XARELTO®
PRESCRIBER GUIDE

This booklet provides important information to assist prescribers in the use of Xarelto (rivaroxaban) with their patients.

This guide is intended for Health Care Professionals only.

Xarelto® rivaroxaban

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SPAF=stroke prevention in atrial fibrillation; DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism.

Introducing Xarelto

Indications

Xarelto (rivaroxaban) is fully funded for all indications from August 1st 2018 - no authority required.[1]

Prevention of stroke in NVAF

Prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA[2]

PE treatment

Treatment of PE and for the prevention of recurrent DVT and PE[2]

VTE prevention in THR

Prevention of VTE in adult patients undergoing elective hip replacement surgery[2]

VTE prevention in TKR

Prevention of VTE in adult patients undergoing elective knee replacement surgery[2]

DVT treatment

Treatment of DVT and for the prevention of recurrent DVT and PE[2]

AF = atrial fibrillation; VTE = venous thromboembolism; PE = pulmonary embolism; DVT = deep vein thrombosis; TIA = transient ischaemic attack; THR = total hip replacement; TKR = total knee replacement.

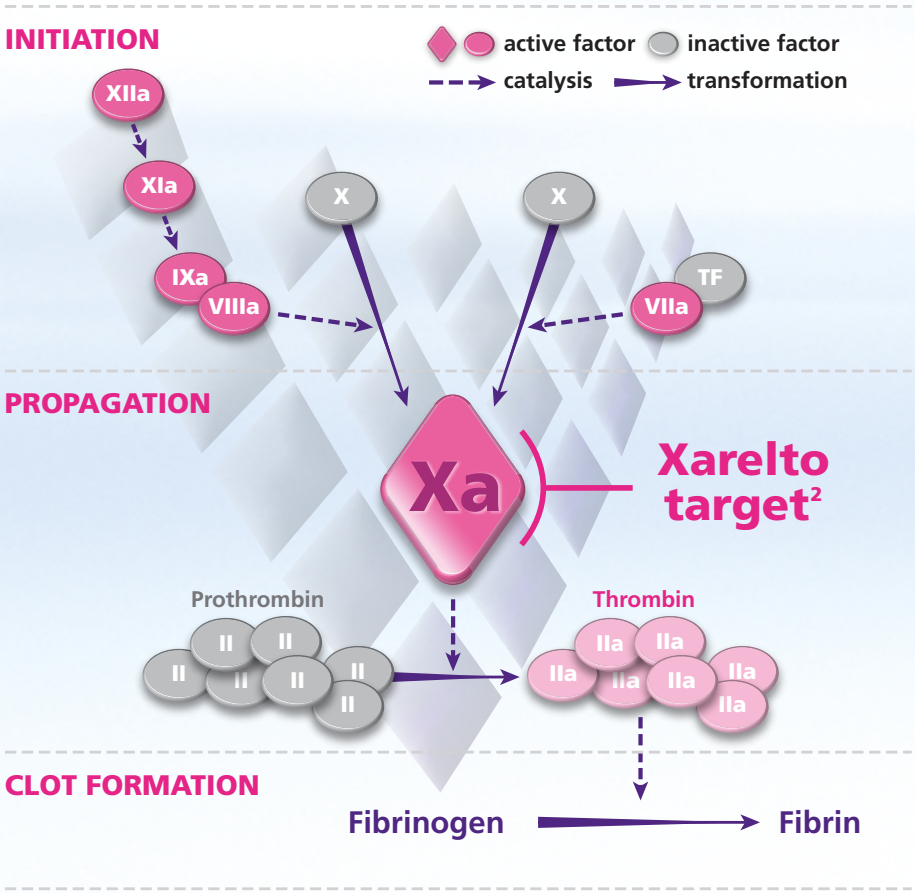
Introducing Xarelto

Mode of action

Xarelto acts as an anticoagulant with a different mechanism to warfarin and dabigatran, by selective inhibition of Factor Xa.[2-4]

- Factor Xa lies within the coagulation pathway and is responsible for thrombin generation[2]
- Factor Xa acts as an amplifier, generating more than 1000 molecules of thrombin for each molecule of Factor Xa[2]
- In theory, Factor Xa may be a better target than thrombin, because it has fewer functions outside coagulation. However, inhibition of Factor Xa has not been shown to have any clinical benefits over thrombin inhibition[3,4]

Figure 1. Xarelto targets Factor Xa in the coagulation cascade[2]



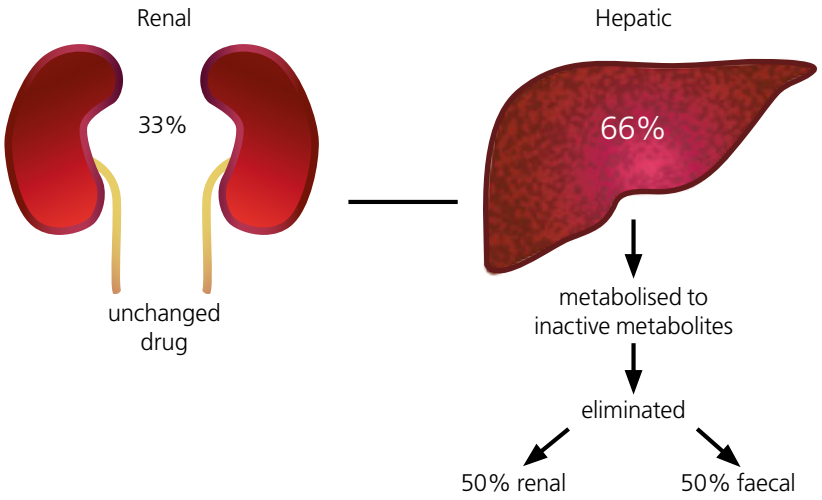
Introducing Xarelto

Absorption and bioavailability

Xarelto has a rapid onset of action (2-4 hours) and offset (12-24 hours). It has an elimination half-life of 5-9 hours in young individuals and 11-13 hours in elderly patients.[2]

In total, 33% of the administered dose undergoes direct renal excretion as unchanged active substance. Approximately 66% undergoes metabolic degradation; half of this is eliminated renally and the other half eliminated by the faecal route as inactive metabolites.[2]

Pharmacokinetic parameters of Xarelto[2]

Bioavailability	80-100%*†
Time to peak plasma concentration	2-4 hours
Plasma protein binding	92-95%
Metabolism	CYP3A4, CYP2J2 CYP-independent mechanisms
Elimination	
Elimination half-life	5-9 hours in young individuals 11-13 hours in elderly (> 65 years)

*For the 10 mg dose irrespective of fasting or fed conditions.

†Oral bioavailability of 20 mg dose is reduced to 66% under fasting conditions, thus Xarelto 15 mg and 20 mg tablets should be taken with food.

Introducing Xarelto

Evidence for Xarelto once daily dosing

- **7 Phase III clinical trials with 28,321 patients[2,5-10]**
  - Strong clinical evidence that once-daily Xarelto has an equivalent safety profile versus warfarin, and effectively prevents:[2,5-10]
    - Stroke in patients with non-valvular atrial fibrillation and at least one additional risk factor[5]
    - Recurrence of VTE following acute DVT/PE treatment[6,7]
    - VTE in patients following major orthopaedic surgery[8-10]
- **Similar pharmacokinetics of Xarelto once and twice daily[11]**
  - Once-daily doses of Xarelto were shown to sufficiently inhibit Factor Xa and thrombin generation compared with Xarelto twice daily[12]
  - Notably, single doses of Xarelto prolong clotting parameters up to 24 hours, irrespective of the short half-life (5-13 hours)[12]

Please refer to pages 9-13 for indication-specific dosing guides.

Xarelto indications

Stroke prevention in atrial fibrillation (SPAF)

Xarelto is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF) and at least one additional risk factor for stroke.[2]

Non-valvular AF refers to AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis (usually of rheumatic origin). Both of these patient types were excluded from all novel oral anticoagulant (NOAC) trials.[13]

Stroke and bleeding risk assessment

CHA_2DS_2-VASc should be used to assess stroke risk in patients with AF.[14,15]

Risk factors	Points assigned $CHADS_2$	CHA_2DS_2-VASc
Congestive heart failure	+1	+1
Hypertension	+1	+1
Age (years)		
65-74		+1
≥ 75		+2
> 75	+1	
Diabetes mellitus	+1	+1
Stroke/TIA	+2	+2
Vascular disease		+1
Females		+1
	Cumulative score: 0-6	**Cumulative score: 0-9**

"The CHA_2DS_2-VASc score is better at identifying 'truly low-risk' patients with AF and is as good as—and possibly better than—scores such as $CHADS_2$ in identifying patients who develop stroke and thromboembolism."[16]

The HAS-BLED score should be used to assess the risk of bleeding in people who are starting or have started anticoagulation.[14,15]

Clinical characteristic	Points
Hypertension (SBP >160 mmHg)*	1
Abnormal renal function	1
Abnormal liver function	1
Stroke	1
Cumulative score	**Range 0-9**

Clinical characteristic	Points
Bleeding	1
Labile INRs*	1
Elderly (age>65 years)	1
Drugs	1
Alcohol*	1
Cumulative score	**Range 0-9**

*Modifiable risk factor. SBP = systolic blood pressure

Xarelto indications

Dosing for SPAF

The recommended dose for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation is **Xarelto 20 mg once daily with food.**[2] For patients with moderate renal impairment (CrCl 30-49mL/min), the recommended dose is **Xarelto 15 mg once daily with food.**[2]

Dosing scheme for Xarelto in patients with non-valvular atrial fibrillation[2]

Renal Function	Dose	Tablet
Normal or mildly impaired: (creatinine clearance ≥ 50 mL/min)	20 mg once daily with food	
Moderate: (creatinine clearance 30–49 mL/min)	15 mg once daily with food	
Severe: (creatinine clearance < 30 mL/min)	Contraindicated	–
For non-valvular AF patients not yet receiving an anticoagulant		
Initiate Xarelto on day 1	Xarelto 20 mg or 15 mg once daily with food‡^	

AF=atrial fibrillation. *Tablets not actual size, representative only.*

‡Dosage depending on renal function.

^Once Xarelto has been commenced, INR measurement is not appropriate to measure the anticoagulation activity of Xarelto, and therefore should not be used for this purpose. Treatment with Xarelto does not require routine coagulation monitoring.

Xarelto indications

Patients with severe renal impairment

Use is contraindicated in patients with a creatinine clearance of <30 mL/min for Xarelto 15 mg and 20 mg tablets.[2] Prior to commencing treatment with Xarelto, an accurate assessment of renal function should be undertaken, especially if there is any suspicion that the person may have a degree of renal impairment.[2] If there is a suspicion of renal impairment, the degree of renal impairment must be determined accurately.[2]

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.[2] No more than one tablet per day should be taken.[2]

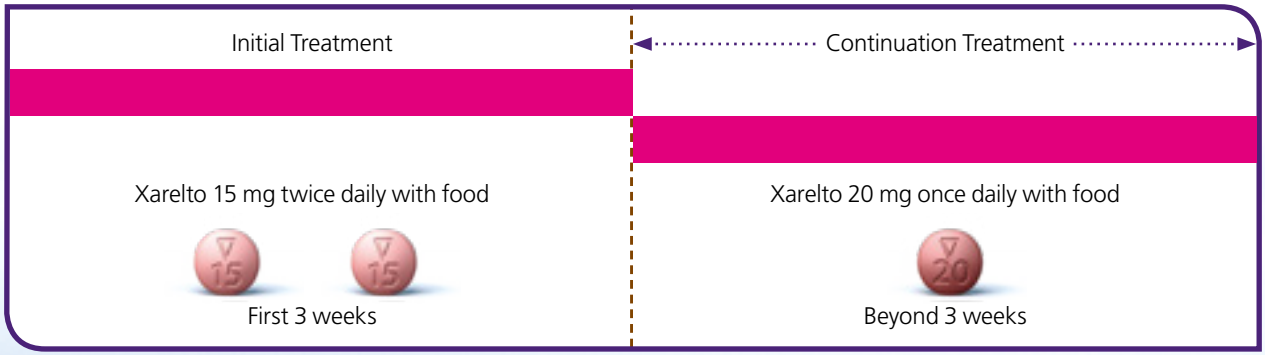
For further information, please refer to the 'Clinical use of Xarelto' section on pages 14-17 of this guide.

Xarelto indications

Xarelto is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and PE.[2]

Dosing for treatment of DVT/PE and prevention of recurrent DVT and PE

Initiating Xarelto for DVT and PE treatment in newly diagnosed patients[2]



Tablets not actual size, representative only.

Patients with severe renal impairment

Use is contraindicated in patients with a creatinine clearance <30 mL/min.[2] It is recommended that renal function is assessed as part of patient follow up.[2]

Duration of therapy

Therapy should be continued as long as the risk of recurrent DVT and PE persists.[2] The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.[2]

Missed dose

- **Twice-daily treatment period (15 mg twice daily for newly diagnosed patients):** If a dose is missed, the patient should take the next dose immediately to ensure intake of 30 mg Xarelto per day.[2] Continue with the regular 15 mg twice-daily intake on the following day. No more than two tablets per day should be taken.[2]
- **Once-daily treatment period (continuation):** If a dose is missed, the patient should take Xarelto immediately and continue on the following day with the once-daily intake as recommended.[2] No more than one tablet per day should be taken.[2]

For further information, please refer to the 'Clinical use of Xarelto' section on pages 14-17 of this guide.

Xarelto indications

Xarelto is indicated for prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks).[2]

Dosing for VTE prevention in total hip and knee replacement

The recommended dose of Xarelto in VTE prevention in major orthopaedic surgery of the lower limbs (elective total hip or knee replacement) is a 10 mg tablet taken once daily.[2] The initial dose should be taken 6–10 hours after surgery provided that haemostasis has been established.[2] Xarelto 10 mg may be taken with or without food.[2]

Dosing scheme for Xarelto for VTE prevention in major orthopaedic surgery of the lower limbs[2]

Renal Function	Dose	Tablet
Normal or mildly impaired: (creatinine clearance > 50 mL/min)	10 mg once daily*	
Moderate: (creatinine clearance 30–49 mL/min)	10 mg once daily*	
Severe: (creatinine clearance 15–29 mL/min)	10 mg once daily* (use with caution)	

*Xarelto 10 mg tablet may be taken with or without food.

Tablets not actual size, representative only.

Patients with severe renal impairment

Use with caution is recommended in patients with a creatinine clearance 15–29 mL/min.[2] Use is contraindicated in patients with creatinine clearance <15 mL/min.[2] It is recommended that renal function is assessed as part of patient follow-up.[2]

Xarelto indications

Duration of therapy

The duration of therapy depends on the type of major orthopaedic surgery.[2]

- For patients undergoing hip replacement surgery, a treatment duration of 5 weeks is recommended.[2]
- For patients undergoing knee replacement surgery, a treatment duration of 2 weeks is recommended.[2]

Dose of 10 mg once daily and duration specified for each type of surgery is not to be exceeded.[2]

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. No more than one tablet per day should be taken.[2]

For further information, please refer to the 'Clinical use of Xarelto' section on pages 14-17 of this guide.

Clinical use of Xarelto

Patient selection

Xarelto is contraindicated in the following patients:[2]

- Undergoing dialysis or patients with severe renal impairment with a creatinine clearance <30 mL/min for Xarelto 15 mg and 20 mg tablets and CrCl <15 mL/min for Xarelto 10 mg tablets[2]
- With clinically significant active bleeding[2]
- With lesions at increased risk of clinically significant bleeding[2]
- With spontaneous impairment of haemostasis[2]
- With significant hepatic disease (including moderate to severe hepatic impairment), which is associated with coagulopathy[2]
- Who are on concomitant systemic treatment with azole anti-mycotics or HIV protease inhibitors[2]
- With increased bleeding risk[2]
- Who are hypersensitive to the active substance or to any of the excipients[2]
- Who are pregnant or breastfeeding[2]

Assessment of renal function

According to the 2018 European Heart Rhythm Association (EHRA) Guidelines on the use of non-vitamin K antagonist oral anticoagulants in atrial fibrillation, renal function should be assessed at least annually in order to identify any changes in renal function. More frequent assessment may be considered for patients with additional risk factors such as elderly or frail patients or those with multiple co-morbidities.[13]

In the clinical trials for Xarelto, renal function was determined by calculating creatinine clearance (CrCl) using the Cockcroft-Gault Formula (Figure 2).[2] CrCl calculators are now available through a number of applications and prescriber software.

Clinical use of Xarelto

Figure 2. Renal function calculations using the Cockcroft-Gault Formula (Xarelto Data Sheet)[2]

For serum creatinine concentration in mg/100 mL:

$$\textit{Creatinine Clearance [mL / min]} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{72 \times \text{serum creatinine [mg / 100 mL]}} \times \textit{(0.85 for women)}$$

For serum creatinine concentration in µmol/L:

$$\textit{Creatinine Clearance [mL / min]} = \frac{1.23 \times (140 - \text{age [years]}) \times \text{weight [kg]}}{\text{serum creatinine [µmol / L]}} \times (0.85 \text{ for women})$$

Caution must be exercised when renal function estimates are based on eGFR. eGFR values may not directly correlate with creatinine clearance.[2]

Coagulation testing

Xarelto does not require routine coagulation monitoring.[2]

However, measuring Xarelto levels may be useful in exceptional situations where knowledge of Xarelto exposure may help to make clinical decisions, e.g. overdose and emergency surgery.[2]

Anti-FXa assays with Xarelto-specific calibrators to measure rivaroxaban levels are now commercially available. Clinically indicated haemostatic status can also be assessed by PT using Neoplastin® as described in the Data Sheet.[2]

The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalised ratio (INR).[2] INR testing was developed to measure warfarin effects and is therefore not appropriate to measure the activity of Xarelto.[2] Dosing or treatment decisions should not be based on results of INR except when converting from Xarelto to warfarin as described on page 19.[2]

Clinical use of Xarelto

Perioperative management

If an invasive procedure or surgical intervention is required, Xarelto should be stopped at least 24 hours before the surgery, depending on the type of surgery and the clinical indication for anticoagulation.[2] If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.[2] Xarelto should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows this and adequate haemostasis has been established.[2]

Peri-operative management with Xarelto [2,13,17]

Bleeding risk surgery	Surgical example	Suggested measure for normal renal function	Suggested measure for moderately impaired renal function
Minimal	Cataract surgery Single tooth extraction/ clean	Continue Xarelto	Continue Xarelto
Low	Percutaneous biopsies Dental surgery	Stop Xarelto 24h before procedure	Stop Xarelto 24–48h before procedure
Moderate or High	Major surgery Spinal surgery Neurosurgery	Stop Xarelto at least 48h before surgery based on specialist recommendation	Stop Xarelto at least 48h before surgery based on specialist recommendation

Timing of resumption of Xarelto

Xarelto should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established.[2]

Management of bleeding

Individualised bleeding management may include:[2]

- Symptomatic treatment, such as mechanical compression, surgical intervention and/or fluid replacement[2]
- Haemodynamic support; blood product or component transfusion[2]
- 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[2] (PCC)
  - activated prothrombin complex concentrate[2] (APCC)
  - recombinant factor VIIa[2] (r-FVIIa).

Due to the high plasma protein binding Xarelto is not expected to be dialysable.[2]

Xarelto use during cardioversion

Xarelto can be initiated or continued in patients who may require cardioversion.[2]

For transoesophageal echocardiogram-guided cardioversion in patients not previously treated with anticoagulants, Xarelto treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation.[2]

For patients who are unable to swallow whole tablets

Xarelto 10 mg, 15 mg, or 20 mg tablets may be crushed and mixed with water or applesauce immediately prior to use and administered orally. After the administration of crushed Xarelto 15 mg or 20 mg tablets, the dose should be immediately followed by food.[2]

The crushed Xarelto 10 mg, 15 mg, or 20 mg tablet may be given through gastric tubes. Gastric placement of the tube should be confirmed before administering Xarelto. 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 tablets, the dose should be immediately followed by enteral feeding.[2]

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.[2] The use of activated charcoal to reduce absorption in case of overdose may be considered.[2]

Should a bleeding complication arise in a patient receiving Xarelto, the next Xarelto administration should be delayed or treatment should be discontinued as appropriate.[2]

There is currently no specific antidote available to Xarelto.[2]

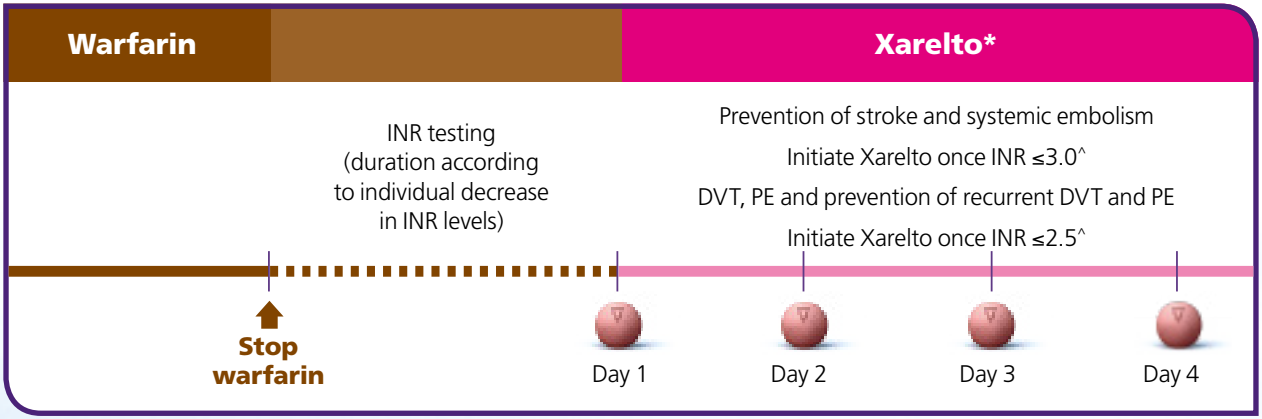
Contact the New Zealand National Poisons Centre 0800 POISON (0800 764 766) for advice on management.[2]

Converting Xarelto from/to other anticoagulants

Converting from warfarin to Xarelto

It is important to ensure adequate anticoagulation while minimising the risk of bleeding during conversion of therapy.[2]

Converting from warfarin to Xarelto*[2]



*See dosing recommendations for required daily dose.

^Once Xarelto has been commenced, INR measurement is not appropriate to measure the anticoagulation activity of Xarelto, and therefore should not be used for this purpose. Treatment with Xarelto does not require routine coagulation monitoring.

Tablets not actual size, representative only.

For patients treated for **prevention of stroke and systemic embolism**, treatment with warfarin should be stopped and Xarelto therapy should be initiated when the **INR is ≤3.0.**[2]

For patients treated for **DVT, PE and prevention of recurrent DVT and PE**, treatment with warfarin should be stopped and Xarelto therapy should be initiated when the **INR is ≤2.5**.[2]

Once Xarelto has been commenced, INR measurement is not appropriate to measure the anticoagulant activity of Xarelto, and therefore should not be used for this purpose.[2] Treatment with Xarelto does not require routine coagulation monitoring.[2]

Converting Xarelto from/to other anticoagulants

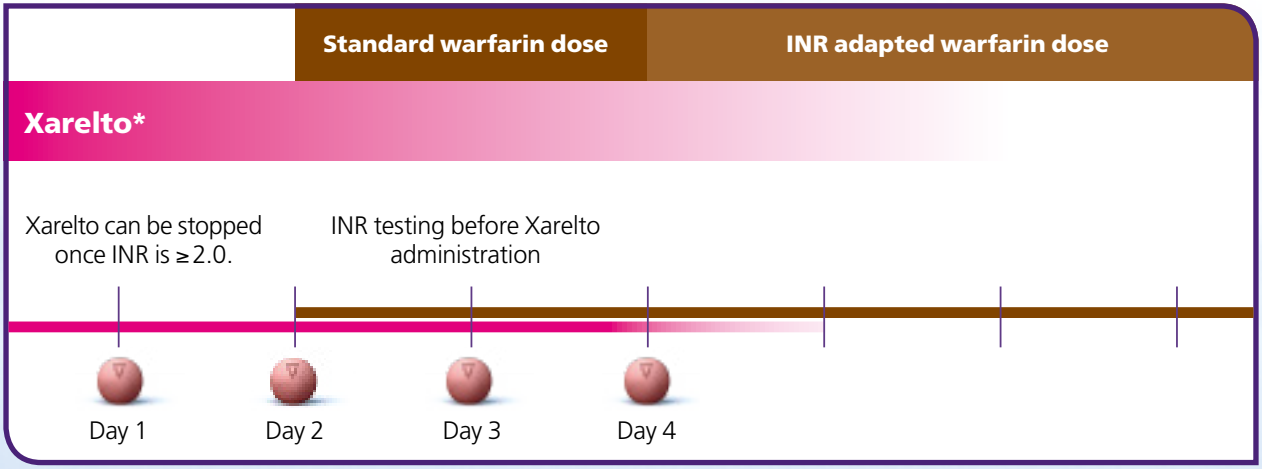
Converting from Xarelto to warfarin

It is important to ensure adequate anticoagulation while minimising the risk of bleeding during conversion of therapy.[2]

When converting to warfarin, Xarelto and warfarin should be given concurrently until the INR is ≥ 2.0.[2] For the first two days of the conversion period, standard initial dosing of warfarin should be used followed by warfarin dosing guided by INR testing.[2]

INR measurement is not appropriate to measure the anticoagulant activity of Xarelto.[2] While patients are on both Xarelto and warfarin, **INR should not be tested earlier than 24 hours after the previous dose, but prior to the next dose, of Xarelto**.[2] Once Xarelto is discontinued, INR testing may be done reliably at least 24 hours after the last dose.[2]

Converting from Xarelto to warfarin*[2]



*See dosing recommendations for required daily dose.

Tablets not actual size, representative only.

Converting Xarelto from/to other anticoagulants

Converting from parenteral anticoagulants to Xarelto

Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Xarelto should be started at the time of discontinuation.[2]

Patients with parenteral drug on a fixed dosing scheme such as low molecular weight heparin: Xarelto should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.[2]

Converting from Xarelto to parenteral anticoagulants

Discontinue Xarelto and give the first dose of parenteral anticoagulant at the time that the next Xarelto dose would be taken.[2]

Converting from/to novel anticoagulants

The European Heart Rhythm Association guidelines 2018 recommend that the alternate novel oral anticoagulant can be initiated when the next dose is due, except in situations where higher-than therapeutic plasma concentrations are expected e.g. patient with impaired renal function.[13]

Additional information

Patient alert card

A patient alert card must be provided to each patient who is prescribed Xarelto. 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, dentists and pharmacists 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 health care provider.

XARELTO® (rivaroxaban)

Xarelto is used in anticoagulation. Prescription Medicine. 10 mg, 15 mg, and 20 mg tablets containing rivaroxaban. **INDICATIONS:** Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. 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 deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and pulmonary embolism (see the PRECAUTIONS for haemodynamically unstable PE patients). **DOSAGE AND ADMINISTRATION:** For VTE prevention in total hip and knee replacement, one 10 mg tablet taken once daily. Initial dose to be taken 6-10 hours after surgery provided haemostasis has been established. Xarelto may be taken with or without food. For stroke prevention in atrial fibrillation, one 20 mg tablet taken once daily. The dose is one 15 mg tablet taken once daily for patients with creatinine clearance 30-49 mL/min. For treatment of acute DVT and PE, the initial dose is one 15 mg tablet taken twice daily for the first 3 weeks followed by one 20 mg tablet taken once daily for the continued treatment and prevention of recurrent DVT and PE. Xarelto 15 mg and 20 mg tablets should be taken with food. Tablets may be crushed and administered orally (mixed with water or applesauce) or given through gastric tubes. **CONTRAINDICATIONS:** Hypersensitivity to rivaroxaban or to any of the excipients, clinically significant active bleeding, lesions at increased risk of clinically significant bleeding and patients with spontaneous impairment of haemostasis, significant hepatic disease which is associated with coagulopathy, severe renal impairment with a creatinine clearance < 15 mL/min for Xarelto 10 mg (< 30 mL/min for Xarelto 15 mg and 20 mg), concomitant treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein such as HIV protease inhibitors (e.g. ritonavir) or systemically administered azole anti-mycotics (e.g. ketoconazole), pregnancy, lactation. **PRECAUTIONS:** Should be used with caution in patients with an increased bleeding risk such as congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, active ulcerative gastrointestinal disease, recent gastrointestinal ulcerations, vascular retinopathy, recent intracranial or intracerebral haemorrhage, intraspinal or intracerebral vascular abnormalities, shortly after brain, spinal or ophthalmological surgery, bronchiectasis or history of pulmonary bleeding, renal impairment, hepatic impairment, surgery and interventions, spinal/epidural anaesthesia or puncture, paediatric use under 18 years not recommended, no clinical data in patients with prosthetic valves, haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy, lactose intolerance, driving and machine use. Pregnancy Category C. **INTERACTIONS WITH OTHER MEDICINES:** Care to be taken if concomitantly used with medicines affecting haemostasis; increased risk of bleeding with concomitant administration with SSRIs, SNRIs, NSAIDs, platelet aggregation inhibitors, other anticoagulants. Strong inhibitors of both CYP3A4 and P-gp. **ADVERSE EFFECTS:** Please refer to Datasheet for a complete list. Common adverse reactions (≥ 1/100 to < 1/10) include post procedural, eye, GI tract and urogenital tract haemorrhage, haemoptysis, increased transaminases, gingival bleeding, constipation, diarrhoea, dyspepsia, nausea, vomiting, pyrexia, oedema peripheral, confusion, pain in extremity, gastrointestinal and abdominal pain, headache, fever, decreased general strength and energy, contusion, dizziness, epistaxis, haematoma, anaemia, renal impairment and ecchymosis, cutaneous and subcutaneous haemorrhage, hypotension, rash and pruritus. Less frequent but serious adverse reactions include: urticaria, cerebral and intracranial haemorrhage, jaundice, angioedema, allergic oedema, cholestasis, hepatitis and thrombocytopaenia. **Based on DS:** Dated 11 December 2017

Xarelto will be fully funded without restrictions from 1st August 2018. Until 1st August 2018, Xarelto is only funded for patients who meet criteria for use after hip or knee replacement. A prescription fee will apply. This medicine has risks and benefits. Before prescribing, please review Data Sheet for further information. Full Data Sheet is available from www.medsafe.govt.nz or Bayer New Zealand Limited, 3 Argus Place Hillcrest North Shore Auckland 0627. Telephone 0800 233 988.

References: 1. PHARMAC website www.pharmac.govt.nz. Accessed May 2018. **2.** Xarelto Data Sheet. **3.** Laux V et al. Thromb Haemost 2009;102: 892–9. **4.** Ansell J. J Thromb Haemast 2007;5(Suppl I):60–4. **5.** Patel MR et al. for the ROCKET AF Investigators. N Engl J Med 2011;365:883–91. **6.** EINSTEIN-DVT Investigators. N Engl J Med 2010;363:2499–510. **7.** EINSTEIN-PE Investigators. N Engl J Med 2012;366:1287–97. **8.** Eriksson BI et al. N Engl J Med 2008;358:2765–75. **9.** Kakkar AK et al. Lancet 2008;372:31–9. **10.** Lassen MR et al. N Engl J Med 2008;358:2776–86. **11.** Mueck W et al. Clin Pharmacokinet 2011;50:675–86. **12.** Kubitza D et al. Clin Pharmacol Ther 2005;78:412–21. **13.** Steffel et al. European Heart Journal (2018) 00, 1-64. **14.** National Institute for Health and Care Excellence. Atrial fibrillation: the management of atrial fibrillation. CG180. London: NICE, June 2014. Available at: www.nice.org.uk/guidance/cg180. Accessed April 2018. **15.** American College of Cardiology. Atrial Fibrillation Toolkit. Available at: http://www.acc.org/tools-and-practice-support/clinical-toolkits/atrial-fibrillation-afib. Accessed April 2018. **16.** Camm AJ et al. Eur Heart J 2012;33:2719-47. **17.** Tran H et al. Intern Med J 2014;44:525–36.

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BY8695 NZ-XAR-00030-05-2018. TAPS NA7491 Prepared April 2018.

Xarelto® rivaroxaban