Quick Guide

Xarelto® approved across multiple indications worldwide[1]

Xarelto® rivaroxaban

139158_1368931_Cross Indication Quick Guide_PRINT_GM_01

Indications and Dosing[1]

Prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation

20 mg OD — Patients with CrCl > 49 ml/min with food

Or

15 mg OD — Patients with CrCl 15–49 ml/min[a] with food

Treatment of pulmonary embolism and deep vein thrombosis

Secondary prevention of recurrent venous thromboembolism[b]

From Day 1 to Day 21

15 mg BID — Patients with CrCl > 15 ml/min[a] with food

At Day 22 Transition to

20 mg OD[c] — Patients with CrCl > 15 ml/min[a,c] with food

Prevention of venous thromboembolism after major orthopaedic surgery of the lower limbs

10 mg OD — Patients with CrCl > 15 ml/min[a]

The initial dose should be taken 6–10 hours after surgery once haemostasis has been established

CrCl, creatinine clearance; BID, twice daily; OD, once daily. [a]Not recommended in patients with CrCl < 15 ml/min; use with caution in patients with CrCl 15–29 ml/min and in patients with renal impairment when concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration. [b]Not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. [c]A reduction of the dose from 20 mg OD to 15 mg OD should be considered in patients with CrCl 15–49 ml/min when the patient's assessed risk of bleeding outweighs the risk of recurrent pulmonary embolism and deep vein thrombosis. The recommendation for the use of 15 mg OD is based on pharmacokinetic modelling and has not been studied in this clinical setting.

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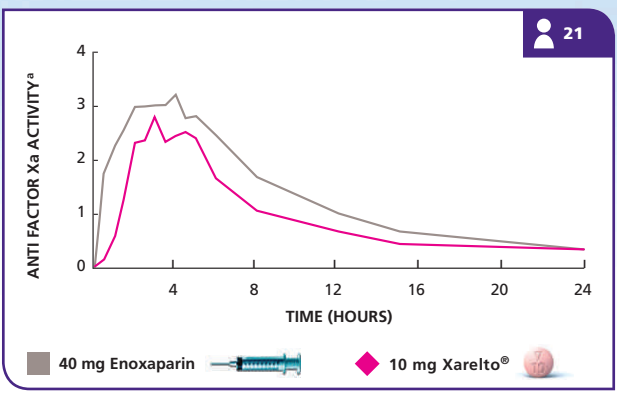
Mode of Action[1,2]

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

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

Fast onset of action[2]

- Xarelto® works as fast as enoxaparin, with no injections required[1,2]



Graph adapted from Kubitza D, *et al.* 2013.[2]

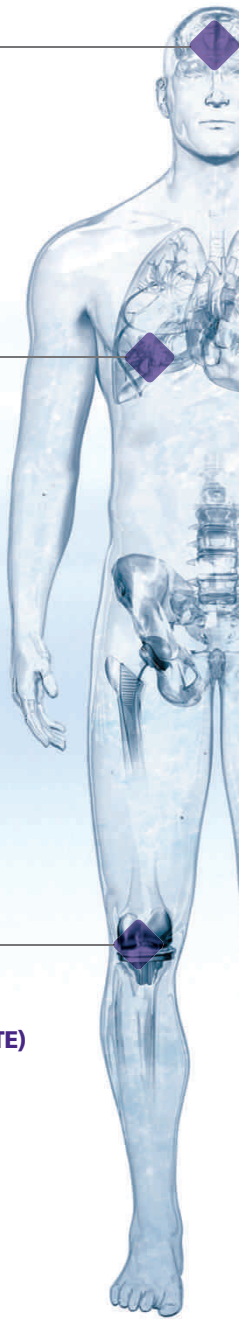
[a]Change from baseline (ng/ml).

Xarelto®: Across Multiple Indications[1]

Stroke Prevention in Non-valvular Atrial Fibrillation
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation[a]

Treatment of Pulmonary Embolism (PE)
Treatment of PE in haemodynamically stable patients

Prevention of Venous Thromboemboli (VTE) after Elective Knee-Replacement Surgery
Prevention of VTE in patients undergoing elective knee-replacement surgery



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Secondary Prevention of Recurrent Venous Thromboemboli (VTE)
Prevention of recurrent VTE following the treatment of deep vein thrombosis and/or pulmonary embolism

Prevention of Venous Thromboemboli (VTE) after Elective Hip-Replacement Surgery
Prevention of VTE in patients undergoing elective hip-replacement surgery

Treatment of Deep Vein Thrombosis (DVT)
Treatment of DVT in patients

Non-Valvular Atrial Fibrillation[1]

Indication[1]

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Treatment[1]

Day 1
Initiate Xarelto®

One 20 mg tablet, once daily with food

No routine coagulation monitoring required[a]

Xarelto®

Creatinine Clearance	Recommended Dosage
30–49 ml/min	15 mg once daily[b]
15–29 ml/min	15 mg once daily, use with caution[b]
< 15 ml/min	Not recommended

Important notes[1]

- Xarelto® provides protection from day 1 and 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

INR, international normalised ratio. [a]INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto®. [b]Use with caution when patient is concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations.

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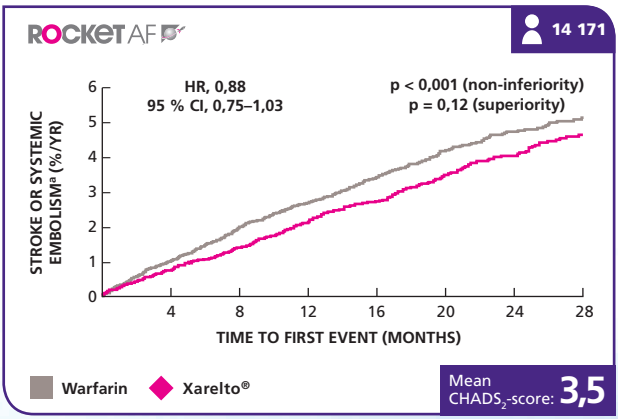
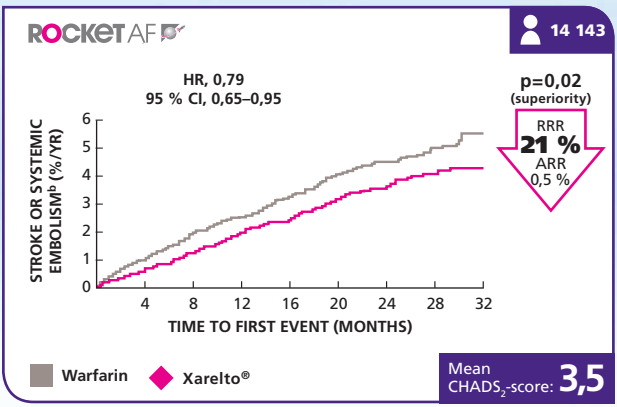
ROCKET AF Study Results[3]

Highly effective protection against stroke and systemic embolism in challenging patients[3]



Intention-to-treat analysis

Graph adapted from Patel M.R., *et al.* 2011.[3]



Safety on-treatment analysis

Graph adapted from Patel M.R., *et al.* 2011.[3,4]

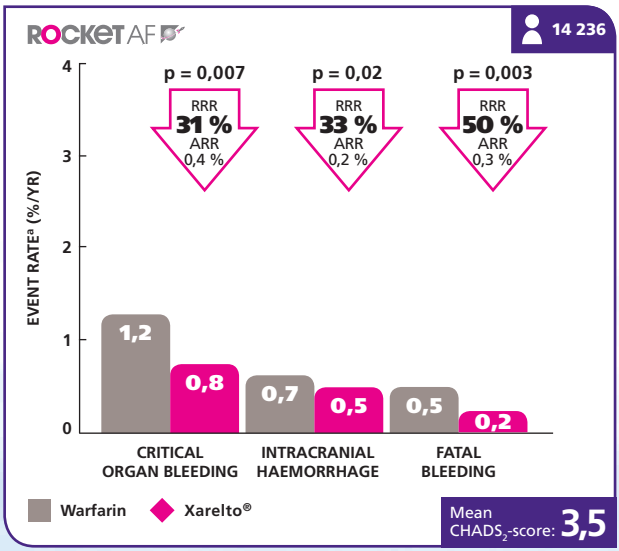
No significant differences in major or clinically relevant non-major bleeding events vs warfarin[c]

Warfarin	Xarelto®
14,5 %/YR	14,9 %/YR
HR, 1,03; 95 % CI, 0,96–1,11; p = 0,44	

AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval; YR, year; RRR, relative risk ratio; ARR, absolute risk ratio. $CHADS_2$-score for atrial fibrillation stroke risk. [a]Primary efficacy endpoint: composite of all stroke (both ischaemic and haemorrhagic) and systemic embolism. [b]Primary safety endpoint. [c]Major or non-major clinically relevant bleeding.

Xarelto® Reduced the Most Serious Bleeding Types[3]

Significant reduction in intracranial haemorrhage, critical organ and fatal bleeding vs warfarin[3]



Safety population during treatment analysis

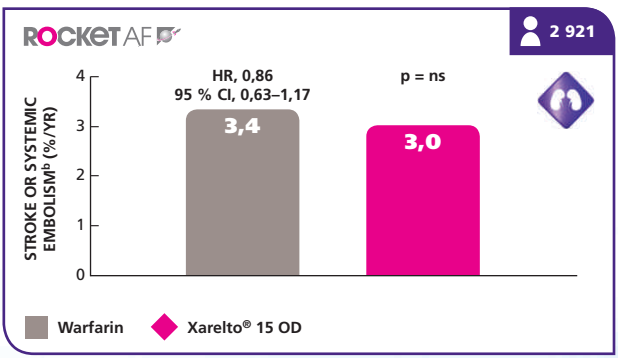
Graph adapted from Patel M.R., *et al.* 2011.[3]

- No significant difference in primary safety endpoint of major or clinically relevant non-major bleeding vs warfarin[3]
- Xarelto® showed significantly more overt bleeding with drops in haemoglobin levels of 2,0 g per decilitre or more, or leading to transfusion of two or more units of blood or red blood cells, than warfarin[3]
- Patients receiving Xarelto® experienced significantly more gastrointestinal (GI) bleeding events, which included upper GI, lower GI and rectal bleeds, than those receiving warfarin[3]

RRR, relative risk reduction; ARR, absolute risk reduction; YR, year; GI, gastrointestinal. $CHADS_2$-score for atrial fibrillation stroke risk. The RRR was calculated as 1–HR by Bayer.
[a]Bleeding was defined as major if it was clinically overt and associated with a decrease in the haemoglobin level of 2.0 g/dl, if bleeding led to the transfusion of 2 or more units of blood or red blood red cells, or if bleeding was intracranial or retroperitoneal, occurred in another critical site or contributed to death.

Protection in Patients with Moderate Renal Impairment[a,5]

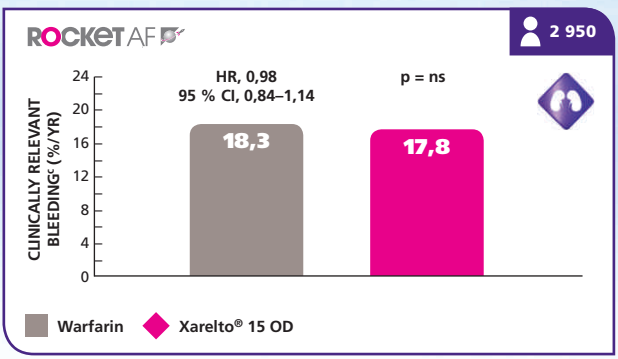
Highly effective stroke prevention in non-valvular atrial fibrillation patients with moderate renal impairment[a,5]



Intention-to-treat analysis

Graph adapted from Fox K.A.A., *et al.* 2011.[5]

Safety in non-valvular atrial fibrillation patients with moderate renal impairment[a,5]



Safety population during treatment analysis

Graph adapted from Fox K.A.A., *et al.* 2011.[5]

- Xarelto® 15 OD – The only non-VKA oral anticoagulant with a prospectively tested, specific renal dose in patients with non-valvular atrial fibrillation[3,5]

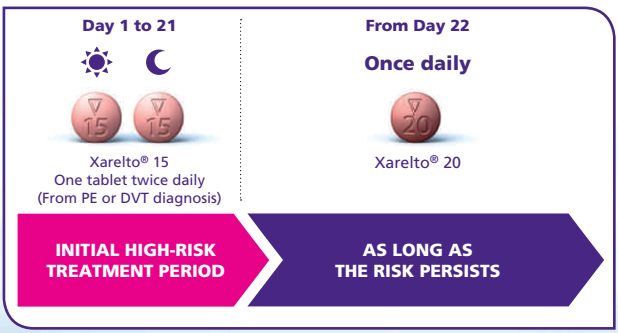
HR, hazard ratio; CI, confidence interval; ns, not significant; YR, year; OD, once daily.
[a]Creatinine clearance: 30–49 ml/min. [b]Primary efficacy endpoint: Composite of all stroke (both ischaemic and haemorrhagic) and systemic embolism. [c]Primary safety endpoint: Composite of major or non-major clinically relevant bleeding.

Pulmonary Embolism and Deep Vein Thrombosis[1,6]

Indication[1]

- Treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT) and prevention of recurrent pulmonary emboli and deep vein thrombosis in adults

Simplified dosing that demonstrated clot regression within 21 days and enduring protection[1,7]



- 15 mg BID for 21 days treats the initial clot and protects against early recurrence[1,6,7]

For renally impaired patients[1]

Creatinine Clearance	Recommended Dosage	
	Weeks 1–3	After 3 Weeks
30–49 ml/min	15 mg twice daily[a]	20 mg once daily[a]
15–29 ml/min	15 mg twice daily, use with caution	20 mg once daily, use with caution
< 15 ml/min	Not recommended	Not recommended

Important notes[1]

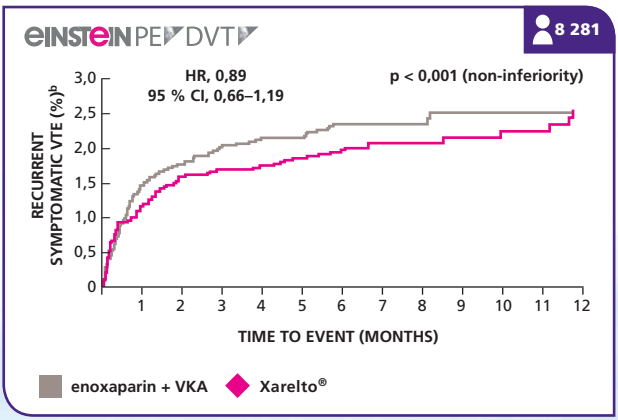
- The duration of therapy should be individualised after careful assessment of the treatment benefit against bleeding risk
- Xarelto® is not recommended as an alternative to UFH in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy
- Xarelto® 15 and 20 tablets are to be taken with food

BID, twice daily; UFH, unfractionated heparin. [a]Use with caution when patient is concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations.

EINSTEIN-PE/DVT Study Results[6]

Highly effective oral single-drug treatment[a,6]

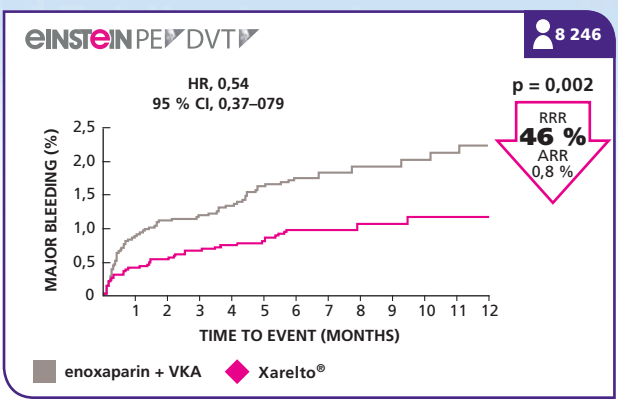
- No need for heparin injections to initiate treatment[1]
- The primary efficacy outcome was symptomatic, recurrent venous thromboembolism (VTE) – the composite of deep vein thrombosis and non-fatal or fatal pulmonary emboli[6]



Intention-to-treat analysis

Graph adapted from Prins M.H., *et al.* 2013.[6]

Significant reduction in risk of major bleeding[6]



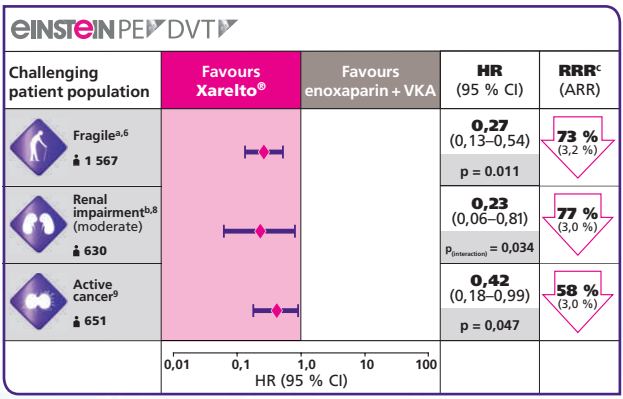
Safety population during treatment analysis

Graph adapted from Prins M.H., *et al.* 2013.[6]

PE, pulmonary embolism; DVT, deep vein thrombosis; HR, hazard ratio; CI, confidence interval; VKA, vitamin K antagonist; RRR, relative risk reduction; ARR, absolute risk reduction. [a]Pooled analysis of EINSTEIN-DVT and EINSTEIN-PE randomised studies. [b]Primary efficacy outcome.

EINSTEIN-PE/DVT Significant Reduction in Major Bleeding[6,8,9]

Safety benefit in your challenging patients[6,8,9]



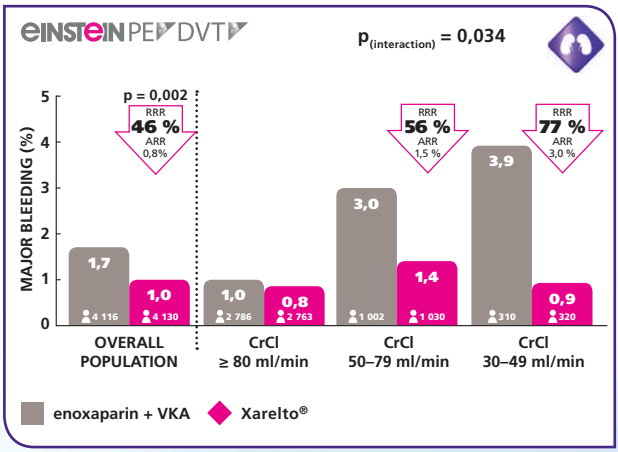
Graph adapted from Prins M.H., *et al*. 2013.[6]

Comparable rate of major or non-major clinically relevant bleeding events[d,6]

enoxaparin + VKA	Xarelto®
412 patients 10,0 %	388 patients 9,4 %
HR, 0,93; 95 % CI, 0,81–1,06; p = 0,27	

PE, pulmonary embolism; DVT, deep vein thrombosis; VKA, vitamin K antagonist; HR, hazard ratio; CI, confidence interval; RRR, relative risk reduction; ARR, absolute risk reduction; CrCl, creatinine clearance. [a]Fragile patients are defined as having one or more of the following risk factors: aged > 75 years, renal impairment (CrCl < 50 ml/min) and low body weight (< 50 kg). [b]Normal renal function: CrCl ≥ 80 ml/min. Mild renal impairment: CrCl 50–79 ml/min. Moderate renal impairment: CrCl 30–49 ml/min. Severe renal impairment: CrCl < 30 ml/min. [c]RRR was calculated as 1–HR by Bayer. [d]Primary safety endpoint: composite of major or non-major clinically relevant bleeding.

Safety Benefit in Renal Impairment[6,8]



Safety population during treatment analysis

Adapted from Bauersachs R.M, *et al.* 2014.[8]

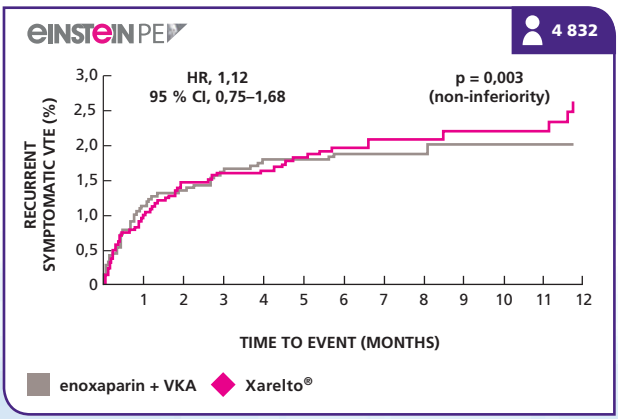
- Overall rates of clinically relevant bleeding were comparable between Xarelto® and enoxaparin + VKA

PE, pulmonary embolism; DVT, deep vein thrombosis; RRR, relative risk reduction; ARR, absolute risk reduction; CrCl, creatinine clearance; VKA, vitamin K antagonist.

The Only Non-VKA Oral Anticoagulant with a Separate Clinical Trial in Pulmonary Embolism[10]

Xarelto® is highly effective at protecting against the life-threatening risk of pulmonary embolism[10]

- The primary efficacy outcome was symptomatic, recurrent venous thromboembolism – the composite of deep vein thrombosis and non-fatal or fatal pulmonary emboli



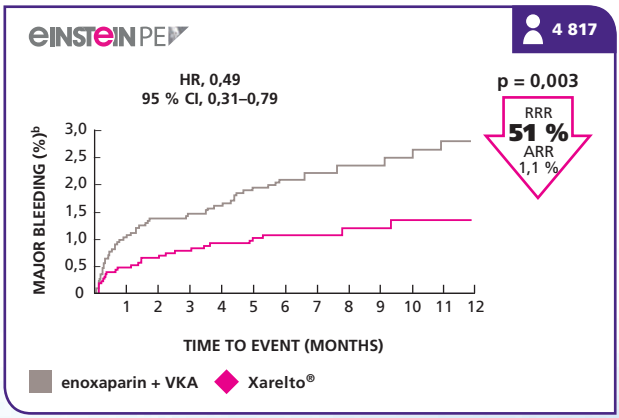
Intention-to-treat analysis

Graph adapted from Büller H.R., *et al.* 2012.[10]

VTE, venous thromboembolism; HR, hazard ratio; CI, confidence interval; VKA, vitamin K antagonist.

EINSTEIN-PE Study Results[10]

Xarelto® significantly lowers the risk of major bleeding[a] vs enoxaparin + VKA[10]



Safety population during treatment analysis

Graph adapted from Büller H.R., *et al.* 2012.[10]

Comparable rates of clinically relevant bleeding vs enoxaparin + VKA[c,10]

enoxaparin + VKA	Xarelto®
274 patients 11,4 %	249 patients 10,3 %
HR, 0,90; 95 % CI, 0,76–1,07; p = 0,23	

PE, pulmonary embolism; VKA, vitamin K antagonist; HR, hazard ratio; CI, confidence interval; RRR, relative risk reduction; ARR, absolute risk reduction. [a]Bleeding was defined as major if it was clinically overt and associated with a decrease in haemoglobin level of 2,0 g/dl, if bleeding led to the transfusion of 2 or more units of blood or red blood cells, or if bleeding was intracranial or retroperitoneal, occurred in another critical site or contributed to death. [b]RRR was calculated as 1–HR by Bayer. [c]Primary safety endpoint: Major and clinically relevant non-major bleeding.

Major Orthopaedic Surgery of the Lower Limbs

Indication[1]

- Prevention of venous thromboembolism after major orthopaedic surgery of the lower limbs

Treatment[1]

Surgery

Day 1
Initiate Xarelto®

One 10 mg tablet, once daily with or without food

Recommended treatment duration after:
- **Hip-replacement surgery: 5 weeks[1]**
- **Knee-replacement surgery: 2 weeks[1]**

No routine coagulation monitoring required[a]

Xarelto®

For renally impaired patients[1]

Creatinine Clearance	Recommended Dosage
30–49 ml/min	10 mg once daily[b]
15–29 ml/min	10 mg once daily, use with caution[b]
< 15 ml/min	Not recommended

Important notes[1]

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

INR, international normalised ratio. [a]INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto®. [b]Use with caution when patient is concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations.

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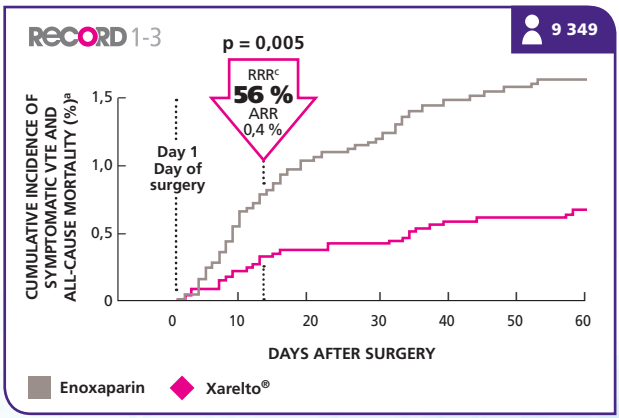
RECORD 1–3
Pooled Study Results[11]

Xarelto® delivers early and more effective prevention of symptomatic venous thromboembolism and all cause mortality, without increasing major bleeding than enoxaparin[a,b,11]

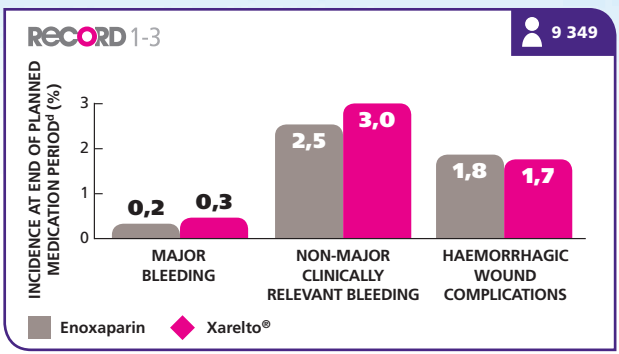


Safety population during treatment analysis
Graph adapted from Eriksson B.I., *et al.* 2009.[11]

- 56 % RRR in the primary efficacy outcome of symptomatic VTE and all-cause mortality at 2 weeks
- 62 % RRR at the end of the planned medication period (0,5 % vs 1,3 %, respectively; OR 0,38; 95 % CI 0,22–0,62; p < 0,001)[d]

Xarelto® vs enoxaparin: Similar rates of the main safety outcome of major bleeding at 2 weeks (0,2 % for both) and at the end of the planned medication period (0,3 % vs 0,2 %)[11]

Xarelto® vs enoxaparin: Comparable rates of bleeding and haemorrhagic wound complications[e,11]



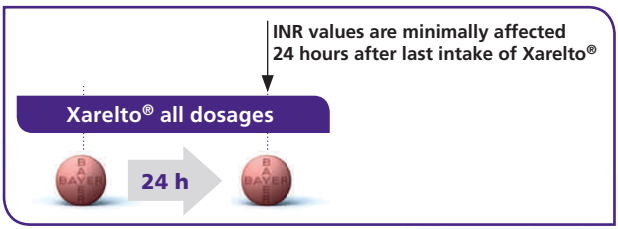
Safety population during treatment analysis
Graph adapted from Eriksson B.I., *et al.* 2009.[11]

VTE, venous thromboembolism; RRR, relative risk reduction; ARR, absolute risk ratio; OR, odds ratio; CI, confidence interval. [a]Kaplan-Meier survival curve: Cumulative incidence of symptomatic VTE and all-cause mortality over the total study duration (planned medication period plus follow-up). [b]Enoxaparin regimen includes placebo phase in RECORD2. [c]RRR was calculated as 1–OR by Bayer. [d]End of the planned medication period was 5 weeks (up to day 42) in RECORD1 and RECORD2, including the placebo-controlled period in RECORD2, and 2 weeks (up to day 17) in RECORD3. [e]Haemorrhagic wound complications were a composite of excessive wound haematoma and reported surgical-site bleeding.

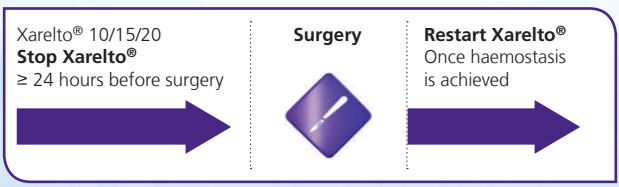
Responsible Use[1]

INR testing was developed for measuring VKA effects[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 hours after the previous intake of Xarelto®) as this test is minimally affected by Xarelto® at this time point.



Perioperative management of patients on Xarelto®[1]



- Xarelto® 10/15/20 should be stopped at least 24 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

INR, international normalised ratio; VKA, vitamin K antagonist.

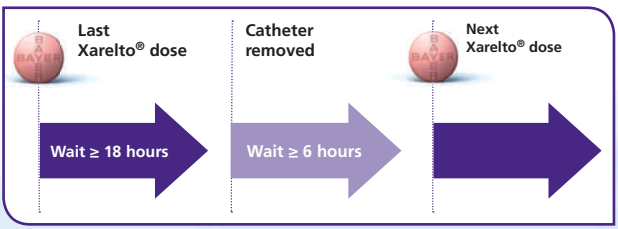
Responsible Use[1]

Neuraxial anaesthesia[1]

Catheters

- At least 2 × half-life, i.e. ≥ 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® should be delayed for 24 hours



There is no clinical experience with the use of Xarelto® 15/20 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.

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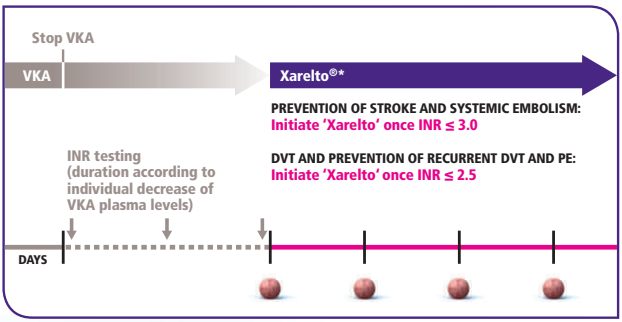
Converting Patients from VKA to Xarelto®[1]



*See dosing recommendations for required daily dose

Converting patients with non-valvular atrial fibrillation 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

Converting patients treated for pulmonary embolism or deep vein thrombosis and to prevent the recurrence of pulmonary embolism or deep vein thrombosis[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

VKA, vitamin K antagonist; INR, international normalised ratio.

Converting Patients from Xarelto® to VKA[1]

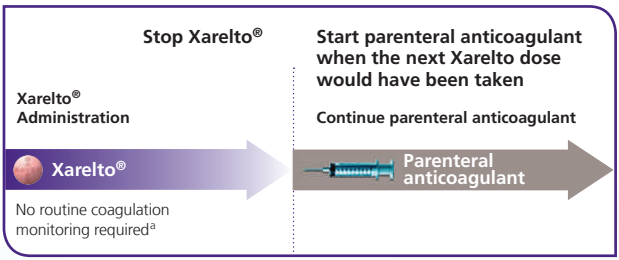
- It is important to ensure adequate anticoagulation while minimising the risk of bleeding during conversion of therapy
- When converting to VKA, administration of Xarelto® and VKA should overlap until INR ≥ 2,0. For the first 2 days of the conversion period, standard initial dosing of VKA should be 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

VKA, vitamin K antagonist; INR, international normalised ratio.

Converting Patients from Xarelto® to Parenteral Anticoagulants[1]

- Give the first dose of parenteral anticoagulant (e.g. subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin) when the next Xarelto® dose would have been taken

No treatment overlap[1]

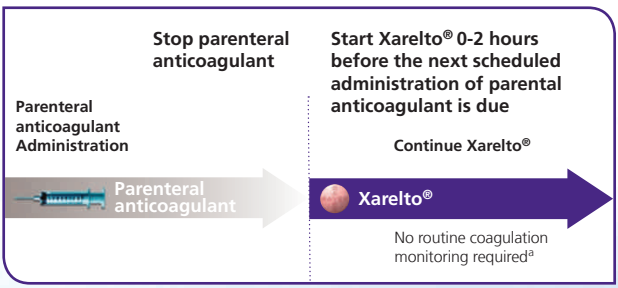


INR, international normalised ratio. [a]INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto®.

Converting Patients from Parenteral Anticoagulants to Xarelto®[1]

- Start Xarelto® 0–2 hours before the next parenteral (e.g. low-molecular-weight heparin) dose would have been given. If a continuously administered intravenous anticoagulant (e.g. unfractionated heparin) is used, start Xarelto® when this treatment is discontinued[1]

No treatment overlap[1]



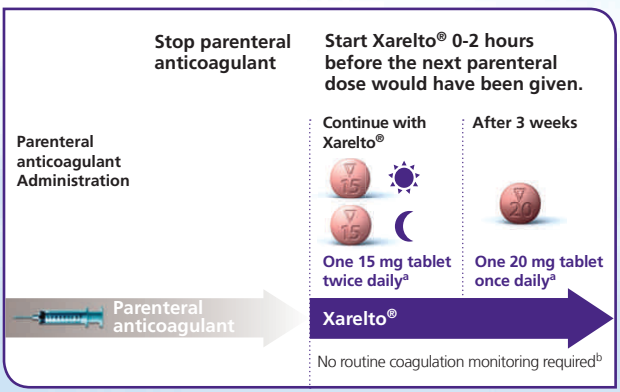
INR, international normalised ratio. [a]INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto®.

Converting Patients from Parenteral Anticoagulants to Xarelto®[1]

Converting patients treated for pulmonary embolism or deep vein thrombosis or prevention of recurrent pulmonary embolism or deep vein thrombosis[1]

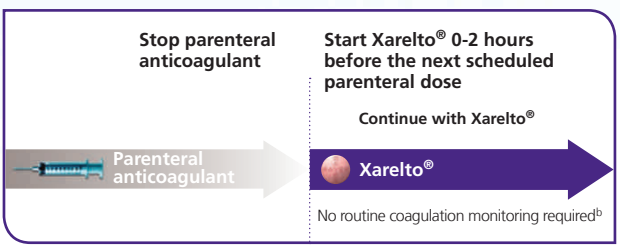
Dosing for patients on anticoagulation therapy for the first 3 weeks

- Start Xarelto® 0–2 hours before the next parenteral dose would have been given
- 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



Dosing for patients on anticoagulation therapy after 3 weeks

- Start Xarelto® 0–2 hours before the time of the next scheduled administration of parenteral anticoagulant



INR, international normalised ratio. [a]For dosing for renally impaired patients, see pages 2, 6, 10, 16 and 18. [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[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[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 twice-daily intake on the following day

Overdose[1]

- 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
- 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

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Bleeding Management[1,14,15]

- Universal strategies are recommended by international guidelines (e.g. ESC or EHRA) and the Xarelto® package insert to stop or reduce bleeding in patients treated with Xarelto®

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®

Due to the high plasma protein binding Xarelto® is not expected to be dialysable.

For more details please refer to the Xarelto® package insert as well as international guidelines (e.g. ESC or EHRA)[14,15]

ESC, European Society of Cardiology; EHRA, European Heart Rhythm Association.
[a]Xarelto® half-life: 5–13 hours. 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 High Risk of Bleeding[1]

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

Several 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: For dosing, refer to pages 2, 6, 10 and 16 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
- Concomitantly receiving certain other drugs affecting haemostasis, such as NSAIDs, ASA, platelet aggregation inhibitors, or increasing rivaroxaban plasma concentrations, such as concomitant inhibitors of CYP3A4 and P-gp
  - Care is to be taken in patients concomitantly receiving drugs affecting haemostasis, such as NSAIDs, ASA and platelet aggregation inhibitors
  - Other anticoagulants are contraindicated in patients treated with Xarelto®
  - Systemic azole antimycotics (e.g ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir): Use of Xarelto® is not recommended

CrCl, creatinine clearance; NSAIDs, non-steroidal anti-inflammatory drugs; ASA, acetylsalicylic acid; CYP3A4, member of the cytochrome P450 family of oxidizing enzymes; P-gp, P-glycoprotein.

Caring for Patients at High Risk of Bleeding[1]

Other haemorrhagic risk factors[1]

As with other antithrombotics, **Xarelto® 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

Xarelto® is not recommended for use in[1]:

- Patients below 18 years of age
- Patients with creatinine clearance < 15 ml/min
- Patients receiving concomitant 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)

CYP3A4, member of the cytochrome P450 family of oxidizing enzymes; P-gp, P-glycoprotein.

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Contraindications[1]

Xarelto® 10 is contraindicated in case of[1]:

- Hypersensitivity to the active substance or to any of the excipients
- Clinically significant active bleeding
- Hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk
- Pregnancy and breastfeeding

Xarelto® 15 and Xarelto® 20 are contraindicated in patients with:

- Hypersensitivity to rivaroxaban or any excipient of the tablets
- Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding)
- Known existing inherited bleeding disorders
- Hepatic disease with or without coagulopathy

Safety and efficacy of Xarelto® 15 and Xarelto® 20 have not been established in pregnant women. Animal data show that rivaroxaban crosses the placental barrier. Therefore the use of Xarelto® 15 and Xarelto® 20 are contraindicated throughout pregnancy.

Safety and efficacy of Xarelto® 15 and Xarelto® 20 have not been established in breastfeeding mothers. Animal data indicate that rivaroxaban is secreted into breast milk. Therefore, Xarelto® 15 and Xarelto® 20 may only be administered after breastfeeding is discontinued.

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XARELTO 10, XARELTO 15 and XARELTO 20

S4 Xarelto 10: Each film-coated tablet contains rivaroxaban 10mg.Reg. No.: 42/8.2/1046; Namibia NS2: 10/8.2/0463. Botswana: BOT1302278; Zimbabwe PP10 Reg. 2017/10.2/5362
S4 Xarelto 15: Each film-coated tablet contains rivaroxaban 15 mg. Reg. No: 46/8.2/0111; Namibia NS2: 12/8.2/0006; S2 Botswana: BOT1302296; Zimbabwe: PP10 Reg. 2017/10.2/5363
S4 Xarelto 20: Each film-coated tablet contains rivaroxaban 20 mg. Reg. No: 46/8.2/0112; Namibia NS2: 12/8.2/0007; S2 Botswana: BOT1302297; Zimbabwe: PP10 Reg. 2017/10.2/5364

PHARMACOLOGICAL CLASSIFICATION: A.8.2 Anticoagulants.

INDICATIONS: (1) Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF); (2) Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE); (3) Treatment of pulmonary embolism (PE) and for the prevention of recurrent pulmonary embolism (PE) and deep vein thrombosis (DVT); (4) Prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

CONTRA-INDICATIONS: Hypersensitivity to rivaroxaban or any excipient of the tablets. ·Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding). Known existing inherited bleeding disorders.· Hepatic disease with or without coagulopathy. Safety and efficacy have not been established in pregnant women. Animal data show that rivaroxaban crosses the placental barrier. Therefore the use is contra-indicated throughout pregnancy. Safety and efficacy have not been established in breastfeeding mothers. Animal data indicate that rivaroxaban is secreted into breast milk. Therefore it may only be administered after breastfeeding is discontinued.

WARNINGS: Patients with prosthetic valves: Safety and efficacy have not been studied in patients with prosthetic heart valves; therefore, there are no data to support the use of XARELTO in this patient population. XARELTO should be used with caution in patients with an increased bleeding risk. Care should be taken if patients are treated concomitantly with medicines affecting haemostasis. Patients at risk of ulcerative gastrointestinal disease, an appropriate prophylactic treatment may be considered. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. XARELTO 15 and XARELTO 20 is to be used with caution in patients with moderate renal impairment (creatinine clearance < 50 to 30 ml/min) receiving co-medications leading to increased rivaroxaban plasma concentrations. No clinical data are available for patients with severe renal impairment (creatinine clearance < 15 ml/min). Therefore the use of XARELTO 15 and XARELTO 20 is not recommended in these patients

SIDE EFFECTS: Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for XARELTO 15 and XARELTO 20. Therefore, the possibility of a haemorrhage should be considered in evaluating the condition in any anticoagulated patient.

Please refer to an approved XARELTO 15 and XARELTO 20 package insert for full information.

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Confidence from Evidence and Real World Experience

♦ Millions of patients across multiple indications worldwide[a,1]

Only approved **once-daily** non-VKA oral anticoagulant for stroke prevention in adult patients with non-valvular atrial fibrillation with over 4 years of real world experience[1]

♦

Oral single-drug approach for treatment of pulmonary embolism or deep vein thrombosis and prevention of recurrent venous thromboembolism with over 3 years of Real World experience[b,1]

♦

First oral Factor Xa inhibitor **licensed in 2010** in venous thromboembolism in patients undergoing major orthopaedic surgery of the lower limbs[1]

♦

Broad real world experience[16–18]

Xarelto® – The World's Most Prescribed Non-VKA Oral Anticoagulant, Across Millions of Patients[a,19]

Please visit ThrombosisAdviser.com

[a]Calculation based on IMS Health MIDAS. Database: Monthly Sales December 2015. [b]Not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.

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Xarelto® rivaroxaban