

PRODUCT MONOGRAPH

Pr XARELTO[®]

rivaroxaban tablet

10 mg

Anticoagulant

Direct Factor Xa Inhibitor

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XARELTO[®]

rivaroxaban tablet

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Film-coated tablet, 10 mg	Lactose Monohydrate <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

XARELTO[®] (rivaroxaban tablet) is indicated for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery.

Geriatrics (> 65 years of age)

In phase III clinical studies, 53% (n = 2486) of the patients treated with XARELTO were aged ≥ 65 years, and 15% (n = 694) were aged >75 years (see **WARNINGS AND PRECAUTIONS – Geriatrics (>65 Years of Age)** and **Renal**, and **DOSAGE AND ADMINISTRATION – Renal Impairment** and **Geriatrics (>65 years of age)**).

Pediatrics (< 18 years of age)

The safety and efficacy of XARELTO have not been established in children less than 18 years of age; therefore, XARELTO is not recommended in this patient population.

CONTRAINDICATIONS

- Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and a clinically relevant bleeding risk (see **WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic**)
- Clinically significant active bleeding, including hemorrhagic manifestations and bleeding diathesis
- Lesions at increased risk of clinically significant bleeding, eg, cerebral infarction (hemorrhagic or ischemic) within the last 6 months, and patients with spontaneous impairment of hemostasis

- Concomitant **systemic** treatment with strong inhibitors of both *CYP3A4* and P-gp (see **WARNINGS AND PRECAUTIONS – General**)
- Pregnancy
- Nursing women
- Hypersensitivity to XARELTO or to any ingredient in the formulation. (For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.)

WARNINGS AND PRECAUTIONS

General

The use of XARELTO is contraindicated in patients receiving concomitant **systemic** treatment with strong inhibitors of both *CYP3A4* and P-gp such as ketoconazole, itraconazole, voriconazole, posaconazole, or ritonavir). These drugs may increase XARELTO plasma concentrations to a clinically relevant degree, which may lead to an increased bleeding risk (see **DRUG INTERACTIONS**).

Strong *CYP3A4* inducers should be administered with caution in combination with XARELTO (see **DRUG INTERACTIONS – Drug-Drug Interactions**).

Care should be taken if patients are treated concomitantly with drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs) and platelet aggregation inhibitors (see **DRUG INTERACTIONS**). Coadministration of XARELTO with other anticoagulants or antithrombotic therapy has not been adequately studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk.

Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site.

Carcinogenesis and Mutagenesis

See **TOXICOLOGY – Carcinogenicity** and **Mutagenesis**.

Cardiovascular

No QTc prolonging effects were observed with XARELTO.

Hematologic

Hemorrhage

XARELTO, like other anticoagulants, should be used with caution in patients with an increased bleeding risk such as congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, vascular retinopathy, or concomitant use of drugs affecting hemostasis.

Due to the pharmacological mode of action, XARELTO may be associated with an increased risk of occult or overt bleeding which may result in posthemorrhagic anemia. The signs, symptoms, and severity will vary according to the location and degree, or extent, of the bleeding.

The possibility of a hemorrhage should be considered in evaluating the condition of any anticoagulated patient. Hemorrhagic complications may present as weakness, asthenia, paleness, dizziness, headache, or unexplained swelling.

Hepatic/Biliary/Pancreatic

Patients with significant hepatic disease (eg, acute clinical hepatitis, chronic active hepatitis, liver cirrhosis) were excluded from clinical trials. Therefore, XARELTO is contraindicated in patients with hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and a clinically relevant bleeding risk.

The limited data available for patients with mild hepatic impairment without coagulopathy indicate that there is no difference in pharmacodynamic response or pharmacokinetics as compared to healthy subjects.

Peri-operative Considerations

Neuraxial (Epidural/Spinal) Anesthesia

When neuraxial (epidural/spinal) anesthesia or spinal puncture is performed, patients treated with antithrombotics for prevention of thromboembolic complications are at risk for developing an epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters or the concomitant use of drugs affecting hemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, the administration of XARELTO should be delayed for 24 hours.

Patients who have undergone epidural puncture and who are receiving XARELTO should be frequently monitored for signs and symptoms of neurological impairment (eg, numbness or weakness of the legs, bowel or bladder dysfunction). If neurological deficits are noted, urgent diagnosis and treatment is necessary.

The physician should consider the potential benefit versus the risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis and use XARELTO only when the benefits clearly outweigh the possible risks. An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of XARELTO. XARELTO should be administered not earlier than 6 hours after the removal of the catheter.

Renal

Following oral dosing with XARELTO, there is a direct relationship between the pharmacodynamic effects and the degree of renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY – Renal Insufficiency**).

There are insufficient safety data in patients with severe renal impairment (CrCl <30 mL/min) as these patients were excluded from pivotal phase III trials. **Therefore, the use of XARELTO is not recommended in patients with severe renal impairment.** Patients who develop acute renal failure while on XARELTO should discontinue such treatment.

XARELTO should be used with caution in patients with moderate renal impairment (CrCl 30-49 mL/min) concomitantly receiving other drugs which increase rivaroxaban plasma concentrations (see **DOSAGE AND ADMINISTRATION – Renal Impairment** and **DRUG INTERACTIONS – Drug-Drug Interactions**).

Physicians should consider the benefit/risk of anticoagulant therapy before administering XARELTO to patients with moderate renal impairment with a creatinine clearance close to the severe renal impairment category (CrCl <30 mL/min) or with a potential to have deterioration of renal function during therapy.

Sensitivity/Resistance

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

Special Populations

Pregnant Women

No data are available on the use of XARELTO in pregnant women.

Based on animal data, use of XARELTO is contraindicated throughout pregnancy (see **CONTRAINDICATIONS** and **TOXICOLOGY – Reproductive Toxicology**).

If XARELTO is to be used in women of childbearing potential, pregnancy should be avoided.

Nursing Women

No data are available on the use of XARELTO in nursing mothers. In rats, XARELTO is secreted into breast milk. Therefore, XARELTO may only be administered after breastfeeding is discontinued (see **CONTRAINDICATIONS** and **TOXICOLOGY – Reproductive Toxicology**).

Pediatrics (<18 Years of Age)

The safety and efficacy of XARELTO have not been established in children less than 18 years of age; therefore, XARELTO is not recommended in this patient population.

Geriatrics (>65 Years of Age)

No dose adjustment is required for the elderly (>65 years of age). Increasing age may be associated with declining renal and hepatic function (see **CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS – Renal** and **Hepatic/Biliary/Pancreatic**; and **DOSAGE**

AND ADMINISTRATION – Renal Impairment and Hepatic Impairment). Physicians should take into consideration that 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.

Monitoring and Laboratory Tests

Prothrombin and activated Partial Thromboplastin Time

XARELTO, at recommended doses, prolongs several global (prothrombin time, activated partial thromboplastin time, Heptest[®]) and specific (inhibition of factor Xa activity) clotting tests. Prothrombin time (PT) is influenced by XARELTO in a dose-dependent way if Neoplastin[®] is used for the assay. In patients undergoing elective total hip replacement or total knee replacement surgery, the 5/95 percentiles for PT (Neoplastin[®]) 2 to 4 hours after tablet intake (ie, at the time of maximum effect) ranged from 13 to 25 sec. In case of excessive doses, the PT is expected to be outside of this range.

Although the activated partial thromboplastin time (aPTT) and HepTest[®] are also both prolonged dose-dependently, neither test is recommended for the assessment of the pharmacodynamic effects of XARELTO. Similarly, antifactor Xa activity as well as inhibition of factor Xa activity are influenced by XARELTO but, as for aPTT and Heptest[®], neither test is recommended to follow the effects of XARELTO (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**).

Hemoglobin

Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of XARELTO 10 mg has been evaluated in three randomized, double-blind, active-control phase III studies (RECORD 1, RECORD 2, and RECORD 3). In the phase III studies, 4657 patients undergoing total hip replacement or total knee replacement surgery were randomized to XARELTO, with 4571 patients actually receiving XARELTO.

In RECORD 1 and 2, a total of 2209 and 1228 THR patients, respectively, were randomized to XARELTO 10 mg od. In RECORD 1, the treatment period for both groups was 35±4 days postoperatively. In RECORD 2, patients randomized to XARELTO were treated for 35 ±4 days postoperatively, and patients randomized to enoxaparin received placebo after day 12±2 until day 35±4 postoperatively. In RECORD 3, a total of 1220 TKR patients were randomized to XARELTO 10 mg od, and both groups received study drug until day 12±2 postoperatively.

The safety profile of XARELTO with regard to adverse events (AE) and serious adverse events (SAE) is similar to that of the active comparator in the RECORD 1, 2, and 3 studies.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The database of RECORD 1, 2, and 3 comprised 4657 patients randomized to treatment with XARELTO 10 mg od and 4692 patients randomized to enoxaparin 40 mg od. Analysis of this pooled database showed that there was no statistically significant difference in bleeding ($P > 0.05$) between XARELTO and the active comparator (see [Table 2](#)). More details are provided in [Table 10](#) and [Table 12](#).

Table 2 - RECORD 1, 2, and 3 – Treatment-Emergent Bleeding Events a (Safety Population with Central Adjudication) in Patients Randomized to XARELTO (First Dose 6 to 8 Hours Postoperatively) or Enoxaparin (First Dose 12 Hours Preoperatively)

		Major Bleeding ^b n (%)	Major Bleeding Including Surgical Site Bleeding Events Associated With Hemoglobin Drops or Transfusions ^c n (%)	Any Bleeding (Major or Nonmajor) ^d n (%)
RECORD 1 (THR)	XARELTO (N=2209) 10 mg od po for 35±4 days	6 (0.3)	40 (1.8)	133 (6.0)
	Enoxaparin (N=2224) 40 mg od SC for 36±4 days	2 (0.1)	33 (1.5)	131 (5.9)
	P Value^e	0.18	0.41	0.90
RECORD 2 (THR)	XARELTO (N=1228) 10 mg od po for 35±4 days	1 (0.1)	23 (1.9)	81 (6.6)
	Enoxaparin (N=1229) 40 mg od SC for 12±2 days	1 (0.1)	19 (1.6)	68 (5.5)
	P Value^e	1.00	0.54	0.273
RECORD 3 (TKR)	XARELTO (N=1220) 10 mg od po for 12±2 days	7 (0.6)	21 (1.7)	60 (4.9)
	Enoxaparin (N=1239) 40 mg od SC for 13±2 days	6 (0.5)	17 (1.4)	60 (4.8)
	P Value^e	0.79	0.52	1.00
Pooled Analysis^f (RECORD 1, 2, 3)	XARELTO (N=4657)	14 (0.3)	84 (1.8)	274 (5.9)
	Enoxaparin (N=4692)	9 (0.2)	69 (1.5)	259 (5.5)
	P Value^e	0.31	0.22	0.48

- a Starts with administration of the first (placebo) tablet or (placebo) injection. Active XARELTO treatment started after surgery. Active enoxaparin treatment started on the day before surgery.
- b Major bleeding events included: (1) fatal, (2) bleeding into a critical organ (eg, retroperitoneal, intracranial, intraocular or intraspinal bleeding/hemorrhagic puncture), (3) bleeding requiring reoperation, (4) clinically overt extra-surgical site bleeding associated with ≥ 2 g/dL fall in hemoglobin or leading to infusion of ≥ 2 units of whole blood or packed cells.
- c Surgical-site bleeding events associated with a decrease in hemoglobin were based on a determination by the investigator. Surgical-site bleeding events requiring transfusion were based on an algorithmic assessment of blood transfusions given within 48 hours of the bleeding event. In addition, both types of surgical-site bleeding events must have been based on bleeding events confirmed by the adjudication committee and reported as overt surgical-site bleeding events by the investigator.
- d Nonmajor bleeding events were bleeding events that did not fulfill the criteria of major bleeding.
- e P value calculated as Fishers two-sided exact test
- f Note that pooling was done despite the shorter duration of therapy with enoxaparin in RECORD 2
See [Table 10](#) and [Table 12](#) for additional details.
- od = once daily
po = oral
SC = subcutaneous

Due to the pharmacological mode of action, XARELTO may be associated with an increased risk of occult or overt bleeding which may result in posthemorrhagic anemia (see **WARNINGS AND PRECAUTIONS – Hematologic**).

The most common treatment-emergent adverse events reported by patients valid for safety analysis in the 3 phase III studies are presented in [Table 3](#).

Table 3 – Treatment-Emergent Drug-Related Adverse Events Occurring in >1% of Any Treatment Group – Pooled Data of RECORD 1, 2, 3 (Patients Valid for Safety Analysis^a)

Medical Entity	XARELTO (N=4571)		Enoxaparin (N=4601)	
	n	(%)	n	(%)
Gastrointestinal disorders				
Nausea	57	(1.25)	70	(1.52)
Injury, poisoning, and procedural complications				
Anemia (including laboratory parameter)	49	(1.07)	51	(1.11)
Post procedural hemorrhage	71	(1.55)	64	(1.39)
Investigations				
Increase in transaminases	91	(1.99)	128	(2.78)
Increase in Gamma-glutamyltransferase	51	(1.12)	72	(1.56)

Note: Incidence = number of events/number at risk, where: number of events = number of patients reporting the event; number at risk = number of patients in reference population

Only treatment emergent adverse events which occurred up to 2 days after the last dose of study medication are included.

a Started after administration of oral study medication (XARELTO or matching placebo tablet).

Less Common Clinical Trial Adverse Drug Reactions

Incidence is $\geq 0.1\%$ to $< 1\%$ unless specified.

Blood and the Lymphatic System Disorders: thrombocythemia (including platelet count increased)

Cardiac Disorders: tachycardia

Gastrointestinal Disorders: abdominal and gastrointestinal pain (including upper abdominal pain, stomach discomfort), constipation, diarrhea, dry mouth, dyspepsia (including epigastric discomfort), vomiting

General Disorders and Administration Site Conditions: edema peripheral, feeling unwell (including fatigue, asthenia), fever, localized edema

Hepatobiliary Disorders: abnormal hepatic function ($\geq 0.01\%$ to $< 0.1\%$)

Immune System Disorders: allergic dermatitis ($\geq 0.01\%$ to $< 0.1\%$)

Injury, Poisoning, and Procedural Complications: wound secretion

Investigations: bilirubin conjugated increased (with or without concomitant increase of ALT) ($\geq 0.01\%$ to $< 0.1\%$), blood bilirubin increased, increased alkaline phosphatase, increased amylase, increased LDH, increased lipase

Musculoskeletal, Connective Tissue, and Bone Disorders: pain in extremity

Nervous System Disorders: dizziness, headache, syncope (including loss of consciousness)

Renal and Urinary Disorders: renal impairment (including serum creatinine increased, blood urea increased)

Skin and Subcutaneous Tissue Disorders: contusion, pruritus (including rare cases of generalized pruritus), rash, urticaria (including rare cases of generalized urticaria)

Vascular Disorders: gastrointestinal tract hemorrhage (including gingival bleeding, rectal hemorrhage, hematemesis), genital tract hemorrhage (including menorrhagia), hematuria (including blood urine present), hemorrhage (including hematoma and rare cases of muscle hemorrhage), hypotension (including blood pressure decreased, procedural hypotension), nose bleed.

In other clinical studies with XARELTO, single cases of adrenal hemorrhage and conjunctival hemorrhage, and fatal gastrointestinal ulcer hemorrhage were reported; jaundice and hypersensitivity were rare and hemoptysis was uncommon. Intracranial bleeding (especially in patients with arterial hypertension and/or on concomitant antihemostatic agents) which in single cases may be potentially life-threatening has been reported.

Abnormal Hematologic and Clinical Chemistry Findings

The incidence rates of laboratory abnormalities in the XARELTO and enoxaparin treatment groups were generally similar. In the RECORD 1, 2, and 3 studies, drug-related increases in transaminases were reported in 2.0% of XARELTO- and 2.8% of enoxaparin-treated patients and drug-related increases in gamma-glutamyltransferase occurred in 1.1% of XARELTO- and 1.6% of enoxaparin-treated patients.

DRUG INTERACTIONS

Overview

CYP Inhibition

XARELTO does not inhibit *CYP3A4* or any other major CYP isoenzymes.

CYP Induction

XARELTO does not induce *CYP3A4* or any other major CYP isoenzymes.

Drug-Drug Interactions

The use of XARELTO is contraindicated in patients receiving concomitant systemic treatment with strong inhibitors of both *CYP3A4* and P-gp such as (ketoconazole, itraconazole, voriconazole, posaconazole, or ritonavir). These drugs may increase XARELTO plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS – General**). Drugs strongly inhibiting only one of the XARELTO elimination pathways, either *CYP3A4* or P-gp, potentially increase XARELTO plasma concentrations. The expected increase is considered not clinically relevant.

Table 4 – Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Reference	Effect on Concentration of XARELTO	Clinical Comment
Azole antimycotic: ketoconazole	CT	↑ XARELTO	Coadministration of XARELTO with the azole-antimycotic ketoconazole (400 mg od) a strong <i>CYP3A4</i> and P-gp inhibitor, led to a 2.6-fold increase in mean XARELTO steady state AUC and a 1.7-fold increase in mean XARELTO C_{max} , with significant increases in its pharmacodynamic effects. The use of XARELTO is contraindicated in patients receiving systemic treatment with ketoconazole (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – General and Renal).
Protease inhibitor: ritonavir	CT	↑ XARELTO	Coadministration of XARELTO with the HIV protease inhibitor ritonavir (600 mg bid), a strong <i>CYP3A4</i> and P-gp inhibitor, led to a 2.5-fold increase in mean XARELTO AUC and a 1.6-fold increase in mean XARELTO C_{max} , with significant increases in its pharmacodynamic effects. The use of XARELTO is contraindicated in patients receiving systemic treatment with ritonavir (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – General and Renal).
Anti-infectives: erythromycin	CT	↑ XARELTO	Erythromycin (500 mg tid), which inhibits <i>CYP3A4</i> and P-gp moderately, led to a 1.3-fold increase in mean XARELTO AUC and C_{max} . This increase is within the magnitude of the normal variability of AUC and C_{max} and is considered not clinically relevant.
rifampicin	CT	↓ XARELTO	Coadministration of XARELTO with the strong <i>CYP3A4</i> and P-gp inducer rifampicin led to an approximate 50% decrease in mean XARELTO AUC, with parallel decreases in its pharmacodynamic effects. Strong <i>CYP3A4</i> inducers should be administered with caution in combination with XARELTO.

Table 4 – Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Reference	Effect on Concentration of XARELTO	Clinical Comment
Antithrombotic: enoxaparin	CT	No effect on XARELTO	After combined administration of enoxaparin (40 mg single dose) with XARELTO (10 mg single dose), an additive effect on antifactor Xa activity was observed, without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the bioavailability and pharmacokinetics of XARELTO (see WARNINGS AND PRECAUTIONS – General).
Nonsteroidal Anti-inflammatory Drugs (NSAIDs): naproxen	CT	No effect on XARELTO	Coadministration with naproxen did not affect XARELTO bioavailability and pharmacokinetics. No clinically relevant prolongation of bleeding time was observed after concomitant administration of XARELTO and 500 mg naproxen. Nevertheless there may be individuals with more pronounced pharmacodynamic response (see WARNINGS AND PRECAUTIONS – General).
acetylsalicylic acid (ASA)	CT	No effect on XARELTO	No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when XARELTO was coadministered with 500 mg acetylsalicylic acid (see WARNINGS AND PRECAUTIONS – General).
Anticonvulsants: phenytoin carbamazepine phenobarbitone	T	↓ XARELTO	The concomitant use of XARELTO with strong <i>CYP3A4</i> inducers (eg, phenytoin, carbamazepine, or phenobarbitone) may also lead to a decreased XARELTO plasma concentration. Strong <i>CYP3A4</i> inducers should be administered with caution in combination with XARELTO.
Antiplatelet drugs: clopidogrel	CT	No effect on XARELTO	Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not affect XARELTO bioavailability and pharmacokinetics, but a relevant increase in bleeding times was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin, or GPIIb/IIIa receptor levels (see WARNINGS AND PRECAUTIONS – General).

Legend: C= Case Study; CT=Clinical Trial; T=Theoretical

Interactions Shown Not to Exist

There were no mutual pharmacokinetic interactions between XARELTO and midazolam (substrate of *CYP3A4*), digoxin (substrate of P-gp), or atorvastatin (substrate of *CYP3A4* and P-gp).

Coadministration of the H₂-receptor antagonist ranitidine, the antacid aluminum hydroxide / magnesium hydroxide, naproxen, clopidogrel, or enoxaparin did not affect XARELTO bioavailability and pharmacokinetics.

Drug-Food Interactions

XARELTO can be taken with or without food (see [ACTION AND CLINICAL PHARMACOLOGY](#)).

Grapefruit juice is a moderate *CYP3A4* inhibitor. Therefore, increase in XARELTO exposure upon grapefruit juice consumption is not expected to be clinically relevant.

Drug-Herb Interactions

The concomitant use of XARELTO with other strong *CYP3A4* inducers (eg, St. John's Wort) may lead to a decreased XARELTO plasma concentration. Strong *CYP3A4* inducers should be administered with caution in combination with XARELTO.

Drug-Laboratory Interactions

Clotting parameter tests (PT, aPTT, HepTest[®]) are affected as expected by the mode of action of XARELTO (see [ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics](#)).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose of XARELTO for VTE prevention in patients following elective total hip replacement or elective total knee replacement surgery is one tablet (10 mg) once daily (see also [Special Populations](#) below). XARELTO may be taken with or without food. The initial dose should be taken within 6 to 10 hours after surgery, provided that hemostasis has been established. If hemostasis is not established, treatment should be delayed.

The duration of treatment depends on the type of surgery:

- After elective total hip replacement surgery, patients should be treated for 35 days.
- After elective total knee replacement surgery, patients should be treated for 14 days.

Special Populations

Hepatic Impairment

XARELTO is contraindicated in patients with hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and a clinically relevant bleeding risk.

The limited clinical data for patients with moderate hepatic impairment indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment (see [CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic](#); and [ACTION AND CLINICAL PHARMACOLOGY – Hepatic Insufficiency](#)).

The limited data available for patients with mild hepatic impairment without coagulopathy indicate that there is no difference in pharmacodynamic response or pharmacokinetics as compared to healthy subjects.

Renal Impairment

The use of XARELTO is not recommended in patients with severe renal impairment.

Patients who develop acute renal failure while on XARELTO should discontinue such treatment.

XARELTO should be used with caution in patients with **moderate** renal impairment (CrCl 30 - 49 mL/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see **WARNINGS AND PRECAUTIONS – Renal** and **DRUG INTERACTIONS – Drug-Drug Interactions**).

Physicians should consider the benefit/risk of anticoagulant therapy before administering XARELTO to patients with moderate renal impairment with a creatinine clearance close to the severe renal impairment category (CrCl <30 mL/min) or with a potential to have deterioration of renal function during therapy. Consideration should be given to follow the renal function in these patients.

Creatinine clearance can be estimated using the Cockcroft-Gault Formula as follows:

Creatinine Clearance (mL/min)=

$$\text{Males: } \frac{(140-\text{age}) (\text{years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females: } \frac{0.85 \times (140-\text{age}) (\text{years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Sex, Ethnicity, or Body Weight

Body Weight: The exposure of 10 mg XARELTO in the extreme underweight group (<50 kg) resulted in a larger C_{max} by 24%, as compared to the normal subjects. The maximal effect of PT prolongation was approximately 20% higher at lower body weight. In overweight subjects with body weight higher than 120 kg, the PT maximal prolongation was less pronounced.

Sex: Sex effect was not observed.

Ethnicity: Ethnicity effect was not observed.

Pediatrics (<18 years of age)

The safety and efficacy of XARELTO have not been established in children less than 18 years of age; therefore, XARELTO is not recommended in this patient population.

Geriatrics (>65 years of age)

No dose adjustment is required for the elderly (>65 years of age). Increasing age may be associated with declining renal and/or liver function (see **CONTRAINDICATIONS**; **WARNINGS AND PRECAUTIONS – Renal** and **Hepatic/Biliary/Pancreatic**; and **DOSAGE AND ADMINISTRATION – Renal Impairment** and **Hepatic Impairment**).

Missed Dose

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

OVERDOSAGE

Overdose following administration of XARELTO may lead to hemorrhagic complications due to its pharmacodynamic properties.

The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Administration of activated charcoal up to 8 hours after overdose may reduce the absorption of XARELTO.

Due to the high plasma protein binding, XARELTO is not expected to be removed by dialysis.

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

Delay of next XARELTO administration or discontinuation of treatment as appropriate. XARELTO has a half-life of approximately 5 to 13 hours (see **ACTION AND CLINICAL PHARMACOLOGY**).

Appropriate symptomatic treatment, eg, mechanical compression (eg, for severe epistaxis), surgical interventions, fluid replacement and hemodynamic support, or blood product or component transfusion should be considered.

If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants:

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

However, there is currently no experience with the use of these products in individuals receiving XARELTO.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of XARELTO. There is no scientific rationale for benefit or experience with systemic hemostatics (eg, desmopressin, aprotinin, tranexamic acid, aminocaproic acid) in individuals receiving XARELTO.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Rivaroxaban is a highly selective, direct, antithrombin independent factor Xa inhibitor with high oral bioavailability.

Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex and, ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation. Selective inhibitors of FXa can terminate the amplified burst of thrombin generation, thereby diminishing thrombin-mediated activation of coagulation.

Pharmacodynamics

There is a clear correlation between plasma rivaroxaban concentration and the degree of anticoagulant effect. The maximal effect (E_{max}) of rivaroxaban on pharmacodynamic parameters occurs at the same time as C_{max} .

- A dose-dependent inhibition of factor Xa activity was observed over the complete dose range closely following the pharmacokinetic profiles which provides the ‘proof of mechanism’ in humans. Inhibition of factor Xa activity versus rivaroxaban plasma concentration follows a maximum effect (E_{max}) model. There is a close correlation between FXa inhibition and plasma concentrations with an r value of 0.97.
- Prothrombin time (PT) is influenced by rivaroxaban in a dose-dependent way with a close correlation to plasma concentrations ($r = 0.98$) if Neoplastin[®] is used for the assay. Other reagents would provide different results. The INR (International Normalized Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing hip replacement surgery or knee replacement surgery, the 5/95 percentiles for PT (Neoplastin[®]) 2 to 4 hours after tablet intake (ie, at the time of maximum effect) ranged from 13 to 25 sec.
- The activated partial thromboplastin time (aPTT) is also prolonged dose-dependently; however, the slope is rather flat and does not allow a sufficient discrimination at the relevant plasma concentrations. Therefore, aPTT is not considered to be adequate for following the pharmacodynamic effects. The r value for aPTT is 0.99.
- HepTest[®] is also prolonged dose-dependently and correlates closely with plasma concentrations, following a curvilinear model. Despite the r value of 0.99 for the relation to plasma concentrations, the HepTest[®] is not considered optimal to assess the pharmacodynamic effects due to the curvilinear relationship.

- Antifactor Xa activity is also influenced by rivaroxaban; however, no standard for calibration is available.

Pharmacokinetics

Absorption

The absolute bioavailability of rivaroxaban is approximately 100% for the 10 mg dose. Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake.

Rivaroxaban 10 mg dose can be taken with or without food. Administration of the 10 mg rivaroxaban tablet with food (high-calorie/high-fat meal) showed no significant food effects (see **DOSAGE AND ADMINISTRATION** and **DETAILED PHARMACOLOGY – Absorption and Bioavailability**).

Rivaroxaban pharmacokinetic parameters behave in a linear fashion; no evidence of bioaccumulation was seen after multiple doses.

Variability in rivaroxaban pharmacokinetics is moderate with interindividual variability (CV%) ranging from 30% to 40%.

Table 5 – Summary of PK Parameters After Oral Administration of 10 mg of Rivaroxaban in Humans

	C_{max} [$\mu\text{g/L}$]	$t_{1/2}$ [h]	AUC [$\mu\text{g}\cdot\text{h/L}$]	Clearance, Urinary Excretion	Volume of Distribution
Healthy (Young) Subjects	~114 ^a	5-9	~817	$CL_{sys} = \sim 10 \text{ L/h}$ $CL_R = 3 - 4 \text{ L/h}$ $Ae_{ur} = 30\% - 40\%$	$V_{ss} = \sim 50 \text{ L}$
Patients	~125	7-11	~1170	N/A (no IV data) ^b $Ae_{ur} = 22\%$	N/A (no IV data)

a = 2 – 4 hours after drug administration (t_{max})

b = not available

AUC = area under the plasma-concentration time curve; Ae_{ur} = amount of drug excreted unchanged into urine; CL_{sys} = systemic clearance (after intravenous administration); CL_R = renal clearance; C_{max} = maximum plasma concentration; $t_{1/2}$ = terminal elimination half-life; t_{max} = time to reach C_{max} ; V_{ss} = volume of distribution at steady state

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 L.

Metabolism

Rivaroxaban is eliminated by metabolic degradation (approximately 2/3 of the administered dose) as well as by direct renal excretion of unchanged compound (approximately 1/3). Rivaroxaban is metabolized 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.

Excretion

Rivaroxaban and metabolites have a dual route of elimination (via renal and fecal routes).

The clearance and excretion of rivaroxaban are as follows:

- 1/3 of the active drug is cleared as unchanged drug by the kidneys
- 1/3 of the active drug is metabolized to inactive metabolites and then excreted by the kidneys
- 1/3 of the active drug is metabolized to inactive metabolites and then excreted by the fecal route

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 low-clearance drug. Elimination of rivaroxaban from plasma occurred with terminal half-lives of 5 to 9 hours in young individuals and with terminal half-lives of 11 to 13 hours in the elderly.

Special Populations and Conditions

Pediatrics (<18 years of age)

The safety and efficacy of XARELTO have not been established in children less than 18 years of age; therefore XARELTO is not recommended in this patient population.

Geriatrics (>65 years of age)

Clinical studies have been conducted in older ages, with results of prolonged terminal half-lives (11 to 13 hours in elderly versus 5 to 9 hours in young subjects) accompanied by increases of XARELTO exposure (approximately 50%) compared to young healthy subjects. This difference may be due to reduced renal function in the elderly (see **CONTRAINDICATIONS**; **WARNINGS AND PRECAUTIONS – Renal**; and **DOSAGE AND ADMINISTRATION – Renal Impairment**).

Sex

There were no clinically relevant differences in pharmacokinetics between male and female patients (see **DETAILED PHARMACOLOGY – Sex**).

Race

No clinically relevant interethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding pharmacokinetics and pharmacodynamics (see **DETAILED PHARMACOLOGY – Race**).

Hepatic Insufficiency

A phase I study investigated the influence of impaired hepatic function in cirrhotic patients (Child-Pugh Class A or B, number of patients 8 per group) on the pharmacodynamics and pharmacokinetics of a single dose of rivaroxaban.

In patients with mild hepatic impairment (Child-Pugh Class A), there was no difference as compared to healthy volunteers with respect to either pharmacodynamics (inhibition of factor Xa activity [1.08-fold for AUC and 0.98-fold for E_{\max}]), prolongation of prothrombin time (1.02-fold for AUC and 1.06-fold for E_{\max}), or pharmacokinetics (both total and unbound AUC [1.15 for total and 0.91-fold increase for unbound] and C_{\max} [0.97 for total and 0.78-fold for unbound]).

Child-Pugh Class B patients had lower baseline factor Xa activity levels (0.64 U/mL) compared to healthy subjects and Child-Pugh Class A patients (0.85 U/mL, for both patient populations). Inhibition of factor Xa activity was more pronounced in Child-Pugh Class B patients compared to both healthy subjects and Child-Pugh Class A patients. The increase of inhibition was 2.6-fold $AUC_{(0-t_n)}$ and 1.2-fold maximal effect (E_{\max}). The group difference was statistically significant, both for $AUC_{(0-t_n)}$ ($P < 0.01$) as well as for E_{\max} ($P < 0.05$) of inhibition of factor Xa activity. In line with these results, a relevant difference in prolongation of PT was observed between healthy subjects and Child-Pugh Class B patients. The increase of prolongation was 2.1-fold ($AUC_{(0-t_n)}$) and 1.4-fold (E_{\max}). A statistically significant group-difference was observed for $AUC_{(0-t_n)}$ ($P < 0.0004$) as well as E_{\max} ($P < 0.0001$).

Pharmacokinetic parameters also indicated a significant increase in Child-Pugh Class B patients as compared to healthy volunteers both on AUC pharmacokinetics (both total and unbound AUC [2.27-fold for total and 2.57-fold increase for unbound]) and C_{\max} (1.27-fold for total and 1.38-fold for unbound).

A PK/PD analysis showed that the slope of the prothrombin time/plasma concentration correlation is increased by more than 2-fold for Child-Pugh Class B patients as compared to healthy volunteers. Since the global clotting test PT assesses the coagulation factors VII, X, V, II which are synthesized in the liver, impaired liver function can also result in prolongations of PT in the absence of anticoagulant therapy.

The PK/PD changes observed in Child-Pugh Class B patients are markers for the severity of the underlying hepatic disease which is expected to lead to a subsequent increased bleeding risk in this patient group.

XARELTO is contraindicated in patients with hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and a clinically relevant bleeding risk (see

CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic).

Renal Insufficiency

As active rivaroxaban is partially cleared via the kidneys (30% to 40% of the dose), there is a direct but moderate correlation of systemic exposure to rivaroxaban with degree of renal impairment.

In a phase I study, following oral single dosing with rivaroxaban 10 mg in subjects with mild (CrCl 50 - 79 mL/min), moderate (CrCl 30 - 49 mL/min), or severe (CrCl 15 - 29 mL/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4-, 1.5-, and 1.6-fold, respectively compared to healthy subjects with normal renal function (CrCl \geq 80 mL/min).

The overall inhibition of factor Xa activity ($AUC_{(0-48h)}$ of effect versus time) was increased in these groups by a factor of 1.5, 1.9, and 2.0, respectively. The relative prolongation of prothrombin time (PT) was also affected by renal impairment and showed even more pronounced effects. $AUC_{(0-48h)}$ of effect versus time was increased by a factor of 1.3, 2.2, and 2.4, respectively.

In phase II, rivaroxaban plasma concentrations (AUC) were increased 1.2- and 1.5-fold in subjects with mild and moderate renal impairment respectively compared to healthy subjects with normal renal function and the peak inhibition of factor Xa activity ($AUC_{(0-48h)}$ of effect versus time) was increased in these groups by a factor of 1.0 and 1.3 respectively. In a pooled analysis of phase III subjects with mild and moderate renal impairment, the peak PT was increased by 1.0-, and 1.1-fold compared to subjects with normal renal function.

There was no evidence of substantial drug accumulation in patients with mild or moderate renal impairment. The phase III trials also showed that the bleeding rate with rivaroxaban in patients with renal impairment was not significantly different than that in patients with normal renal function.

The use of XARELTO is not recommended in patients with severe renal impairment.

XARELTO should be used with caution in patients with moderate renal impairment (CrCl 30 - 49 mL/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see **WARNINGS AND PRECAUTIONS – Renal**; and **DETAILED PHARMACOLOGY – Renal Insufficiency**).

Different Weight Categories

Extremes in body weight (<50 kg or >120 kg) caused less than a 25% change in the plasma concentration of rivaroxaban (see **DETAILED PHARMACOLOGY – Body Weight**).

STORAGE AND STABILITY

Store at 15°C to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Excipients

Cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium lauryl sulfate

Film-coating

Ferric oxide red, hypromellose 15 cP, polyethylene glycol, titanium dioxide

Film-coated, round, biconvex, light red immediate release tablets of 6 mm diameter for oral use.

Each tablet has the Bayer Cross on one side and 10 and a triangle on the other side.

XARELTO tablets are supplied in HDPE bottles of 50 and 120, and in blisters of 10, 30, and 100.

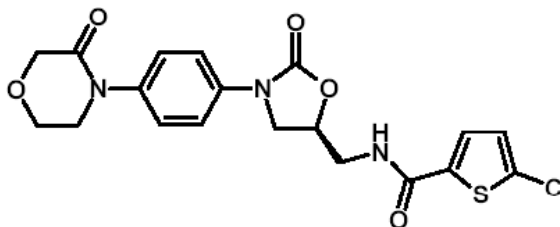
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Rivaroxaban
Common Name:	5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide
Molecular Formula and Molecular Mass:	C ₁₉ H ₁₈ Cl N ₃ O ₅ S 435.89

Structural Formula:



Physicochemical Properties:	Rivaroxaban is a pure (S)-enantiomer. It is an odorless, nonhygroscopic, white to yellowish powder. Rivaroxaban is practically insoluble in water (7 mg/L, pure water) and remains so in aqueous acidic medium (5 mg/L, in 0.1 M and 0.01 M hydrochloric acid) or buffer systems, pH 3 to 9 (5 mg/L)
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CLINICAL TRIALS

Study Demographics and Trial Design

The XARELTO pivotal studies were designed to demonstrate the efficacy of XARELTO for the prevention of venous thromboembolic events (VTE), ie, proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing elective total hip replacement (THR) or total knee replacement (TKR) surgery. A once-daily dose of 10 mg was selected for all phase III studies in the prevention of VTE in patients undergoing THR or TKR surgery, based on clinical data generated in phase II studies. Over 9,500 patients (7,050 in THR surgery; 2,531 in TKR surgery) were studied in these controlled randomized double-blind studies (RECORD 1, 2, and 3).

Pivotal Studies

The RECORD 1 and 3 studies were multicenter, multinational, prospective, double-blind, double-dummy studies in patients randomized to XARELTO or to enoxaparin (see [Table 6](#)). A noninferiority design was adopted with the prespecification that, if noninferiority was shown, a second analysis would be undertaken to determine if the efficacy of XARELTO was superior to that of enoxaparin. RECORD 1 was conducted in patients undergoing elective THR surgery while RECORD 3 was conducted in patients undergoing elective TKR surgery. In both studies, XARELTO 10 mg once daily started not earlier than 6 hours postoperatively was compared with an enoxaparin dosage regimen of 40 mg once daily started 12 hours preoperatively, as recommended in many countries worldwide. The dose of enoxaparin sodium approved for use in thromboprophylaxis in conjunction with elective THR or TKR surgery in Canada is subcutaneous 30 mg twice daily with the first dose to be administered 12 to 24 hours postoperatively. The primary endpoint was Total VTE a composite of any DVT (distal or proximal), nonfatal PE, or death from any cause. The main secondary endpoint was Major VTE, a composite endpoint comprising proximal DVT, nonfatal pulmonary embolism (PE), and VTE-related death. Other prespecified secondary efficacy endpoints included the incidence of DVT (any thrombosis, including proximal and distal) and the incidence of symptomatic VTE.

Men and women of 18 years or older scheduled for elective surgery could be enrolled provided that they had no active or high risk of bleeding or other conditions contraindicating treatment with low-molecular-weight heparin, no significant liver disease, were not pregnant or breastfeeding women, or were not using HIV-protease inhibitors.

In RECORD 1 and 3, demographic and surgical characteristics were similar between the two groups except for a significantly larger number of females in RECORD 3 (XARELTO 70% and enoxaparin 66%, $P = 0.03$). The reasons for exclusion of patients from various analyses in both studies were also similar.

Table 6 – Summary of the Pivotal Studies for the Prevention of Venous Thromboembolic Events (VTE) in Patients Undergoing Elective Total Hip Replacement (THR) or Total Knee Replacement (TKR) Surgery

Study	Study Design	Treatment Regimen	Patient Populations
RECORD 1 ^a	THR patients prospectively randomized to XARELTO or enoxaparin; noninferiority, double-blind, double-dummy design; multinational study.	XARELTO 10 mg od oral for 35±4 days (first dose administered 6 to 8 h postoperatively) Enoxaparin 40 mg od SC for 36±4 days (first dose administered 12 h preoperatively)	Randomized 4541 (2266 XARELTO, 2275 enoxaparin) Safety Population 4433 (2209 XARELTO, 2224 enoxaparin) mITT 3153 (1595 XARELTO, 1558 enoxaparin) mITT (for Major VTE) 3364 (1686 XARELTO, 1678 enoxaparin) Per Protocol 3028 (1537 XARELTO, 1492 enoxaparin)
RECORD 3 ^a	TKR patients prospectively randomized to XARELTO or enoxaparin; noninferiority, double-blind, double-dummy design; multinational study.	XARELTO 10 mg od oral for 12±2days (first dose administered 6 to 8 h postoperatively) Enoxaparin 40 mg od SC for 13±2 days (first dose administered 12 h preoperatively)	Randomized 2531 (1254 XARELTO, 1277 enoxaparin) Safety Population 2459 (1220 XARELTO, 1239 enoxaparin) mITT 1702 (824 XARELTO, 878 enoxaparin) mITT (for Major VTE) 1833 (908 XARELTO, 925 enoxaparin) Per Protocol 1631 (793 XARELTO, 838 enoxaparin)

a The mean age of patients in RECORD 1 and 3 was 63.2±11.4 and 67.6±9 years, respectively.

Safety population = The safety population comprised those subjects who received at least 1 dose of study drug.

mITT = A subject was considered valid for the modified intent-to-treat (MITT) analysis if the subject was (1) valid for safety analysis; (2) had undergone the appropriate surgery; and (3) had an adequate assessment of thromboembolism.

mITT (for Major VTE) = A subject was valid for MITT analysis of major VTE, if the subject was (1) valid for safety analysis; had undergone the appropriate surgery; and (3) had an adequate assessment of thromboembolism for major VTE.

Per Protocol = the per-protocol (PP) population was to include subjects who were (1) valid for the MITT analysis; (2) had an adequate assessment of thromboembolism that, in case of a positive finding, was done not later than 36 h after stop of active study drug, in case of no finding, was done not later than 72 h after the end of active study drug; and (3) had no major protocol deviations.

Major VTE = composite of proximal DVT, nonfatal PE, or VTE-related death

od = once daily

SC = subcutaneous

Study Results

The results of the noninferiority analysis of Total VTE for RECORD 1 and 3 are presented in [Table 7](#). For the primary efficacy analysis, the difference between the incidences in the XARELTO group and the enoxaparin group were estimated, after stratification according to

country using the Mantel-Haenszel weighting, and the corresponding asymptomatic two-sided 95% confidence interval was determined. Tests for noninferiority and superiority were both based on the 95% confidence interval. Noninferiority was shown if the lower limit of the CI was above the prespecified noninferiority margin; -3.5% in RECORD 1 and -4% in RECORD 3.

Table 7 – RECORD 1 (THR) and RECORD 3 (TKR): Noninferiority Analysis of Total VTE^a, the Primary Composite Efficacy Endpoint, and its Components –Per Protocol (PP)^b Population Through the Double-Blind Treatment Period

	RECORD 1 (THR)		RECORD 3 (TKR)	
	XARELTO 10 mg N=1537 n (%)	Enoxaparin 40 mg N=1492 n (%)	XARELTO 10 mg N=793 n (%)	Enoxaparin 40 mg N=838 n (%)
Total VTE^a (primary composite endpoint)	13 (0.9%)	50 (3.4%)	74 (9.3%)	152 (18.1%)
	Absolute Risk Reduction ^c 2.5% (1.5% to 3.6%; <i>P</i> <0.001)		Absolute Risk Reduction ^c 8.7% (5.4% to 12.0%; <i>P</i> <0.001)	
DVT (proximal and/or distal)	11 (0.7)	47 (3.2)	74 (9.3)	147 (17.5)
Nonfatal PE	2 (0.1)	1 (<0.1)	0	3 (0.4)
Death from all causes	1 (<0.1)	2 (0.1)	0	2 (0.2)

- a Total VTE = DVT (proximal and/or distal), nonfatal PE, or death from all causes
- b PP = the per-protocol (PP) population was to include subjects who were (1) valid for the MITT analysis; (2) had an adequate assessment of thromboembolism that, in case of a positive finding, was done not later than 36 h after stop of active study drug, in case of no finding, was done not later than 72 h after the end of active study drug; and (3) had no major protocol deviations
- c Mantel-Haenszel Weighted Reduction to Enoxaparin (Noninferiority was shown if the lower limit of the CI was above the prespecified noninferiority margin; -3.5% in RECORD 1 and -4% in RECORD 3)

In both pivotal studies, the per-protocol analysis for the primary endpoint showed that XARELTO 10 mg/day (first dose 6 to 8 hours postoperatively) was not inferior to enoxaparin 40 mg/day (first dose 12 to 24 hours preoperatively).

Since noninferiority was shown, a prespecified superiority analysis was undertaken to determine if the efficacy of XARELTO was superior to that of enoxaparin in the modified intent-to-treat population (mITT). The superiority analysis of Total VTE and data for the main secondary endpoint (Major VTE) and other secondary endpoints for RECORD 1 and 3 are presented in [Table 8](#) and [Table 9](#), respectively.

Table 8 – RECORD 1 (THR): Superiority Analysis for Total VTE (Primary Composite Endpoint)^a, Major VTE (Main Secondary Endpoint)^b and Their Components, and Other Selected Efficacy Endpoints – Modified ITT^c (MITT) Population Through the Double-Blind Treatment Period

Parameter	XARELTO 10 mg		Enoxaparin 40 mg		Absolute Risk Reduction ^d	P Value	Relative Risk Reduction	P Value
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)		% (95% CI)	
Total VTE	18/1595	1.1% (0.7% to 1.8%)	58/1558	3.7% (2.8% to 4.8%)	2.6% (1.5% to 3.7%)	<0.001	70% (49%-82%)	P <0.001
Major VTE	4/1686	0.2% (0.1% to 0.6%)	33/1678	2.0% (1.4% to 2.8%)	1.7% (1.0% to 2.5%)	<0.001	88% (66%-96%)	P <0.001
Death from all causes	4/1595	0.3% (0.1% to 0.6%)	4/1558	0.3% (0.1% to 0.7%)	0.0% (-0.4% to 0.4%)	1.00	--	--
Nonfatal PE	4/1595	0.3% (0.1% to 0.6%)	1/1558	0.1% (<0.1% to 0.4%)	-0.2% (-0.6% to 0.1%)	0.37	--	--
DVT (proximal and/or distal)	12/1595	0.8% (0.4% to 1.3%)	53/1558	3.4% (2.6% to 4.4%)	2.7% (1.7% to 3.7%)	<0.001	--	--
Proximal DVT	1/1595	0.1% (<0.1% to 0.4%)	31/1558	2.0% (1.4% to 2.8%)	1.9% (1.2% to 2.7%)	<0.001	--	--
Distal DVT only	11/1595	0.7% (0.3% to 1.2%)	22/1558	1.4% (0.9% to 2.1%)	0.7% (0.0% to 1.5%)	0.04	--	--
VTE-related death	0/1595	0%	1/1558	<0.1%	--	--	--	--
Symptomatic VTE^e	6/2193	0.3% (0.1% to 0.6%)	11/2206	0.5% (0.3% to 0.9%)	0.2% (-0.1% to 0.6%)	0.22	--	--

a Total VTE = composite of DVT (proximal and/or distal), nonfatal PE, or death from all causes.

b Major VTE = composite of proximal DVT, nonfatal PE, or VTE-related death

c MITT = subject valid for safety analysis, has undergone appropriate surgery, has adequate assessment of thromboembolism

d Mantel-Haenszel Weighted Reduction to Enoxaparin given for all endpoints except nonfatal PE and death from all causes, for which unweighted (exact) estimates were given. Superiority was shown if the lower limit of the CI was above zero.

e Safety population for Symptomatic VTE (patients valid for safety analysis who underwent the appropriate surgery). The safety population was used because assessment of symptomatic events is possible in the greater population, regardless of the availability of an adequate venographic assessment.

Table 9 – RECORD 3 (TKR): Superiority Analysis for Total VTE (Primary Composite Endpoint)^a, Major VTE (Main Secondary Endpoint)^b and Their Components, and Other Selected Efficacy Endpoints – Modified ITT (MITT)^c Population Through the Double-Blind Treatment Period

Parameter	XARELTO 10 mg		Enoxaparin 40 mg		Absolute Risk Reduction ^d	P Value	Relative Risk Reduction	P Value
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)		% (95% CI)	
Total VTE	79/824	9.6% (7.7% to 11.8%)	166/878	18.9% (16.4% to 21.7%)	9.2% (5.9% to 12.4%)	<0.001	49% (35%-61%)	<0.001
Major VTE	9/908	1.0% (0.5% to 1.9%)	24/925	2.6% (1.7% to 3.8%)	1.6% (0.4% to 2.8%)	0.01	62% (18%-82%)	0.016
Death from all causes	0/824	0% (0.0% to 0.5%)	2/878	0.2% (0.0% to 0.8%)	0.2% (-0.2% to 0.8%)	0.23	--	--
Nonfatal PE	0/824	0% (0.0% to 0.3%)	4/878	0.5% (0.1% to 1.2%)	0.5% (0.0% to 1.2%)	0.06	--	--
DVT (proximal and/or distal)	79/824	9.6% (7.7% to 11.8%)	160/878	18.2% (15.7% to 20.9%)	8.4% (5.2% to 11.7%)	<0.001	--	--
Proximal DVT	9/824	1.1% (0.5% to 2.1%)	20/878	2.3% (1.4% to 3.5%)	1.1% (-0.1% to 2.3%)	0.07	--	--
Distal DVT only	70/824	8.5% (6.7% to 10.6%)	140/878	15.9% (13.6% to 18.5%)	7.3% (4.3% to 10.4%)	<0.001	--	--
VTE-related death	0/824	0%	0/878	0%	--	--	--	--
Symptomatic VTE^e	8/1201	0.7% (0.3% to 1.3%)	24/1217	2.0% (1.3% to 2.9%)	1.3% (0.4% to 2.2%)	0.005	--	--

a Total VTE = composite of DVT (proximal and/or distal), nonfatal PE, or death from all causes.

b Major VTE = composite of proximal DVT, nonfatal PE, or VTE-related death

c MITT = subject valid for safety analysis, has undergone appropriate surgery, has adequate assessment of thromboembolism

d Mantel-Haenszel Weighted Reduction to Enoxaparin given for all endpoints except nonfatal PE and death from all causes, for which unweighted (exact) estimates were given. Superiority was shown if the lower limit of the CI was above zero.

e Safety population for Symptomatic VTE (patients valid for safety analysis who underwent the appropriate surgery). The safety population was used because assessment of symptomatic events is possible in the greater population, regardless of the availability of an adequate venographic assessment.

The efficacy results of the prespecified analysis using a modified intent-to-treat population indicate that XARELTO 10 mg administered postoperatively once daily is superior in preventing DVT to enoxaparin 40 mg once daily (first dose 12 hours preoperatively). The Canadian approved dosage regimen for enoxaparin is 30 mg every 12 hours (first dose is to be administered 12 to 24 hours postoperatively). There are no definitive head-to-head studies to compare the safety and efficacy of the Canadian approved enoxaparin dosage regimen to the enoxaparin dosage regimen used in the RECORD 1 and 3 studies.

In the safety population of 3429 subjects treated with XARELTO and 3463 subjects treated with enoxaparin in the pivotal studies (RECORD 1 and 3), the results observed for bleeding events have been summarized in [Table 10](#). In RECORD 1, serious drug-related treatment-emergent adverse events were reported in 26 (1.2%) for XARELTO and 23 (1.0%) for enoxaparin. In RECORD 3, serious drug-related treatment-emergent adverse events were reported in 26 (2.1%) for XARELTO and 19 (1.5%) for enoxaparin.

Table 10 – RECORD 1 and 3: Detailed Overview of Treatment-Emergent Bleeding Events (Safety Population)^a

	RECORD 1 (THR)			RECORD 3 (TKR)		
	XARELTO 10 mg od N=2209	Enoxaparin 40 mg od N=2224	P Value	XARELTO 10 mg od N=1220	Enoxaparin 40 mg od N=1239	P Value
Any Bleeding n (%) (95% CI)	133 (6.0%) (5.1% to 7.1%)	131 (5.9%) (5.0% to 7.0%)	0.90	60 (4.9%) (3.8%-6.3%)	60 (4.8%) (3.7%-6.2%)	1.0
Major Bleeding^b n (%) (95% CI)	6 (0.3%) (0.1%-0.6%)	2 (0.1%) (<0.1%-0.3%)	0.18	7 (0.6%) (0.2%-1.2%)	6 (0.5%) (0.2%-1.1%)	0.79
Fatal Bleeding^c	1 (<0.1%) ^b	0 (0.0%)	--	0 (0.0%)	0 (0.0%)	--
Bleeding into a critical organ n (%)	1 (<0.1%)	0 (0.0%)	--	1 (0.1%)	2 (0.2%)	--
Bleeding leading to reoperation n (%)	2 (0.1%)	1 (<0.1%)	--	5 (0.4%)	4 (0.3%)	--
Clinically overt extra- surgical site bleeding leading to a fall in hemoglobin n (%)	2 (0.1%)	1 (<0.1%)	--	1 (0.1%)	0 (0.0%)	--
Clinically overt extra- surgical site bleeding leading to transfusion of ≥2 units of blood n (%)	2 (0.1%)	1 (<0.1%)	--	1 (0.1%)	0 (0.0%)	--
Nonmajor Bleeding^d n (%)	128 (5.8%)	129 (5.8%)	--	53 (4.3%)	54 (4.4%)	--
Clinically relevant nonmajor bleeding n (%)	65 (2.9%)	54 (2.4%)	--	33 (2.7%)	28 (2.3%)	--
Hemorrhagic wound complications^e n (%)	34 (1.5%)	38 (1.7%)	--	25 (2.0%)	24 (1.9%)	--

a Patients may have had more than one type of event, and an event could fall into more than one category; adjudicated treatment-emergent bleeding events included those beginning after the initiation of the study drug and up to 2 days after last dose of the study drug.

b Major bleeding events included: (1) fatal, (2) bleeding into a critical organ (eg, retroperitoneal, intracranial, intraocular, or intraspinal bleeding/hemorrhagic puncture), (3) bleeding requiring reoperation, (4) clinically overt extra-surgical site bleeding associated with ≥2 g/dL fall in hemoglobin or leading to infusion of ≥2 units of whole blood or packed cells.

c The event occurred before the administration of the first dose of rivaroxaban.

d Nonmajor bleeding events were bleeding events that did not fulfill the criteria of major bleeding.

e Composite of excessive wound hematoma and reported surgical-site bleeding.

Phase III Supportive Study

RECORD 2 was a randomized, double-blind, double-dummy, prospective study conducted in 2509 randomized patients (safety population = 2457; mITT = 1733) undergoing THR. The aim of RECORD 2 was to assess extended thromboprophylaxis with XARELTO for 35±4 days. RECORD 2 was similar in study design, inclusion/exclusion criteria and endpoints to RECORD 1, except that enoxaparin 40 mg once daily (first dose given preoperatively) was given for a shorter duration (12±2 days) than XARELTO 10 mg od (35±4 days). Comparative efficacy claims to enoxaparin may not be drawn from this study, due to the differences in the treatment duration of XARELTO and enoxaparin.

Table 11 – RECORD 2 (THR): Superiority Analysis for Total VTE (Primary Composite Endpoint)^a, Major VTE (Main Secondary Endpoint)^b and Their Components, and Other Selected Efficacy Endpoints – Modified ITT^c (MITT) Population Through the Double-Blind Treatment Period

Parameter	XARELTO 10 mg od for 35±4 days		Enoxaparin 40 mg for 12±2 days		Absolute Risk Reduction	P Value	Relative Risk Reduction	P Value
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)		% (95% CI)	
Total VTE	17/864	2.0% (1.2% to 3.1%)	81/869	9.3% (7.5% to 11.5%)	7.3% (5.2% to 9.4%)	<0.0001	79% (65% to 87%)	< 0.001
Major VTE	6/961	0.6% (0.2% to 1.4%)	49/962	5.1% (3.8% to 6.7%)	4.5% (3.0% to 6.0%)	<0.0001	88% (71% to 95%)	< 0.001
Death from all causes	2/864	0.2% (<0.1% to 0.8%)	6/869	0.7% (0.3% to 1.5%)	0.5% (-0.2% to 1.3%)	0.29	--	--
Nonfatal PE	1/864	0.1% (<0.1% to 0.6%)	4/869	0.5% (0.1% to 1.2%)	0.3% (-0.2% to 1.1%)	0.37	--	--
DVT (proximal and/or distal)	14/864	1.6% (0.9% to 2.7%)	71/869	8.2% (6.4% to 10.2%)	6.5% (4.5% to 8.5%)	<0.0001	--	--
Proximal DVT	5/864	0.6% (0.2% to 1.3%)	44/869	5.1% (3.7% to 6.7%)	4.5% (2.9% to 6.0%)	<0.0001	--	--
Distal DVT only	9/864	1.0% (0.5% to 2.0%)	27/869	3.1% (2.1% to 4.5%)	2.0% (0.7% to 3.3%)	0.0025	--	--
VTE-related death	0/864	0%	1/869	0.1%	--	--	--	--
Symptomatic VTE^c	3/1212	0.2% (<0.1% to 0.7%)	15/1207	1.2% (0.7% to 2.0%)	1.0% (0.3% to 1.8%)	0.0040	--	--

a Total VTE = composite of DVT (proximal and/or distal), nonfatal PE, or death from all causes.

b Major VTE = composite of proximal DVT, nonfatal PE, or VTE-related death

c MITT = subject valid for safety analysis, has undergone appropriate surgery, has adequate assessment of thromboembolism

d Mantel-Haenszel Weighted Reduction to Enoxaparin given for all endpoints except nonfatal PE and death from all causes, for which unweighted (exact) estimates were given. Superiority was shown if the lower limit of the CI was above zero.

e Safety population for Symptomatic VTE (patients valid for safety analysis who underwent the appropriate surgery). The safety population was used because assessment of symptomatic events is possible in the greater population regardless of the availability of an adequate venographic assessment.

Table 12 – RECORD 2: Detailed Overview of Treatment-Emergent Bleeding Events (Safety Population)^a

	XARELTO 10 mg od for 35±4 days N=1228	Enoxaparin 40 mg od for 12±2 days N=1229	P Value
Any Bleeding n (%) (95% CI)	81 (6.6%) (5.3% to 8.1%)	68 (5.5%) (4.3% to 7.0%)	0.27
Major Bleeding^b n (%) (95% CI)	1 (0.1%) (0.0–0.5)	1 (0.1%) (0.0–0.5)	1.00
Fatal bleeding	0 (0.0%)	0 (0.0%)	--
Bleeding into a critical organ n (%)	0 (0.0%)	1 (0.1%)	--
Bleeding leading to reoperation n (%)	0 (0.0%)	0 (0.0%)	--
Clinically overt extra-surgical site bleeding leading to a fall in hemoglobin n (%)	1 (0.1%)	0 (0.0%)	--
Clinically overt extra-surgical site bleeding leading to transfusion of ≥2 units of blood n (%)	1 (0.1%)	0 (0.0%)	--
Nonmajor Bleeding^c n (%)	80 (6.5%)	67 (5.5%)	--
Clinically relevant nonmajor bleeding n (%)	40 (3.3%)	33 (2.7%)	--
Hemorrhagic wound complications^d n (%)	20 (1.6%)	21 (1.7%)	--

a Patients may have had more than one type of event, and an event could fall into more than one category; adjudicated treatment-emergent bleeding events included those beginning after the initiation of the study drug and up to 2 days after last dose of the study drug.

b Major bleeding events included: (1) fatal, (2) bleeding into a critical organ (eg, retroperitoneal, intracranial, intraocular, or intraspinal bleeding/hemorrhagic puncture), (3) bleeding requiring reoperation, (4) clinically overt extra-surgical site bleeding associated with ≥2 g/dL fall in hemoglobin or leading to infusion of ≥2 units of whole blood or packed cells.

c Nonmajor bleeding events were bleeding events that did not fulfill the criteria of major bleeding.

d Composite of excessive wound hematoma and reported surgical-site bleeding.

The results from this study demonstrate that extended duration prophylaxis with 10 mg XARELTO od for 35 days provided clinically meaningful decreases in Total VTE, Major VTE, and symptomatic VTE in THR patients without an increased risk of bleeding.

DETAILED PHARMACOLOGY

Animal Pharmacology

In Vitro

Rivaroxaban is a competitive, selective, and direct, antithrombin independent FXa inhibitor. It potently inhibits free human FXa, prothrombinase, and clot associated FXa. Rivaroxaban inhibits human FXa with >10 000-fold greater selectivity than for other serine proteases. Its effect on FXa resulted in a prolongation of clotting times in human plasma.

In Vivo

Rivaroxaban given prophylactically showed consistent, dose-dependent antithrombotic activity in both venous (platelet-poor, fibrin-rich) and arterial (platelet-rich, fibrin-poor) thrombosis models in mice, rats, and rabbits, with higher potency in the venous model.

In a rabbit model of venous thrombus growth, oral rivaroxaban given nonprophylactically reduced thrombus growth to a similar extent as observed with known efficacious doses of the control agents nadroparin and fondaparinux.

In a murine model of thromboembolic death, rivaroxaban provided effective protection with greater potency than enoxaparin.

PT values correlated strongly with the plasma concentrations of rivaroxaban.

The antihemostatic effect of rivaroxaban was evaluated in bleeding time models in rats and rabbits. Bleeding times were not significantly affected at antithrombotic doses below the ED50 required for antithrombotic efficacy in the arterial thrombosis models. Rivaroxaban showed an antithrombotic activity/bleeding risk ratio comparable to enoxaparin.

Safety Pharmacology

Safety pharmacology investigation on vital organ systems (cardiovascular system, respiratory system, and central nervous system) as well as on supplemental organ systems (hematology and blood coagulation, gastrointestinal function, renal function, and metabolism) revealed no adverse effect of rivaroxaban.

Studies on ventricular repolarization (hERG K⁺ current and action potential of isolated rabbit Purkinje fibers in vitro, ECG recordings in dogs) showed no evidence for a proarrhythmic risk in humans.

Human Pharmacology

Pharmacokinetics

Rivaroxaban pharmacokinetics are linear with no relevant accumulation beyond steady state after multiple doses. Variability in pharmacokinetics is moderate with interindividual variability (coefficient of variation) ranging from 30% to 40%.

Absorption and Bioavailability

Rivaroxaban is a low solubility, high permeability compound. Rivaroxaban is readily absorbed after oral administration as solution (C_{max} after approximately 30 min) as well as tablet (C_{max} after 2 to 4 hours). Oral bioavailability of rivaroxaban is high due to almost complete absorption with/without food (at doses up to 15 mg) and lack of relevant presystemic first-pass extraction of this low-clearance drug.

Distribution

Plasma protein binding for rivaroxaban in humans is high at approximately 92% to 95% in vitro, with serum albumin being the main binding component. No concentration dependency and no sex difference in fraction unbound were detected. Mean rivaroxaban protein-bound fractions determined ex vivo in healthy subjects ranged from 90% to 95%.

Due to its high plasma protein binding, rivaroxaban is not expected to be removed by dialysis.

The binding of rivaroxaban to plasma proteins is fully reversible. In accordance with other species, rivaroxaban is mainly located in plasma; the human plasma-to-blood partition coefficient is 1.40.

Metabolism

Rivaroxaban is eliminated by metabolic degradation (approximately 2/3 of administered dose) as well as by direct renal excretion of unchanged active compound (approximately 1/3 of administered dose). In all investigated species, the oxidative degradation of the morpholinone moiety (catalyzed via *CYP3A4/CYP3A5* and *CYP2J2* and leading via cleavage of the ring and further oxidation to metabolite M-1) was the major site of biotransformation of rivaroxaban. Unchanged rivaroxaban is the most important compound in human plasma with no major or active circulating metabolites being present. No metabolic conversion of rivaroxaban to its enantiomer was observed in humans.

Taking excretion data and metabolite profiles derived from the mass balance study in man into consideration, present data from the CYP reaction phenotyping study suggests that contribution of *CYP3A4/CYP3A5* accounts for approximately 18% and *CYP2J2* for approximately 14% of total rivaroxaban elimination, respectively. Besides this oxidative biotransformation, hydrolysis of the amide bonds (approximately 14%) and active, transporter-mediated renal excretion of unchanged drug (approximately 30%) play important roles as elimination pathways.

Excretion

Rivaroxaban and its metabolites have a dual route of elimination, via both renal (66% in total) and biliary/fecal routes; 36% of the administered dose is excreted unchanged via the kidneys via glomerular filtration and active secretion.

The clearance and excretion of rivaroxaban is as follows:

- 1/3 of the active drug is cleared as unchanged drug by the kidneys
- 1/3 of the active drug is metabolized to inactive metabolites and then excreted by the kidneys
- 1/3 of the active drug is metabolized to inactive metabolites and then excreted by the fecal route.

Rivaroxaban has been identified in vitro to be a substrate both of the active transporter P-glycoprotein (P-gp) and of the multidrug transport protein Bcrp ('breast cancer resistance protein').

With an average systemic plasma clearance of approximately 10 L/h, rivaroxaban is a low-clearance drug lacking relevant first-pass extraction. Mean terminal elimination half-lives of rivaroxaban are in the range of 5 h to 9 h after steady-state tablet dosing regimens in young subjects. Mean terminal elimination half-lives between 11 h to 13 h were observed in the elderly.

Special Populations and Conditions

Geriatrics (>65 Years of Age)

Results from a set of phase I studies indicate for the target population of elderly higher mean AUC values by 52% in males and by 39% in females when compared to young subjects of the same sex, accompanied by an increase in C_{max} by 35% in both sexes and by terminal half-lives between 11 and 13 h. Investigating subjects older than 75 years confirmed the expectation, leading to approximately 41% higher AUC values in comparison to young subjects (90% CI [1.20 – 1.66]), mainly due to reduced (apparent) total body clearance and renal clearance. No relevant age effects could be observed for C_{max} (C_{max} ratio 1.08; 90% CI [0.94-1.25]) or t_{max} .

Pediatrics (<18 Years of Age)

No clinical data are available for children.

Sex

There were no relevant differences in pharmacokinetics and pharmacodynamics between male and female subjects, especially when taking into account body weight differences.

Body Weight

Extremes in body weight (<50 kg or >120 kg) had only a small influence (increase in maximum concentration by <25% on rivaroxaban plasma concentrations and pharmacodynamics).

Race

Differences in rivaroxaban exposure observed between the various investigated ethnic groups — Caucasians, African-Americans, Hispanics, Chinese and Japanese — were within the normal magnitude of interindividual variability.

With respect to factor Xa activity and coagulation parameters, eg, prothrombin time (PT Neoplastin[®]), neither age, sex, nor body weight affected the PD parameter/rivaroxaban

concentration relationship, ie, all observed changes in pharmacodynamics were driven by the respective underlying plasma exposure in these specific subject populations. This is also true for the various investigated ethnic groups — Caucasians, African-Americans, Hispanics, Chinese and Japanese.

Renal Insufficiency

In subjects with severe renal impairment, rivaroxaban plasma concentrations (AUC) were significantly increased (1.6-fold on average; range: 1.2 - 2.2) compared to healthy subjects. The increase in AUC was inversely correlated to creatinine clearance. A close correlation existed between rivaroxaban renal and total body clearance and creatinine clearance. The unbound fraction of rivaroxaban was not affected by renal impairment. Increased overall plasma concentrations in subjects with moderate and severe renal impairment were associated with an increased sensitivity of PT prolongation towards rivaroxaban exposure which was not observed for the inhibition of FXa activity. This difference may reflect the impact of the underlying renal disease on anticoagulant therapy which may be detected by the global clotting test PT Neoplastin[®].

Hepatic Insufficiency

Cirrhotic patients with mild liver impairment exhibited only minor changes in rivaroxaban pharmacokinetics (1.2-fold increase in average rivaroxaban AUC), comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment, rivaroxaban plasma concentrations (AUC) were significantly increased (2.3-fold on average). The increase in exposure was driven by both reduced hepatic and renal clearance. Elevations in PT Neoplastin[®] both at baseline and under rivaroxaban treatment were even more pronounced due to the underlying hepatic disease which impairs the ability of the liver to synthesize clotting factors. Baseline PT values were 12.6 seconds for healthy subjects, 13.1 seconds for cirrhotic patients with mild liver impairment, and 16.0 seconds for cirrhotic patients with moderate hepatic impairment. As the global clotting test PT Neoplastin[®] assesses the extrinsic pathway (coagulation factors VII, X, V, II), a significantly altered sensitivity in anticoagulant activity towards rivaroxaban plasma exposure (increase in slope for PT Neoplastin[®]/rivaroxaban plasma concentration relationship by more than 2 fold: 3.1 seconds/[100 µg/L] for healthy subjects vs 7.8 seconds/[100 µg/L] for cirrhotic patients with moderate hepatic impairment) was observed, which again reflects the underlying disease. Cirrhotic patients with severe hepatic impairment were not studied.

Pharmacokinetic Interaction Studies

Rivaroxaban 10 mg tablet is not sensitive to interactions with respect to absorption processes. Lack of relevant food effect could be demonstrated for the 10 mg dose, and neither changes in gastric pH nor the concomitant medication of chelating agents (by coadministration with the H₂ receptor antagonist ranitidine, 150 mg bid, or the antacid aluminum hydroxide/magnesium hydroxide [MAALOX[®]], 10 mL) had any relevant impact on pharmacokinetic and hence pharmacodynamic parameters of rivaroxaban.

Coadministration of enoxaparin (40 mg), acetylsalicylic acid (500 mg followed by 100 mg on two consecutive days), naproxen (500 mg), and clopidogrel (300 mg), respectively, did not affect rivaroxaban pharmacokinetics.

The absence of a clinically relevant interaction potential by rivaroxaban through induction or inhibition of major CYP isoforms or the P-gp transporter was confirmed by lack of mutual pharmacokinetic interactions in vivo between rivaroxaban and midazolam (cosubstrate of *CYP3A4/3A5*), digoxin (cosubstrate of P-glycoprotein), or atorvastatin (cosubstrate of both *CYP3A4* and P-gp).

The azole antifungal ketoconazole (400 mg od), classified as a strong *CYP3A4* and P-gp inhibitor, led to a 2.6-fold increase in mean rivaroxaban steady-state AUC and a 1.7-fold increase in mean C_{max} . Ketoconazole 200 mg od led to a 1.8-fold increase in rivaroxaban AUC and a 1.5-fold increase in C_{max} .

The HIV protease inhibitor ritonavir (600 mg bid), classified as a strong *CYP3A4* and P-gp inhibitor and also reported to strongly inhibit Bcrp, led to a 2.5-fold increase in mean rivaroxaban AUC and a 1.6-fold increase in mean C_{max} .

The macrolide antibiotic erythromycin (500 mg tid), classified as a weak-to-moderate *CYP3A4* and P-gp inhibitor, led to a 1.3-fold increase both in mean rivaroxaban AUC and in mean C_{max} .

Rifampicin (600 mg od), classified as a strong *CYP3A4* and P-gp inducer, led to a significant decrease in rivaroxaban elimination half-life and an approximately 50% reduction in rivaroxaban plasma exposure.

TOXICOLOGY

Acute Toxicity

Rivaroxaban showed low acute toxicity in rats and mice.

Repeated Dose Toxicity

Rivaroxaban was tested in repeat-dose studies up to 6 months in rats and up to 12 months in dogs. Based on the pharmacological mode of action, a NOEL could not be established due to effects on clotting time. All adverse findings, except for a slight body weight gain reduction in rats and dogs, could be related to an exaggerated pharmacological mode of action of the compound. In dogs, at very high exposures, severe spontaneous bleedings were observed. The NOAELs after chronic exposure are 12.5 mg/kg in rats and 5 mg/kg in dogs.

Carcinogenicity

Because rivaroxaban is to be used only for short-term treatment, assessment of carcinogenicity in animals is not required.

Reproductive Toxicology

Rivaroxaban was tested in developmental toxicity studies at exposure levels of up to 38-fold (rat) and up to 89-fold (rabbit) above the therapeutic exposure in humans. The toxicological profile is mainly characterized by maternal toxicity due to exaggerated pharmacodynamic effects.

Up to the highest dose tested, no primary teratogenic potential was identified.

[¹⁴C]Rivaroxaban-related radioactivity penetrated the placental barrier in rats. In none of the fetal organs and tissues did the exposure in terms of maximum concentrations or AUC exceed the maternal blood exposure. The average exposure in the fetuses based on AUC₍₀₋₂₄₎ reached about 20% of the exposure in maternal blood. The AUC in the mammary glands was approximately equivalent to the AUC in the blood, which indicates secretion of radioactivity into milk (see **CONTRAINDICATIONS**).

Rivaroxaban did not show an effect on male or female fertility up to 200 mg/kg.

Lactation

[¹⁴C]Rivaroxaban was administered orally to lactating Wistar rats (day 8 to 10 post partum) as a single oral dose of 3 mg/kg body weight.

[¹⁴C]Rivaroxaban-related radioactivity was secreted into the milk of lactating rats only to a low extent in relation to the administered dose: The estimated amount of radioactivity excreted with milk was 2.12% of the maternal dose within 32 hours after administration (see **CONTRAINDICATIONS**).

Mutagenesis

No genotoxicity was observed in a test for gene mutation in bacteria (Ames-Test), in an in vitro test for chromosomal aberrations, or in the in vivo micronucleus test.

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PART III: CONSUMER INFORMATION

PrXARELTO®
rivaroxaban tablets

This leaflet is Part 3 of a three-part "Product Monograph" published when XARELTO was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about XARELTO. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

XARELTO is used to prevent blood clots in your veins after a major operation on your legs, either on your hip or your knee. These blood clots could dislodge and travel to the lungs causing serious health risks. Your doctor has prescribed this medicine for you because after an operation you are at an increased risk of getting blood clots.

What it does:

XARELTO belongs to a group of medicines called anticoagulants (blood thinners). XARELTO works by directly inhibiting clotting factor Xa, an essential component to the blood-clotting process. It helps to prevent the development of unwanted blood clots (thrombosis) in blood vessels.

When it should not be used:

Do not take XARELTO:

- if you have severe liver disease which leads to an increased risk of bleeding
- if you have severely reduced kidney function. Your doctor will know how to determine your kidney function
- if you are bleeding excessively
- if you are aware of body lesions at risk of bleeding, including bleeding in the brain within the last 6 months
- if you are pregnant or breastfeeding
- if you are allergic (hypersensitive) to rivaroxaban (active ingredient of XARELTO) or any of the other ingredients of XARELTO. The ingredients are listed in the "**What the nonmedicinal ingredients are**" section of this leaflet

What the medicinal ingredient is:

The active substance is rivaroxaban.

What the nonmedicinal ingredients are:

cellulose microcrystalline, croscarmellose sodium, ferric oxide red, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sodium lauryl sulfate, titanium dioxide

What dosage forms it comes in:

Film coated tablets, 10 mg

XARELTO 10 mg film-coated tablets are light red, round, film-coated tablets marked with the Bayer Cross on one side and 10 and a triangle on the other side.

WARNINGS AND PRECAUTIONS

It has been reported that taking XARELTO may result in bleeding, which can be serious or life-threatening. Stroke (bleeding inside the brain) and bleeding into the body cavity below the diaphragm, which contains the stomach, intestine, liver, and other organs, can occur.

Lactose is a nonmedicinal ingredient in XARELTO. Do not take XARELTO if a doctor has told you that you have one of the following rare hereditary diseases:

- Galactose intolerance
- Lapp lactase deficiency
- glucose-galactose malabsorption

Take special care with XARELTO:

- if you have an increased risk of bleeding such as
 - bleeding disorders
 - very high blood pressure, not controlled by medical treatment
 - active ulcer or a recent ulcer of your stomach or bowel
 - a problem with the blood vessels in the back of your eyes (retinopathy)
 - recent bleeding in your brain (stroke, intracranial or intracerebral bleeding)
 - a recent operation on your brain, spinal column or eye

Tell your doctor before you take XARELTO, if any of these apply to you. Your doctor may decide to keep you under closer observation.

If your operation involves a catheter or injection into your spinal column (eg, for epidural or spinal anesthesia or pain reduction):

- it is very important to take XARELTO before and after the injection or removal of the catheter exactly at the times you have been told by your doctor
- tell your doctor immediately if you get numbness or weakness of your legs, or problems with your bowel or bladder after the end of anesthesia, because urgent care is necessary

Pregnancy and breastfeeding

If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking XARELTO. If you become pregnant while you are taking XARELTO, immediately tell your doctor, who will decide how you should be treated.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you are taking:

- some medicines for fungal infections (eg, ketoconazole) unless they are only applied to the skin
- antiretroviral medicines for HIV/AIDS (eg, ritonavir [NORVIR[®]] and lopinavir/ritonavir [KALETRA[®]])
- other medicines to reduce blood clotting (eg, enoxaparin [LOVENOX[®]] or clopidogrel [PLAVIX[®]])
- anti-inflammatory and pain relieving medicines (eg, naproxen [NAPROSYN[®]] or acetylsalicylic acid [ASPIRIN[®]])

Tell your doctor before taking XARELTO, because its effect may be increased. Your doctor may decide to keep you under closer observation.

PROPER USE OF THIS MEDICATION

Usual dose

Always take XARELTO exactly as your doctor has told you. You should continue taking the tablets until they are finished. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one tablet (10 mg) once a day.

Swallow the tablet preferably with water. It can be taken with or without food.

Take the first tablet 6 to 10 hours after your operation. Then take a tablet every day until your doctor tells you to stop. Try to take the tablet at the same time every day to help you to remember it.

If you have had a major hip operation, you will usually take the tablets for 35 days.

If you have had a major knee operation, you will usually take the tablets for 14 days.

Children and adolescents

Don't give XARELTO tablets to people under 18 years of age. There is not enough information on its use in children and adolescents.

Overdose

Contact your doctor or your regional Poison Control Centre immediately if you have taken too many XARELTO tablets. Taking too much XARELTO increases the risk of bleeding.

Missed Dose

If you have missed a dose, take it as soon as you remember. Take the next tablet on the following day and then carry on taking a tablet once a day as normal.

Do not take a double dose to make up for a forgotten tablet.

Stopped Treatment

Don't stop taking XARELTO without talking to your doctor first, because XARELTO prevents the development of a serious condition.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, XARELTO can cause side effects, although not everybody gets them.

Like other similar medicines (blood thinners), XARELTO may cause bleeding. In some cases bleeding may not be obvious, such as unexplained swelling.

The most common side effect seen with XARELTO is nausea.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/ Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Bleeding from the surgical wound, an injury or other procedure		✓	
	Anemia (Exceptional weakness, tiredness, paleness, dizziness, headache)		✓	
Un-common	Liquid oozing from the surgical wound		✓	
	Unexpected bruising or bleeding after operation		✓	
	Bleeding from bowel, blood in stools/ black stools, or when you vomit		✓	
	Genital bleeding in elderly and patients at risk of extensive abnormal menstrual bleeding		✓	
	Genital bleeding in all other groups excluding the above population	✓		
	Nose bleed (with a duration of >5 minutes)		✓	
	Bleeding gums when you brush your teeth (with a duration of >5 minutes)		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/ Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Blood in your urine, red/pink tinge to urine		✓	
	Low blood pressure (lightheadedness, dizziness, and/or fainting)		✓	
	Localized swelling, swelling in your limbs		✓	
	Itchy skin or rash		✓	
Rare	Impaired liver function (jaundice/ yellowing of the skin or eyes, dark urine)		✓	
	Bleeding into a joint (stiff, sore, hot or painful joint)		✓	
	Bleeding into the rectum or from hemorrhoids		✓	

You should be aware that prescription medicines carry some risks and that all possible risks may not be known at this stage.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

If you think you have an allergic reaction to XARELTO (symptoms such as red and lumpy skin, rash, hives, swelling, trouble breathing), it is important that you seek medical advice from your doctor straight away.

This is not a complete list of side effects. For any unexpected effects while taking XARELTO, contact your doctor or pharmacist.

HOW TO STORE IT

Keep at room temperature (15°C-30°C).

Keep out of the reach and sight of children.

Do not use XARELTO after the expiry date which is stated on the bottle and on each blister after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:

Toll-free telephone:	866-234-2345
Toll-free fax:	866-678-6789
Online:	www.healthcanada.gc.ca/medeffect
By email:	CanadaVigilance@hc-sc.gc.ca
By regular mail:	Canada Vigilance National Office Marketed Health Products Safety and Effectiveness Information Bureau Marketed Health Products Directorate Health Products and Food Branch Health Canada Tunney's Pasture, AL 0701C Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at: <http://www.bayer.ca> or obtained by contacting the sponsor, Bayer Inc., at 1-800-265-7382.

This leaflet was prepared by:

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