

PRODUCT INFORMATION

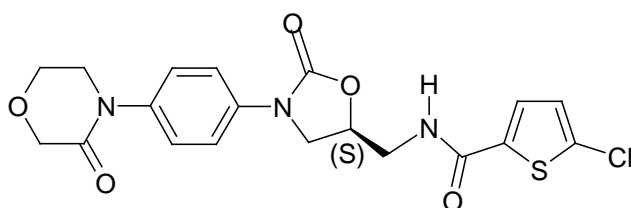
XARELTO® (rivaroxaban)

NAME OF THE MEDICINE

Xarelto (rivaroxaban) is a selective, direct acting Factor Xa inhibitor.

Rivaroxaban is 5-Chloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl)methyl)-2-thiophene-carboxamide. The empirical formula is C₁₉H₁₈ClN₃O₅S, molecular weight is 435.89 g / mole and CAS number is 366789-02-8.

Rivaroxaban has the following structural formula:



DESCRIPTION

Rivaroxaban is an odourless, non-hygroscopic white to yellowish powder. Rivaroxaban is practically insoluble in water and aqueous media in the pH range 1 to 9. An amount of approximately 5 - 7 mg/L rivaroxaban is pH-independently soluble in aqueous media at 25 °C. Rivaroxaban is only slightly soluble in organic solvents (e.g. acetone, polyethylene glycol 400).

Each film-coated tablet contains 10 mg, or 15 mg or 20 mg of rivaroxaban.

In addition, each Xarelto tablet contains:

Tablet core: Microcrystalline cellulose, croscarmellose sodium, lactose, hypromellose, sodium lauryl sulfate, magnesium stearate.

Filmcoat: Macrogol 3350, hypromellose, titanium dioxide, iron oxide red.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent

Mechanism of Action

Rivaroxaban is a highly selective direct Factor Xa inhibitor with oral bioavailability.

Activation of Factor X to Factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to

generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation. Selective inhibitors of FXa can terminate the amplified burst of thrombin generation. Consequently, several specific and global clotting tests are affected by rivaroxaban. Dose dependent inhibition of Factor Xa activity was observed in humans.

Pharmacodynamic effects

Dose dependent inhibition of Factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin[®] is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant

Table 1: 5/95 percentiles for PT (Neoplastin[®]) after tablet intake

	VTE Prevention in total hip and knee replacement	DVT Treatment and prevention of recurrent DVT and PE*		Stroke Prevention in Atrial Fibrillation	
Dosage	10 mg	15 mg bid	20 mg od	15 mg od	20 mg od
5/95 percentiles for PT (Neoplastin [®]) 2 – 4 hours after tablet intake (seconds)	13 – 25	16 – 33	15 – 30	10 – 50	14 – 40

*measurements of 5/95 percentiles for PT were recorded 1 – 4 hours after tablet intake
od = once daily, bid = twice daily

The activated partial thromboplastin time (aPTT) and HepTest[®] are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. Anti-Factor Xa activity is influenced by rivaroxaban (see “Effect on Laboratory Tests”).

There is no need for monitoring of coagulation parameters while using Xarelto.

No QTc prolonging effect was observed with rivaroxaban.

Pharmacokinetic properties

Absorption and Bioavailability

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake. The absolute bioavailability of rivaroxaban is high (80-100 %) for the 10 mg dose irrespective of fasting/fed conditions. Under fed conditions Xarelto 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. Oral bioavailability of Xarelto 20 mg tablet is reduced to 66% under fasting conditions. When Xarelto 20 mg tablet is taken with food mean AUC is increased by 39% compared to tablet taken under fasting conditions. This indicates almost complete absorption and high oral bioavailability.

Xarelto 10 mg tablets can be taken with or without food. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose. (see DOSAGE AND ADMINISTRATION).

Xarelto 15 mg and 20 mg tablets should be taken with food (see DOSAGE AND ADMINISTRATION). The data regarding food effect is limited.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %, apart from the day of surgery and the following day when variability in exposure is high (70%) in patients who underwent hip or knee replacement.

Distribution

Plasma protein binding in human is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 L.

Metabolism and Elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then eliminated renally and the other half eliminated by the fecal route. The other 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation.

Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma with no major or active circulating metabolites being present. With a systemic clearance of about 10 L/h rivaroxaban can be classified as a low-clearance drug. Elimination of rivaroxaban from plasma occurred with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Gender / Elderly (above 65 years)

Whilst elderly patients exhibited higher plasma concentrations than younger patients with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance, no dose adjustment is necessary (see DOSAGE AND ADMINISTRATION).

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients (see DOSAGE AND ADMINISTRATION).

Different weight categories

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Children and adolescents (from birth to 18 years)

No data are available for this patient population (see DOSAGE AND ADMINISTRATION).

Interethnic differences

No clinically relevant interethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics (see DOSAGE AND ADMINISTRATION).

Hepatic impairment

The critical aspect of liver impairment is the reduced synthesis of normal coagulation factors in the liver, which is captured by only one of the five clinical/biochemical measurements composing the Child Pugh classification system. The bleeding risk in patients may not clearly correlate with this classification scheme. Therefore, the decision to treat patients with an anticoagulant should be made independently of the Child Pugh classification.

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2-fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. No relevant difference in pharmacodynamic properties was observed between these groups. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3-fold compared to healthy volunteers, due to significantly impaired drug clearance which indicates significant liver disease. Unbound AUC was increased 2.6-fold. There are no data in patients with severe hepatic impairment. The inhibition of FXa activity was increased by a factor of 2.6 as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1.

The global clotting test PT assesses the extrinsic pathway that comprises of coagulation Factors VII, X, V, II, and I, which are synthesised in the liver. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT. The elevated PT at baseline and a significantly altered sensitivity in anti-coagulant activity towards rivaroxaban plasma exposure (increase in slope for PT/rivaroxaban plasma concentration relationship by more than 2-fold) in cirrhotic patients with moderate hepatic impairment indicate the decreased ability of the liver to synthesize coagulation factors. The PK/PD changes in these patients are markers for the severity of the underlying hepatic disease which is expected to lead to a subsequent increased bleeding risk in this patient group.

Therefore Xarelto is contraindicated in patients with significant hepatic disease (including moderate and severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk. No data are available for severe hepatic impairment (Child Pugh C patients) (see DOSAGE AND ADMINISTRATION). Xarelto may be used with caution in cirrhotic patients with moderate hepatic impairment if it is not associated with coagulopathy.

Renal impairment

Rivaroxaban exposure was inversely correlated to the decrease in renal function, as assessed via creatinine clearance (CrCl) measurements. In individuals with mild (creatinine clearance 50 - 80 mL/min), moderate (creatinine clearance 30 - 49 mL/min) and severe (creatinine clearance 15 - 29 mL/min) renal impairment, rivaroxaban plasma concentrations

(AUC) were 1.4, 1.5 and 1.6-fold increased respectively as compared to healthy volunteers (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Corresponding increases in pharmacodynamic effects were more pronounced (see DOSAGE AND ADMINISTRATION and PRECAUTIONS) in individuals with mild, moderate or severe renal impairment; the overall inhibition of FXa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers. Prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively.

There are no data in patients with CrCl < 15 mL/min. Use is contraindicated in patients with creatinine clearance < 15 mL/min (see CONTRAINDICATIONS). Xarelto 10 mg is to be used with caution in patients with severe renal impairment creatinine clearance 15 - 29 mL/min. Xarelto 15 mg and 20 mg are contraindicated in patients with CrCl < 30 mL/min. (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS and PRECAUTIONS).

Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis. The increased exposure to rivaroxaban further increases the risk of bleeding in these patients. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

If there is a suspicion of renal impairment, the degree of renal impairment must be determined accurately. Caution must be exercised when renal function estimates are based on eGFR. In clinical trials, renal function was determined using the calculated creatinine clearance, using the Cockcroft-Gault Formula as follows:

For serum creatinine concentration in mg/100 mL:

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

For serum creatinine concentration in µmol/L:

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

CLINICAL TRIALS

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs

The RECORD clinical program was designed to demonstrate the efficacy of rivaroxaban for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9,500 patients (7,050 in total hip replacement surgery and 2,531 in total knee replacement surgery) were studied in controlled randomised double-blind Phase III clinical studies, known as the RECORD-program.

RECORD 1 and 2 were conducted in patients undergoing elective total hip replacement surgery (THR) and RECORD 3 was performed in patients undergoing elective total knee replacement (TKR) surgery. Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery.

Table 2: Patient demographics – RECORD studies

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

Study	No of patients	N (%) / Sex		Mean age ± SD (years)
RECORD 1 (THR)	2209 rivaroxaban 2224 enoxaparin	1971(44.5)/ male	2462 (55.5)/ female	63.2 ± 11.4
RECORD 2 (THR)	1228 rivaroxaban 1229 enoxaparin	1139 (46)/ male	1318 (54)/ female	61.5 ± 13.4
RECORD 3 (TKR)	1220 rivaroxaban 1239 enoxaparin	781 (31.8)/ male	1678 (68.2)/ female	67.6 ± 9.0

The respective studies were heterogeneous with respect to their composition of participating countries (centres from Europe, North and South America, Asia and Australia). Men and women of 18 years or older scheduled for hip or knee replacement surgery could be enrolled provided that they had no active or high risk of bleeding or other conditions contraindicating treatment with low-molecular weight heparin, no significant liver disease, were not pregnant or breastfeeding, or were not using HIV protease inhibitors.

In all three pivotal studies, rivaroxaban 10 mg once daily started not earlier than 6 hours postoperatively was compared with enoxaparin 40 mg once daily started 12 hours preoperatively.

The primary efficacy analysis in all studies was based on stratified (by geographical region) risk difference between rivaroxaban and enoxaparin and corresponding 2-sided 95% confidence intervals. Efficacy was assessed in two steps; first a non-inferiority test was performed based on the per protocol population. Since non-inferiority was shown, a pre-specified superiority analysis was performed subsequently based on the modified ITT population.

In all three phase III studies (see Table 3) rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non-fatal PE or death) and major VTE (proximal DVT, non-fatal PE or VTE-related death), the pre-specified primary and major secondary efficacy endpoints. The results were clinically meaningful and statistically significant. Relative risk reductions in total VTE were 49% (RECORD 3) and 70% (RECORD 1) in comparison to enoxaparin and 79% (RECORD 2) in comparison to enoxaparin/placebo. Furthermore in all three studies the rate of symptomatic VTE (symptomatic DVT, non-fatal PE, VTE-related death) was lower in rivaroxaban treated patients compared to patients treated with enoxaparin.

The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

The analysis of the pooled results of the Phase III trials corroborated the data obtained in the individual studies regarding reduction of total VTE, major VTE and symptomatic VTE with rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily.

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

Table 3: Efficacy and safety results from Phase III RECORD (VTE Prevention in THR, TKR)

	RECORD 1			RECORD 2			RECORD 3		
Study Population	4541 patients undergoing total hip replacement surgery			2509 patients undergoing total hip replacement surgery			2531 patients undergoing total knee replacement surgery		
Treatment dosage and duration after surgery	Rivaroxaban 10 mg od 35 ± 4 days n (%)	Enoxaparin 40 mg od 35 ±4 days n (%)	p value	Rivaroxaban 10 mg od 35 ±4 days n (%)	Enoxaparin 40 mg od 12 ± 2 days n (%)	p value	Rivaroxaban 10 mg od 12± 2 days n (%)	Enoxaparin 40 mg od 12 ±2 days n (%)	p value
Total VTE	18 (1.1%)	58 (3.7%)	<0.001	17 (2.0%)	81 (9.3%)	<0.001	79 (9.6%)	166 (18.9%)	<0.001
Major VTE	4 (0.2%)	33 (2.0%)	<0.001	6 (0.6%)	49 (5.1%)	<0.001	9 (1.0%)	24 (2.6%)	0.01
Symptomatic VTE	6 (0.4%)	11 (0.7%)	--	3 (0.4%)	15 (1.7 %)	--	8 (1.0%)	24 (2.7%)	--
Major bleedings	6 (0.3 %)	2 (0.1%)	--	1 (0.1%)	1 (0.1%)	--	7 (0.6%)	6 (0.5%)	--
PE (non-fatal)	4 (0.3%)	1 (<0.1%)	--	1 (0.1%)	4 (0.5%)	--	0 (0.0)	4 (0.5%)	--
Death (any cause)	4 (0.3%)	4 (0.3%)	--	2 (0,2%)	6 (0.7%)	--	0 (0.0)	2 (0.2%)	--
VTE related death	0 (0%)	1 (<0.1%)	--	0 (0%)	1 (0.1%)	--	0 (0%)	0 (0%)	--

n = number of events; (%) = percentage

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

The ROCKET-AF clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF).

In the pivotal randomised, double-blind, double-dummy, parallel-group, event-driven, non-inferiority ROCKET-AF study comparing once daily oral rivaroxaban with adjusted-dose oral warfarin, 14,264 patients were assigned either to rivaroxaban 20 mg orally once daily (15 mg orally once daily in patients with CrCl 30 - 49 mL/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

Patients included in the trial had non-valvular atrial fibrillation and a history of prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or two or more of the following risk factors without prior stroke:

- age \geq 75 years,
- hypertension,
- heart failure or left ventricular ejection fraction \leq 35%, or
- diabetes mellitus

The mean age of patients was 71 years with 44% > 75 years. The population was 60% male, 83% Caucasian, 13% Asian and 4% other. There was a history of stroke, TIA, or non-CNS systemic embolism in 55% of patients, and 38% of patients had not taken a vitamin K antagonist (VKA) within 6 weeks at time of screening. At baseline, 37% of patients were on aspirin (almost exclusively at a dose of 100 mg or less). A few patients were on clopidogrel and 11.4 % on class III antiarrhythmics including amiodarone. The study included patients with co morbidities e.g. 55% secondary prevention population (prior stroke/ TIA/ Systemic embolism), hypertension 91%, diabetes 40%, congestive heart failure 63%, and prior myocardial infarction 17%. Patients with various degree of renal impairment were included in the study, see Table 4 for details.

Table 4: Baseline patient numbers for creatinine clearance groups

CrCl ml/min (degree of renal impairment)	rivaroxaban n = 7123	warfarin n = 7124
<30 (severe)	4 (0.1)	4 (0.1)
30 - 49 (moderate)	1503 (21.1)	1475 (20.7)
50 - 80 (mild)	3321 (46.6)	3414 (47.9)
> 80 (normal)	2295 (32.2)	2231 (31.3)

Exclusion criteria included:

- cardiac related conditions (haemodynamically significant mitral valve stenosis, prosthetic heart valve, planned cardioversion, transient atrial fibrillation caused by reversible disease, known presence of atrial myxoma or left ventricular thrombus and active endocarditis),
- haemorrhage risk related conditions (active internal bleeding, major surgical procedure or trauma within 30 days before randomisation, clinically significant gastrointestinal (GI) bleeding within 6 months of randomisation, history of intracranial, intraocular, spinal or atraumatic intra-articular bleeding, chronic haemorrhagic disorder, known intracranial neoplasm, arteriovenous malformation, or aneurysm)
- planned invasive procedure with potential for uncontrolled bleeding

- sustained uncontrolled hypertension (>180/100 mm Hg)
- concomitant conditions and therapies listed under CONTRAINDICATIONS as well as severe disabling stroke (modified Rankin score 4-5) or any stroke within 14 days, TIA within 3 days, >100 mg acetylsalicylic acid (ASA), anticipated need for chronic NSAIDs treatment, known HIV infection at the time of screening, significant hepatic impairment or (ALT > 3 x ULN)

The Principal Investigators were instructed to dose their patients with warfarin orally once daily, dose-adjusted to a target International Normalised Ratio [INR] of 2.5 [range 2.0 to 3.0, inclusive]. During the study, INR monitoring (using a Hemosense® point-of-care INR device [INRatio®]) was to occur as clinically indicated but at least every 4 weeks. Unblinded INR measurements were not performed while subjects were on study drug, except in case of a medical emergency.

In order to maintain the integrity of the blind, local unblinded INR measurements (i.e., not using the study Hemosense INRatio® device) were discouraged for at least 3 days after subjects stopped receiving study drug (after the start of open-label VKA therapy), including when the subject discontinued study medication, or completed the study. After 3 days, VKA dosing was managed using local unblinded INR measurements.

Comparative efficacy with standard of care (warfarin) in the double blind clinical trial setting provides evidence that rivaroxaban is as effective as warfarin. There is insufficient experience to determine how Xarelto and warfarin compare when warfarin therapy is well controlled.

Unlike some other contemporary trials, these committees did not provide detailed and focused direction to the sites about their handling of individual patient INRs, since one goal of the trial was to run the study as close to usual care as possible, to maximize generalisability of the final results to standard practice.

The primary objective of the study was met, as Xarelto was shown to be non-inferior to warfarin in the primary efficacy endpoint, composite of stroke and systemic embolism (HR 0.79, 95% CI 0.66 – 0.96, $p < 0.001$). As non-inferiority was met, Xarelto was tested, as per the pre-specified analysis, for superiority in primary and secondary endpoints. Xarelto demonstrated superiority over warfarin for stroke and systemic embolism in the on treatment, safety population (HR 0.79, 95% CI 0.65 – 0.95, $p = 0.015$). Major secondary endpoints; composite of stroke, systemic embolism and vascular death and composite of stroke, systemic embolism, myocardial infarction (MI) and vascular death were also reduced significantly (see Table 5).

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 6).

Table 5: Efficacy results from Phase III ROCKET AF (Stroke Prevention in AF)

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

Study Population	Patients with non-valvular atrial fibrillation (AF) ^		
Treatment Dosage	Rivaroxaban 20 mg orally od (15 mg orally od in patients with CrCl 30 to 49 mL/min) N=7061 Event Rate (100 Pt-yr)#	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) N=7082 Event Rate (100 Pt-yr) #	Hazard Ratio (95% CI) p-value
Stroke and Non-CNS Systemic embolism	189 (1.70)	243 (2.15)	0.79 (0.65-0.95) 0.015*
Stroke, Non-CNS Systemic embolism and Vascular Death	346 (3.11)	410 (3.63)	0.86 (0.74-0.99) 0.034*
Stroke, Non-CNS Systemic embolism, Vascular Death and MI	433 (3.91)	519 (4.62)	0.85 (0.74-0.96) 0.010*
Stroke	184 (1.65)	221 (1.96)	0.85 (0.70 - 1.03) 0.092
Non-CNS Systemic Embolism	5 (0.04)	22 (0.19)	0.23 (0.09 - 0.61) 0.003**
All-cause Mortality	208 (1.87)	250 (2.21)	0.85 (0.70 - 1.02) 0.073 ^a

^ Safety population, on treatment = All ITT subjects who take at least 1 dose of study medication after randomisation during double-blind treatment period or within 2 days after discontinuation (site 042012 was excluded for efficacy analysis)

Number of events per 100 patient years of follow up

* Statistically significant at 0.025 (one-sided) for non-inferiority and 0.05 (two-sided) for superiority in favour of rivaroxaban

** Statistically significant at nominal alpha = 0.05 (two sided)

a p value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio

Table 6: Safety results from Phase III ROCKET AF (Stroke Prevention in AF)

Study Population	Patients with non-valvular atrial fibrillation (AF) ^		
Treatment Dosage	Rivaroxaban 20 mg orally od (15 mg orally od in patients with CrCl 30 to 49 mL/min) N=7111 Event Rate (100 Pt-yr) #	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) N=7125 Event Rate (100 Pt-yr) #	Hazard Ratio (95% CI) p-value
Major and Non-major Clinically Relevant bleeding events	1475 (14.91)	1449 (14.52)	1.03 (0.96 - 1.11) 0.442
Major bleeding events	395 (3.60)	386 (3.45)	1.04 (0.90 - 1.20) 0.576
Death due to bleeding	27 (0.24)	55 (0.48)	0.50 (0.31,0.79) 0.003*
Critical Organ Bleeding	91 (0.82)	133 (1.18)	0.69 (0.53 - 0.91) 0.007*
Intracranial haemorrhage	55 (0.49)	84 (0.75)	0.67 (0.47-0.93) 0,019*

Study Population	Patients with non-valvular atrial fibrillation (AF) ^		
Treatment Dosage	Rivaroxaban 20 mg orally od (15 mg orally od in patients with CrCl 30 to 49 mL/min) N=7111 Event Rate (100 Pt-yr) #	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) N=7125 Event Rate (100 Pt-yr) #	Hazard Ratio (95% CI) p-value
Haemoglobin drop	305 (2.77)	254 (2.26)	1.22 (1.03 - 1.44) 0.019*
Transfusion of 2 or more units of packed red blood cells or whole blood.	183 (1.65)	149 (1.32)	1.25 (1.01 - 1.55) 0.044*
Non-major Clinically Relevant bleeding events	1185 (11.80)	1151 (11.37)	1.04 (0.96 - 1.13) 0.345

^ Safety population, on treatment = All ITT subjects who take at least 1 dose of study medication after randomisation during double-blind treatment period or within 2 days after discontinuation (site 042012 was excluded for efficacy analysis)

Number of events per 100 patient years of follow up

* Statistically significant at nominal alpha = 0.05 (two sided)

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) and prevention of recurrent DVT and Pulmonary Embolism

The EINSTEIN clinical program was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrent DVT and PE. Over 9400 patients were studied in three randomised controlled Phase III clinical studies (EINSTEIN DVT, EINSTEIN PE and EINSTEIN Extension) and additionally a predefined analysis of the pooled EINSTEIN DVT and EINSTEIN PE studies was conducted (see Table 10). The overall combined treatment duration in all studies was up to 21 months.

All Phase III studies used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all-cause mortality.

EINSTEIN DVT and EINSTEIN PE studies

In the EINSTEIN DVT and EINSTEIN PE, open label, randomised, event driven non-inferiority studies, 3449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE; 4832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. Concomitant conditions listed under CONTRAINDICATIONS as well as subjects who had significant liver disease or ALT > 3 x ULN, bacterial endocarditis, VKA treatment indicated other than DVT and/or PE were excluded from these studies.

Based on the clinical judgement of the investigator, the treatment duration was up to 12 months in both studies, assigned prior to randomisation, For the initial 3 week treatment of acute DVT and acute PE, 15 mg of Xarelto was administered twice daily. This was followed by 20 mg of Xarelto once daily. Patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) were treated with the same dose as patients with creatinine clearance above 50 mL/min (i.e. 15 mg twice daily for the first three weeks and 20 mg once daily from day 22 onwards). The comparator treatment regimen consisted of enoxaparin administered for at

least 5 days in combination with vitamin K antagonist treatment until the prothrombin time/international normalised ratio (PT/INR) was in therapeutic range (≥ 2.0). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

After randomisation, subjects allocated to the comparator arm received enoxaparin twice daily for at least 5 days in combination with VKA (overlap 4 to 5 days) and continued with VKA only after the INR had been ≥ 2 for two consecutive measurements at least 24 hours apart. Warfarin and acenocoumarol were allowed as VKAs. Warfarin and acenocoumarol were to be started not later than 48 hours after randomisation. VKA dosages were individually titrated and adjusted to achieve a target INR of 2.5 and maintain the INR within the therapeutic range (range 2.0-3.0) for either 3, 6 or 12 months. The INR had to be measured initially every 2 to 3 days, and at least once monthly once stable. Each centre had to specify before study start which VKA compound (warfarin or acenocoumarol) would be used during the study.

In the ITT analysis of EINSTEIN DVT, subjects were comparable between treatment groups. About 57% of subjects were male. The race of about 77% of subjects was described as white, about 13% as Asian, and about 2% as black. Age ranged from 18-95 years in the rivaroxaban and from 18-97 years in the enoxaparin/VKA group, with a mean of approximately 56 years in both groups. Mean body weight was about 82 kg, with ranges from 33 to 193 kg.

In the ITT analysis of EINSTEIN PE, subjects were comparable between treatment groups. 54.1% and 51.7% were men in the rivaroxaban and enoxaparin / VKA groups respectively. The race of about 66% of subjects was described as white. Age ranged from 18 to 97 years, with a mean of approximately 58 years in both treatment groups. Mean body weight was about 83 kg, ranging from 35 to 220 kg.

Table 7: Baseline patient numbers for creatinine clearance groups in EINSTEIN DVT and EINSTEIN PE

Creatinine clearance (mL/min)	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban n = 1525	Enox/VKA n = 1571	Rivaroxaban n = 2419	Enox/VKA n = 2413
< 30 mL/min (severe)	6 (0.3%)	9 (0.5%)	4 (0.2%)	2 (< 0.1%)
30 - 49 mL/min (moderate)	115 (6.6%)	120 (7.0%)	207 (8.6%)	191 (7.9%)
50 - 80 mL/min (mild)	393 (22.7%)	399 (23.2%)	637 (26.3%)	593 (24.6%)
> 80 mL/min (normal)	1193 (68.9%)	1170 (68.1%)	1555 (64.3%)	1617 (67.0%)

EINSTEIN-DVT (see Table 8) met its principal objective, demonstrating that Xarelto was non-inferior to enoxaparin/VKA for the primary outcome of symptomatic recurrent VTE (HR of 0.68 [95% CI = 0.44 – 1.04], $p < 0.001$). The pre-specified test for superiority was not statistically significant ($p = 0.0764$). The incidence rates for the principal safety outcome (major or clinically relevant non-major bleeding events), as well as the secondary safety outcome (major bleeding events), were similar for both groups (HR of 0.97 [95% CI = 0.76 – 1.22], $p = 0.77$ and HR of 0.65 [95% CI = 0.33 – 1.30], $p = 0.21$, respectively). The pre-defined secondary outcome of net clinical benefit, (the composite of the primary efficacy outcome and major bleeding events), was reported with a HR of 0.67 ([95% CI = 0.47 – 0.95], $p = 0.03$) in favour of Xarelto.

The relative efficacy and safety findings were consistent regardless of pre-treatment (none, LMWH, unfractionated heparin or fondaparinux) as well as among the 3, 6 and 12-month durations. In terms of other secondary outcomes, vascular events occurred in 12 patients (0.7%) in the Xarelto arm and 14 patients (0.8%) in the enoxaparin/VKA group (HR of 0.79 [95% CI = 0.36 – 1.71], p = 0.55), and total mortality accounted for 38 (2.2%) vs. 49 (2.9%) patients in the Xarelto vs. enoxaparin/VKA arms, respectively (p = 0.06).

Table 8: Efficacy and safety results from Phase III EINSTEIN DVT (DVT treatment)

Study Population	3449 patients with symptomatic acute deep vein thrombosis	
Treatment Dosage and Duration	Xarelto 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N=1731	Enoxaparin for 5 days followed by VKA 3, 6 or 12 months N=1718
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/Death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major bleeding events	14 (0.8%)	20 (1.2%)
All-cause Mortality	38 (2.2%)	49 (2.9%)

*p: < 0.0001 (non-inferiority), 0.076 (superiority), HR: 0.680 (0.443 - 1.042)

In the EINSTEIN PE study (see Table 9) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p = 0.0026 (test for non-inferiority); hazard ratio: 1.12 (0.75 – 1.68)). The pre-specified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.85 ((95% CI: 0.63 - 1.14), nominal p value p = 0.275).

The incidence rate for the primary safety outcome (major or clinically relevant non-major bleeding events) was slightly lower in the rivaroxaban treatment group (10.3% (249/2412)) than in the enoxaparin/VKA treatment group (11.4% (274/2405)). The incidence of the secondary safety outcome (major bleeding events) was lower in the rivaroxaban group (1.1% (26/2412)) than in the enoxaparin/VKA group (2.2% (52/2405)) with a hazard ratio 0.49 (95% CI: 0.31 - 0.79; p-value for superiority 0.0032).

Table 9: Efficacy and safety results from Phase III EINSTEIN PE (PE treatment)

Study population	4,832 patients with an acute symptomatic PE	
Treatment dosage and duration	Xarelto 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N = 2419	Enoxaparin for 5 days followed by VKA 3, 6 or 12 months N = 2413
Symptomatic recurrent VTE*	50 (2.1%)	44 (1.8%)
Symptomatic recurrent PE	23 (1.0%)	20 (0.8%)

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

Study population	4,832 patients with an acute symptomatic PE	
Treatment dosage and duration	Xarelto 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N = 2419	Enoxaparin for 5 days followed by VKA 3, 6 or 12 months N = 2413
Symptomatic recurrent DVT	18 (0.7%)	17 (0.7%)
Symptomatic PE and DVT	0	2 (< 0.1%)
Fatal PE/Death where PE cannot be ruled out	11 (0.5%)	7 (0.3%)
Major bleeding events	26 (1.1%)	52 (2.2%)

* p < 0.0026 (non-inferiority); hazard ratio: 1.12 (0.75 – 1.68)

A prespecified pooled analysis of the outcome of the EINSTEIN DVT and PE studies was conducted (see Table 10).

Table 10: Efficacy and safety results from pooled analysis of Phase III EINSTEIN DVT and EINSTEIN PE

Study population	8,281 patients with an acute symptomatic DVT or PE	
Treatment dosage and duration	Xarelto 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N = 4,150	Enoxaparin for 5 days followed by VKA 3, 6 or 12 months N = 4,131
Symptomatic recurrent VTE*	86 (2.1%)	95 (2.3%)
Symptomatic recurrent PE	43 (1.0%)	38 (0.9%)
Symptomatic recurrent DVT	32 (0.8%)	45 (1.1%)
Symptomatic PE and DVT	1 (<0.1%)	2 (<0.1%)
Fatal PE/Death where PE cannot be ruled out	15 (0.4%)	13 (0.3%)
Major bleeding events	40 (1.0%)	72 (1.7%)

* p < 0.001 (non-inferiority); hazard ratio: 0.89 (0.66 – 1.19)

EINSTEIN Extension study

EINSTEIN Extension, a double blind, randomised, event driven superiority study included 1,197 patients with confirmed symptomatic DVT or PE. Xarelto 20 mg once daily was compared with placebo for an additional 6 to 12 months in patients who had completed initial treatment for DVT or PE for 6 to 14 months; where clinical uncertainty with respect to the need for continued anticoagulation existed. Patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) were treated with the same dose as patients with creatinine clearance above 50 mL/min (i.e. 20 mg once daily). The treatment duration, assigned prior to randomisation, was based on the clinical judgement of the investigator.

In the EINSTEIN-Extension study (see Table 11), Xarelto was superior to placebo for the primary efficacy outcome with a HR of 0.18 [95% CI = 0.09 – 0.39], p <0.001 (i.e. a relative risk reduction of 82%). For the principal safety outcome (major bleeding events) there was no significant difference between patients treated with Xarelto compared to placebo (p = 0.11). Therefore, the pre-defined secondary outcome of net clinical benefit, defined as the composite

of the primary efficacy outcome and major bleeding events, was reported with a HR of 0.28 ([95% CI = 0.15 – 0.53], $p < 0.001$) in favour of Xarelto.

Table 11: Efficacy and safety results from Phase III EINSTEIN EXTENSION (Prevention of recurrent DVT and PE)

Study Population	1197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment Dosage and Duration	Xarelto 20 mg OD 6 or 12 months N = 602	Placebo 6 or 12 months N = 594
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Fatal PE/Death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
All-cause mortality	38 (2.2%)	49 (2.9%)

* $p < 0.0001$ (superiority), HR: 0.185 (0.087 - 0.393)

In terms of other secondary outcomes, vascular events occurred in 3 patients in the Xarelto arm and 4 patients in the placebo group (HR of 0.74 [95% CI = 0.17 – 3.3], $p = 0.69$), and total mortality accounted for 1 (0.2%) vs. 2 (0.3%) of patients in the Xarelto vs. placebo arms, respectively.

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).
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and PE.

CONTRAINDICATIONS

Xarelto is contraindicated in patients:

- who are hypersensitive to the active substance or to any of the excipients,
- with clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding),
- with lesions at increased risk of clinically significant bleeding and patients with spontaneous impairment of haemostasis,
- with significant hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk (see PRECAUTIONS and Pharmacokinetic properties),

- undergoing dialysis or patients with severe renal impairment with a creatinine clearance < 30 mL/min for Xarelto 15 mg and 20 mg tablets, (CrCl < 15 mL/min for Xarelto 10 mg) due to increased plasma levels which may lead to an increased risk of bleeding (see Pharmacokinetic properties and PRECAUTIONS),
- concomitantly treated 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) (see Interactions with Other Medicines).
- who are pregnant (see Use in Pregnancy)
- who are breast-feeding (see Use in Lactation)

PRECAUTIONS

Haemorrhagic risk

Like other anticoagulants, Xarelto increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe Xarelto to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding. Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding which may result in posthaemorrhagic anaemia (see ADVERSE EFFECTS). Several sub-groups of patients as detailed below are at increased risk of bleeding. These patients are to be carefully monitored for signs of bleeding complications after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Haemorrhagic complications may present as weakness, paleness, dizziness, headache, or unexplained swelling, dyspnoea, and unexplained shock.

Patients at high risk of bleeding should not be prescribed Xarelto (see CONTRAINDICATIONS).

Close clinical surveillance is recommended in presence of multiple risk factors for bleeding including pharmacokinetic factors (renal impairment, hepatic impairment, drug interactions), pharmacodynamic interactions (NSAIDs, platelet aggregation inhibitors), and general haemorrhagic risk factors (see below).

General haemorrhagic risk factors

Xarelto like other antithrombotics 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
- concomitant use of medicines affecting haemostasis

- bronchiectasis or history of pulmonary bleeding

For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

Other risk factors

Renal impairment

Xarelto is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) receiving co-medications (including moderate inhibitors of CYP3A4 or P-gp) leading to increased rivaroxaban plasma concentrations (see Interactions with Other Medicines). In patients with severe renal impairment (creatinine clearance < 30 mL/min) rivaroxaban plasma levels may be significantly increased, which may lead to an increased bleeding risk. Due to the underlying disease these patients are also at an increased risk of both bleeding and thrombosis. Due to limited clinical data Xarelto 10 mg should be used with caution in patients with CrCl 15 - 29 mL/min. Xarelto 15 mg and 20 mg should not be used in patients with CrCl < 30 mL/min. Patients on dialysis have not been studied, Xarelto should not be used in this population (see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, PHARMACOLOGY).

No clinical data are available for patients with creatinine clearance less than 15 mL/min. Therefore use of Xarelto is contraindicated in these patients (see CONTRAINDICATIONS).

Hepatic impairment

Xarelto is contraindicated in patients with significant hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk. Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity. Xarelto may be used in cirrhotic patients with moderate hepatic (Child Pugh B) impairment if it is not associated with coagulopathy (see PHARMACOLOGY and CONTRAINDICATIONS).

Strong CYP 3A4 and P-gp inhibitors

Xarelto is contraindicated in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP 3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES). However, fluconazole, a less potent CYP3A4 and P-gp inhibitor has less effect on rivaroxaban and may be co-administered (see Table 12 and Table 13).

Concomitant medications

Non-steroidal anti-inflammatory drugs

Care should be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs) as these drugs may impact haemostasis (see INTERACTION WITH OTHER MEDICINES).

Anticoagulants

Co administration of Xarelto with other anticoagulants has not been studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk (see INTERACTION WITH OTHER MEDICINES).

Platelet aggregation inhibitors

Care should be taken if patients are treated concomitantly with platelet aggregation inhibitors (e.g. clopidogrel and acetylsalicylic acid) as it may lead to an increased bleeding risk (see INTERACTION WITH OTHER MEDICINES). For patients on antiplatelet therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases.

Management of bleeding

Should bleeding occur, management of the haemorrhage may include the following steps:

- Identify and treat the underlying cause of the bleeding
- Where no source of bleeding can be identified, delay of next rivaroxaban administration or discontinuation of treatment as appropriate. Rivaroxaban has a terminal half-life between 5 and 13 hours (see Pharmacokinetic properties). Management should be individualised according to the severity and location of the haemorrhage. A specific agent to reverse the anti-coagulant effect of rivaroxaban is not yet available. Because of high plasma protein binding, rivaroxaban is not expected to be dialysable. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.
- appropriate symptomatic treatment, e.g. mechanical compression, surgical interventions, fluid replacement and haemodynamic support, blood product (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If life threatening bleeding cannot be controlled by the above measures, administration of one of the following procoagulants may be considered:

- activated prothrombin complex concentrate (APCC)
- prothrombin complex concentrate (PCC)
- recombinant factor VIIa.

While there is currently no experience with the use of these products in individuals receiving Xarelto, all three procoagulants have demonstrated significant reductions in rivaroxaban-induced bleeding time prolongation in nonclinical studies.

There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving Xarelto. There is neither scientific rationale for benefit nor experience with the systemic haemostatics desmopressin and aprotinin in individuals receiving Xarelto.

Surgery and interventions

If an invasive procedure or surgical intervention is required, based on clinical judgement of the physician, Xarelto should be stopped at least 24 hours before the intervention if possible. Individual patient factors will need to be taken into account in the decision as to how long Xarelto should be stopped prior to surgery. Consider longer duration of treatment cessation

based on benefit/risk with patients at higher risk of bleeding or in cases of major surgery where complete haemostasis may be required.

A specific agent to reverse the anti-coagulant effect of rivaroxaban is not yet available. 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 (see Metabolism and Elimination and Effect of Laboratory Tests).

Patients with prosthetic valves

Safety and efficacy of Xarelto has not been studied in patients with prosthetic heart valves. Therefore, there are no data to support that Xarelto 20 mg (15 mg in patients with moderate renal impairment) provides adequate anti-coagulation in this patient population.

Spinal / epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal / epidural anaesthesia) or spinal /epidural puncture is performed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention, the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

An epidural catheter is not to be removed earlier than 18 hours after the last administration of Xarelto. The next Xarelto dose is to be administered not earlier than 6 hours after the removal of the catheter.

If traumatic puncture occurs the administration of Xarelto is to be delayed for 24 hours.

Hip fracture surgery

Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, Xarelto is not recommended in these patients.

DVT and PE treatment: Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Xarelto is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Xarelto have not been established in these clinical situations.

Lactose intolerance

Xarelto contains lactose. Patients with rare hereditary problems of lactose or galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Xarelto.

Information for the Patient

A Consumer Medicine Information leaflet is available. Please advise your patient to read this information carefully.

Effects on Fertility

Rivaroxaban did not affect male or female fertility at oral doses up to 200 mg/kg/day in Wistar rats, which corresponds to 33-fold (males) and 49-fold (females) the unbound rivaroxaban AUC in humans at the maximum recommended dose.

Use in Pregnancy

Pregnancy Category C

There are no data from the use of rivaroxaban in pregnant women. Thrombolytic agents can produce placental haemorrhage and subsequent prematurity and fetal loss.

Studies in rats and rabbits were affected by the anticoagulant effects of rivaroxaban on the mother. In rats, altered placental appearance and necrosis were observed at doses ≥ 10 mg/kg/day (4 times human exposure based on unbound plasma AUC). A NOAEL in rats for embryofetal development was established at 35 mg/kg/day (17 times human exposure based on unbound plasma AUC).

In rabbits, abortions occurred at doses ≥ 10 mg/kg/day (11 times human exposure based on unbound plasma AUC), while deaths occurred at doses ≥ 40 mg/kg/day (52 times human exposure based on unbound plasma AUC). Changes in placental appearance (course, grained and/or necrotic) were also noted at doses ≥ 10 mg/kg/day. A NOAEL in rabbits for embryofetal development was established at 2.5 mg/kg/day (3 times human exposure based on unbound plasma AUC). In rats and rabbits rivaroxaban showed pronounced maternal toxicity with placental changes related to its pharmacological mode of action (e.g., haemorrhagic complications) leading to reproductive toxicity. No primary teratogenic potential was identified. Due to the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated in pregnancy (see CONTRAINDICATIONS). Xarelto should be used in women of childbearing potential only with effective contraception.

Use in Lactation

No data on the use of rivaroxaban in nursing mothers are available. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-feeding (see CONTRAINDICATIONS).

[¹⁴C] rivaroxaban was administered orally to lactating Wistar rats (day 8 to 10 post partum) as a single oral dose of 3 mg/kg body weight. [¹⁴C] rivaroxaban-related radioactivity was secreted into the milk of lactating rats only to a low extent in relation to the administered dose. The estimated amount of radioactivity excreted into milk was 2.12 % of the maternal dose within 32 hours after administration.

Paediatric Use

Xarelto is not recommended for use in children or adolescents below 18 years of age due to a lack of data on safety and efficacy (see DOSAGE AND ADMINISTRATION and Pharmacokinetic properties).

Use in Elderly

No dose adjustment is required for the elderly (> 65 years of age). It should be taken into consideration that increasing age may be associated with declining renal and hepatic function (see CONTRAINDICATIONS, PRECAUTIONS and Pharmacokinetic properties).

Different Gender and Different Weight Categories

No dose adjustment is required for these patient populations (see Pharmacokinetic properties).

Carcinogenicity

Testing was performed by oral dosing for 2 years at up to 60 mg/kg/day reaching unbound plasma rivaroxaban exposure levels similar to humans (mice) or up to 3.6-fold higher (rats) than in humans.

Rivaroxaban showed no carcinogenic potential in either species.

Genotoxicity

Rivaroxaban showed no genotoxicity potential in bacterial mutagenicity tests, chromosomal aberration assays in Chinese hamster cells or in an *in vivo* mouse micronucleus assay.

Effect on Laboratory Tests

Xarelto at recommended doses prolongs the global clotting tests prothrombin time (PT), activated partial thromboplastin time (aPTT), HepTest[®], as well as the specific clotting test, anti-Factor Xa activity. PT is influenced by Xarelto in a dose-dependent manner if Neoplastin[®] is used for the assay. The 5/95 percentiles of PT (Neoplastin[®]) 2 to 4 hours after tablet intake (i.e. at the time of maximum effect) is described in Table 1 (see Pharmacodynamic effects). In case of excessive doses, the PT is expected to be outside of this range. Although aPTT, anti-Factor Xa activity and HepTest[®] are also prolonged dose-dependently, none of these reliably assesses the pharmacodynamic effects of Xarelto.

During any conversion period when warfarin and Xarelto are overlapped, the pharmacodynamic effects of rivaroxaban can be tested with the anti-Factor Xa activity, PiCT (Prothrombinase-induced Clotting Time), and HepTest[®] assays, as these tests were not affected by warfarin. Four days after cessation of warfarin and onwards, all tests (including PT, aPTT, anti-Factor Xa activity and ETP) only reflected the effect of rivaroxaban (see DOSAGE AND ADMINISTRATION and Pharmacodynamic properties).

INR is not a valid measure for the anticoagulant activity of rivaroxaban, and therefore should not be used. If measurement of rivaroxaban exposure is required in special clinical situations (such as suspected overdose, or emergency settings), both prothrombin time and chromogenic anti-Factor Xa assays using validated rivaroxaban calibrators and controls have the potential to assess rivaroxaban plasma concentrations gravimetrically (ng/mL or µg/L). The pharmacokinetic profile of rivaroxaban has to be taken into account when interpreting results of these tests.

Effects on ability to drive and use machines

Syncope and dizziness have been reported and may affect the ability to drive and use machines (see ADVERSE EFFECTS). Patients experiencing these adverse reactions should not drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Pharmacokinetic interactions

Rivaroxaban is cleared mainly via cytochrome P450-mediated (CYP 3A4, CYP 2J2) hepatic metabolism and renal excretion of the unchanged drug, involving the P-glycoprotein (P-gp) / breast cancer resistance protein (Bcrp) transporter systems.

CYP Inhibition

Rivaroxaban does not inhibit CYP 3A4 or any other major CYP isoforms.

CYP Induction

Rivaroxaban does not induce CYP 3A4 or any other major CYP isoforms.

Effects on rivaroxaban

Strong inhibitors of both CYP3A4 and P-gp

The concomitant use of Xarelto with substances that strongly inhibit both CYP 3A4 and P-gp may lead to reduced hepatic and renal clearance and thus significantly increased systemic exposure of rivaroxaban.

Co-administration of Xarelto with the azole-antimycotic ketoconazole (400 mg od), a strong CYP 3A4 and P-gp inhibitor, led to a 2.6-fold increase in mean rivaroxaban steady state AUC and a 1.7-fold increase in mean rivaroxaban C_{max} , with significant increases in its pharmacodynamic effects.

Co-administration of Xarelto with the HIV protease inhibitor ritonavir (600 mg bid), a strong CYP 3A4 and P-gp inhibitor, led to a 2.5-fold increase in mean rivaroxaban AUC and a 1.6-fold increase in mean rivaroxaban C_{max} , with significant increases in its pharmacodynamic effects.

Therefore Xarelto is contraindicated in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (see CONTRAINDICATIONS). However, fluconazole (400 mg once daily) considered a less potent CYP3A4 and P-gp inhibitor led to an increase in rivaroxaban AUC and C_{max} within the magnitude of normal variability (see PRECAUTIONS and Table 12, Table 13 below).

Strong inhibitors of CYP3A4 or P-gp

Drugs strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP 3A4 or P-gp, increase rivaroxaban plasma concentrations to a level which is considered not clinically relevant (see Table 12, Table 13 below).

Patients with renal impairment taking P-gp and weak to moderate CYP3A4 inhibitors may have significant increases in exposure, which may increase bleeding risk.

Xarelto is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) receiving co-medications (including moderate inhibitors of CYP3A4 or P-gp) leading to increased rivaroxaban plasma concentrations (see PRECAUTIONS).

CYP3A4 inducers

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

The concomitant use of rivaroxaban with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced rivaroxaban plasma concentrations. Caution should be taken when Xarelto 15 and 20 mg tablets are co-administered with strong CYP3A4 inducers (see Table 13 below)

Table 12: Established or potential interactions which are clinically relevant

<i>Class (effect)</i> Examples	Effect on rivaroxaban plasma concentration	Clinical comment
<i>Strong CYP3A4 and strong P-gp inhibitor</i> Azole-antimycotics e.g. ketoconazole, itraconazole, voriconazole, posaconazole or HIV-protease inhibitors e.g. ritonavir	↑ rivaroxaban	Concomitant treatment with systemic azole-antimycotics or HIV-protease inhibitors is contraindicated.

Table 13: Established or potential interactions which are not clinically relevant

<i>Class (effect)</i> Examples	Effect on rivaroxaban plasma concentration	Clinical comment
CYP3A4 and P-gp inhibitor Fluconazole	↑ rivaroxaban	Fluconazole (400 mg once daily), considered as moderate CYP 3A4 inhibitor, led to a 1.4-fold increase in mean rivaroxaban AUC and a 1.3-fold increase in mean C _{max} . This increase is within the magnitude of the normal variability of AUC and C _{max} and is considered not clinically relevant.
<i>Strong CYP 3A4 and moderate P-gp inhibitor</i> Clarithromycin	↑ rivaroxaban	500 mg bid led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in C _{max} . This increase, which is close to the magnitude of the normal variability of AUC and C _{max} , is considered to be not clinically relevant.
<i>Moderate CYP3A4 and moderate P-gp inhibitor</i> Erythromycin	↑ rivaroxaban	500 mg tid led to a 1.3-fold increase in mean rivaroxaban steady state AUC and C _{max} . This increase is within the magnitude of the normal variability of AUC and C _{max} and is considered not clinically relevant.
<i>Other P-gp inhibitors</i> Cyclosporine, Amiodarone, Quinidine, Diltiazem, Verapamil	↑ rivaroxaban	Theoretically, due to the inhibition of P-gp mediated renal excretion, concomitant administration with Xarelto may lead to increased plasma rivaroxaban to a level which is considered not clinically relevant.
<i>Strong CYP 3A4 and P-gp inducer</i> Rifampicin	↓ rivaroxaban	Led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The decrease in rivaroxaban plasma concentration is considered not clinically relevant.
<i>Other CYP 3A4 inducers</i>	↓ rivaroxaban	Concomitant use with Xarelto may lead to a

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

<i>Class (effect)</i> Examples	Effect on rivaroxaban plasma concentration	Clinical comment
Anticonvulsants e.g. Phenytoin, Carbamazepine, Phenobarbitone or St John's Wort		decreased plasma rivaroxaban concentration.

Pharmacodynamic Interactions

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose), an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Co administration of Xarelto with other anticoagulant therapy has not been studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk (see PRECAUTIONS).

Converting patients from warfarin (INR 2.0 to 3.0) to Xarelto 20 mg or from Xarelto (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin[®]) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of Factor Xa activity and endogenous thrombin potential were additive. It should be noted that the anticoagulant effect of rivaroxaban does not correlate to INR values and therefore INR should not be used.

If it is desired to test the pharmacodynamic effects of Xarelto during the conversion period, anti-Factor Xa activity, PiCT, and HepTest can be used as these tests were not affected by warfarin. From day 4 after stopping warfarin onwards, all tests (including PT, aPTT, inhibition of Factor Xa activity and ETP) reflected only the effect of Xarelto (see DOSAGE AND ADMINISTRATION).

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and Xarelto.

Non-steroidal anti-inflammatory drugs

Bleeding time was prolonged after co-administration of naproxen (500 mg) and rivaroxaban (mean 11.3 minutes) as compared to naproxen (500 mg) alone (7.9 minutes) and rivaroxaban alone (6.1 minutes, normal range of bleeding time: 2 to 8 minutes). In the three Phase III trials (RECORD 1, 2, and 3) more than 70 % of subjects received concomitant NSAIDs with a similar risk of bleeding as compared to comparator treatment. However, due to the general impact on haemostasis, care should be taken if anticoagulated patients are treated concomitantly with NSAIDs (see PRECAUTIONS).

No clinically relevant prolongation of bleeding time was observed after concomitant administration of Xarelto (15 mg) and 500 mg naproxen. Nevertheless there may be individuals with more pronounced pharmacodynamic response (see PRECAUTIONS).

Platelet aggregation inhibitors

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction (with Xarelto 15 mg). Bleeding time was prolonged after co-administration of clopidogrel and rivaroxaban (mean 21.7 minutes) as compared to clopidogrel

alone (12.7 minutes) and rivaroxaban alone (7.7 minutes, normal range of bleeding time: 2 to 8 minutes) This increase in the combined treatment group was driven by a subset of patients in whom pronounced prolongations of bleeding times were observed. These prolongations of bleeding time did not correlate to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels. For patients on antiplatelet therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases. (see PRECAUTIONS).

Food and dairy products

Xarelto 10 mg can be taken with or without food (see Pharmacokinetic properties).

Xarelto 15 mg and 20 mg tablets should be taken with food (see Pharmacokinetic properties).

Interactions shown not to exist

There were no mutual pharmacokinetic interactions between rivaroxaban and midazolam (substrate of CYP 3A4), digoxin (substrate of P-gp) or atorvastatin (substrate of CYP 3A4 and P-gp).

Co-administration of the H₂ receptor antagonist ranitidine, the antacid aluminium hydroxide / magnesium hydroxide, naproxen, clopidogrel or enoxaparin did not affect rivaroxaban bio-availability and pharmacokinetics.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid (see PRECAUTIONS).

ADVERSE EFFECTS

The safety of rivaroxaban has been evaluated in nine Phase III studies including 18,403 patients exposed to rivaroxaban (see Table 14).

Table 14: Number of patients studied and treatment duration in Phase III studies

Indication	Number of patients	Maximum daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Treatment of DVT, PE and prevention of recurrent DVT and PE	4,556	Day 1 – 21: 30 mg Day 22 and onwards: 20mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

In total about 74% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events (regardless of causality). About 25% of patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients.

In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue and organ which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity (including possible fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. The risk of bleedings may be increased in certain patient groups e.g. patients with uncontrolled severe arterial hypertension and/or taking concomitant medications affecting haemostasis (see PRECAUTIONS). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, asthenia, 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. Therefore, the possibility of a haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

VTE Prevention in total hip and knee replacement

The safety of Xarelto has been evaluated in three Phase III studies including 4571 patients undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement) treated up to 39 days. In the population of subjects who have taken at least one dose of Xarelto 10 mg od, a total of 1191 subjects were included in the knee replacement trial with a scheduled treatment period of about 2 weeks and 3380 subjects included in the total hip replacement trials with a scheduled treatment period of about 5 weeks. The two treatment groups, rivaroxaban and enoxaparin/placebo showed very similar demographic and baseline characteristics.

The incidence of common treatment-emergent adverse reactions reported in the safety population was similar in both treatment groups for the three Phase III studies irrespective of treatment duration and for treatment period until Day 12 ± 2. The most frequently reported treatment-emergent adverse reactions in both treatment groups during both treatment periods were gastrointestinal disorders, in particular nausea; procedural complications such as post operative anaemia; and investigations, in particular related to liver function tests.

The adverse events and adverse reactions are presented within each system organ class; and should be interpreted within the surgical setting.

Adverse events and adverse reactions as reported by the investigators in the three Phase III studies are listed in Table 15 below by system organ class (in MedDRA). RECORD 1-3 trials were similar in study design and patient population, the dose regimen tested was rivaroxaban 10 mg od compare to enoxaparin 40 mg od.

Table 15: Treatment-emergent adverse events (AE) ≥1% (regardless of causality) and treatment emergent adverse reactions (ADR) starting after initiation of rivaroxaban, as reported by the investigators in patients in three Phase III studies (RECORD 1 to 3) 11354, 11357, 11356

Xarelto (10 mg od) N = 4657	Enoxaparin/Placebo (40 mg od) N = 4692
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Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

System Organ Class Medical Entity / Preferred Term	AE	ADR	AE	ADR
Blood and lymphatic system disorders				
Anaemia (incl. respective lab parameters)		54 (1.16%)		55 (1.17%)
Cardiac disorders				
Hypertension	77 (1.65%)		86 (1.83%)	
Hypotension	244 (5.24%)		238 (5.07%)	
Tachycardia	74 (1.59%)		71 (1.51%)	
Procedural hypotension	47 (1.01%)		34 (0.72%)	
Endocrine disorders				
Hyperglycaemia	43 (0.92%)		53 (1.13%)	
Gastrointestinal disorders				
Nausea	517 (11.10%)	69 (1.48%)	519 (11.06%)	86 (1.83%)
Constipation	318 (6.83%)		335 (7.14%)	
Diarrhoea	106 (2.28%)		137 (2.92%)	
Dyspepsia	42 (0.90%)		51 (1.09%)	
GI and abdominal pain	89 (1.91%)		93 (1.98%)	
Vomiting	452 (9.71%)		482 (10.27%)	
General disorders and administration site conditions				
Feeling unwell	92 (1.98%)		81 (1.73%)	
Fever	430 (9.23%)		444 (9.46%)	
Headache	108 (2.32%)		108 (2.30%)	
Peripheral Oedema	202 (4.34%)		168 (3.58%)	
Unspecific pain	285 (6.12%)		295 (6.29%)	
Infections and infestations				
Urinary tract infection	82 (1.76%)		90 (1.92%)	
Injury, Poisoning and Procedural Complications				
Arthralgia	65 (1.40%)		81 (1.73%)	
Post procedural haemorrhage (incl. postoperative anaemia and wound haemorrhage)	292 (6.27%)	123 (2.64%)	279 (5.95%)	109 (2.32%)
Wound healing complications	199 (4.27%)		161 (3.43%)	
Investigations				
Increase in blood alkaline phosphatase	38 (0.82%)		57 (1.21%)	
Increase in transaminases (incl. ALT increase, AST	150 (3.22%)	102 (2.19%)	208 (4.43%)	137 (2.92%)

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

increase)				
Increased gamma-glutamyltransferase	84 (1.80%)	56 (1.20%)	126 (2.69%)	73 (1.56%)
Increased lactate dehydrogenase	45 (0.97%)		56 (1.19%)	
Musculoskeletal and connective tissue disorders				
Increased muscle tone and cramping	62 (1.33%)		39 (0.83%)	
Nervous system disorders				
Dizziness	156 (3.35%)		144 (3.07%)	
Sleep disorders	191 (4.10%)		196 (4.18%)	
Syncope	60 (1.29%)		33 (0.70%)	
Renal and urinary disorders				
Urinary retention	84 (1.80%)		84 (1.79%)	
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	49 (1.05%)		58 (1.24%)	
Skin and subcutaneous tissue disorders				
Pruritus	110 (2.36%)		87 (1.85%)	
Rash	60 (1.29%)		57 (1.21%)	
Unspecific blistering	68 (1.46%)		43 (0.92%)	
Social circumstances				
Anxiety reaction	52 (1.12%)		39 (0.83%)	
Vascular disorders				
Haemorrhage	67 (1.44%)		72 (1.53%)	
Thrombocythaemia	79 (1.70%)		87 (1.85%)	
Deep vein thrombosis	198 (4.25%)		363 (7.74%)	

Less frequent Clinical Trial Adverse Drug Reactions < 1% in the Phase III studies; 11354, 11357, 11356 (RECORD 1 to 3):

Blood and the Lymphatic System Disorders: Thrombocythaemia (incl. platelet count increased)

Cardiac Disorders: Tachycardia

Gastrointestinal Disorders: Constipation, diarrhoea, abdominal and gastrointestinal pain (incl. upper abdominal pain, stomach discomfort), dyspepsia

	(incl. epigastric discomfort), dry mouth, vomiting
General Disorders and Administration Site Conditions:	Localised oedema, decreased general strength and energy (incl. fatigue, asthenia), feeling unwell (incl. malaise)
Hepatobiliary disorders:	Hepatic function abnormal
Immune system disorders:	Dermatitis allergic
Injury, Poisoning and Procedural Complications:	Wound secretion
Investigations:	Increased lipase, increased amylase, blood bilirubin increased, increased LDH, increased alkaline phosphatase, bilirubin conjugated increased (with or without concomitant increase of ALT)
Musculoskeletal, Connective Tissue and Bone Disorders:	Pain in extremity
Nervous System Disorders:	Dizziness, headache, syncope (incl. loss of consciousness)
Renal and Urinary Disorders:	Renal impairment (incl. blood creatinine increased, blood urea increased)
Skin and Subcutaneous Tissue Disorders:	pruritus (incl. rare cases of generalised pruritus), rash, urticaria (incl. rare cases of generalised urticaria), contusion
Vascular Disorders:	hypotension (incl. blood pressure decrease, procedural hypotension), haematoma (incl. rare cases of muscle haemorrhage), gastrointestinal tract haemorrhage (incl. gingival bleeding, rectal haemorrhage, haematemesis), urogenital tract haemorrhage, nose bleed

Treatment of DVT, PE and Prevention of Recurrent VTE

The safety of Xarelto has been evaluated in three Phase III trials with 4556 patients treated up to 21 months and exposed to either 15 mg Xarelto twice daily for 3 weeks followed by 20 mg once daily (EINSTEIN DVT and EINSTEIN PE) or 20 mg once daily (EINSTEIN Extension).

Treatment-emergent drug-related adverse events were reported by 28.5% of rivaroxaban treated subjects and by 28.6% of enoxaparin/VKA treated subjects (pooled studies 11702 DVT and 11702 PE). The respective incidence rates for the study 11899 were 16% rivaroxaban vs. 11% placebo .

The most common treatment-emergent adverse reactions reported in patients valid for safety analysis in the three Phase III studies for DVT or PE treatment and prevention of recurrent VTE are presented in Table 16.

Table 16: Treatment-Emergent Adverse Reactions grouped by System Organ Class occurring in > 1% of any treatment group – pooled EINSTEIN-DVT and EINSTEIN-PE studies (11702-DVT and 11702-PE) and EINSTEIN-Extension (11899) (patients valid for safety analysis)

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

System Organ Class /PT MedDRA	Pooled EINSTEIN-DVT and EINSTEIN-PE		EINSTEIN-Extension	
	XARELTO (N = 4130) n (%)	ENOXAPARIN /VKA (N = 4116) n (%)	XARELTO (N = 598) n (%)	Placebo (N = 590) n(%)
Blood and lymphatic system disorders				
Anaemia	84 (2.03%)	62 (1.51%)	4 (0.67%)	2 (0.34%)
Cardiac disorder				
Tachycardia	55 (1.33%)	43 (1.04%)	2 (0.33%)	0
Eye disorders				
Conjunctival haemorrhage	12 (0.70%)	21 (1.23%)	6 (1.00%)	0
Gastrointestinal disorders				
Gingival bleeding	93 (2.25%)	104 (2.53%)	11 (1.84%)	2 (0.34%)
Rectal haemorrhage	90 (2.18%)	56 (1.36%)	4 (0.67%)	4 (0.68%)
Abdominal pain	69 (1.67%)	53 (1.29%)	2 (0.33%)	7 (1.19%)
Abdominal pain upper	71 (1.72%)	50 (1.21%)	10 (1.67%)	1 (0.17%)
Constipation	187 (4.53%)	174 (4.23%)	6 (1.00%)	5 (0.85%)
Diarrhoea	179 (4.33%)	164 (3.98%)	7 (1.17%)	8 (1.36%)
Dyspepsia	60 (1.45%)	54 (1.31%)	8 (1.34%)	4 (0.68%)
Nausea	153 (3.70%)	160 (3.89%)	7 (1.17%)	6 (1.02%)
Vomiting	69 (1.67%)	96 (2.33%)	3 (0.50%)	6 (1.02%)
General disorders and administration site conditions				
Pyrexia	111 (2.69%)	108 (2.62%)	5 (0.84%)	7 (1.19%)
Oedema peripheral	128 (3.10%)	135 (3.28%)	13 (2.17%)	17 (2.88%)
Asthenia	61 (1.48%)	60 (1.46%)	4 (0.67%)	6 (1.02%)
Fatigue	90 (2.18%)	68 (1.65%)	6 (1.00%)	3 (0.51%)
Injury, poisoning and postprocedural complications				
Wound haemorrhage	59 (1.43%)	65 (1.58%)	11 (1.84%)	7 (1.19%)
Contusion	145 (3.51%)	197 (4.79%)	19 (3.18%)	16 (2.71%)
Subcutaneous haematoma	44 (1.07%)	61 (1.48%)	0	2 (0.34%)
Investigations				
Alanine aminotransferase increased	72 (1.74%)	129 (3.13%)	2 (0.33%)	4 (0.68%)
Aspartate aminotransferase increased	32 (0.77%)	44 (1.07%)	4 (0.67%)	3 (0.51%)

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

System Organ Class /PT MedDRA	Pooled EINSTEIN-DVT and EINSTEIN-PE		EINSTEIN-Extension	
	XARELTO (N = 4130) n (%)	ENOXAPARIN /VKA (N = 4116) n (%)	XARELTO (N = 598) n (%)	Placebo (N = 590) n(%)
Musculoskeletal, connective tissue and bone disorders				
Pain in extremity	230 (5.57%)	221 (5.37%)	29 (4.85%)	35 (5.93%)
Nervous system disorders				
Headache	284 (6.88%)	242 (5.88%)	18 (3.01%)	15 (2.54%)
Dizziness	102 (2.47%)	108 (2.62%)	6 (1.00%)	8 (1.36 %)
Renal and urinary disorders				
Haematuria	111 (2.69%)	113 (2.75%)	13 (2.17%)	2 (0.34%)
Reproductive system and breast disorders				
Menorrhagia [#]	122 (2.95%)	64 (1.55%)	5 (0.84%)	2 (0.34%)
Vaginal haemorrhage	54 (1.31%)	23 (0.56%)	1 (0.17%)	5 (0.85%)
Respiratory, thoracic and mediastinal disorders				
Epistaxis	307 (7.43%)	271 (6.58%)	24 (4.01%)	11 (1.86%)
Haemoptysis	100 (2.42%)	98 (2.38%)	1 (0.17%)	1 (0.17%)
Skin and subcutaneous tissue disorders				
Pruritus	83 (2.01%)	58 (1.41%)	2 (0.33 %)	2 (0.34%)
Rash	97 (2.35%)	89 (2.16%)	5 (0.84%)	7 (1.19%)
Vascular disorders				
Haematoma	91 (2.20%)	150 (3.64%)	7 (1.17%)	8 (1.36%)

[#] observed as very common for rivaroxaban in women < 55 years in Study 11702

Less frequent ADRs ≥ 0.1% to <1% unless otherwise specified (pooled EINSTEIN-DVT, EINSTEIN-PE and EINSTEIN-Extension)

Eye disorders

eye haemorrhage

Gastrointestinal Disorders:

anal haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haemorrhoidal haemorrhage, lower gastrointestinal haemorrhage, melaena, lip haemorrhage, mouth haemorrhage, tongue haemorrhage, abdominal discomfort, abdominal pain lower, dry mouth

General Disorders and Administration Site Conditions:

feeling abnormal (≥ 0.01% to < 0.1%), malaise

Hepatobiliary Disorders:

hepatic function abnormal, jaundice (≥ 0.01% to < 0.1%)

Immune System Disorders:	hypersensitivity
Injury, poisoning and postprocedural complications:	operative haemorrhage, postprocedural haemorrhage, traumatic haematoma, traumatic haemorrhage, subdural haematoma (≥ 0.01% to < 0.1%)
Investigations:	haemoglobin decreased, liver function test abnormal, hepatic enzyme increased, transaminases increased, blood bilirubin increased, bilirubin conjugated increased (with or without concomitant increase of ALT), gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood amylase increased, occult blood positive
Nervous System Disorders:	syncope, cerebellar haemorrhage (≥ 0.01% to < 0.1%), cerebral haemorrhage (≥ 0.01% to < 0.1%), haemorrhage intracranial (≥ 0.01% to < 0.1%), haemorrhagic transformation stroke (≥ 0.01% to < 0.1%)
Reproductive system and breast disorders:	menometrorrhagia (≥ 0.01% to < 0.1%), metrorrhagia
Skin and Subcutaneous Tissue Disorders:	urticaria, ecchymosis, skin haemorrhage, drug eruption, dermatitis allergic, pruritus generalised
Vascular Disorders:	hypotension

Prevention of stroke and systemic embolism in patients with atrial fibrillation

In the pivotal double-blind ROCKET AF study, a total of 14,264 unique subjects with non-valvular atrial fibrillation who were at risk for stroke and non-CNS systemic embolism were randomly assigned to treatment with either rivaroxaban (7,131 subjects) or warfarin (7,133 subjects) in 45 countries. Patients received Xarelto 20 mg orally once daily (15 mg orally once daily in patients with moderate (CrCl: 30-49 mL/min) renal impairment) or warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The safety population included subjects who were uniquely randomised and took at least 1 dose of study medication.

In total, 14,236 subjects were included in the safety population (used for the safety analyses), with 7,111 and 7,125 subjects in rivaroxaban and warfarin groups, respectively. The median time on treatment was 19 months and overall treatment duration was up to 41 months. The mean duration of Xarelto treatment exposure was 572 days.

The treatment-emergent adverse reactions reported in patients valid for safety analysis in ROCKET AF are presented in Table 17.

Table 17: Incidence of treatment-emergent adverse reactions grouped by System Organ Class occurring > 1% of any treatment group – Subjects Valid for Safety Analysis – ROCKET AF SN11630

MedDRA System organ Class Preferred Term	Rivaroxaban N = 7111 (100%)	Warfarin N = 7125 (100%)
Blood and lymphatic system disorders		

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

MedDRA System organ Class Preferred Term	Rivaroxaban N = 7111 (100%)	Warfarin N = 7125 (100%)
Anaemia	219 (3.08%)	143 (2.01%)
Eye disorders		
Conjunctival haemorrhage	104 (1.46)	151 (2.12)
Gastrointestinal disorders		
Diarrhoea	379 (5.33%)	397 (5.57%)
Gingival bleeding	263 (3.70%)	155 (2.18%)
Nausea	194 (2.73%)	153 (2.15%)
Constipation	163 (2.29%)	153 (2.15%)
Rectal haemorrhage	149 (2.10%)	102 (1.43%)
Abdominal pain upper	127 (1.79%)	120 (1.68%)
Vomiting	114 (1.60%)	111 (1.56%)
Dyspepsia	111 (1.56%)	91 (1.28%)
Abdominal pain	107 (1.50%)	118 (1.66%)
Gastrointestinal haemorrhage	100 (1.41%)	70 (0.98%)
General disorders and administration site conditions		
Oedema peripheral	435 (6.12%)	444 (6.23%)
Fatigue	223 (3.14)	221 (3.10)
Asthenia	125 (1.76)	106 (1.49)
Pyrexia	72 (1.01%)	87 (1.22%)
Injury, poisoning and postprocedural complications		
Contusion	196 (2.76)	291 (4.08)
Investigations		
Alanine amino transferase increased	144 (2.03)	112 (1.57)
Musculoskeletal, connective tissue and bone disorders		
Pain in extremity	191 (2.69)	208 (2.92)
Nervous system disorders		
Dizziness	433 (6.09)	449 (6.30)
Headache	324 (4.56)	363 (5.09)

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

MedDRA System organ Class Preferred Term	Rivaroxaban N = 7111 (100%)	Warfarin N = 7125 (100%)
Syncope	130 (1.83)	108 (1.52)
Renal and urinary disorders		
Haematuria	296 (4.16)	242 (3.40)
Respiratory tract disorders		
Epistaxis	721 (10.14)	609 (8.55)
Haemoptysis	99 (1.39)	100 (1.40)
Skin and subcutaneous tissue disorders		
Ecchymosis	159 (2.24)	234 (3.28)
Pruritus	120 (1.69)	118 (1.66)
Rash	112 (1.58)	129 (1.81)
Vascular disorders		
Haematoma	216 (3.04)	330 (4.63)
Hypotension	141 (1.98)	130 (1.82)

Less frequent ADRs \geq 0.1% to < 1% unless otherwise specified – ROCKET AF

Cardiac disorders:	Tachycardia
Eye disorders:	Eye haemorrhage, vitreous haemorrhage
Gastrointestinal Disorders:	Melaena, upper gastrointestinal haemorrhage, haemorrhoidal haemorrhage, haematochezia, Mouth haemorrhage, lower gastrointestinal haemorrhage, anal haemorrhage, gastric ulcer haemorrhage, gastritis haemorrhagic, Gastric haemorrhage, haematemesis, abdominal discomfort, abdominal pain lower, dry mouth
General Disorders and Administration Site Conditions:	Malaise
Hepatobiliary Disorders:	Hepatic function abnormal, hyperbilirubinaemia, jaundice (\geq 0.01% to <0.1%)
Immune System Disorders:	Hypersensitivity
Injury, Poisoning, and Procedural Complications:	Post procedural haemorrhage, wound haemorrhage, traumatic haematoma, incision site haemorrhage, subdural haematoma, subcutaneous haematoma, periorbital haematoma
Investigations:	Haemoglobin decreased, haematocrit decreased, blood bilirubin increased, liver function test abnormal, aspartat aminotransferase increased, hepatic enzyme increased, blood urine present, creatinine renal clearance decreased, blood creatinine increased, blood urea increased, blood alkaline phosphatase increased, lipase increased, bilirubin conjugated increased (with or without concomitant increase of ALT) (\geq 0.01% to <0.1%)

Renal and urinary disorders:	Renal impairment
Reproductive system disorders:	Vaginal haemorrhage, metrorrhagia
Musculoskeletal, Connective Tissue, and Bone Disorders:	Haemarthrosis, muscle haemorrhage ($\geq 0.01\%$ to $< 0.1\%$)
Nervous system disorders:	Loss of consciousness, haemorrhagic stroke, haemorrhage intracranial
Skin and Subcutaneous Tissue Disorders:	Dermatitis allergic, rash pruritic, rash erythematous, rash generalized, pruritus generalized, urticaria, skin haemorrhage
Vascular disorders:	Haemorrhage, bleeding varicose vein

In other clinical studies, vascular pseudoaneurysm formation following percutaneous intervention has been reported.

Post-marketing Observations

Angioedema and allergic oedema have been reported post-marketing in temporal association with the use of Xarelto. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.

DOSAGE AND ADMINISTRATION

VTE Prevention in total hip and knee replacement

The recommended dose of Xarelto for VTE prevention in major orthopaedic surgery of the lower limbs (elective total hip or knee replacement) is a 10 mg tablet taken once daily.

The initial dose should be taken 6 - 10 hours after surgery provided that haemostasis has been established. Xarelto may be taken with or without food.

The duration of treatment depends on the type of major orthopaedic surgery.

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

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

Stroke Prevention in Atrial Fibrillation

The recommended dose is 20 mg once daily.

For patients with moderate renal impairment (Creatinine clearance: 30 – 49 mL/min), one 15 mg tablet of Xarelto should be taken once daily.

Xarelto 20 mg tablets and Xarelto 15 mg tablets should be taken with food (see Pharmacokinetic Properties).

Treatment of DVT and PE and prevention of recurrent DVT and PE

The recommended dose for the initial treatment of acute DVT and PE is 15 mg Xarelto **twice daily** for the first three weeks followed by 20 mg Xarelto **once daily** for the continued treatment and the prevention of recurrent DVT and PE.

During the initial 3 weeks of acute treatment 15 mg of Xarelto should be taken twice daily.

After the initial 3 weeks treatment Xarelto should be continued at 20 mg once daily. Therapy should be continued as long as the VTE risk persists. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Experience with Xarelto in this indication for more than 12 months is limited.

Xarelto 15 mg tablets and Xarelto 20 mg tablets should be taken with food.

Special Populations

Hepatic impairment

Xarelto is contraindicated in patients with significant hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk (see CONTRAINDICATIONS). No dose adjustment is necessary in patients with other hepatic diseases (see Pharmacokinetic Properties).

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment (Child Pugh C) (see CONTRAINDICATIONS and Pharmacokinetic Properties).

Renal impairment

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. (See Pharmacokinetic Properties)

No clinical data are available for patients with (CrCl < 15 mL/min) or patients on dialysis. Therefore, use of Xarelto is contraindicated in this patient population (see CONTRAINDICATIONS).

Please refer to Table 18 below for dosing instructions for patients with renal impairment by indications.

Table 18: Dosage and administration advice for patients with reduced renal function

Indication Creatinine Clearance (CrCl)	VTE Prevention in total hip and knee replacement	Stroke Prevention in Atrial Fibrillation	Treatment of DVT and PE and prevention of recurrent DVT and PE
Normal > 80 mL/min	10 mg once daily	20 mg once daily	15 mg twice daily for 3 weeks, followed by 20 mg once daily
Mild 50 – 80 mL/min			
Moderate 30 – 49 mL/min	10 mg once daily	15 mg once daily	15 mg twice daily for 3 weeks, followed by 20 mg once daily

Attachment 1: Product information for AusPAR Xarelto; Rivaroxaban; Bayer Australia Ltd PM-2012-01179-3-3 Date of Finalisation 2 October 2013. This Product Information was approved at the time this AusPAR was published.

Indication Creatinine Clearance (CrCl)	VTE Prevention in total hip and knee replacement	Stroke Prevention in Atrial Fibrillation	Treatment of DVT and PE and prevention of recurrent DVT and PE
Severe 15 – 29 mL/min	10 mg once daily (Use with caution)	Xarelto is contraindicated	
Severe < 15 mL/min	Xarelto is contraindicated		

Patients above 65 years

Based on clinical data, no dose adjustment is required for these patient populations (see Pharmacokinetic properties).

Increasing age is associated with declining renal function.

Body weight

No dose adjustment is required for these patient populations (see Pharmacokinetic properties).

Gender

No dose adjustment is required for these patient populations (see Pharmacokinetic properties).

Children and adolescents

Xarelto is not recommended for use in children or adolescents below 18 years of age due to a lack of data on safety and efficacy.

Ethnic differences

No dose adjustment is required based on ethnic differences (see Pharmacokinetic properties).

Transition Xarelto from and to Vitamin K Antagonists (VKA) or Parenteral Anticoagulants

Anticoagulant	Transition From Xarelto	Transition To Xarelto
Vitamin K Antagonists (VKA)	<p>Transition from Xarelto to VKAs</p> <p>There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Limited clinical trial data is available to guide the process whereby patients are converted from Xarelto to VKAs.</p> <p>Continuous adequate anticoagulation should be ensured during transition to an alternate anticoagulant.</p> <p>In patients converting from Xarelto to VKA, VKA should be given concurrently</p>	<p>Transition from VKA to Xarelto:</p> <p>For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is ≤ 3.0.</p> <p>For patients treated for DVT and prevention of recurrent DVT and PE, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is ≤ 2.5.</p>

	<p>until the INR is ≥ 2.0. It should be noted that Xarelto can contribute to an elevated INR and so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of VKA. Therefore, INR measurements should be made in accordance with the following guidance during the transition from Xarelto to VKA:</p> <p>For the first two days of the conversion period, standard initial dosing of VKA should be used and, after the first two days, VKA dosing should be guided by INR testing. While patients are on both Xarelto and VKA, INR should be tested just prior to the next dose of Xarelto (not earlier than 24 hours after the previous dose). Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the last dose.</p>	<p>The INR is not a valid measure for the anticoagulant activity of Xarelto, and therefore should not be used. The INR is only calibrated and validated for VKAs and cannot be used for any other anticoagulant. When switching patients from VKAs to Xarelto, INR values will be elevated after the intake of Xarelto but this is not indicative of the anticoagulant effect of Xarelto (see Interactions with Other Medicines).</p>
<p>Parenteral Anticoagulants</p>	<p>Transition from Xarelto to Parenteral Anticoagulants:</p> <p>Discontinue Xarelto and give the first dose of parenteral anticoagulant at the time that the next Xarelto dose would be taken</p>	<p>Transition from Parenteral Anticoagulants to Xarelto:</p> <p>For patients currently receiving a parenteral anticoagulant, start Xarelto 0 to 2 hours before the time of the next scheduled administration of the parenteral drug (e.g., LMWH) or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).</p>

Missed Dose

It is essential to adhere to the dosage schedule provided.

- Xarelto 10 mg, 15 mg, or 20 mg tablets taken **once** a day:

If a dose is missed, the patient should take Xarelto immediately on the same day and continue on the following day with the once daily intake as before. A double dose should not be taken to make up for a missed tablet.

- Xarelto 15 mg tablets taken **twice** a day:

If a dose is missed during the 15 mg twice daily treatment phase the patient should take the next dose immediately to ensure the intake of 30 mg total dose per day. In this case two 15

mg tablets may be taken at once. The following day the patient should continue with the regular 15 mg twice daily intake schedule as recommended.

OVERDOSAGE

Overdose following administration of Xarelto may lead to haemorrhagic complications due to its pharmacodynamic properties.

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg or above.

A specific antidote antagonising the pharmacological effect of rivaroxaban is not available.

Activated charcoal may reduce absorption of the drug if given within up to 8 hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Protamine sulphate and Vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Xarelto 10 mg - One tablet contains 10 mg rivaroxaban. The tablets are film-coated round, biconvex, light red immediate release tablets of 6 mm diameter marked with a Bayer cross on one side and "10" and a triangle on the other side. The tablets are supplied in packs of 3, 5, 10, 15, 30, 100 tablets.

Xarelto 15 mg - One tablet contains 15 mg rivaroxaban. The tablets are film-coated round, biconvex, red immediate release tablets of 6 mm diameter marked with a Bayer cross on one side and "15" and a triangle on the other side. The tablets are supplied in packs of 7, 14, 28, 42, 84, 98, 100 tablets.

Xarelto 20 mg - One tablet contains 20 mg rivaroxaban. The tablets are film-coated round, biconvex, brown red immediate release tablets of 6 mm diameter marked with a Bayer cross on one side and "20" and a triangle on the other side. The tablets are supplied in packs of 7, 28, 84, 98, 100 tablets.

Not all pack sizes may be marketed.

The tablets are packed in thermoformed PP/Aluminium foil blisters or PVC/PVDC/Aluminium foil blisters. Store below 30 °C.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LTD

ABN 22 000 138 714

875 Pacific Highway

PYMBLE, NSW 2073

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POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG: 24 November 2008

DATE OF MOST RECENT AMENDMENT: 27 June 2013

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