XARELTO®

Film-coated tablet

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS
Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[Posology and method of administration, Special warnings and precautions for use, and Clinical efficacy and safety]*.

B. SPINAL/EPIDURAL HEMATOMA
Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of XARELTO and neuraxial procedures is not known**

[see Special warnings and precautions for use and Undesirable effects].

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Special warnings and precautions for use]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Special warnings and precautions for use]*.

Important information, please read carefully!

Composition

Xarelto 10 mg
1 film-coated tablet contains 10 mg rivaroxaban.

Xarelto 15 mg
1 film-coated tablet contains 15 mg rivaroxaban.

Xarelto 20 mg
1 film-coated tablet contains 20 mg rivaroxaban.

Pharmaceutical form

Film-coated tablet (tablet).

Xarelto 10 mg
Light red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and "10" and a triangle on the other side.

Xarelto 15 mg
Red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and “15” and a triangle on the other side.

Xarelto 20 mg

Brown-red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and “20” and a triangle on the other side.

Pharmacological Properties

Pharmacodynamic properties

Pharmacotherapeutic group: Other antithrombotic agents, ATC code: B01AF01

Mechanism of action
Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

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. In patients undergoing major orthopedic surgery , the 5/95 percentiles for PT (Neoplastin) 2-4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 s (baseline values before surgery 12 to 15s).
In patients receiving rivaroxaban for treatment of DVT and haemodynamically stable PE, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.
In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.
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. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see ‘Pharmacokinetic properties’).

Clinical efficacy and safety
Xarelto is indicated for prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.
The rivaroxaban clinical programme was designed to demonstrate the efficacy of Xarelto® for the prevention of 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 randomized double-blind phase III clinical studies, the RECORD-programme.
Xarelto® 10 mg once daily (od) started no sooner than 6 hours post-operatively was compared with enoxaparin 40 mg once daily started 12 hours pre-operatively.
In all three phase III studies (see table 1), rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non fatal PE and death) and major VTE (proximal DVT, non fatal PE and VTE-related death), the pre-specified primary and major secondary efficacy endpoints. Furthermore, in all three studies the rate of symptomatic VTE (symptomatic DVT, non fatal PE and VTE-related death) was lower in Xarelto® treated patients compared to patients treated with enoxaparin.
The main safety endpoint, major bleeding, showed comparable rates for patients treated with Xarelto® 10 mg compared to enoxaparin 40 mg.

Table 1: Efficacy and safety results from phase III clinical studies

Study Population	RECORD 1 4,541 patients undergoing total hip replacement surgery			RECORD 2 2,509 patients undergoing total hip replacement surgery			RECORD 3 2,531 patients undergoing total knee replacement surgery		
Treatment Dosage and Duration	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 35 ± 4 days	p	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 12 ± 2 days	p	Rivaroxaban 10 mg od 12 ± 2 days	Enoxaparin 40 mg od 12 ± 2 days	p
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 rate	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%)	

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 Xarelto® 10 mg once daily compared to enoxaparin 40 mg once daily.

In addition to the phase III RECORD program, a post-authorization, non-interventional, open-label cohort study (XAMOS) has been conducted in 17,413 patients undergoing major orthopaedic surgery of the hip or knee, to compare rivaroxaban with other pharmacological thromboprophylaxis (standard-of-care) under real-life setting. Symptomatic VTE occurred in 57 (0.6%) patients in the rivaroxaban group (n=8,778) and 88 (1.0%) of patients in the standard-of-care group (n=8,635; HR 0.63; 95% CI 0.43-0.91); safety population). Major bleeding occurred in 35 (0.4%) and 29 (0.3%) of patients in the rivaroxaban and standard-of-care groups (HR 1.10; 95% CI 0.67-1.80). Thus, the results were consistent with the results of the pivotal randomised studies.

Xarelto is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation:

- *with previous history of stroke or TIA*
- *with $CHADS_2$ Score ≥ 2*

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto in reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to Xarelto 20 mg once daily (15 mg once daily in patients with creatinine clearance 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.
34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.

Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 – 0.96; P<0.001 for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 – 1.03; P<0.001 for non-inferiority; P=0.117 for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 2.
Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).
The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 3).

Table 2: Efficacy results from phase III ROCKET AF

Study population	ITT analyses of efficacy in patients with non-valvular atrial fibrillation		
Treatment dosage	Xarelto 20 mg od (15 mg od in patients with moderate renal impairment) Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value, test for superiority
Stroke and non-CNS systemic embolism	269 (2.12)	306 (2.42)	0.88 (0.74 - 1.03) 0.117
Stroke, non-CNS systemic embolism and vascular death	572 (4.51)	609 (4.81)	0.94 (0.84 - 1.05) 0.265
Stroke, non-CNS systemic embolism, vascular death and myocardial infaction	659 (5.24)	709 (5.65)	0.93 (0.83 - 1.03) 0.158
Stroke	253 (1.99)	281 (2.22)	0.90 (0.76 - 1.07) 0.221
Non-CNS systemic embolism	20 (0.16)	27 (0.21)	0.74 (0.42 - 1.32) 0.308
Myocardial infaction	130 (1.02)	142 (1.11)	0.91 (0.72 - 1.16) 0.464

Table 3: Safety results from phase III ROCKET AF

Study population	Patients with non-valvular atrial fibrillation[a]		
Treatment dosage	Xarelto 20 mg once a day (15 mg once a day in patients with moderate renal impairment) Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value
Major and non-major clinically relevant bleeding events	1,475 (14.91)	1,449 (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 (0.74)	0.67 (0.47 - 0.93) 0.019
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	1,185 (11.80)	1,151 (11.37)	1.04 (0.96 - 1.13) 0.345
All cause mortality	208 (1.87)	250 (2.21)	0.85 (0.70 - 1.02) 0.073

a) Safety population, on treatment
* Nominally significant

In addition to the phase III ROCKET AF study, a prospective, single-arm, post-authorization, non-interventional, open-label cohort study (XANTUS) with central outcome adjudication including thromboembolic events and major bleeding has been conducted. 6,704 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism in clinical practice. The mean $CHADS_2$ score was 1.9 and HAS-BLED score was 2.0 in XANTUS, compared to a mean $CHADS_2$ and HAS-BLED score of 3.5 and 2.8 in ROCKET AF, respectively. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years.
These observations in clinical practice are consistent with the established safety profile in this indication.

Patients undergoing cardioversion
A prospective, randomized, open-label, multicenter, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naive and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomized 2:1), for the prevention of cardiovascular events. TEE- guided (1 - 5 days of pretreatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischemic attack, non-CNS systemic embolism, MI and cardiovascular death) occurred in 5 (0.5 %) patients in the rivaroxaban group (n = 978) and 5 (1.0 %) patients in the VKA group (n = 492; RR 0.50; 95 % CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6 %) and 4 (0.8 %) patients in the rivaroxaban (n = 988) and VKA (n = 499) groups, respectively (RR 0.76; 95 % CI 0.21- 2.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKA treatment groups in the setting of cardioversion.

Treatment of DVT in which duration of treatment should be based on the underlying disease and treatment of haemodynamically stable pulmonary embolism (PE) which is must be confirmed by spiral CT imaging
The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto in the initial and continued treatment of DVT in which duration of treatment should be based on the underlying disease and treatment of haemodynamically stable pulmonary embolism (PE) which is must be confirmed by spiral CT imaging.
Over 12,800 patients were studied in three randomised controlled phase III clinical studies (Einstein DVT, Einstein PE and Einstein Extension and Einstein Choice) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and to reduce the risk of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and to reduce the risk of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

In both the Einstein DVT and the Einstein PE study, the comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range ($\geq$ 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.

In Einstein Extension 1,197 patients with DVT or PE were studied for reducing the risk of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Xarelto 20 mg once daily was compared with placebo.

Einstein DVT, PE and Extension 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.

In Einstein Choice, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomization date (median : 351 days). Xarelto 20 mg once daily and Xarelto 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily.
The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE.

In the Einstein DVT study (see Table 4) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ($p < 0.0001$ (test for non-inferiority); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of

0.67 ((95% CI: 0.47 - 0.95), nominal p value p=0.027) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 – 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (P=0.932 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35 - 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

Table 4: Efficacy and safety results from phase III Einstein DVT

Study population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment dosage and duration	Xarelto[a] 3, 6 or 12 months N=1,731	Enoxaparin/VKA[b] 3, 6 or 12 months N=1,718
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 or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified hazard ratio of 2.0); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (superiority)

In the Einstein PE study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for non-inferiority); hazard ratio: 1.123 (0.749 – 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.849 ((95% CI: 0.633 - 1.139), nominal p value p= 0.275). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 – 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (p=0.082 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).

The incidence rates 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 0.493 (95% CI: 0.308 - 0.789).

Table 5: Efficacy and safety results from phase III Einstein PE

Study population	4,832 patients with an acute symptomatic PE	
Treatment dosage and duration	Xarelto[a] 3, 6 or 12 months N=2,419	Enoxaparin/VKA[b] 3, 6 or 12 months N=2,413
Symptomatic recurrent VTE*	50 (2.1%)	44 (1.8%)
Symptomatic recurrent PE	23 (1.0%)	20 (0.8%)
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 or clinically relevant non-major bleeding	249 (10.3%)	274 (11.4%)

Major bleeding events	26 (1.1%)	52 (2.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0026$ (non-inferiority to a prespecified hazard ratio of 2.0); hazard ratio: 1.123 (0.749 – 1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 6).

Table 6: 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[a] 3, 6 or 12 months N=4,150	Enoxaparin/VKA[b] 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 or clinically relevant non-major bleeding	388 (9.4%)	412 (10.0%)
Major bleeding events	40 (1.0%)	72 (1.7%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified hazard ratio of 1.75); hazard ratio: 0.886 (0.661 – 1.186)

The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) of the pooled analysis was reported with a hazard ratio of 0.771 ((95% CI: 0.614 – 0.967), nominal p value p= 0.0244).

In the Einstein Extension study (see Table 7) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

Table 7: Efficacy and safety results from phase III Einstein Extension

Study population	1,197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment dosage and duration	Xarelto[a] 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%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily
* $p < 0.0001$ (superiority), hazard ratio: 0.185 (0.087 - 0.393)

In the Einstein Choice study (see table 8) Xarelto 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with Xarelto 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

Table 8: Efficacy and safety results from phase III Einstein Choice

Study population	3,396 patients continued prevention of recurrent venous thromboembolism		
Treatment dosage	Xarelto 20 mg od N=1,107	Xarelto 10 mg od N=1,127	ASA 100 mg od N=1,131
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5%)*	13 (1.2%)**	50 (4.4%)
Symptomatic recurrent PE	6 (0.5%)	6 (0.5%)	19 (1.7%)
Symptomatic recurrent DVT	9 (0.8%)	8 (0.7%)	30 (2.7%)
Fatal PE/death where PE cannot be ruled out	2 (0.2%)	0	2 (0.2%)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7%)	18 (1.6%)	56 (5.0%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Clinically relevant non-major bleeding	30 (2.7)	22 (2.0)	20 (1.8)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1%)+	17 (1.5%)++	53 (4.7%)

* p<0.001(superiority) Xarelto 20 mg od vs ASA 100 mg od; HR=0.34 (0.20–0.59)
** p<0.001 (superiority) Xarelto 10 mg od vs ASA 100 mg od; HR=0.26 (0.14–0.47)
+ Xarelto 20 mg od vs. ASA 100 mg od; HR=0.44 (0.27–0.71), p=0.0009 (nominal)
++ Xarelto 10 mg od vs. ASA 100 mg od; HR=0.32 (0.18–0.55), p<0.0001 (nominal)

In addition to the phase III EINSTEIN program, a prospective, non-interventional, open-label cohort study (XALIA) with central outcome adjudication including recurrent VTE, major bleeding and death has been conducted. 5,142 patients with acute DVT were enrolled to investigate the long-term safety of rivaroxaban compared with standard-of-care anticoagulation therapy in clinical practice. Rates of major bleeding, recurrent VTE and all-cause mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively. There were differences in patient baseline characteristics including age, cancer and renal impairment. A pre-specified propensity score stratified analysis was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted hazard ratios comparing rivaroxaban and standard-of-care for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40 - 1.50), 0.91 (95% CI 0.54 - 1.54) and 0.51 (95% CI 0.24 - 1.07), respectively.
These results in clinical practice are consistent with the established safety profile in this indication.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events. See 'Posology and method of administration' for information on paediatric use.

Patients with prosthetic heart valves having recently undergone TAVR
In the randomised, open label, active-controlled, event-driven multicenter phase III GALILEO study 1644 patients were randomized to either a rivaroxaban-based strategy or an antiplatelet-based strategy 1-7 days after a successful transcatheter aortic valve replacement. Patients with previous atrial fibrillation or with an ongoing indication for oral anticoagulation were excluded.

The main objective was to assess the efficacy and safety of a rivaroxaban-based treatment strategy (10 mg rivaroxaban od plus 75-100 mg acetylsalicylic acid (ASA) od for 90 days followed by rivaroxaban 10 mg od) compared to standard of care (clopidogrel 75 mg od plus 75-100 mg ASA od for 90 days followed by ASA od). The study was terminated early due to an imbalance in death and thromboembolic events.
In the intention-to-treat (ITT) analysis the primary efficacy endpoint, i.e. death and thromboembolic events, occurred in 105 patients (9.8 per 100 patient years) in the rivaroxaban arm and in 78 patients (7.21 per 100 patient years) in the antiplatelet arm; the HR was 1.35 (95% CI: 1.01; 1.81). In the on-treatment analysis the primary efficacy outcome occurred in 68 patients (8.11 per 100 patient years) in the rivaroxaban arm compared to 63 (6.6 per 100 patient years) in the antiplatelet arm; the HR was 1.21 (95% CI: 0.86; 1.70).
In the ITT analysis the primary safety endpoint, i.e. composite of life-threatening, disabling or major bleeding, occurred in 46 patients (4.29 per 100 patient years) in the rivaroxaban arm compared to 31 (2.83 per 100 patient years) in the antiplatelet arm; the HR was 1.50 (95% CI 0.95; 2.37).

Patient with high risk triple positive antiphospholipid syndrome
In an investigator sponsored ranomized open-label multicenter study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, 3 antiphospholipid test: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The tiral was terminated prematurely after the enrollment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomized to rivaroxaban 20 mg (15 mg for patients with cretainine clearance<50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomized to rivaroxaban (4 ischemic stroke and 3 myocardial infarction). No events were reported in patients randomized to warfarin . Major bleeding occurred in 4 patients (7 %) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

Pharmacokinetic properties

Absorption
Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.
Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose. Xarelto® 10 mg tablets can be taken with or without food. Rivaroxaban pharmacokinetics are approximatelty linear up to about 15 mg once daily.
Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When Xarelto 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Xarelto 15 mg and 20 mg are to be taken with food (see 'Posology and method of administration').
Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions Xarelto 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state.
Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Distribution
Plasma protein binding in humans 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 litres.

Biotransformation and elimination
Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal 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 substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs 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.

Special populations
Gender
There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

Elderly population
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.

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.

Inter-ethnic differences
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

Hepatic impairment
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. 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. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.
The inhibition of Factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.
Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see 'Contraindications').

Renal impairment
There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance 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 increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa 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 creatinine clearance < 15 ml/min.
Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.
Use is not recommended in patients with creatinine clearance < 15 ml/min. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see 'Special warnings and precautions for use').

Pharmacokinetic data in patients
In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) µg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (Factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and Factor Xa activity was best described by an E_{max} model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects. In patients, baseline Factor Xa and PT were influenced by the surgery resulting in a difference in the concentration-PT slope between the day post-surgery and steady state.

Paediatric population
Safety and efficacy have not been established for children and adolescents up to 18 years.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and reproductive toxicity.
Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.
In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

Carcinogenicity

Rivaroxaban was tested up to 60 mg/kg/day reaching exposure levels similar to humans (mice) or up to 3.6-fold higher (rats) than in humans.
Rivaroxaban showed no carcinogenic potential in rats and mice.

Indications

Xarelto is indicated for prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery

Xarelto is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation:

- with previous history of stroke or TIA
- with $CHADS_2$ Score ≥ 2

Xarelto is indicated for the treatment of Deep Vein Thrombosis (DVT) in which duration of treatment should be based on the underlying disease.

Xarelto is indicated for the treatment of patients with haemodynamically stable pulmonary embolism (PE) which is must be confirmed by spiral CT imaging.

Posology and method of administration

Posology

For prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
The recommended dose is 10 mg Xarelto taken orally once daily.The initial dose should be taken 6 to10 hours after surgery, provided that haemostasis has been established.

The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

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

Missed Dose
If a dose is missed the patient should take Xarelto immediately and then continue the following day with once daily intake as before.

To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation:

- with previous history of stroke or TIA
- with $CHADS_2$ score ≥ 2

The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Xarelto should be continued long term provided the benefit of reducing the risk of stroke and systemic embolism outweighs the risk of bleeding (see 'Special warnings and precautions for use').

If a dose is missed the patient should take Xarelto immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

For the treatment of Deep Vein Thrombosis (DVT) in which duration on treatment should be based on the underlying disease and the treatment of patients with haemodynamically stable pulmonary embolism (PE), the recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment, as indicated in the table below.

Following completion of six to twelve months therapy, based on an individual assessment of the risk of recurrent DVT or PE against the risk for bleeding, dose reduction to 10 Xarelto once daily may be considered.

	Time period	Dosing schedule	Total dosing
For the treatment of Deep Vein Thrombosis (DVT) in which duration on treatment should be based on the underlying disease and the treatment of patient with haemodinamically stable	Day 1 – 21	15 mg twice daily	30 mg
	Day 22 and onwards	20 mg once daily	20 mg
	Following completion of 6 – 12 month treatment for DVT or PE	10 mg once daily	10 mg

pulmonary embolism (PE)			

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see 'Special warnings and precautions for use'). Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Xarelto immediately to ensure intake of 30 mg Xarelto per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take Xarelto immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to Xarelto
For patients treated for reducing the risk of stroke and systemic embolism, VKA treatment should be stopped and Xarelto therapy should be initiated when the INR is ≤ 3.0.
For patients treated for DVT or PE, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is ≤ 2.5.
When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see 'Interaction with other medicinal products and other forms of interaction').

Converting from Xarelto to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both Xarelto and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto. Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the last dose (see 'Interaction with other medicinal products and other forms of interaction' and 'Pharmacokinetic properties').

Converting from parenteral anticoagulants to Xarelto
For patients currently receiving a parenteral anticoagulant, Xarelto should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

Converting from Xarelto to parenteral anticoagulants
Give the first dose of parenteral anticoagulant at the time the next Xarelto dose would be taken.

Special populations

Renal impairment
Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see 'Special warnings and precautions for use' and 'Pharmacokinetic properties').

- For the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery, when the recommended dose is 10 mg once daily, no dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) (see 'Pharmacokinetic properties').
- For reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, when the recommended dose is 20 mg once daily, no dose adjustment from the recommended dose is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see 'Pharmacokinetic properties').
  In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment: the recommended dose is 15 mg once daily (see 'Pharmacokinetic properties').
- For the treatment of DVT or PE, when the recommended dose is 15 mg twice daily for the first 3 weeks followed by 20 mg once daily, no dose adjustment from the recommended dose is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see 'Pharmacokinetic properties').
  In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment: patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is

15 mg once daily based on PK modelling (see 'Special warnings and precautions for use' and 'Pharmacokinetic properties').
Following completion of 6 – 12 month treatment for DVT or PE, when dose reduction to 10 mg once daily is considered, no dose adjustment is necessary.

Hepatic impairment
Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see 'Contraindications' and 'Pharmacokinetic properties').

Elderly population
No dose adjustment (see 'Pharmacokinetic properties').

Body weight
No dose adjustment (see 'Pharmacokinetic properties').

Gender
No dose adjustment (see 'Pharmacokinetic properties').

Paediatric population
The safety and efficacy of Xarelto in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto is not recommended for use in children below 18 years of age.

Patients undergoing cardioversion
Xarelto can be initiated or continued in patients who may require cardioversion.
For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Xarelto treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation (see 'Pharmacodynamic properties').

Method of administration
For oral use.
Xarelto 10 mg can be taken with or without food.
Xarelto 15 & 20 mg are to be taken with food (see 'Pharmacokinetic properties').

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Clinically significant active bleeding.

Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, apixaban, dabigatran, etc.) except under the circumstances of switching therapy to or from rivaroxaban (see 'Posology and method of administration') or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see 'Pharmacokinetic properties').

Pregnancy and breast feeding (see 'Fertility, pregnancy and breast feeding').

Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Increased Risk of Thrombotic Events after Premature Discontinuation
Premature discontinuation of any oral anticoagulant, including Xarelto, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If Xarelto is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Posology and method of administration and Clinical efficacy and safety]*.

Haemorrhagic risk

As with other anticoagulants, patients taking Xarelto are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Xarelto administration should be discontinued if severe haemorrhage occurs.

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see 'Undesirable effects'). This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.
Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see 'Pharmacodynamic properties' and 'Pharmacokinetic properties').

Renal impairment
In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see 'Posology and method of administration' and 'Pharmacokinetic properties').
The Azole anti-mycotic fluconazole, a moderate Cyp3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered (*see section 'Interactions with other medicinal products and other forms of interaction')*
Xarelto® is to be used with caution in patients with moderate renal impairment (creatinine clearance <50-30 mL/min) concomitantly receiving other medicinal products which increase Xarelto® plasma concentrations (see section *'Interaction with other medicinal products and other forms of interaction'*).
Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.

Hepatic impairment
In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), Xarelto® plasma levels may be significantly increased which may lead to an increased bleeding risk. Xarelto® is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Xarelto® may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not assoc-iated with coagulopathy. (see sections *'Posology and method of administration', 'Contraindication' and 'Pharmacokinetic properties'*).

Interaction with other medicinal products
The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see 'Interaction with other medicinal products and other forms of interaction').
Fluconazole is expected to have less effect on Xarelto exposure and can be co-administered with caution.
Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors, or selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibotors (SNRIs), (see section *'Interaction with other medicinal products and other forms of interaction'*).
For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see 'Interaction with other medicinal products and other forms of interaction').

Other haemorrhagic risk factors
As with other antithrombotics, rivaroxaban is not recommended 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
- intra spinal or intracerebral vascular abnormalities
- recent brain, spinal or ophthalmological surgery
- bronchiectasis or history of pulmonary bleeding

Bleeding during antithrombotic treatment may unmask underlying yet unknown malignancy, in particular in the gastrointestinal or genitourinary tract. Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumor location, antineoplastic therapy and stage of disease.

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

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see 'Pharmacodynamic properties' and 'Pharmacokinetic properties').

Patients with prosthetic valves
Xarelto is not recommended for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR) based on data from a randomized controlled clinical study comparing a Xarelto-regimen to an antiplatelet regimen (*see section* 'Pharmacodynamic properties').
The safety and efficacy of Xarelto have not been studied in patients with other prosthetic heart valves or other valve procedures; therefore, there are no data to support that Xarelto provides adequate anticoagulation in those patient populations.

Patients with antiphospholipid syndrome
Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Hip fracture surgery
Xarelto has not been studied in interventional clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety.

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.

Dosing recommendations before and after invasive procedures and surgical intervention
If an invasive procedure or surgical intervention is required, Xarelto should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.
If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Xarelto should be restarted a as soon as possible after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see 'Pharmacokinetic properties').

Spinal/epidural anaesthesia or puncture
When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 15 mg and 20 mg rivaroxaban in these situations.
To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 'Pharmacokinetic properties'). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

Interaction with CYP3A4 inducers
The concomitant use of Xarelto® with strong CYP3A4 inducers (e.g.rifampicin, phenytoin, carbamazepine, Phenobarbital or St.John's Wort) may lead to reduced Xarelto® plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution (see section *'Interaction with other medicinal products and other forms of interaction'*).

Elderly population
Increasing age may increase haemorrhagic risk

Dermatological reactions
Serious skin reactions, including Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section '*Undesirable effects*'). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

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

Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors
Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban C_{max}, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see 'Special warnings and precautions for use').

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in C_{max}. The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients.

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and C_{max}. This increase is not considered clinically relevant. The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients.

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean C_{max}. The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients.

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

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.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see 'Special warnings and precautions for use').

NSAIDs/platelet aggregation inhibitors
No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see 'Special warnings and precautions for use').

SSRIs/SNRIs
As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Warfarin
Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (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.
If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.
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 rivaroxaban.

CYP3A4 inducers
Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

Other concomitant therapies
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.
For Xarelto 10 mg, no clinically relevant interaction with food was observed (see section *'Posology and method of administration'*).

Laboratory parameters
Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see 'Pharmacodynamic properties').

Fertility, pregnancy and breast feeding

Pregnancy
Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see 'Preclinical safety data'). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see 'Contraindications').
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast feeding
Safety and efficacy of Xarelto have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast feeding (see 'Contraindications'). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Fertility
No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see 'Preclinical safety data').

Effects on ability to drive and use machines

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope and dizziness have been reported to be common (see 'Undesirable effects'). Patients experiencing these adverse reactions should not drive or use machines.

Undesirable effects

Summary of the safety profile
The safety of rivaroxaban has been evaluated in eight phase III studies including 18,403 patients exposed to rivaroxaban (see Table 9).

Table 9: Number of patients studied, maximum daily dose 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 in which duration on treatment should be based on the underlying disease and the treatment of patients with haemodynamically stable pulmonary embolism (PE)	4,556	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg Following completion of 6 – 12 month treatment for DVT or PE, 10 mg may be considered	21 months
Xarelto is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: • with previous history of stroke or TIA • with $CHADS_2$ score ≥ 2	7,750	20 mg	41 months

*Patients exposed to at least one dose of rivaroxaban

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the 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 PE bleeding events occurred in approximately 27.8% of patients and anaemia occurred in approximately 2.2% of patients. In patients treated for reducing the risk 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.

Tabulated list of adverse reactions
The frequencies of adverse reactions reported with Xarelto are summarised in table 10 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:
common (≥ 1/100 to < 1/10)
uncommon (≥ 1/1,000 to < 1/100)
rare (≥ 1/10,000 to < 1/1,000)
Not known: cannot be estimated from the available data.

Table 10: All treatment-emergent adverse reactions reported in patients in phase III studies

Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			
Anaemia (incl. respective laboratory parameters)	Thrombocythemia (incl. platelet count increased)[A]		
Immune system disorders			
	Allergic reaction, dermatitis allergic		
Nervous system disorders			
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope		
Eye disorders			
Eye haemorrhage (incl. conjunctival haemorrhage)			
Cardiac disorders			
	Tachycardia		
Vascular disorders			

Common	Uncommon	Rare	Not known
Hypotension, haematoma			Pseudoaneurysm formation following percutaneous intervention*
Respiratory, thoracic and mediastinal disorders			
Epistaxis Haemoptysis			
Gastrointestinal disorders			
Gingival bleeding Gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth		
Hepatobiliary disorders			
	Hepatic function abnormal	Jaundice	
Skin and subcutaneous tissue disorders			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		
Musculoskeletal and connective tissue disorders			
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
Renal and urinary disorders			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]) Renal impairment (incl. blood creatinine increased, blood urea increased)[A]			Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions			
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]	
Investigations			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase[A], increased LDH[A], increased lipase[A], increased amylase[A], increased GGT[A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
Injury, poisoning and procedural complications			

Common	Uncommon	Rare	Not known
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion Wound secretion[A]			

A: observed in prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT and PE in which duration of treatment should be based on the underlying disease as very common in women < 55 years
*) These reactions ocurred in other clinical studies than the phase III studies in patients undergoing major orthopaedic surgery of the lower limbs, patients treated for DVT, or patients treated for the reducing the risk of stroke and systemic embolism

Description of selected adverse reactions
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 or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see 'Overdose' Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in 'Special warnings and precautions for use'). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.
Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Post-marketing observations
The following adverse reactions 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.
Immune system disorders: Angioedema and allergic oedema (In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)).
Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury) (In the pooled phase III trials, these events were rare (≥ 1/10,000 to < 1/1,000)).
Blood and lymphatic system disorders: Thrombocytopenia (In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)).
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (In the pooled phase III trials, these events were estimated as very rare (<1/10,000)).
Respiratory, thoracic and mediastinal disorders: Eosinophilic pneumonia (In the pooled phase III trials, these events were very rare (< 1/10,000).)
Renal and urinary disorders: Anticoagulant-related nephropathy (In the pooled phase III trials, the frequency cannot be estimated)

Overdose

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 rivaroxaban or above.
A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.
The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding
Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see 'Pharmacokinetic properties'). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.
If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or

recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Hypromellose
Sodium laurilsulfate
Magnesium stearate

Macrogol 3350
Hypromellose
Titanium dioxide (E171)
Iron oxide red (E172)

Incompatibilities

Not applicable

Storage

Do not store above 30 °C

Presentation

Xarelto 10 mg
Box, 1 Blister @ 10 Film-coated tablets : Reg. No. XXXXX

Xarelto 15 mg
Box, 2 Blisters @ 14 Film-coated tablets : Reg. No. XXXXX

Xarelto 20 mg
Box, 2 Blisters @ 14 Film-coated tablets : Reg. No. XXXXX

Instruction for use/handling :

None

Harus dengan resep dokter

Manufactured by Bayer AG, Leverkusen – Germany
Imported by PT Bayer Indonesia, Depok – Indonesia

LEMBAR INFORMASI UNTUK PASIEN

Xarelto 10 mg tablet salut selaput
Xarelto 15 mg tablet salut selaput
Xarelto 20 mg tablet salut selaput
Rivaroxaban

Bacalah semua bagian lembar informasi ini sebelum mulai minum obat
- Simpanlah lembar informasi ini. Anda mungkin perlu membacanya kembali.
- Jika ada pertanyaan lebih lanjut, tanyalah kepada dokter atau apoteker anda.
- Obat ini telah diresepkan oleh dokter untuk anda. Jangan berikan kepada orang lain. Obat ini mungkin berbahaya buat orang lain, meskipun mereka memiliki gejala penyakit yang sama dengan anda.
- Jika efek samping yang anda alami menjadi semakin serius, atau jika anda menyadari bahwa anda mengalami efek samping yang tidak tercantum pada lembar informasi ini, segera beritahukan dokter atau apoteker anda.

Yang akan anda temukan dalam lembar informasi ini :

1. APAKAH XARELTO ITU DAN APA KEGUNAANNYA

Xarelto digunakan pada orang dewasa untuk :
- **Mencegah bekuan darah di pembuluh darah balik setelah operasi penggantian sendi panggul atau lutut.** Dokter anda telah meresepkan obat ini karena setelah operasi, anda mengalami peningkatan risiko terjadinya bekuan darah.
- **Mengurangi risiko terjadinya bekuan darah di otak (*stroke*) dan pembuluh darah lainnya di tubuh anda** jika anda menderita kelainan irama jantung yang dikenal sebagai fibrilasi atrium yang non – valvular (bukan disebabkan oleh gangguan pada katup jantung).
- **Mengobati bekuan darah di pembuluh darah balik di kaki anda (sumbatan di pembuluh darah balik bagian dalam / *deep vein thrombosis*)**. Lamanya pemberian obat akan sangat bergantung pada penyakit yang mendasari terjadinya bekuan darah tersebut.
- **Mengobati pasien emboli paru yang secara hemodinamik stabil, yang harus dikonfirmasi dengan menggunakan pencitraan CT Spiral**

Xarelto termasuk dalam kelompok obat yang dikenal sebagai obat anti trombosis (pencegah terjadinya bekuan darah). Obat ini bekerja dengan menghambat faktor pembekuan darah (yang dikenal sebagai faktor Xa) sehingga menurunkan kecenderungan darah untuk membeku.

2. YANG PERLU ANDA KETAHUI SEBELUM MINUM XARELTO

Jangan minum Xarelto
- **jika anda alergi** (*hipersensitif*) terhadap rivaroxaban atau kandungan lainnya yang terdapat dalam Xarelto (terdaftar pada bagian ke – 6 dari lembar informasi ini)
- **jika anda mengalami perdarahan yang berlebihan**
- **jika anda memiliki penyakit di dalam organ tubuh yang meningkatkan risiko perdarahan serius**
- **jika anda mengkonsumsi obat untuk mencegah pembekuan darah (misalnya warfarin, dabigatran, apixaban atau heparin), kecuali saat mengganti pengobatan antikoagulan atau bila anda dipasang infus pada vena atau arteri dan anda memperoleh heparin pada infus itu**
- **jika anda menderita penyakit pada hati** yang dapat meningkatkan resiko perdarahan,
- **jika anda sedang hamil atau menyusui**

Jangan minum Xarelto dan beritahu dokter anda jika salah satu hal tersebut di atas terjadi pada anda.

Peringatan dan perhatian
Bicara dengan dokter atau apoteker anda sebelum minum Xarelto

Hati-hati dalam menggunakan Xarelto

- jika anda mengalami **peningkatan risiko untuk terjadinya perdarahan**, seperti pada keadaan-keadaan sebagai berikut :
  - **penyakit ginjal berat**
  - **jika anda mengkonsumsi obat lain untuk mencegah pembekuan darah (misalnya warfarin, dabigatran, apixaban atau heparin)**
  - **kelainan perdarahan**
  - **tekanan darah yang sangat tinggi,** dan tidak terkontrol dengan menggunakan obat
  - **terdapat ulkus (luka) yang masih aktif atau ulkus baru** pada lambung atau usus anda
  - **masalah pada pembuluh darah di bagian belakang mata anda** (*retinopati*)
  - **penyakit paru-paru di mana bronkus (saluran pernapasan) anda melebar dan terisi nanah** (*bronkiektasis*), atau **pernah mengalami perdarahan di paru-paru**
- jika anda memiliki katup jantung prostetik
- jika dokter sudah menginformasikan bahwa anda menderita sindrom anti fosfolipid berat, suatu penyakit yang dapat menyebabkan bekuan darah
- jika dokter anda menetapkan bahwa tekanan darah anda tidak stabil atau pengobatan lain atau prosedur operasi untuk menghilangkan bekuan darah dari paru-paru sedang direncanakan

Hati-hati jika anda menderita kanker aktif yang memiliki resiko peningkatan perdarahan. Yang dimaksud dengan kanker aktif adalah dalam 6 bulan terakhir anda :

- didiagnosis kanker
- mengalami kekambuhan kanker
- sedang diobati karena kanker

Beri tahu dokter anda sebelum anda minum Xarelto, jika anda mengalami salah satu hal yang tersebut di atas. Dokter anda kemudian akan memutuskan jika anda tetap akan diberikan Xarelto dan jika anda memerlukan pengawasan ketat oleh dokter selama pengobatan.

Jika anda perlu mengalami operasi :

- sangat penting untuk mengkonsumsi Xarelto sebelum dan sesudah operasi tepat pada waktu yang diinstruksikan oleh dokter anda.

Jika operasi anda menggunakan kateter atau injeksi ke dalam kolom tulang belakang

(contoh : untuk anestesi epidural atau spinal atau pereda nyeri):

- Sangat penting untuk minum Xarelto sebelum dan sesudah injeksi atau pencabutan kateter tepat pada saat anda diberitahukan oleh dokter anda.
- Beritahu dokter anda segera jika anda mengalami kebas atau lemas pada kaki atau masalah pada usus atau kandung kemih setelah anestesi habis, karena diperlukan perawatan secepatnya.

Anak-anak dan remaja

Xarelto **tidak direkomendasikan untuk digunakan pada orang dengan usia kurang dari 18 tahun.** Tidak ada informasi yang cukup untuk penggunaan pada anak-anak dan remaja.

Menggunakan obat lain

Informasikan dokter atau apoteker anda jika anda sedang atau baru saja menggunakan obat-obatan lain, termasuk obat-obat yang dapat digunakan tanpa resep dokter.

- **Jika anda menggunakan :**
  - beberapa jenis **obat untuk infeksi jamur** (misal : ketoconazole, itraconazole, voriconazole, posaconazole), kecuali jika obat-obatan tersebut hanya digunakan sebagai obat luar pada kulit
  - beberapa jenis **obat anti virus untuk HIV / AIDS** (contoh : ritonavir)
  - obat-obatan lain yang digunakan untuk **mengurangi pembekuan darah** (contoh : enoxaparin, clopidogrel atau antagonis vitamin K seperti warfarin dan acenocoumarol)
  - **obat anti peradangan dan pereda rasa sakit** (misal : naproxen atau asam asetil salisilat)
  - dronedarone, obat untuk mengobati denyut jantung yang tidak normal
  - **Beberapa jenis obat untuk mengobati depresi** (*selective serotonin reuptake inhibitors* (SSRI) atau *serotonin norepinephrine reuptake inhibitors* (SNRI))

  Beri tahu dokter anda sebelum minum Xarelto, karena efek dari Xarelto dapat mengalami peningkatan. Dokter anda kemudian akan memutuskan jika anda tetap akan diberikan Xarelto dan jika anda memerlukan pengawasan ketat oleh dokter selama pengobatan.
  Jika dokter anda berpikir bahwa anda mengalami peningkatan risiko terjadinya ulkus (luka) di lambung atau usus, dokter anda mungkin akan menggunakan juga obat-obatan untuk mengobati ulkus sebagai pencegahan.

- **Jika anda menggunakan :**
  - beberapa jenis **obat-obatan untuk pengobatan epilepsi** (fenitoin, karbamazepin, fenobarbital)
  - **St John's Wort,** produk herbal yang digunakan untuk depresi
  - **rifampicin,** suatu jenis antibiotika

  Beri tahu dokter anda sebelum minum Xarelto, karena efek dari Xarelto dapat mengalami penurunan. Dokter anda kemudian akan memutuskan jika anda tetap akan diberikan Xarelto dan jika anda memerlukan pengawasan ketat oleh dokter selama pengobatan.

Kehamilan dan menyusui
Jika anda hamil atau menyusui jangan minum Xarelto. Jika ada kemungkinan anda menjadi hamil, gunakan kontrasepsi yang dapat dipercaya selama menggunakan Xarelto. Jika anda menjadi hamil pada saat anda sedang minum Xarelto, segera beri tahu dokter anda, yang kemudian akan segera memutuskan bagaimana anda akan diobati.

Mengemudi dan menggunakan mesin
Xarelto dapat menyebabkan efek samping seperti pusing (frekuensi : sering dijumpai) atau merasa mau pingsan (frekuensi: tidak sering dijumpai) (lihat bagian 4, "Kemungkinan Efek Samping"). Anda sebaiknya tidak mengemudi atau menggunakan mesin jika mengalami gejala-gejala tersebut.

Xarelto mengandung laktosa
Jika anda telah diinformasikan oleh dokter anda bahwa anda mengalami intoleransi terhadap beberapa jenis gula tertentu, hubungi dokter anda sebelum minum Xarelto.

3. BAGAIMANA CARA MINUM XARELTO

Selalu minum Xarelto seperti yang diinstruksikan oleh dokter anda. Anda harus bertanya kepada dokter atau apoteker anda jika anda masih ragu-ragu.

Berapa banyak yang harus diminum

- **Untuk mencegah bekuan darah di pembuluh darah balik setelah operasi penggantian sendi panggul atau lutut**
  Dosis rekomendasinya adalah 10 mg, satu tablet, sekali sehari.

- **Untuk mengurangi risiko terjadinya bekuan darah di otak (*stroke*) dan pembuluh darah lain di tubuh anda**
  Dosis rekomendasinya adalah 20 mg, satu tablet, sekali sehari.
  Jika anda memiliki masalah pada ginjal, dosisnya dapat dikurangi menjadi 15 mg, satu tablet, sekali sehari.

- **Untuk mengobati bekuan darah di pembuluh darah balik di kaki anda dan bekuan darah di dalam pembuluh darah paru-paru anda**
  Dosis rekomendasinya adalah 15 mg, satu tablet, dua kali sehari untuk 3 minggu pertama. Untuk penggunaan setelah 3 minggu, dosis rekomendasinya adalah 20 mg, satu tablet, sekali sehari.
  Setelah pengobatan selama 6 sampai 12 bulan, dokter anda bisa memutuskan untuk melanjutkan pengobatan dengan menggunakan dosis 20 mg, satu tablet, satu kali sehari atau dapat mempertimbangkan penggunaan dosis 10 mg, satu tablet, satu kali sehari berdasarkan penilaian individual berdasarkan risiko terjadinya rekurensi sumbatan di pembuluh darah balik bagian dalam atau emboli paru terhadap risiko terjadinya perdarahan.
  Jika anda memiliki masalah pada ginjal, dosis rekomendasinya adalah 15 mg, satu tablet, dua kali sehari untuk 3 minggu pertama. Untuk penggunaan setelah 3 minggu, dosisnya dapat dikurangi dari 20 mg, satu tablet, sekali sehari menjadi 15 mg, satu tablet, sekali sehari. Setelah pengobatan selama 6 sampai 12 bulan, jika dokter anda memutuskan untuk melanjutkan pengobatan dengan dosis 10 mg satu kali sehari, tidak diperlukan adanya penyesuaian dosis.
  Lamanya pemberian obat akan sangat bergantung pada penyakit yang mendasari terjadinya bekuan darah tersebut.

Telan tablet, sebaiknya dengan air putih.
Konsumsi Xarelto 10 mg dengan atau tanpa makanan.
Konsumsi Xarelto 15 mg atau 20 mg bersama-sama dengan makanan.

Kapan harus minum Xarelto
Minum Xarelto setiap hari sampai dokter anda meminta anda untuk berhenti. Usahakan untuk mengkonsumsi obat pada waktu yang sama setiap harinya supaya anda mudah mengingatnya. Dokter anda akan memutuskan berapa lama pengobatan akan berlangsung.

Untuk mencegah bekuan darah di pembuluh darah balik setelah operasi penggantian sendi panggul atau lutut
Tablet pertama diminum 6 -10 jam setelah operasi.
Jika anda mengalami operasi penggantian sendi panggul, biasanya anda harus mengkonsumsi obat selama 5 minggu.
Jika anda mengalami operasi penggantian sendi lutut, biasanya anda harus mengkonsumsi obat selama 2 minggu.

Untuk mengurangi risiko terjadinya bekuan darah di otak (*stroke*) dan pembuluh darah lain di tubuh anda
Jika irama jantung anda perlu dikembalikan ke normal dengan suatu prosedur Kardioversi, konsumsilah Xarelto pada waktu yang telah diinstruksikan oleh dokter anda.

Jika anda menggunakan lebih dari dosis yang dianjurkan
Hubungi dokter anda segera jika anda menggunakan Xarelto lebih dari dosis yang dianjurkan. Minum Xarelto terlalu banyak akan meningkatkan risiko terjadinya perdarahan.

Jika anda lupa minum Xarelto
- **Jika anda menggunakan dosis 10 mg sekali sehari** dan lupa minum satu dosis, segera minum obat begitu anda ingat. Jangan minum lebih dari satu tablet dalam satu hari untuk menggantikan dosis yang terlupa. Konsumsi tablet berikutnya pada hari berikutnya, kemudian lanjutkan penggunaan sekali sehari.

- **Jika anda menggunakan dosis 20 mg atau 15 mg sekali sehari** dan lupa minum satu dosis, segera minum obat begitu anda ingat. Jangan minum lebih dari satu tablet dalam satu hari untuk menggantikan dosis yang terlupa. Konsumsi tablet berikutnya pada hari berikutnya, kemudian lanjutkan penggunaan sekali sehari.

- **Jika anda menggunakan dosis 15 mg tablet, dua kali sehari** dan lupa minum satu dosis, segera konsumsi obat begitu anda ingat. Jangan minum lebih dari dua tablet 15 mg dalam satu hari. Jika anda lupa mengkonsumsi satu dosis anda dapat menggunakan dua tablet 15 mg pada waktu yang sama untuk memperoleh dosis total dua tablet (30 hari) dalam satu hari. Pada hari berikutnya anda harus melanjutkan menggunakan satu tablet 15 mg dua kali sehari.

Jika anda berhenti minum Xarelto
Jangan berhenti menggunakan Xarelto tanpa berkonsultasi dengan dokter anda terlebih dahulu, karena Xarelto digunakan untuk mencegah dan mengobati kondisi yang serius.

Jika anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter atau apoteker anda.

4. KEMUNGKINAN EFEK SAMPING

Seperti obat-obatan lainnya, Xarelto dapat menyebabkan efek samping, meskipun tidak semua orang akan mengalaminya.

Seperti obat lain yang sejenis (obat anti trombosis), Xarelto dapat menyebabkan perdarahan yang berpotensi dapat mengancam jiwa. Perdarahan berlebihan dapat menyebabkan penurunan mendadak tekanan darah (*shock*). Pada beberapa kasus perdarahan yang terjadi mungkin tidak terlihat dengan jelas.

Kemungkinan efek samping yang dapat menjadi tanda perdarahan :
Beritahu dokter anda segera jika anda mengalami efek samping berikut ini :
- **perdarahan yang lama atau berlebihan**
- **rasa lelah, lemah, pucat, pusing, sakit kepala, pembengkakan yang tidak dapat dijelaskan alasannya, sesak napas, nyeri dada atau angina pektoris,** yang dapat merupakan tanda terjadinya perdarahan**.**

Dokter anda dapat memutuskan anda akan berada dalam pengawasan ketat atau mengubah pengobatan untuk anda.

Kemungkinan efek samping yang dapat menjadi tanda adanya reaksi kulit berat :
Beritahu dokter anda segera jika anda mengalami reaksi kulit seperti ruam kulit hebat, lecet atau luka pada lapisan kulit misal pada mulut atau mata (*Stevens-Johnson syndrome/Toxic Epidermal Necrolysis*). Frekuensi dari efek samping ini sangat jarang (kurang dari 1 dalam 10.000)

Daftar kemungkinan efek samping:
Efek samping yang sering ditemukan
(terjadi pada 1 dari 10 orang)
- perdarahan di lambung atau usus, saluran kemih (termasuk darah pada urin atau menstruasi yang hebat), hidung, dan gusi
- perdarahan di mata (termasuk perdarahan dari bagian berwarna putih di mata)
- perdarahan pada jaringan atau rongga tubuh (hematoma, memar)
- batuk darah
- perdarahan dari kulit atau bagian bawah kulit
- perdarahan setelah operasi
- merembesnya darah atau cairan dari luka operasi
- pembengkakan pada tungkai
- rasa nyeri di tungkai
- demam
- penurunan kadar sel darah merah yang dapat membuat kulit menjadi pucat dan menyebabkan rasa lemas atau sulit bernapas
- sakit perut, gangguan pencernaan, merasa sakit, konstipasi, diare
- tekanan darah rendah (gejalanya dapat berupa pusing atau seperti mau pingsan saat berdiri)
- penurunan kekuatan dan energi secara umum (rasa lemah, lelah), sakit kepala, pusing
- ruam dan rasa gatal pada kulit
- kerusakan fungsi ginjal (mungkin dapat terlihat pada pemeriksaan yang dilakukan oleh dokter anda)
- pemeriksaan darah dapat menunjukkan peningkatan beberapa enzim hati

Efek samping yang lebih jarang ditemukan
(terjadi pada 1 dari 100 orang)
- perdarahan pada otak atau bagian dalam tulang tengkorak
- perdarahan pada sendi yang mengakibatkan rasa nyeri dan pembengkakan
- mau pingsan
- merasa tidak sehat
- mulut terasa kering
- peningkatan denyut jantung
- reaksi alergi, termasuk reaksi alergi kulit
- gatal-gatal
- gangguan fungsi hati (mungkin dapat terlihat pada pemeriksaan yang dilakukan oleh dokter anda)
- pemeriksaan darah mungkin dapat menunjukkan terjadinya peningkatan kadar bilirubin, pankreas, atau hati, atau jumlah trombosit

Efek samping yang lebih jarang ditemukan
(terjadi pada 1dari 1000 orang)
- perdarahan pada otot
- pembengkakan lokal
- pengumpulan darah (*hematoma*) sebagai komplikasi dari operasi jantung di mana kateter dimasukkan untuk mengobati arteri koroner yang menyempit (*pseudoaneurisme*)
- kulit dan mata menjadi berwarna kekuningan (*jaundice*)

Efek samping yang frekuensinya tidak diketahui
(frekuensi tidak dapat diperkirakan dari data yang ada)
- peningkatan tekanan pada otot kaki atau lengan setelah perdarahan, yang dapat menyebabkan rasa nyeri, pembengkakan, perubahan sensasi, mati rasa, atau kelumpuhan (sindrom kompartemen setelah perdarahan)
- gagal ginjal setelah perdarahan berat

Berikut efek samping yang dilaporkan setelah otorisasi:
- Angioedema dan edema alergi (pembengkakan wajah, bibir, mulut, lidah atau tenggorokan)
- Kolestasis (penurunan aliran empedu), Hepatitis termasuk luka sel hati (inflamasi hati termasuk luka pada hati)
- Trombositopenia (rendahnya jumlah platelet, yaitu sel yang membantu pembekuan darah).
- Akumulasi eosinofil, suatu jenis sel darah putih granulositik yang menyebabkan peradangan pada paru (pneumonia eosinofil)
- Perdarahan di ginjal kadang disertai adanya darah di urin yang menyebabkan ketidakmampuan ginjal bekerja dengan baik (nefropati yang berhubungan dengan antikoagulan)

Jika anda mengalami efek samping apa pun, beri tahu dokter atau apoteker anda. Ini termasuk efek samping yang tidak terdaftar pada lembar informasi ini.

5. BAGAIMANA CARA MENYIMPAN XARELTO

Jauhkan dari jangkauan dan pandangan anak-anak.

Jangan minum Xarelto setelah tanggal kadaluarsa yang tercantum pada karton pembungkus dan pada setiap blister obat, setelah tulisan EXP.
Tanggal kadaluarsa merujuk pada hari terakhir pada bulan tersebut.

Obat ini tidak memerlukan kondisi penyimpanan khusus.

Obat ini tidak boleh dihancurkan melalui sistem pembuangan air atau sampah rumah tangga. Tanyakan pada apoteker anda bagaimana cara menghancurkan atau membuang obat-obatan yang tidak lagi digunakan. Hal ini dapat membantu melindungi lingkungan anda.

6. INFORMASI LEBIH LANJUT

Kandungan Xarelto
- Bahan aktifnya adalah rivaroxaban. Setiap tablet mengandung rivaroxaban 10 mg, 15 mg atau 20 mg.
- Kandungan yang lain adalah :
  Inti tablet : *selulosa mikrokristalin, natrium kroskarmelosa, laktosa monohidrat, hipromelosa, natrium laurilsulfat, magnesium stearat*.
  Lapisan selaput : *makrogol 3350, hipromelosa, titanium dioksida (E171), besi oksida merah (E172)*.

Seperti apa bentuk Xarelto dan isi kemasannya
Xarelto 10 mg tablet salut selaput berwarna merah muda, bundar, bikonveks dan ditandai dengan *BAYER-cross* pada satu sisi dan tulisan “10” dan sebuah segi tiga pada sisi lainnya.
Xarelto tersedia dalam kemasan :
Dus, 1 blister @ 10 tablet salut selaput, No. Reg. XXXXX

Xarelto 15 mg tablet salut selaput berwarna merah, bundar, bikonveks dan ditandai dengan *BAYER-cross* pada satu sisi dan tulisan “15” dan sebuah segi tiga pada sisi lainnya.
Xarelto tersedia dalam kemasan :
- Dus, 2 blister @ 14 tablet salut selaput; No. Reg. XXXXX

Xarelto 20 mg tablet salut selaput berwarna merah kecoklatan, bundar, bikonveks dan ditandai dengan *BAYER-cross* pada satu sisi dan tulisan “20” dan segi tiga pada sisi lainnya.
Xarelto tersedia dalam kemasan :
- Dus, 2 blister @ 14 tablet salut selaput; No. Reg. XXXXX

Harus dengan resep dokter

Dibuat oleh Bayer AG, Leverkusen – Germany
Diimpor oleh PT Bayer Indonesia, Depok – Indonesia