mg OD[b,c]**	**10 mg OD[b,d]** or 20 mg[b,c]
CrCl <15 ml/min	**Not recommended**		

Initial high-risk treatment period[1,10] → Continued treatment[1] → As long as the risk persists[1]

Important notes[1]

- 15 mg BID for 21 days treats the initial clot and protects against early recurrence[1,8,9]
- Xarelto® is not recommended as an alternative to UFH in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy
- The duration of therapy should be individualised after careful assessment of the treatment benefit against bleeding risk
- When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months of 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[a] a dose of Xarelto 20 mg once daily should be considered

Xarelto 15 mg and 20 mg should be taken with food
Xarelto 10 mg can be taken with or without food

[a]While on Xarelto 10 mg once daily. [b]Use with caution in patients with CrCl 15–29 ml/min and in patients with CrCl 30–49 ml/min concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations. [c]In patients with CrCl 15–49 ml/min 15 mg OD should be considered if the patient's assessed risk of bleeding outweighs the risk of recurrent PE/DVT. The recommendation for the use of 15 mg OD is based on pharmacokinetic modelling and has not been studied in this clinical setting. [d]When the recommended dose is 10 mg OD, no dose adjustment from the recommended dose is necessary.

Hip or Knee Replacement Surgery[1]

Indication[1]

- Prevention of VTE after elective hip or knee replacement surgery in adults

Treatment[1]

Simple dosing for patients with normal renal function or impaired renal function[1]

Adults

Normal renal function CrCl ≥50 ml/min	 **10 mg OD**
Impaired renal function CrCl 15–49 ml/min	**10 mg OD[a]**
CrCl <15 ml/min	**Not recommended**

Hip replacement surgery: 5 weeks[1]

Knee replacement surgery: 2 weeks[1]

Important notes[1]

- No preoperative anticoagulation necessary
- Initiate Xarelto® 6–10 h after surgery, provided that haemostasis has been established
- Do NOT start earlier than 6 h after surgery in order not to interfere with haemostasis

Xarelto 10 mg can be taken with or without food

[a]Use with caution in patients with CrCl 15–29 ml/min and in patients with CrCl 30–49 ml/min concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations.

Chronic Coronary or Symptomatic Peripheral Artery Disease[1]

Indication[1]

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

Treatment[1]

Dual pathway inhibition with Xarelto® vascular dose 2.5 mg BID plus aspirin

Adults		
Normal renal function CrCl ≥50 ml/min	 **Aspirin** low dose OD[a]	**Xarelto vascular dose** 2.5 mg BID
Impaired renal function CrCl 15–49 ml/min	**Aspirin** low dose OD[a] +	**Xarelto vascular dose** 2.5 mg BID[b]
CrCl <15 ml/min	**Not recommended**	

Important notes[1]

- Contraindicated in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month
- Use with caution in patients aged ≥75 years or with lower body weight (<60kg)
- Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus bleeding risk
- In patients with an acute thrombotic event or vascular procedure, and a need for dual antiplatelet therapy, the continuation of Xarelto 2.5 mg BID should be evaluated depending on the type of event or procedure and antiplatelet regimen

Xarelto 2.5 mg can be taken with or without food

[a]75–100 mg OD. In CAD/PAD patients, Xarelto vascular dose 2.5 mg BID has only been studied in combination with aspirin; dual antiplatelet therapy has not been studied in combination with Xarelto vascular dose 2.5 mg BID in these patients. [b]Use with caution in patients with CrCl 15–29 ml/min and in patients with CrCl 30–49 ml/min concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations.

Acute Coronary Syndrome[1]

Indication[1]

- Xarelto® 2.5 mg BID, co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers[a]

Treatment[1]

Ensure responsible use: Xarelto 2.5 mg BID for 12 months

Adults			
Normal renal function CrCl ≥50 ml/min	**Antiplatelet therapy[b]**	+	 **Xarelto vascular dose** 2.5 mg BID
Impaired renal function CrCl 15–49 ml/min	**Antiplatelet therapy[b]**	+	**Xarelto vascular dose** 2.5 mg BID[c]
CrCl <15 ml/min	**Not recommended**		

Important notes[1]

- Contraindicated in patients with history of stroke or TIA
- Use with caution in patients aged ≥75 years or with lower body weight (<60kg)
- Treatment should be regularly evaluated in the individual patient, weighing the risk for ischaemic events against the bleeding risk
- Initiate Xarelto 2.5 mg BID as soon as possible after stabilisation of the ACS event
  - Xarelto should be administered, at the earliest, 24 h after admission to hospital
  - Xarelto should be initiated when parenteral anticoagulation therapy would normally be discontinued
- Treatment beyond 12 months (up to 24 months) should be implemented on an individual patient basis[d]

Xarelto 2.5 mg can be taken with or without food

[a]Troponin-I/T; creatine kinase-muscle and brain isoenzyme (CK-MB). [b]ASA alone or ASA plus clopidogrel or ticlopidine. Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended. [c]Use with caution in patients with CrCl 15–29 ml/min and in patients with CrCl 30–49 ml/min concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations. [d]Experience up to 24 months is limited.

Practical Management[1]

INR testing was developed for measuring effects of VKA[1]

If the pharmacodynamic effects of VKA during a conversion period need to be determined, INR measurement can be used at the C_{trough} of Xarelto® (24 h after the previous intake of Xarelto) as this test is minimally affected by Xarelto at this time point.

Xarelto — **24 hours** — INR values are minimally affected 24 h after last intake of Xarelto

Perioperative management of patients on Xarelto[1]

Xarelto 10/15/20 mg
Stop Xarelto
≥24 h before surgery

Surgery

Restart Xarelto
Once haemostasis is achieved

Xarelto 2.5 mg
Stop Xarelto
≥12 h before surgery

Surgery

Restart Xarelto
Once haemostasis is achieved

- 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

Practical Management[1]

Neuraxial anaesthesia[1]

Catheters

- At least 2 × half-life, i.e. ≥18 h should elapse after the last administration of Xarelto® before removal of an epidural catheter
- Following removal of the catheter, at least 6 h should elapse before the next Xarelto dose is administered

If traumatic puncture occurs, the administration of Xarelto should be delayed for 24 h

There is no clinical experience with the use of Xarelto 2.5 mg with ASA alone or with ASA plus clopidogrel or ticlopidine or the use of 15 mg/20 mg Xarelto 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 rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Switching Patients

From VKA to Xarelto®[1]

Stop VKA

Start Xarelto

Prevention of stroke and systemic embolism:

Initiate Xarelto once INR ≤3.0

Treatment of PE/DVT and prevention of recurrent PE/DVT:

Initiate Xarelto once INR ≤2.5

VKA → **Xarelto**

See dosing recommendations for required daily dose

Switching patients with NVAF treated for prevention of stroke and systemic embolism[1]

- Treatment with VKAs should be stopped
- To assess the residual effect of VKAs, closely monitor the INR
- Xarelto therapy should be initiated once INR ≤3.0
- After intake of Xarelto, INR values will be falsely elevated and should not be used

Switching patients treated for PE or DVT or treated to prevent the recurrence of PE or DVT[1]

- Treatment with VKAs should be stopped
- To assess the residual effect of VKAs, closely monitor the INR
- Xarelto therapy should be initiated once INR ≤2.5
- After intake of Xarelto, INR values will be falsely elevated and should not be used

From Xarelto to VKA[1]

- It is important to ensure adequate anticoagulation while minimising the risk of bleeding during switching of therapy
- When switching to VKA, administration of Xarelto and VKA should overlap until INR ≥2.0. For the first 2 days of the switching 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 h after the previous dose, but prior to the next dose of Xarelto. Once Xarelto is discontinued, INR values obtained at least 24 h after the last dose reliably reflect the VKA dosing

Switching Patients

From parenteral anticoagulants to Xarelto®[1]

Switching all patients

- Start Xarelto 0–2 h before the time of the next scheduled administration of parenteral anticoagulant (e.g. LMWH). If a continuously administered intravenous anticoagulant (e.g. UFH) is used, start Xarelto when this treatment is discontinued

No treatment overlap[1]

Stop parenteral anticoagulant	Start Xarelto
Parenteral anticoagulant	Xarelto
Start Xarelto 0–2 h before the time of the next scheduled administration of parenteral anticoagulant[1]	No routine coagulation monitoring required[a]

Switching patients treated for PE or DVT or prevention of recurrent PE/DVT[1]

Dosing for patients on anticoagulation therapy for the first 3 weeks

- Start Xarelto following the general guidance for switching all patients
- Continue the twice-daily regimen of Xarelto until patients have received a total of 3 weeks of anticoagulant therapy, taking any previous parenteral anticoagulant therapy into account. Then switch to the once-daily regimen of Xarelto according to the label

No treatment overlap[1]

Stop parenteral anticoagulant	Start Xarelto
	 15 mg BID[b] 20 mg OD[b]
Parenteral anticoagulant	Xarelto
Start Xarelto 0–2 h before the time of the next scheduled administration of parenteral anticoagulant[1]	No routine coagulation monitoring required[a]

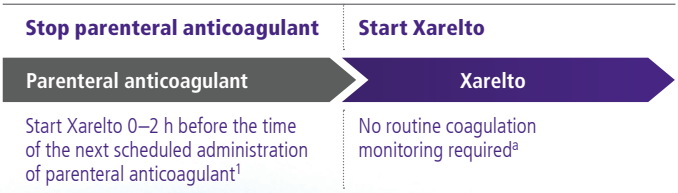
[a]INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto. [b]For dosing for renally impaired patients, see page 8.

Switching Patients

Switching patients treated for PE or DVT or prevention of recurrent PE/DVT[1]

Dosing for patients on anticoagulation therapy after 3 weeks[1]

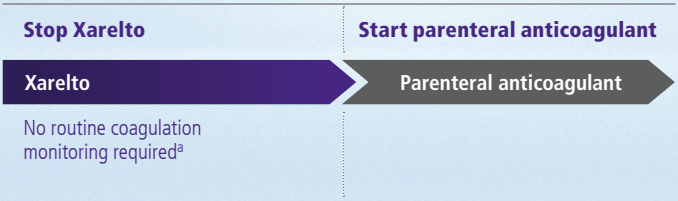
No treatment overlap[1]



From Xarelto® to parenteral anticoagulants[1]

- Give the first dose of parenteral anticoagulant (e.g. subcutaneous LMWH or intravenous UFH) when the next Xarelto dose would have been taken

No treatment overlap[1]



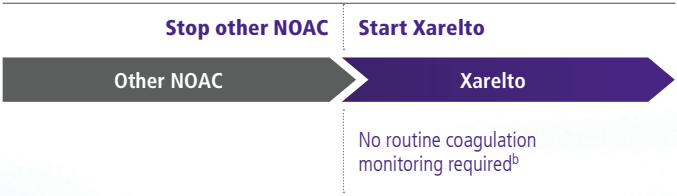
[a]INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto.

Switching Patients

From another NOAC to Xarelto®[11]

- Give the first dose of Xarelto when the next dose of the other NOAC would have been taken
- In situations where higher than therapeutic plasma concentrations of NOAC are expected (e.g. patients with renal impairment), a longer time interval between stopping the first NOAC and starting Xarelto may be considered[a]

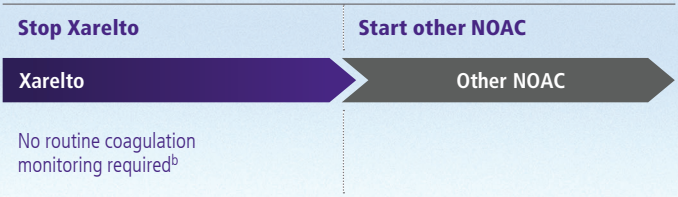
No treatment overlap[1]



From Xarelto to another NOAC[11]

- Give the first dose of the alternative NOAC when the next Xarelto dose would have been taken
- In situations where higher than therapeutic plasma concentrations of NOAC are expected (e.g. patients with renal impairment), a longer time interval between stopping Xarelto and starting the alternative NOAC may be considered[a]

No treatment overlap[1]



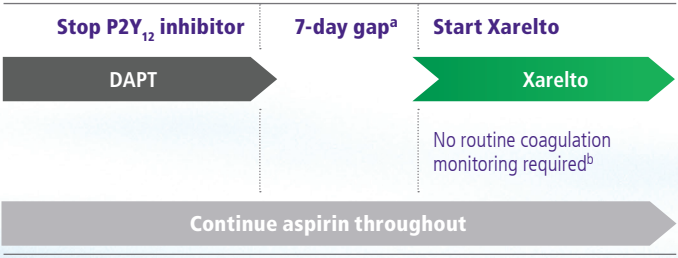
[a]Length of time interval to be determined by the physician, after appropriate medical assessment. [b]INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto.

Switching Patients

From DAPT to Xarelto® vascular dose plus aspirin

- Low-dose aspirin should be continued throughout the switch
- A short gap between DAPT and Xarelto vascular dose is essential to avoid the increased bleeding risk associated with triple therapy
- The length of the gap should be based on what the manufacturer advises when stopping $P2Y_{12}$ inhibitor before surgery. For the $P2Y_{12}$ inhibitors clopidogrel,[12] prasugrel[13] and ticagrelor[14] that is at least 7 days

No treatment overlap[1]



[a]Or equal to manufacturer's advice on stopping $P2Y_{12}$ inhibitor before surgery. [b]INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto.

Missed Dose[1]

Once-daily treatment of Xarelto® 10/15/20 mg[1]

- If a dose is missed, the patient should take Xarelto immediately
- 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

Twice-daily treatment phase of Xarelto 15 mg[1]

- 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 BID intake on the following day

Twice-daily treatment of Xarelto 2.5 mg[1]

- If a dose is missed, the patient should continue with the regular dose as recommended at the next scheduled time
- The dose should not be doubled to make up for a missed dose

Overdose[1]

- Owing 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
- A specific reversal agent antagonising the pharmacodynamic effect of Xarelto is not available
- The use of activated charcoal to reduce absorption in case of Xarelto overdose may be considered

Bleeding Management[1,5,11]

- Universal strategies are recommended by international guidelines (e.g. ESC or EHRA) and the Xarelto® SmPC to stop or reduce bleeding in patients treated with Xarelto[1,5,11]

These strategies are dependent on the severity of bleeding[1]

1. Delay next dose or discontinue Xarelto[a] and reconsider concomitant medication as appropriate

2. Symptomatic and local measures and general volume management

- Mechanical compression (e.g. for severe epistaxis)
- Surgical intervention/haemostasis
- General volume management (fluid replacement, haemodynamic support)
- Blood products (packed red cells or fresh frozen plasma, as appropriate) or platelets

In rare cases of life-threatening bleeding that cannot be controlled with the above measures or for urgent surgical interventions

3. Special haemostatic management:

- Consider a specific procoagulant reversal agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant Factor VIIa (r-FVIIa)
- However, there is currently very limited clinical experience with the use of these products in individuals receiving Xarelto

Owing to the high plasma protein binding, Xarelto is not expected to be dialysable.

For more details please refer to the Xarelto SmPC as well as international guidelines (e.g. ESC or EHRA)[1,5,11]

[a]Xarelto half-life: 5–13 h. Temporary or permanent discontinuation should always balance the risk of bleeding against the increased risk of ischaemia occasioned by the discontinuation.

Caring for Patients at Increased Risk of Bleeding[1]

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

The following subgroups of patients are at increased risk and **should be carefully monitored for signs and symptoms of bleeding complications.** Treatment decisions in these patients should be taken after assessment of treatment benefit against the risk of bleeding.

- Elderly
- Decreased renal function: **Refer to pages 5 and 8–12 for patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment.** Use with caution in patients with CrCl 15–29 ml/min and in patients with CrCl 30–49 ml/min when concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations. Use of Xarelto is not recommended in patients with CrCl <15 ml/min
- Concomitantly receiving certain other drugs affecting haemostasis or increasing rivaroxaban plasma concentrations
  - Use with caution in patients concomitantly receiving drugs affecting haemostasis, such as NSAIDs, ASA, platelet aggregation inhibitors and SSRIs and SNRIs
  - Concomitant use of other anticoagulants is contraindicated with the exception of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
  - Use of Xarelto is not recommended in patients receiving strong concomitant inhibitors of CYP3A4 and P-gp such as systemic azole antimycotics (e.g ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir) as these substances may increase rivaroxaban plasma concentration
  - 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

Other haemorrhagic risk factors[1]

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
- 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

Use with caution in ACS and CAD/PAD patients:

- Aged ≥75 years, and the benefit-risk should be individually assessed on a regular basis
- With lower body weight (<60 kg)

Patients in whom Xarelto® is Not Recommended for use[1]

- Under 18 years of age
- CrCl <15 ml/min
- Those with implanted prosthetic heart valves
- As an alternative to UFH in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy
- Concomitantly receiving treatment with strong CYP3A4 inducers – unless they are closely observed for signs and symptoms of thrombosis
- Concomitantly receiving systemic treatment with strong inhibitors of both CYP3A4 and P-gp such as azole antimycotics (ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)
- Given the limited clinical data available with dronedarone, co-administration with Xarelto should be avoided
- ACS patients treated with Xarelto vascular dose 2.5 mg BID in combination with antiplatelet agents other than ASA or ASA plus clopidogrel/ticlopidine (e.g. prasugrel or ticagrelor).

Contraindications[1]

Xarelto is contraindicated in the following cases[1]

- Hypersensitivity to the active substance or to any of the excipients
- Active clinically significant bleeding
- Lesion or condition, if considered to be a significant risk of 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
- Concomitant treatment with any other anticoagulants e.g. UFH; LMWHs (enoxaparin, dalteparin, etc.); heparin derivatives (fondaparinux, etc.); oral anticoagulants (warfarin, dabigatran, 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
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including Child-Pugh class B and C cirrhotic patients
- Pregnancy and breastfeeding. Women of child-bearing potential should avoid becoming pregnant during treatment with Xarelto. The safety and efficacy of Xarelto have not been established in breastfeeding women. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy

Xarelto vascular dose 2.5 mg BID is also contraindicated in case of[1]

- ACS patients with prior stroke and/or TIA
- CAD/PAD patients with previous haemorrhagic or lacunar stroke, or any stroke within a month

References

1. Xarelto® (rivaroxaban). Summary of Product Characteristics, as approved by the European Commission.
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6. Cappato R., *et al. Eur Heart J.* 2015;36(28):1805–11.
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8. Prins M.H., *et al. Thromb J.* 2013;11(1):21.
9. Van Es J., *et al. J Thromb Haemost.* 2013;11(4):679–85.
10. Limone B.L., *et al. Thromb Res.* 2013;132(4):420–6.
11. Steffel J. *et al. Eur Heart J.* 2018;39(16):1330–93.
12. Clopidogrel. Summary of Product Characteristics, as approved by the European Commission.
13. Prasugrel. Summary of Product Characteristics, as approved by the European Commission.
14. Ticagrelor. Summary of Product Characteristics, as approved by the European Commission.

NVAF, non-valvular atrial fibrillation; OD, once daily; CrCl, creatinine clearance; PE, pulmonary embolism; DVT, deep vein thrombosis; BID, twice daily; VTE, venous thromboembolism; CAD, coronary artery disease; PAD, peripheral artery disease; ACS, acute coronary syndrome; ASA, acetylsalicylic acid; TIA, transient ischaemic attack; VKA, vitamin K antagonist; TEE, transoesophageal echocardiography; AF, atrial fibrillation; ICE, intracardiac echocardiogram; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; UFH, unfractionated heparin; INR, international normalised ratio; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; DAPT, dual antiplatelet therapy; NSAID, non-steroidal anti-inflammatory drug; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors.

Xarelto 2.5 mg film-coated tablets
(Refer to full SmPC before prescribing.)

▼ **This medicinal product is subject to additional monitoring.**

Composition: *Active ingredient:* 2.5 mg rivaroxaban. *Excipients*: Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate, macrogol 3350, titanium dioxide (E171), iron oxide yellow (E172). **Indication:** 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. **Contraindications:** Hypersensitivity to the active substance or any of the excipients; active clinically significant bleeding; lesion or condition 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; 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; 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; *not recommended due to lack of data*: treatment in combination with antiplatelet agents other than ASA and clopidogrel/ticlopidine; in patients below 18 years of age; in patients concomitantly treated with dronedarone; in patients with prosthetic heart valves. *Use with caution*: in conditions with increased risk of haemorrhage; in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) or with moderate renal impairment (creatinine clearance 30 – 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicinal products affecting haemostasis; in patients ≥ 75 years of age or with lower body weight; when neuraxial anaesthesia or spinal/epidural puncture is employed. 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. 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. Xarelto contains lactose. **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, renal impairment, fever, peripheral oedema, decreased general strength and energy, post-procedural haemorrhage, contusion, wound secretion. *Uncommon*: thrombocytosis, thrombocytopenia, allergic reaction, dermatitis allergic, angioedema and allergic oedema, cerebral and intracranial haemorrhage, syncope, tachycardia, dry mouth, hepatic impairment, increases in bilirubin, blood alkaline phosphatase and GGT, urticaria, haemarthrosis, feeling unwell, increases in LDH, lipase, amylase. *Rare*: jaundice, bilirubin conjugated increased, cholestasis, hepatitis (incl hepatocellular injury), muscle haemorrhage, localised oedema, vascular pseudoaneurysm (*uncommon* in prevention therapy in ACS following percutaneous intervention). *Very rare*: anaphylactic reactions incl. shock, Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome. *Frequency not known*: compartment syndrome or (acute) renal failure secondary to a bleeding.

Classification for supply: Medicinal product subject to medical prescription.
Marketing Authorisation Holder: Bayer AG, 51368 Leverkusen, Germany
Further information available from: *xarelto.medinfo@bayer.com*
Version: EU/8

Xarelto® 10 mg / 15 mg / 20 mg film-coated tablets
(Refer to full SmPC before prescribing.)

▼ This medicinal product is subject to additional monitoring.

Composition: *Active ingredient:* 10 mg / 15 mg / 20 mg rivaroxaban. ***Excipients:*** Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate, macrogol 3350, titanium dioxide (E171), iron oxide red (E172). **Indications:** *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 pulmonary embolism 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. **Contraindications:** 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; *not recommended due to lack of data:* in patients below 18 years of age, in patients concomitantly treated with dronedarone; in patients with prosthetic heart valves, 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) or with moderate renal impairment (creatinine clearance 30 - 49 ml/min) 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. Xarelto contains lactose. **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 and allergic oedema, cerebral and intracranial haemorrhage, syncope, tachycardia, dry mouth, hepatic impairment, increases in bilirubin, blood alkaline phosphatase and GGT, urticaria, haemarthrosis, feeling unwell, increases in LDH, lipase, amylase. *Rare:* jaundice, bilirubin conjugated increased, cholestasis, hepatitis (incl hepatocellular injury), muscle haemorrhage, localised oedema, vascular pseudoaneurysm. *Very rare:* anaphylactic reactions incl. shock, Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome. *Frequency not known:* compartment syndrome or (acute) renal failure secondary to a bleeding.

Classification for supply: Medicinal product subject to medical prescription.
Marketing Authorisation Holder: Bayer AG, 51368 Leverkusen, Germany
Further information available from: xarelto.medinfo@bayer.com
Version: EU/9

Xarelto®: Tailored Protection for Your Cardio-Vascular Patients[1]

Stroke Prevention

Prevention of stroke and systemic embolism[1]

In adults with non-valvular atrial fibrillation (NVAF) with one or more risk factors[a]

20 mg OD
CrCl ≥50 ml/min

or

15 mg OD
CrCl 15–49 ml/min[b]

Venous Protection

Treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT), and prevention of recurrent PE/DVT (in adults)[c,1]

Day 1 to 21	From day 22	After month 6
		Individual risk assessment
		 **or** 
15 mg BID[b]	**20 mg OD[b,d]**	**10 mg OD[b]** **or** **20 mg OD[b,d,e]**

Vascular Protection

Prevention of atherothrombotic events[1]

In adults with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events

Aspirin
low dose OD[f]

Xarelto vascular dose
2.5 mg BID[b]

NEW – INDICATED FOR **CAD** OR **SYMPTOMATIC PAD**

Xarelto 15 mg and 20 mg should be taken with food
Xarelto 2.5 mg and 10 mg can be taken with or without food

[a]Such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack. [b]Not recommended in patients with CrCl <15 ml/min; use with caution in patients with CrCl 15–29 ml/min and in patients with CrCl 30–49 ml/min concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations. [c]Not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. [d]In patients with CrCl 15–49 ml/min 15 mg OD should be considered if the patient's assessed risk of bleeding outweighs the risk of recurrent PE/DVT. The recommendation for the use of 15 mg OD is based on pharmacokinetic modelling and has not been studied in this clinical setting. [e]If high risk of VTE recurrence (complicated comorbidities and/or recurrent PE/DVT on extended prevention) while on Xarelto 10 mg once daily. [f]75–100 mg OD.