PRODUCT MONOGRAPH

PrXARELTO®

Rivaroxaban tablets

Tablets 2.5 mg, 10 mg, 15 mg and 20 mg

Rivaroxaban granules for oral suspension

Granules for oral suspension, 1mg/mL when reconstituted

Anticoagulant

(ATC Classification: B01AF01)

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XARELTO®

rivaroxaban

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Nonmedicinal Ingredients
Oral	Film-coated tablet, 2.5 mg 10 mg, 15 mg and 20 mg	Cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium lauryl sulphate, ferric oxide yellow (2.5 mg), ferric oxide red (10 mg, 15 mg, 20 mg), hypromellose 15 cP, polyethylene glycol, titanium dioxide
	Granules for oral suspension, 1 mg/mL	Citric acid (anhydrous), flavor sweet and creamy, hypromellose 5 cP, mannitol, microcrystalline cellulose and carmellose sodium, sodium benzoate, sucralose, xanthum gum

INDICATIONS AND CLINICAL USE

XARELTO® (rivaroxaban) film-coated tablet (10 mg, 15 mg, 20 mg) is indicated for the:

- prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery.
- treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.
- prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.

XARELTO® (rivaroxaban) film-coated tablet (2.5 mg), in combination with 75 mg – 100 mg acetylsalicylic acid (ASA), is indicated for the:

- prevention of stroke, myocardial infarction and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with coronary artery disease (CAD) with or without peripheral artery disease (PAD).
- prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of major adverse limb events (MALE) or major adverse cardiovascular and cerebrovascular events (MACCE).

XARELTO® (rivaroxaban) granules for oral suspension (1mg/mL) is indicated for the:

- treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment (see **DOSAGE AND ADMINISTRATION**).

XARELTO® (rivaroxaban) film-coated tablet (15 mg) is indicated for the:

- treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment (see **DOSAGE AND ADMINISTRATION**).

XARELTO® (rivaroxaban) film-coated tablet (20 mg) is indicated for the:

- treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment (see **DOSAGE AND ADMINISTRATION**).

Acute Pulmonary Embolus in hemodynamically unstable patients, or in those requiring thrombolysis or pulmonary embolectomy

For the treatment of VTE, XARELTO is **not** recommended as an alternative to unfractionated heparin in patients with pulmonary embolus who are hemodynamically unstable, or who may receive thrombolysis or pulmonary embolectomy, since the safety and efficacy of XARELTO have not been established in these clinical situations (see **DOSAGE AND ADMINISTRATION**).

Geriatrics

Clinical studies have included patients with an age > 65 years (see **WARNINGS AND PRECAUTIONS** – ***Geriatrics (>65 Years of Age)*** and **Renal Impairment,** and **DOSAGE AND ADMINISTRATION** – ***Renal Impairment*** and ***Geriatrics*** *(>65 years of age))*.

Safety and efficacy data are available (see **CLINICAL TRIALS**).

Pediatrics

In children less than 18 years of age, the safety and efficacy of XARELTO have not been established for indications other than treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence. Therefore, XARELTO is not recommended for use in children below 18 years of age for indications other than the treatment of VTE and prevention of VTE recurrence.

The safety and efficacy of XARELTO 2.5 mg and 10 mg film-coated tablets have not been established in children less than 18 years of age; therefore, XARELTO 2.5 mg and 10 mg film-coated tablets are not recommended in this patient population (see **WARNINGS AND PRECAUTIONS - Special Populations - *Pediatrics (<18 Years of Age)***).

CONTRAINDICATIONS

- Clinically significant active bleeding, including gastrointestinal bleeding
- Lesions or conditions at increased risk of clinically significant bleeding, e.g, recent cerebral infarction (hemorrhagic or ischemic), active peptic ulcer disease with recent bleeding, patients with spontaneous or acquired impairment of hemostasis

- Concomitant **systemic** treatment with strong inhibitors of **both** CYP 3A4 and P-glycoprotein (P-gp), such as cobicistat, ketoconazole, itraconazole, posaconazole, or ritonavir (see **WARNINGS AND PRECAUTIONS – Drug Interactions**)
- Concomitant treatment with any other anticoagulant, including
    - unfractionated heparin (UFH), except at doses used to maintain a patent central venous or arterial catheter,
    - low molecular weight heparins (LMWH), such as enoxaparin and dalteparin,
    - heparin derivatives, such as fondaparinux, and
    - oral anticoagulants, such as warfarin, dabigatran, apixaban, edoxaban, except under circumstances of switching therapy to or from XARELTO.
- Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy, and having clinically relevant bleeding risk (see **WARNINGS AND PRECAUTIONS – Hepatic Impairment**)
- Pregnancy (see **WARNINGS AND PRECAUTIONS – Special Populations**, ***Pregnant Women***)
- Nursing women (see **WARNINGS AND PRECAUTIONS – Special Populations, *Nursing Women***)
- Hypersensitivity to XARELTO (rivaroxaban) or to any ingredient in the formulation, (see **DOSAGE FORMS, COMPOSITION AND PACKAGING)**.

WARNINGS AND PRECAUTIONS

PREMATURE DISCONTINUATION OF ANY ORAL ANTICOAGULANT, INCLUDING XARELTO, INCREASES THE RISK OF THROMBOTIC EVENTS.

To reduce this risk, consider coverage with another anticoagulant if XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

Bleeding

XARELTO, like other anticoagulants, should be used with caution in patients with an increased bleeding risk. Bleeding can occur at any site during therapy with XARELTO. The possibility of a hemorrhage should be considered in evaluating the condition of any anticoagulated patient. Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site. Patients at high risk of bleeding should not be prescribed XARELTO (see **CONTRAINDICATIONS**).

Should severe bleeding occur, treatment with XARELTO must be discontinued and the source of bleeding investigated promptly.

Close clinical surveillance (looking for signs of bleeding or anemia) is recommended throughout the treatment period, especially in the presence of multiple risk factors for bleeding (see Table 2 below).

Table 2 – Factors Which Increase Hemorrhagic Risk

Factors increasing rivaroxaban plasma levels	Severe renal impairment (CrCl < 30 mL/min)
	Concomitant **systemic** treatment with strong inhibitors of **both** CYP 3A4 and P-gp
Pharmacodynamic interactions	NSAID
	Platelet aggregation inhibitors, including ASA, clopidogrel, prasugrel, ticagrelor
	Selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRIs)
Diseases / procedures with special hemorrhagic risks	Congenital or acquired coagulation disorders
	Thrombocytopenia or functional platelet defects
	Uncontrolled severe arterial hypertension
	Active ulcerative gastrointestinal disease
	Recent gastrointestinal bleeding
	Vascular retinopathy, such as hypertensive or diabetic
	Recent intracranial hemorrhage
	Intraspinal or intracerebral vascular abnormalities
	Recent brain, spinal or ophthalmological surgery
	Bronchiectasis or history of pulmonary bleeding
Others	Age > 75 years

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. Care should be taken if patients are treated concomitantly with drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRIs) (see also **DRUG INTERACTIONS**). Patients on treatment with XARELTO 2.5 mg and ASA should only receive chronic concomitant treatment with NSAIDS, if the benefit outweighs the bleeding risk.

In patients with atrial fibrillation and having a condition that warrants single or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with XARELTO.

XARELTO 2.5 mg BID has not been studied in combination with, or as replacement of dual antiplatelet therapy (DAPT) for the prevention of stroke, myocardial infarction and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with coronary artery disease (CAD) with or without peripheral artery disease (PAD). The combination has also not been studied for the prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of major adverse limb events (MALE) or major adverse cardiovascular and cerebrovascular events (MACCE).

XARELTO 2.5 mg BID is not indicated in patients with unstable atherosclerotic disease when DAPT is indicated.

Concomitant ASA use (almost exclusively at a dose of 100 mg or less) with either XARELTO or warfarin during the ROCKET-AF trial was identified as an independent risk factor for major bleeding (see also **DRUG INTERACTIONS**).

The antiplatelet agents, prasugrel and ticagrelor, have not been studied with XARELTO, and are not recommended as concomitant therapy.

The use of thrombolytics should generally be avoided during acute myocardial infarction (AMI) or acute stroke in patients treated with rivaroxaban, due to expected increased risk of major bleeding (see **DOSAGE AND ADMINISTRATION – *Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation*, Other situations requiring thrombolytic therapy**).

Cardiovascular

See **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**.

Patients with valvular disease

XARELTO is not indicated and is not recommended for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Results from a randomized controlled clinical study (GALILEO) showed that the XARELTO regimen failed to demonstrate clinical benefit compared with an antiplatelet strategy. In the intention-to-treat analysis, all-cause mortality, thromboembolic and bleeding events occurred more frequently in patients randomized to the XARELTO regimen. A causal relationship between XARELTO and all-cause mortality could not be established.

Safety and efficacy of XARELTO have not been studied in patients with other prosthetic heart valves or other valve procedures, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis. There are no data to support that XARELTO provides adequate anticoagulation in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of XARELTO is not recommended in this setting.

Of note, in the pivotal Phase III ROCKET AF trial that evaluated XARELTO in the prevention of stroke in atrial fibrillation, 14% of patients had other valvular disease including aortic stenosis, aortic regurgitation, and/or mitral regurgitation. Patients with a history of mitral valve repair were also not excluded from the study. Mitral valve repair rates are not known in ROCKET AF, since information on mitral valve repair status was not specifically collected in this study.

Patients with antiphospholipid syndrome

XARELTO is not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients who are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with rivaroxaban is associated with an increased rate of recurrent thrombotic events compared with vitamin K antagonists.

Patients with nonvalvular atrial fibrillation who undergo PCI (Percutaneous Coronary Intervention) with stent placement

Clinical data are available from an open label interventional study with the primary objective to assess safety in patients with nonvalvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited (see **DOSAGE AND ADMINISTRATION – *Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation*; ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics, *Patients with nonvalvular atrial fibrillation who undergo PCI with stent placement***).

Patients with hemorrhagic or lacunar stroke

CAD / PAD patients with a history of previous haemorrhagic or lacunar stroke were not studied. Treatment with XARELTO 2.5 mg twice daily in combination with ASA should be avoided in these patients.

Patients with ischemic, non-lacunar stroke

CAD / PAD patients who have experienced an ischemic, non-lacunar stroke within the previous month were not studied. Treatment with XARELTO 2.5 mg twice daily in combination with ASA should be avoided in the first month after stroke (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**).

Drug Interactions

Drug interaction studies have only been performed in adults. The information in this section, should be taken into account for the pediatric population (see **DRUG INTERACTIONS**).

Interaction with strong inhibitors of both CYP 3A4 and P-gp

The use of XARELTO is contraindicated in patients receiving concomitant **systemic** treatment with strong inhibitors of **both** CYP 3A4 and P-gp, such as cobicistat, ketoconazole, itraconazole, posaconazole, or ritonavir. These drugs may increase XARELTO plasma concentrations to a clinically relevant degree, i.e, 2.6-fold on average, which increases bleeding risk.

Dronedarone should not be used concomitantly with rivaroxaban since it may increase exposure of rivaroxaban through P-gp and CYP3A4 inhibition, and thereby the risk of bleeding.

Interaction with moderate CYP 3A4 inhibitors

The azole anti-mycotic, fluconazole, a moderate CYP 3A4 inhibitor, or erythromycin, have no clinically relevant effect on rivaroxaban exposure (1.4-fold and 1.3-fold increase, respectively) and may be co-administered with XARELTO in patients with normal renal function (see **DRUG INTERACTIONS**).

The use of XARELTO in subjects with mild and moderate renal impairment concomitantly treated with combined P-gp and moderate CYP 3A4 inhibitors such as erythromycin increased exposure to rivaroxaban by 1.8- and 2.0-fold, respectively, compared to subjects with normal renal function without comedication. If such use must be undertaken, caution is required.

Interaction with strong CYP 3A4 inducers

The concomitant use of XARELTO with strong inducers of CYP 3A4, such as rifampicin, and the anticonvulsants, phenytoin, carbamazepine, phenobarbital, reduces rivaroxaban exposure (see **DRUG INTERACTIONS – Drug-Drug Interactions**). Combined use of XARELTO with strong inducers should generally be avoided, since efficacy of XARELTO may be compromised (see **DRUG INTERACTIONS – Drug-Drug Interactions**).

Hepatic Impairment

Patients with significant hepatic disease (e.g, 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 having 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.

No clinical data are available in children with hepatic impairment.

Surgery / Procedural Interventions

As with any anticoagulant, patients on XARELTO who undergo surgery or invasive procedures are at increased risk for bleeding. In these circumstances, temporary discontinuation of XARELTO may be required.

If a patient concomitantly receiving platelet aggregation inhibitors is to undergo elective surgery and anti-platelet effect is not desired, platelet aggregation inhibitors should be discontinued as directed by the manufacturer's prescribing information.

Limited clinical data are available for patients undergoing fracture-related surgery of the lower limbs. These patients were from a subgroup which was not pre-specified for enrollment in an international, non-interventional (no exclusion criteria), open label cohort study designed to compare the incidence of symptomatic thromboembolic events in patients undergoing elective hip or knee surgery while not randomly assigned to treatment with XARELTO or any local standard-of-care pharmacological therapy.

Pre-Operative Phase

If an invasive procedure or surgical intervention is required, XARELTO 10 mg, 15 mg and 20 mg should be stopped at least 24 hours before the intervention, if possible, due to increased risk of bleeding, and based on clinical judgment of the physician. XARELTO 2.5 mg should be stopped at least 12 hours before the intervention. If a patient is to undergo elective surgery and anti-platelet effect is not desired, platelet aggregation inhibitors should be discontinued as per current treatment guidelines. If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention. Although there are limited data, in patients at higher risk of bleeding or in major surgery where complete hemostasis may be required, consider stopping XARELTO two to four days before surgery, depending on clinical circumstances.

Peri-Operative Spinal/Epidural Anesthesia, Lumbar Puncture

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 even further increased by the use of indwelling epidural catheters or the concomitant use of drugs affecting hemostasis. Accordingly, the use of XARELTO, at doses greater than 10 mg, is not recommended in patients undergoing anesthesia with post-operative indwelling epidural catheters. 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 10 mg should be frequently monitored for signs and symptoms of neurological impairment (e.g, numbness or weakness of the legs, bowel or bladder dysfunction). If neurological 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 10 mg 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 in adults.

There is no clinical experience with the use of XARELTO 15 mg and 20 mg, or XARELTO 2.5 mg in combination with ASA in these situations for adults. There is no clinical experience with the use of XARELTO in these situations for children.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anesthesia or lumbar 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 and should be weighed against the urgency of a diagnostic procedure.

No data are available on the timing of the placement or removal of neuraxial catheter in children while on XARELTO. Discontinue XARELTO and consider a short acting parenteral anticoagulant in these patients.

Post-Procedural Period

XARELTO should be restarted following an invasive procedure or surgical intervention as soon as adequate hemostasis has been established and the clinical situation allows, in order to avoid unnecessary increased risk of thrombosis.

Renal Impairment

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

Determine estimated creatinine clearance (eCrCl) in all patients before instituting XARELTO (see **DOSAGE AND ADMINISTRATION**).

XARELTO should be used with caution in patients with moderate renal impairment (CrCl 30-49 mL/min), especially in those 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 having a creatinine clearance close to the severe renal impairment category (CrCl < 30 mL/min), or in those with a potential to have deterioration of renal function to severe impairment during therapy.

In patients with severe renal impairment (CrCl 15 - < 30 mL/min), rivaroxaban plasma levels may be significantly elevated compared to healthy volunteers (1.6-fold on average) which may lead to an increased bleeding risk. Due to limited clinical data, XARELTO must be used with caution in these patients. No clinical data are available for patients with CrCl < 15 mL/min. Use is not recommended in patients with CrCl < 15ml/min. Patients who develop acute renal failure while on XARELTO should discontinue such treatment.

Due to the high plasma protein binding, i.e, about 95%, rivaroxaban is not expected to be removed by dialysis.

XARELTO is not recommended in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2), as no clinical data are available.

XARELTO is not recommended in children younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available.

Lactose Sensitivity

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

Information About Excipients

XARELTO granules for oral suspension contains 1.8 mg sodium benzoate in each mL oral suspension.

Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

XARELTO granules for oral suspension contains less than 1 mmol sodium (23 mg) per milliliter.

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** and **Lactation**).

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 should only be administered after breastfeeding is discontinued (see **CONTRAINDICATIONS**, and **TOXICOLOGY – Reproductive Toxicology** and **Lactation**).

Geriatrics (>65 Years of Age)

Increasing age is associated with declining renal function. Both of these factors have been observed to result in increased systemic exposure to rivaroxaban, and consequently increased bleeding (see **WARNINGS AND PRECAUTIONS – Renal Impairment,** and **DOSAGE AND ADMINISTRATION – *Renal Impairment***).

Increasing age may increase hemorrhagic risk. XARELTO 2.5 mg BID + ASA should be used with caution in patients with chronic CAD with or without PAD or in patients with symptomatic PAD at demonstrated high risk of MALE or MACCE who are ≥ 75 years of age. The benefit-risk of the treatment should be individually assessed on a regular basis.

Use with caution in elderly patients, especially those taking concomitant medications that increase systemic exposure of XARELTO (see **WARNINGS AND PRECAUTIONS**, **Drug Interactions**, and **DRUG INTERACTIONS**).

Pediatrics (<18 Years of Age)

The safety and efficacy of XARELTO 2.5 mg and 10 mg film-coated tablets have not been established in children less than 18 years of age. Therefore, XARELTO 2.5 mg and 10 mg film-coated tablets are not recommended in this patient population for any indication.

In children less than 18 years of age, the safety and efficacy of XARELTO have not been established for indications other than treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence. Therefore, XARELTO is not recommended for use in children below 18 years of age for indications other than the treatment of VTE and prevention of VTE recurrence.

There is limited data in children with cerebral vein and sinus thrombosis (CVST) who have a central nervous system infection. The risk of bleeding should be carefully evaluated before and during therapy with XARELTO.

Dosing of XARELTO cannot be reliably determined and was not studied in children less than 6 months of age who: at birth had less than 37 weeks of gestation, have a body weight of less than 2.6 kg, or had less than 10 days of oral feeding. XARELTO is therefore not recommended in these children.

Monitoring and Laboratory Tests

The prothrombin time (PT), measured in seconds, is influenced by XARELTO in a dose-dependent way with a close correlation to plasma concentration if the Neoplastin® reagent is used. In patients who are bleeding, measuring the PT using the Neoplastin® reagent may be useful to assist in determining an excess of anticoagulant activity (see **DOSAGE AND**

ADMINISTRATION – ***Considerations for INR Monitoring of VKA Activity during Concomitant XARELTO Therapy***).

Although XARELTO therapy will lead to an elevated INR, depending on the timing of the measurement (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics), the INR is not a valid measure to assess the anticoagulant activity of XARELTO. The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant, including XARELTO.

At recommended doses, XARELTO affects the measurement of the aPTT and Heptest®. These tests are not recommended for the assessment of the pharmacodynamic effects of XARELTO (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**).

Converting patients from warfarin to XARELTO, or from XARELTO to warfarin, increases prothrombin time by the Neoplastin® reagent in seconds (or INR values) more than additively (e.g, individual INR values up to 12 may be observed) during concomitant therapy, whereas effects on aPTT and endogenous thrombin potential are additive (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**).

Anti-Factor-Xa activity is influenced by XARELTO in a dose-dependent fashion. If it is desired to test the pharmacodynamic effects of XARELTO during the switching period, tests of anti-Factor-Xa activity can be used as they are not affected by warfarin. Use of these tests to assess the pharmacodynamic effects of XARELTO requires calibration and should not be done unless XARELTO-specific calibrators and controls are available (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**).

Although there is no need for routine monitoring of anticoagulation effect of XARELTO during clinical practice, in certain infrequent situations such as overdosage, acute bleeding, urgent surgery, in cases of suspected non-compliance, or in other unusual circumstances, assessment of the anticoagulant effect of rivaroxaban may be appropriate. Accordingly, measuring PT using the Neoplastin reagent, or Factor-Xa assay using rivaroxaban-specific calibrators and controls, may be useful to inform clinical decisions in these circumstances.

ADVERSE REACTIONS

Prevention of VTE after THR or TKR

The safety of XARELTO (rivaroxaban) 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.

Treatment of VTE and Prevention of Recurrent DVT and PE

The safety of XARELTO has been evaluated in four Phase III trials with 6790 patients treated up to 21 months. Patients were exposed to 15 mg XARELTO twice daily for 3 weeks followed by:

- 20 mg once daily (EINSTEIN DVT, EINSTEIN PE) or
- 20 mg once daily after at least 6 months of treatment for DVT or PE (EINSTEIN Extension), or
- 20 mg or 10 mg XARELTO once daily after at least 6 months of treatment for DVT or PE (EINSTEIN CHOICE).

The mean treatment duration was 194 days in EINSTEIN DVT, 183 days in EINSTEIN PE, 188 days in EINSTEIN Extension and 290 days in EINSTEIN CHOICE.

The incidence of adverse events resulting in permanent discontinuation of study drug was 5.0% for XARELTO and 4.4% for enoxaparin/VKA (pooled data from EINSTEIN DVT and EINSTEIN PE), 6.5% for XARELTO and 3.4% for placebo (EINSTEIN Extension) and 4.5% for XARELTO 10 mg, 4.5% for XARELTO 20 mg and 4.2% for ASA (EINSTEIN CHOICE).

Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation (SPAF)

In the pivotal double-blind ROCKET AF study, a total of 14,264 patients with atrial fibrillation at risk for stroke and systemic embolism were randomly assigned to treatment with either rivaroxaban (7,131) or warfarin (7,133) in 45 countries. Patients received XARELTO 20 mg orally once daily (15 mg orally once daily in patients with moderate renal impairment [CrCl: 30-49 mL/min]) or dose-adjusted warfarin titrated to a target INR of 2.0 to 3.0. The safety population included patients who were randomized and took at least 1 dose of study medication. In total, 14,236 patients were included in the safety population, with 7,111 and 7,125 patients in rivaroxaban and warfarin groups, respectively. The median time on treatment was 19 months and overall treatment duration was up to 41 months.

The incidence of adverse events resulting in permanent discontinuation of study drug was 15.8% in the rivaroxaban group and 15.2% in the warfarin group.

Prevention of Stroke, Myocardial Infarction, Cardiovascular Death, and Prevention of Acute Limb Ischemia and Mortality in Patients with CAD with or without PAD or prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of MALE or MACCE

COMPASS, a pivotal Phase III event-driven, randomized, controlled study with a 3 x 2 partial factoral design, randomized 27,395 subjects to receive XARELTO 2.5 mg bid in combination with ASA 100 mg od (9,152), XARELTO 5 mg bid alone (9,117) or ASA 100 mg od (9,126). The intention-to-treat (ITT) analysis set includes all randomized subjects. The median duration of treatment for any of the antithrombotic study drugs was 615 days and was similar for all 3 treatment groups.

The incidence of treatment emergent adverse events leading to permanent discontinuation of antithrombotic study medication was 3.4% in the XARELTO 2.5 mg bid plus ASA 100 mg od arm, and 2.6% in the ASA 100 mg od arm.

Bleeding

Due to the pharmacological mode of action, XARELTO is associated with an increased risk of occult or overt bleeding from any tissue and organ (see **WARNINGS AND PRECAUTIONS – Bleeding**, and **Drug Interactions**). The risk of bleeding may be increased in certain patient groups, e.g, patients with uncontrolled severe arterial hypertension and/or on concomitant medication affecting hemostasis (see Table 2**)**. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anemia. Hemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnea, and unexplained shock. In some cases, as a consequence of anemia, symptoms of cardiac ischemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for XARELTO. Therefore, the possibility of a hemorrhage should be considered in evaluating the medical condition in any anticoagulated patient.

Major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Since the adverse event profiles of the patient populations treated with XARELTO for different indications are not interchangeable, a summary description of major and total bleeding is provided by indication, in Table 3 for VTE prevention in patients undergoing elective THR or TKR surgery, in Table 4 for Treatment of VTE and prevention of recurrent DVT and PE, in Table 5 for stroke prevention in atrial fibrillation, and in Table 6 for prevention of stroke, myocardial infarction (MI), cardiovascular (CV) death, acute limb ischemia (ALI) and mortality in patients with CAD with or without PAD or prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of major adverse limb events (MALE) or major adverse cardiovascular and cerebrovascular events (MACCE).

Table 3 - RECORD 1, 2, and 3 (VTE Prevention After THR or TKR) – Treatment-Emergent Bleeding Events (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[a] n (%)	Major Bleeding Including Surgical Site Bleeding Events Associated With Hemoglobin Drops or Transfusions n (%)	Any Bleeding (Major or Nonmajor) 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	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	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	0.79	0.52	1.00
Pooled Analysis (RECORD 1, 2, 3)	XARELTO (N=4657)	14 (0.3)	84 (1.8)	274 (5.9)
	Enoxaparin (N=4692) 40 mg od SC	9 (0.2)	69 (1.5)	259 (5.5)
	P-Value	0.31	0.22	0.48

a Major bleeding events included: (1) fatal, (2) bleeding into a critical organ (e.g, 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.

See Table 23 and Table 25 for additional details.

od = once daily, po = oral, SC = subcutaneous

Table 4 - Treatment-Emergent Bleeding Events and Results – Safety Population with Central Adjudication - Pooled Analysis, EINSTEIN DVT, EINSTEIN PE, EINSTEIN Extension and EINSTEIN CHOICE (Treatment of VTE and Prevention of Recurrent DVT and PE)

	Pooled EINSTEIN DVT and EINSTEIN PE			EINSTEIN Extension		EINSTEIN CHOICE		
Bleeding event	**XARELTO N=4130**	**Enox/VKA N=4116**	**HR (95%CI) *P*-value for superiority**	**20 mg od N=598**	**Placebo N=590**	**XARELTO 10 mg N=1127**	**XARELTO 20 mg N=1107**	**ASA 100 mg N=1131**
	n (%)	**n (%)**		**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Major and Clinically Relevant Non-major Bleeding[a]	388 (9.4)	412 (10.0)	0.93 (0.81-1.06) *P*=0.27	36 (6.0)	7 (1.2)	27 (2.4)	36 (3.3)	23(2.0)
Major bleeding[b]	40 (1.0)	72 (1.7)	0.54 (0.37-0.80) *P*=0.0018*	4 (0.7)[b]	0	5 (0.4)	6 (0.5)	3 (0.3)
Fatal Bleeding	3 (<0.1)	8 (0.2)	-	0	0	0	1 (<0.1)	1 (<0.1)
Intracranial	2 (<0.1)	4 (<0.1)	-	0	0	0	0	1 (<0.1)
Non-Fatal Critical Organ Bleeding	10 (0.2)	29 (0.7)	-	0	0	2 (0.2)	4 (0.4)	1 (<0.1)
Intracranial	3 (<0.1)	10 (0.2)	-	0	0	1 (<0.1)	3 (0.3)	1 (<0.1)
Non-Fatal Non-Critical Organ Bleeding (Fall in Hb ≥ 2 g/dL and/or Transfusions ≥ 2 Units	27 (0.7)	37 (0.9)	-	4	0	3 (0.3)	1 (<0.1)	1 (<0.1)
Gastrointestinal	12 (0.3)	20 (0.5)	-	3	0	2 (0.2)	1 (<0.1)	1 (<0.1)
Clinically Relevant Non-Major Bleeding	357 (8.6)	357 (8.7)	0.99 (0.85-1.14) *P*=0.84	32 (5.4)[b]	7 (1.2)	22 (2.0)	30 (2.7)	20 (1.8)

a Primary safety outcome for Pooled EINSTEIN DVT and EINSTEIN PE.

b Primary safety outcome for EINSTEIN Extension and EINSTEIN CHOICE. Major bleeding event was defined as overt bleeding associated with a fall in hemoglobin of 2 g/dL or more; or leading to a transfusion of 2 or more units of packed red blood cells or whole blood; or that occurred in a critical site: intracranial, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or contributing to death. In EINSTEIN Extension, some patients had more than one event.

See Table 3 for definition of other footnotes.

Clinically relevant non-major bleeding pooled from both EINSTEIN DVT and EINSTEIN PE from a mucosal site occurred in 7.2 % of patients in the XARELTO group and 6.0 % of subjects in the enoxaparin/VKA group. Major bleeding from a mucosal site was observed in 0.6 % of the XARELTO group and 0.7 % of the enoxaparin/VKA group.

Table 5 – ROCKET AF (Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation (SPAF))–Time to the First Occurrence of Bleeding Events While on Treatment (up to Last Dose Plus 2 Days) - Safety Analysis

	XARELTO	Warfarin	
	n (%/year)	n (%/year)	HR (95% CI); *P*-value
Major and Non-major Clinically Relevant Bleeding	1475 (14.91)	1449 (14.52)	1.03 (0.96,1.11); 0.442
Major Bleeding[a]	395 (3.60)	386 (3.45)	1.04 (0.90,1.20); 0.576
Hemoglobin Drop	305 (2.77)	254 (2.26)	1.22 (1.03,1.44); 0.019*
Transfusion (> 2 units)	183 (1.65)	149 (1.32)	1.25 (1.01,1.55); 0.044*
Critical Organ Bleed	91 (0.82)	133 (1.18)	0.69 (0.53,0.91); 0.007*
Intracranial Hemorrhage	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94); 0.019*
Fatal Bleed	27 (0.24)	55 (0.48)	0.50 (0.31,0.79); 0.003*
Non-major Clinically Relevant Bleeding	1185 (11.80)	1151 (11.37)	1.04 (0.96,1.13); 0.345

a See Table 3 and Table 4 for definition of other footnotes.
* Statistically significant at nominal 0.05 (two-sided).
See Table 34, Table 38, and Table 40 for additional details.

Mucosal major bleeding was more common in the XARELTO group (2.4%/year) as compared to the warfarin group (1.6%/year; HR 1.52 (1.25, 1.83) $P < 0.001$). Most of the mucosal major bleeding was from a gastrointestinal site.

Intracranial hemorrhage and upper gastrointestinal hemorrhage resulting in death were observed in 24/55 (43.6%) and 1/204 (0.5%) XARELTO patients who experienced these adverse events, respectively, compared to 42/84 (50.0%) and 3/125 (2.4%) warfarin patients who experienced these same events, respectively.

Table 6- COMPASS (patients with chronic CAD with or without PAD or symptomatic PAD at demonstrated high risk of MALE or MACCE) – Modified ISTH Major Bleeding and Minor Bleeding (Time to First Event[a]) – Intention-to-Treat Analysis

Study Population	**Patients with CAD or PAD[b]**		
Treatment Dosage	**XARELTO 2.5 mg bid in combination with ASA 100 mg od, N=9152**	**ASA 100 mg od N=9126**	**Hazard Ratio (95 % CI) p-value[c]**
Primary safety outcome: Modified ISTH major bleeding	288 (3.1%)	170 (1.9%)	1.70 (1.40;2.05) p < 0.00001*
- Fatal bleeding event	15 (0.2%)	10 (0.1%)	1.49 (0.67;3.33) p = 0.32164
- Symptomatic bleeding in critical organ (non-fatal)	63 (0.7%)	49 (0.5%)	1.28 (0.88;1.86) p = 0.19679

Table 6- COMPASS (patients with chronic CAD with or without PAD or symptomatic PAD at demonstrated high risk of MALE or MACCE) – Modified ISTH Major Bleeding and Minor Bleeding (Time to First Event[a]) – Intention-to-Treat Analysis

Study Population	**Patients with CAD or PAD[b]**		
Treatment Dosage	**XARELTO 2.5 mg bid in combination with ASA 100 mg od, N=9152**	**ASA 100 mg od N=9126**	**Hazard Ratio (95 % CI) p-value[c]**
- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)	10 (0.1%)	8 (0.1%)	1.24 (0.49;3.14) p = 0.65119
- Bleeding leading to hospitalization (non-fatal, non-critical organ, not leading to reoperation)	208 (2.3%)	109 (1.2%)	1.91 (1.51;2.41) p<0.00001*
- Hospitalization where admission date < discharge date	172 (1.9%)	90 (1.0%)	1.91 (1.48;2.46) p<0.00001*
- Hospitalization where admission date = discharge date[d]	36 (0.4%)	21 (0.2%)	1.70 (0.99;2.92) p=0.04983
mISTH Major gastrointestinal bleeding	140 (1.5%)	65 (0.7%)	2.15 (1.60;2.89) p < 0.00001*
mISTH Major intracranial bleeding	28 (0.3%)	24 (0.3%)	1.16 (0.67;2.00) p = 0.59858
Minor Bleeding	838 (9.2%)	503 (5.5%)	1.70 (1.52;1.90) p < 0.001*

[a] For each outcome, the first event experienced per subject is considered; therefore, subsequent events of the same type are not shown.
[b] Intention-to-treat analysis set, primary analyses.
[c] XARELTO 2.5 mg plus ASA 100 mg vs. ASA 100 mg; Log-Rank p-value.
[d] Refers to hospitalization or presentation to an acute care facility with discharge the same day.
bid: twice daily; od: once daily; CI: confidence interval; modified ISTH = Modified International Society of Thrombosis and Hemostasis (ISTH) major bleeding is defined as fatal bleeding, symptomatic bleeding into critical area or organ, bleeding into surgical site requiring reoperation or bleeding leading to hospitalization.
- Table includes events that are classified as major bleedings during the adjudication process.
- Each event is counted in the most severe hierarchical category (fatal; critical organ bleeding; bleeding into surgical site requiring re-operation; bleeding leading to hospitalization) only.
* Statistically significant at nominal 0.05 (two-sided).

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 most common treatment-emergent adverse events in the three Phase III studies for VTE prevention in elective THR and TKR surgery are presented below in Table 7.

Table 7 – Treatment-Emergent Adverse Drug Reactions Occurring in >1% of Any Treatment Group – Pooled Data of RECORD 1, 2, 3 (VTE Prevention After THR or TKR) – (Patients Valid for Safety Analysis[a])

	XARELTO (N=4571)		Enoxaparin (N=4601)	
	n	(%)	n	(%)
Blood and lymphatic system disorders				
Thrombiocytosis (including platelet count increased)	77	(1.68)	86	(1.87)
Gastrointestinal disorders				
Nausea	402	(8.79)	402	(8.74)
Diarrhea	101	(2.21)	134	(2.91)
Abdominal and gastrointestinal pain (including upper abdominal pain, stomach discomfort)	88	(1.93)	88	(1.91)
Dyspepsia (including epigastric discomfort)	40	(0.88)	49	(1.06)
Vomiting	371	(8.12)	392	(8.52)
Constipation	293	(6.41)	319	(6.93)
General Disorders and Administration Site Conditions				
Fever	420	(9.19)	427	(9.28)
Decreased general strength and energy (including asthenia, fatigue)	56	(1.23)	45	(0.98)
Edema peripheral	190	(4.16)	160	(3.48)
Injury, poisoning, and post-procedural complications				
Anemia (including laboratory parameter)	263	(5.75)	292	(6.35)
Post procedural hemorrhage	200	(4.38)	192	(4.17)
Wound secretion	125	(2.73)	92	(2.00)
Investigations				
Increase in LDH	37	(0.81)	49	(1.06)
Increase in transaminases	123	(2.69)	190	(4.13)
Increase in Gamma-glutamyltransferase	74	(1.62)	121	(2.63)
Increase in alkaline phosphatase	35	(0.77)	56	(1.22)
Musculoskeletal, Connective Tissue, and Bone Disorders				
Pain in extremity	74	(1.62)	55	(1.20)
Nervous System Disorders				
Dizziness	149	(3.26)	142	(3.09)
Headache	105	(2.30)	96	(2.09)
Syncope (including loss of consciousness)	71	(1.55)	37	(0.80)
Skin and subcutaneous tissue disorders				
Pruritus (including uncommon cases of generalized pruritus)	97	(2.12)	73	(1.59)
Rash	56	(1.23)	57	(1.24)
Vascular disorders				
Hypotension (including blood pressure decreased)	146	(3.19)	147	(3.19)
Haematoma	47	(1.03)	53	(1.15)

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).

The most common treatment-emergent adverse events reported by patients valid for safety analysis in the 3 Phase III studies for treatment of VTE and prevention of recurrent DVT and PE are presented in Table 8.

Table 8 - Treatment-Emergent Adverse Reactions occurring in >1% of Any Treatment Group – pooled EINSTEIN DVT (11702 DVT) and EINSTEIN PE (11702 PE); EINSTEIN Extension (11899); EINSTEIN CHOICE (16416) [b] (Treatment of VTE and Prevention of Recurrent DVT and PE) - Safety Analysis

	Pooled EINSTEIN DVT and EINSTEIN PE		EINSTEIN Extension		EINSTEIN CHOICE		
	XARELTO (N=4130) n (%)	ENOXAPARIN/ VKA (N=4116) n (%)	XARELTO (N=598) n (%)	Placebo (N=590) n (%)	XARELTO 10 mg (N=1127) n (%)	XARELTO 20 mg (N=1107) n (%)	ASA 100 mg (N=1131) n (%)
Blood and lymphatic system disorders							
Anemia	84 (2.03)	62 (1.51)	4 (0.67)	2 (0.34)	1 (<0.1)	3 (0.3)	0
Cardiac disorder							
Tachycardia	55 (1.33)	43 (1.04)	2 (0.33)	0	0	1 (<0.1)	0
Eye disorders							
Conjunctival hemorrhage	39 (0.94)	47 (1.14)	6 (1.00)	0	2 (0.2)	6 (0.5)	4 (0.4)
Gastrointestinal disorders							
Gingival bleeding	93 (2.25)	104 (2.53)	11 (1.84)	2 (0.34)	14 (1.2)	28 (2.5)	12 (1.1)
Rectal hemorrhage	90 (2.18)	56 (1.36)	4 (0.67)	4 (0.68)	9 (0.8)	6 (0.2)	7 (0.6)
Abdominal pain	69 (1.67)	53 (1.29)	2 (0.33)	7 (1.19)	1 (<0.1)	3 (0.3)	2 (0.2)
Abdominal pain upper	71 (1.72)	50 (1.21)	10 (1.67)	1 (0.17)	2 (0.2)	2 (0.2)	5 (0.4)
Constipation	187 (4.53)	174 (4.23)	6 (1.00)	5 (0.85)	2 (0.2)	0	7 (0.6)
Diarrhea	179 (4.33)	164 (3.98)	7 (1.17)	8 (1.36)	4 (0.4)	4 (0.4)	1 (<0.1)
Dyspepsia	60 (1.45)	54 (1.31)	8 (1.34)	4 (0.68)	1 (<0.1)	3 (0.3)	4 (0.4)
Nausea	153 (3.70)	160 (3.89)	7 (1.17)	6 (1.02)	3 (0.3)	3 (0.3)	2 (0.2)
Vomiting	69 (1.67)	96 (2.33)	3 (0.50)	6 (1.02)	0	4 (0.4)	2 (0.2)
General disorders and administration site conditions							
Pyrexia	111 (2.69)	108 (2.62)	5 (0.84)	7 (1.19)	1 (<0.1)	2 (0.2)	0
Edema peripheral	128 (3.10)	135 (3.28)	13 (2.17)	17 (2.88)	0	0	1 (<0.1)
Asthenia	61 (1.48)	60 (1.46)	4 (0.67)	6 (1.02)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Fatigue	90 (2.18)	68 (1.65%)	6 (1.00)	3 (0.51)	1 (<0.1)	1 (<0.1)	3 (0.3)
Injury, poisoning and post-procedural complications							
Wound hemorrhage	59 (1.43)	65 (1.58)	11 (1.84)	7 (1.19)	11 (1.0)	11(1.0)	8 (0.7)
Contusion	145 (3.51)	197 (4.79)	19 (3.18)	16 (2.71)	0	2 (0.2)	0
Subcutaneous hematoma	44 (1.07)	61 (1.48)	0	2 (0.34)	33 (2.9)	24 (2.2)	33 (2.9)

Table 8 - Treatment-Emergent Adverse Reactions occurring in >1% of Any Treatment Group – pooled EINSTEIN DVT (11702 DVT) and EINSTEIN PE (11702 PE); EINSTEIN Extension (11899); EINSTEIN CHOICE (16416)[b] (Treatment of VTE and Prevention of Recurrent DVT and PE) - Safety Analysis

	Pooled EINSTEIN DVT and EINSTEIN PE		EINSTEIN Extension		EINSTEIN CHOICE		
	XARELTO (N=4130) n (%)	ENOXAPARIN/ VKA (N=4116) n (%)	XARELTO (N=598) n (%)	Placebo (N=590) n (%)	XARELTO 10 mg (N=1127) n (%)	XARELTO 20 mg (N=1107) n (%)	ASA 100 mg (N=1131) n (%)
Investigations							
Alanine aminotransferase increased[c]	72 (1.74)	129 (3.13)	2 (0.33)	4 (0.68)	-	-	-
Aspartate aminotransferase increased[c]	32 (0.77)	44 (1.07)	4 (0.67)	3 (0.51)	-	-	-
Musculoskeletal, connective tissue and bone disorders							
Pain in extremity	230 (5.57)	221 (5.37)	29 (4.85)	35 (5.93)	4 (0.4)	2 (0.2)	1 (<0.1)
Nervous system disorders							
Headache	284 (6.88)	242 (5.88)	18 (3.01)	15 (2.54)	3 (0.3)	4 (0.4)	3 (0.3)
Dizziness	102 (2.47)	108 (2.62)	6 (1.00)	8 (1.36)	5 (0.4)	4 (0.4)	3 (0.3)
Renal and urinary disorders							
Hematuria	111 (2.69)	113 (2.75)	13 (2.17)	2 (0.34)	0	3 (0.3)	0
Reproductive system and breast disorders							
Menorrhagia[a]	122 (2.95)	64 (1.55)	5 (0.84)	2 (0.34)	10 (0.9)	15 (1.4)	2 (0.2)
Vaginal hemorrhage	54 (1.31)	23 (0.56)	1 (0.17)	5 (0.85)	4 (0.4)	5 (0.5)	2 (0.2)
Respiratory, thoracic and mediastinal disorders							
Epistaxis	307 (7.43)	271 (6.58)	24 (4.01)	11 (1.86)	41 (3.6)	41 (3.7)	29 (2.6)
Hemoptysis	100 (2.42)	98 (2.38)	1 (0.17)	1 (0.17)	0	6 (0.5)	1 (<0.1)

Table 8 - Treatment-Emergent Adverse Reactions occurring in >1% of Any Treatment Group – pooled EINSTEIN DVT (11702 DVT) and EINSTEIN PE (11702 PE); EINSTEIN Extension (11899); EINSTEIN CHOICE (16416) [b] (Treatment of VTE and Prevention of Recurrent DVT and PE) - Safety Analysis

	Pooled EINSTEIN DVT and EINSTEIN PE		EINSTEIN Extension		EINSTEIN CHOICE		
	XARELTO (N=4130) n (%)	ENOXAPARIN/ VKA (N=4116) n (%)	XARELTO (N=598) n (%)	Placebo (N=590) n (%)	XARELTO 10 mg (N=1127) n (%)	XARELTO 20 mg (N=1107) n (%)	ASA 100 mg (N=1131) n (%)
Skin and subcutaneous tissue disorders							
Pruritus	83 (2.01)	58 (1.41)	2 (0.33)	2 (0.34)	8 (0.7)	3 (0.3)	3 (0.3)
Rash	97 (2.35)	89 (2.16)	5 (0.84)	7 (1.19)	5 (.4)	3 (0.3)	4 (0.4)
Vascular disorders							
Hematoma	91 (2.20)	150 (3.64)	7 (1.17)	8 (1.36)	0	1 (<0.1)	1 (<0.1)

NB: - Percentages calculated with the number of subjects in each group as denominator
- Incidence is based on number of subjects, not number of events
- Treatment-Emergent (pooled EINSTEIN DVT and EINSTEIN PE) = events that start after randomization and up to 2 days after the last dose of study medication
- Treatment-Emergent (EINSTEIN Extension) = events that start on or after the first dose of study medication and up to 2 days after the last dose of study medication

a Observed as very common for rivaroxaban in women <55 years in pooled 11702 DVT and 11702 PE studies

b According to the protocol, a targeted AE reporting was applied in this study, i.e. all serious adverse events (SAEs), all AEs of special interest, independent if serious or not, all non-serious AEs leading to a permanent study medication discontinuation, and all pregnancies (and their outcomes) in a patient or of the patient's partner needed to be captured on the eCRF and were reported to PV within 24 hours. Investigators could collect AEs on the eCRF, if deemed important.

c As laboratory measurements related to AST/ALT in Einstein CHOICE were not scheduled but performed as needed, the information is not available

The most common identified treatment-emergent adverse drug reactions in the EINSTEIN Junior Phase III study, for the treatment of VTE and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18 years, are presented in Table 9.

Table 9 - Treatment-Emergent Adverse Drug Reactions occurring in ≥1% of Any Treatment Group - EINSTEIN Junior Phase III study(14372) (safety analysis)

	XARELTO (n=329)		Comparator (n=162)	
	n	(%)	n	(%)
Blood and lymphatic system disorders				
Increased tendency to bruise	1	(0.3%)	2	(1.2%)
Gastrointestinal disorders				
Gingival bleeding	10	(3.0%)	0	0
General disorders and administration site conditions				
Injection site bruising	0	0	2	(1.2%)
Puncture site haemorrhage	0	0	4	(2.5%)
Injury, poisoning and procedural complications				
Contusion	9	(2.7%)	1	(0.6%)
Subcutaneous haematoma	7	(2.1%)	0	0
Reproductive system and breast disorder				
Menorrhagia	20	(6.1%)	4	(2.5%)
Respiratory, thoracic and mediastinal disorders				

	XARELTO (n=329)		Comparator (n=162)	
	n	(%)	n	(%)
Epistaxis	20	(6.1%)	8	(4.9%)
Skin and subcutaneous tissue disorders				
Alopecia	4	(1.2%)	1	(0.6%)

NB: Incidence is based on number of subjects, not number of events
A subject is counted only once within each preferred term or any primary SOC.
Treatment-Emergent = an event that occurred after randomization until last intake of study medication plus 2 days.

The most common identified treatment-emergent adverse drug reactions in the pivotal Phase III study, ROCKET AF, for prevention of stroke and systemic embolism in patients with atrial fibrillation are presented in Table 10.

Table 10 – Treatment-Emergent Adverse Reactions Occurring in >1% of Any Treatment Group – ROCKET AF (Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation (SPAF)) - Safety Analysis

	XARELTO (N=7111)		Warfarin (N=7125)	
	n	(%)	n	(%)
Blood and lymphatic system disorders				
Anemia	219	(3.08)	143	(2.01)
Eye disorders				
Conjunctival hemorrhage	104	(1.46)	151	(2.12)
Gastrointestinal disorders				
Diarrhea	379	(5.33)	397	(5.57)
Gingival bleeding	263	(3.70)	155	(2.18)
Nausea	194	(2.73)	153	(2.15)
Rectal hemorrhage	149	(2.10)	102	(1.43)
Abdominal pain upper	127	(1.79)	120	(1.68)
Vomiting	114	(1.60)	111	(1.56)
Dyspepsia	111	(1.56)	91	(1.28)
Abdominal pain	107	(1.50)	118	(1.66)
Gastrointestinal hemorrhage	100	(1.41)	70	(0.98)
General Disorders and Administration Site Conditions				
Edema peripheral	435	(6.12)	444	(6.23)
Fatigue	223	(3.14)	221	(3.10)
Asthenia	125	(1.76)	106	(1.49)
Pyrexia	72	(1.01)	87	(1.22)
Injury, poisoning and post-procedural complications				
Contusion	196	(2.76)	291	(4.08)
Investigations				
Alanine aminotransferase increased	144	(2.03)	112	(1.57)
Musculoskeletal, Connective Tissue, and Bone Disorders				
Pain in extremity	191	(2.69)	208	(2.92)
Nervous System Disorders				
Dizziness	433	(6.09)	449	(6.30)
Headache	324	(4.56)	363	(5.09)
Syncope	130	(1.83)	108	(1.52)
Renal and urinary disorders				
Hematuria	296	(4.16)	242	(3.40)
Respiratory tract disorders				

Table 10 – Treatment-Emergent Adverse Reactions Occurring in >1% of Any Treatment Group – ROCKET AF (Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation (SPAF)) - Safety Analysis

	XARELTO (N=7111)		Warfarin (N=7125)	
	n	(%)	n	(%)
Epistaxis	721	(10.14)	609	(8.55)
Hemoptysis	99	(1.39)	100	(1.40)
Skin and subcutaneous tissue disorders				
Ecchymosis	159	(2.24)	234	(3.28)
Pruritus	120	(1.69)	118	(1.66)
Rash	112	(1.58)	129	(1.81)
Vascular disorders				
Hematoma	216	(3.04)	330	(4.63)
Hypotension	141	(1.98)	130	(1.82)

NB: Incidence is based on number of subjects, not number of events
Treatment-Emergent = events that start on or after the first dose of study medication and up to 2 days after the last dose of study medication

The most common identified treatment-emergent adverse drug reactions in the pivotal Phase III study, COMPASS, are presented in Table 11. The COMPASS protocol utilized a selective, or targeted approach to safety data collection. Therefore, efficacy and safety outcomes as well as events expected in this population as specified in the study protocol were not reported as (S)AEs, but were captured on the respective eCRF. This section includes the results of reported TE(S)AEs.

Table 11 – Treatment-Emergent Adverse Reactions Occurring in > 1% of Any Treatment Group – COMPASS (patients with chronic CAD with or without PAD or symptomatic PAD at demonstrated high risk of MALE or MACCE) (Safety Analysis)

	XARELTO 2.5 mg bid plus ASA 100 mg od (n=9134)		ASA 100 mg (n=9107)	
	n	(%)	n	(%)
Infections and infestations				
Viral upper respiratory tract infection	187	2.0%	193	2.1%

NB: Incidence is based on number of subjects, not number of events

Less Common Clinical Trial Adverse Drug Reactions

Incidence is ≥0.1% to <1% unless specified.

VTE Prevention in Elective THR and TKR Surgery

Cardiac Disorders: tachycardia

Gastrointestinal Disorders: dry mouth, gastrointestinal tract hemorrhage (including gingival bleeding, rectal hemorrhage, hematemesis)

General Disorders and Administration Site Conditions: feeling unwell (including malaise), localized edema

Hepatobiliary Disorders: hepatic impairment (≥0.01% to <0.1%)

Immune System Disorders: hypersensitivity, anaphylaxis, allergic edema and angioedema, dermatitis allergic

Investigations: bilirubin conjugated increased (with or without concomitant increase of ALT) (≥ 0.01% to < 0.1%), blood bilirubin increased, increased amylase, increased lipase

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

Respiratory Tract Disorders: epistaxis

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

Vascular Disorders: urogenital tract hemorrhage

Treatment of VTE and Prevention of Recurrent DVT and PE:

Incidence is ≥ 0.1% to < 1% (pooled EINSTEIN DVT, EINSTEIN PE and EINSTEIN Extension) unless specified. Patients rolled over from EINSTEIN DVT or EINSTEIN PE into EINSTEIN Extension are considered as one patient (N=4556).

Cardiac disorder: tachycardia

Gastrointestinal Disorders: gastrointestinal hemorrhage, hematochezia, hemorrhoidal hemorrhage, melena, mouth hemorrhage, abdominal discomfort, abdominal pain lower, dry mouth

General Disorders and Administration Site Conditions: asthenia, feeling abnormal, malaise

Hepatobiliary Disorders: hepatic impairment

Immune System Disorders: hypersensitivity

Injury, poisoning and post-procedural complications: post-procedural hemorrhage, traumatic hematoma, traumatic hemorrhage, subcutaneous haematoma

Investigations: hemoglobin decreased, aspartate aminotransferase increased, liver function test abnormal, hepatic enzyme increased, transaminases increased, blood bilirubin increased, bilirubin conjugated increased (with or without concomitant increase of ALT), gamma-glutamyl transferase increased, blood alkaline phosphatase increased

Nervous System Disorders: syncope, cerebral and intra cranial hemorrhage (≥ 0.01% to < 0.1%)

Reproductive system and breast disorders: menometrorrhagia, metrorrhagia

Skin and Subcutaneous Tissue Disorders: urticaria, ecchymosis, skin hemorrhage, dermatitis allergic (≥0.01% to <0.1%)

Vascular Disorders: hypotension

In other clinical studies with XARELTO, occurrences of vascular pseudoaneurysm formation following percutaneous intervention have been observed. Very rare cases of adrenal hemorrhage have been reported.

Treatment of VTE and Prevention of VTE Recurrence in Term Neonates, Infants and Toddlers, Children, and Adolescents aged less than 18 years

Blood and Lymphatic System Disorders: hemorrhagic diathesis, increased tendency to bruise

Eye Disorders: retinal hemorrhage

Gastrointestinal Disorders: abdominal discomfort, abdominal pain, abdominal pain upper, diarrhea, diarrhea hemorrhagic, enterocolitis hemorrhagic, gastric hemorrhage, mouth hemorrhage, nausea, vomiting

General Disorders and Administration Site Conditions: catheter site hemorrhage, fatigue, feeling abnormal, feeling cold

Hepatobiliary Disorders: gallbladder disorder, hepatic function abnormal

Infections and Infestations: oral herpes

Injury, Poisoning and Procedural Complications: accidental overdose, accidental underdose, incision site hemorrhage, procedural hemorrhage, stoma site hemorrhage, wound hemorrhage

Investigations: activated partial thromboplastin time prolonged, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin, fibrin D dimer increased, gamma-glutamyltransferase increased, hepatic enzyme increased, prothrombin time prolonged, weight increased

Metabolism and Nutrition Disorders: decreased appetite

Musculoskeletal and Connective Tissue Disorders: arthralgia

Nervous System Disorders: dizziness, headache, paraesthesia, seizure

Renal and Urinary Disorders: Hematuria, urinary bladder hemorrhage, urinary retention

Reproductive System and Breast Disorders: dysmenorrhea, metrorrhagia, vaginal hemorrhage

Respiratory, Thoracic and Mediastinal Disorders: pulmonary hemorrhage

Skin and Subcutaneous Tissue Disorders: alopecia areata, dermatitis allergic, rash, skin hemorrhage

Vascular Disorders: hemorrhage

Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation (SPAF)

Cardiac disorders: tachycardia

Eye disorders: eye hemorrhage, vitreous hemorrhage

Gastrointestinal Disorders: melena, upper gastrointestinal hemorrhage, hemorrhoidal hemorrhage, hematochezia, mouth hemorrhage, lower gastrointestinal hemorrhage, anal

hemorrhage, gastric ulcer hemorrhage, gastritis hemorrhagic, gastric hemorrhage, hematemesis, abdominal discomfort, abdominal pain lower, dry mouth

General Disorders and Administration Site Conditions: malaise

Hepatobiliary Disorders: hepatic impairment, hyperbilirubinemia, jaundice (≥ 0.01% to < 0.1%)

Immune System Disorders: hypersensitivity, anaphylaxis (≥ 0.01% to < 0.1%), allergic edema and angioedema

Injury, Poisoning, and Post-procedural Complications: post-procedural hemorrhage, wound hemorrhage, traumatic hematoma, incision site hemorrhage, subdural hematoma, subcutaneous hematoma, periorbital hematoma

Investigations: hemoglobin decreased, hematocrit decreased, blood bilirubin increased, liver function test abnormal, aspartate aminotransferase increased, hepatic enzyme increased, blood urine present, creatinine renal clearance decreased, blood creatinine increased, blood urea increased, blood alkaline phosphatase increased, lipase increased, bilirubin conjugated increased (with or without concomitant increase of ALT) (≥ 0.01% to < 0.1%)

Musculoskeletal, Connective Tissue, and Bone Disorders: hemarthrosis, muscle hemorrhage (≥ 0.01% to < 0.1%)

Nervous system disorders: loss of consciousness, hemorrhagic stroke, hemorrhage intracranial

Renal and urinary disorders: renal impairment

Reproductive system disorders: vaginal hemorrhage, metrorrhagia

Skin and Subcutaneous Tissue Disorders: dermatitis allergic, rash pruritic, rash erythemateous, rash generalized, pruritus generalized, urticaria, skin hemorrhage

Vascular disorders: hemorrhage, bleeding varicose vein

Prevention of Stroke, Myocardial Infarction and Cardiovascular Death and Prevention of Acute Limb Ischemia and Mortality in Patients with CAD with or without PAD or prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of MALE or MACCE

Blood and Lymphatic System Disorders: anaemia

Cardiac Disorders: atrial fibrillation

Ear and Labyrinth Disorders: vertigo

Eye Disorders: cataract, conjunctivial hemorrhage

Gastrointestinal Disorders: abdominal discomfort, abdominal pain, abdominal pain upper, constipation, dental caries, diarrhea, dyspepsia, gastritis, gingival bleeding, large intestine polyp, lip hemorrhage, melaena, nausea, stomatitis,

General Disorders and Administration Site Conditions: chest pain

Infections and Infestations: bronchitis, cellulitis, gastroenteritis, herpes zoster, influenza, periodontitis, pharyngitis, pneumonia, sepsis,

Injury, poisoning and procedural complications: confusion

Investigations: occult blood positive

Metabolism and Nutrition Disorders: diabetes mellitus

Musculoskeletal and Connective tissue disorders: arthralgia, back pain, lumbar spinal stenosis, musculoskeletal pain, osteoarthritis, pain in extremity, spinal osteoarthritis

Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps): lung neoplasm malignant, prostate cancer

Nervous System Disorders: dizziness, headache

Renal and Urinary Disorders: acute kidney injury, hematuria, renal failure

Reproductive System and Breast Disorders: benign prostatic hyperplasia

Respiratory, Thoracic and Mediastinal Disorders: epistaxis, hemoptysis, upper respiratory tract inflammation

Skin and Subcutaneous Tissue Disorders: eczema, hemorrhage subcutaneous, pruritus, rash, urticarial

Postmarketing Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of XARELTO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and the Lymphatic System Disorders: agranulocytosis, thrombocytopenia

Hepatobiliary Disorders: cholestasis, hepatitis (including hepatocellular injury)

Immune System Disorders: anaphylaxis, allergic edema and angioedema (with or without urticaria)

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS)

Abnormal Hematologic and Clinical Chemistry Findings

In Phase III clinical trials, in VTE prevention, Treatment of VTE and prevention of recurrent DVT and PE, and SPAF the incidence of increases in transaminases in the XARELTO and comparator arms were similar, see Table 7, Table 8, and Table 10 above.

Clinical Trial Adverse Reactions (Pediatrics)

The safety assessment is based on the safety data from two Phase II and one Phase III open-label active controlled trials in a total of 412 pediatric VTE patients aged from birth to less than 18 years. The safety findings were generally similar between XARELTO and comparator in the various pediatric age groups. Overall, the safety profile in the 412 children treated with

rivaroxaban was similar to that observed in the adult population and consistent across age subgroups, although assessment is limited by the small number of patients.

In pediatric VTE patients, headache (very common, 16.7%), fever (very common, 11.7%), epistaxis (very common, 11.2%), vomiting (very common, 10.7%), tachycardia (common, 1.5%), increase in bilirubin (common, 1.5%) and bilirubin conjugated increased (uncommon, 0.7%) were reported more frequently as compared to adults. Consistent with adult population, menorrhagia was observed in 6.6% (common) of female adolescents after menarche. Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in pediatric clinical trials. The adverse drug reactions in pediatric patients were primarily mild to moderate in severity.

DRUG INTERACTIONS

Drug interaction studies have only been performed in adults. The extent of interactions in the pediatric population is not known. The information in this section should be taken into account for the pediatric population (see **WARNINGS AND PRECAUTIONS - Drug Interactions**).

XARELTO (rivaroxaban) neither inhibits nor induces CYP 3A4 or any other major CYP isoenzymes.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. Care should be taken if patients are treated concomitantly with drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, and platelet aggregation inhibitors. Due to the increased bleeding risk, generally avoid concomitant use with other anticoagulants (see **WARNINGS AND PRECAUTIONS – Bleeding**).

Drug-Drug Interactions

The use of XARELTO is contraindicated in patients receiving concomitant **systemic** treatment with strong inhibitors of **both** CYP 3A4 and P-gp such as cobicistat, ketoconazole, itraconazole, posaconazole, or ritonavir). These drugs may increase XARELTO plasma concentrations to a clinically relevant degree, i.e, 2.6-fold on average, which may lead to bleeding. The azole anti-mycotic, fluconazole, a moderate CYP 3A4 inhibitor, has less effect on rivaroxaban exposure and may be co-administered with caution (see **CONTRAINDICATIONS**, and **WARNINGS AND PRECAUTIONS – Drug Interactions)**.

In the ROCKET AF clinical trial in patients with atrial fibrillation, no apparent increase in major bleeding was observed in patients in whom amiodarone, a moderate CYP 3A4 inhibitor, was co-administered with rivaroxaban.

Drugs strongly inhibiting only one of the XARELTO elimination pathways, either CYP 3A4 or P-gp, are expected to increase XARELTO plasma concentrations to a lesser extent. The expected increase is considered less clinically relevant, see Table 12.

Table 12 – Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Reference	Effect	Clinical Comment
Azole antimycotic: ketoconazole	CT	Co-administration of XARELTO with the azole-antimycotic ketoconazole (400 mg od) a strong CYP 3A4 and P-gp inhibitor, led to a 2.6-fold increase in mean 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 – Drug Interactions** and **Renal Impairment**).
Cobicistat	C	Cobicistat is a strong CYP 3A4 and P-gp inhibitor. Coadministration with cobicistat may result in increased plasma concentration of rivaroxaban, leading to an increased bleeding risk.	**The use of XARELTO is contraindicated in patients receiving systemic treatment with cobicistat** (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS – Drug Interactions**).
Dronedarone	C	In a retrospective cohort study using the Truven Health MarketScan database in the US, a significantly increased risk of ICD-diagnoses of bleeding leading to hospitalization or emergency department visit was observed, driven by gastrointestinal bleeding, in NVAF patients with the concomitant use of rivaroxaban and dronedarone compared to those taking rivaroxaban alone.	Dronedarone should not be used concomitantly with XARELTO since it may increase exposure of XARELTO through P-gp and CYP3A4 inhibition, and thereby the risk of bleeding.
fluconazole	CT	Administration of the moderate CYP 3A4 inhibitor fluconazole (400 mg once daily) led to a 1.4-fold increase in mean XARELTO AUC and a 1.3-fold increase in mean C_{max}.	No dose adjustment is required.
Protease inhibitor: ritonavir	CT	Co-administration of XARELTO with the HIV protease inhibitor ritonavir (600 mg bid), a strong CYP 3A4 and P-gp inhibitor, led to a 2.5-fold increase in mean 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 – Drug Interactions** and **Renal Impairment**).
Anti-infectives: erythromycin	CT	Erythromycin (500 mg tid), which inhibits CYP 3A4 and P-gp moderately, led to a 1.3-fold increase in mean XARELTO AUC and C_{max}.	No dose adjustment is required. For patients with renal impairment see **WARNINGS AND PRECAUTIONS – Drug Interactions** and **DETAILED PHARMACOLOGY – Special Populations and Conditions – *Renal Insufficiency*.**

Table 12 – Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Reference	Effect	Clinical Comment
clarithromycin	CT	Clarithromycin (500 mg bid), considered a strong CYP 3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5-fold increase in mean rivaroxaban, and a 1.4-fold increase in C_{max}.	The use of XARELTO in combination with clarithromycin may increase the risk of bleeding particularly in patients with underlying disease conditions, and elderly. Caution is required.
rifampicin	CT	Co-administration of XARELTO with the strong CYP 3A4 and P-gp inducer rifampicin led to an approximate 50% decrease in mean XARELTO AUC, with parallel decreases in its pharmacodynamic effects.	Strong CYP 3A4 inducers should generally be avoided in combination with XARELTO, as such use can be expected to result in inadequate anticoagulation.
Anticonvulsants: phenytoin carbamazepine phenobarbital	T	The concomitant use of XARELTO with strong CYP 3A4 inducers (e.g, phenytoin, carbamazepine, or phenobarbital) may also lead to a decreased XARELTO plasma concentration.	Strong CYP 3A4 inducers should generally be avoided in combination with XARELTO, as such use can be expected to result in inadequate anticoagulation.
Nonsteroidal Anti-inflammatory Drugs (NSAID): naproxen	CT	Co-administration with naproxen did not affect XARELTO bioavailability and pharmacokinetics. No clinically relevant prolongation of bleeding time was observed when 500 mg naproxen was pre-administered 24 hours before concomitant administration of single doses of XARELTO 15 mg and naproxen 500 mg in healthy subjects.	Concomitant use with XARELTO may increase the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss (see **WARNINGS AND PRECAUTIONS – Drug Interactions**).
acetylsalicylic acid (ASA)	CT	No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when 500 mg ASA was pre-administered 24 hours before concomitant administration of single doses of XARELTO 15 mg and ASA 100 mg in healthy subjects.	Concomitant use with XARELTO increases the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss (see **WARNINGS AND PRECAUTIONS – Drug Interactions**). For patients in the ROCKET AF trial, concomitant ASA use (almost exclusively at 100 mg or less) was identified as an independent risk factor for major bleeding with both XARELTO and warfarin.

Table 12 – Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Reference	Effect	Clinical Comment
Antiplatelet drugs: clopidogrel	CT	In two drug interaction studies of 11 and 13 healthy subjects, clopidogrel 300 mg was pre-administered 24 hours before concomitant administration of single doses of XARELTO 15 mg and clopidogrel 75 mg in healthy subjects. Clopidogrel with or without XARELTO led to an approximately 2-fold increase in the median bleeding time (normal range 2 - 8 minutes). In these studies, between 30% and 40% of subjects who received both XARELTO and clopidogrel had maximum bleeding times of up to 45 minutes. XARELTO alone did not lead to a change in bleeding time at 4 hours or 2 days after administration. There was no change in the pharmacokinetics of either drug.	Concomitant use with XARELTO increases the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss (see **WARNINGS AND PRECAUTIONS – Drug Interactions**).
Antithrombotic: enoxaparin	CT	After combined administration of enoxaparin (40 mg single dose) with XARELTO (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 bioavailability and pharmacokinetics of XARELTO.	Co-administration of XARELTO at doses ≥10 mg with other anticoagulants or antithrombotic therapy has not been adequately studied in clinical trials. Due to the increased bleeding risk, generally avoid concomitant use with other anticoagulants (see **WARNINGS AND PRECAUTIONS – Drug Interactions**).
Selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRIs)	T, CT	When concomitantly used in the XARELTO clinical program, numerically higher rates of major or non-major clinically relevant bleeding were observed	As with other anticoagulants, patients on XARELTO are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets.

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

No pharmacokinetic interaction was observed between warfarin and XARELTO.

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

Co-administration of the proton pump inhibitor, omeprazole, the H_2-receptor antagonist, ranitidine, the antacid, aluminum hydroxide / magnesium hydroxide, or naproxen, clopidogrel, or enoxaparin did not affect XARELTO bioavailability or pharmacokinetics.

Drug-Food Interactions

XARELTO 2.5 mg and 10 mg may be taken with or without food. XARELTO 15 mg and 20 mg should be taken with food. XARELTO oral suspension should be taken with a feeding or with food. (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics**).

Grapefruit juice is a moderate CYP 3A4 inhibitor. Therefore, an increase in XARELTO exposure following grapefruit juice consumption is not expected to be clinically relevant.

Drug-Herb Interactions

The concomitant use of XARELTO with strong CYP 3A4 inducers (e.g, St. John's Wort) may lead to a decreased XARELTO plasma concentration. Strong CYP 3A4 inducers should generally be avoided in combination with XARELTO, as such use can be expected to result in inadequate anticoagulation.

Drug-Laboratory Interactions

Although various clotting parameter tests (PT, aPTT, Heptest®) are affected by the mode of action of XARELTO, none of these clotting tests have been demonstrated to reliably assess the anticoagulant activity of rivaroxaban following XARELTO administration under usual conditions (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**, and **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**).

The prothrombin time (PT), measured in seconds, is influenced by XARELTO in a dose-dependent way with a close correlation to plasma concentrations if the Neoplastin® reagent is used. In patients who are bleeding, measuring the PT (Neoplastin® reagent) in seconds, but not INR, may be useful to assist in determining an excess of anticoagulant activity (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**).

DOSAGE AND ADMINISTRATION

As for any non-vitamin K antagonist oral anticoagulant (NOAC) drug, before initiating XARELTO (rivaroxaban), ensure that the patient understands and is prepared to accept adherence to NOAC therapy, as directed.

Determine estimated creatinine clearance (eCrCl) in all patients before instituting XARELTO (rivaroxaban), and monitor renal function during XARELTO treatment, as clinically appropriate. Determination of renal function by eCrCl should occur at least once per year, and especially during circumstances when renal function may be expected to be compromised, i.e, acute myocardial infarction (AMI), acute decompensated heart failure (AHF), increased use of diuretics, dehydration, hypovolemia, etc. Clinically relevant deterioration of renal function may require dosage adjustment or discontinuation of XARELTO (see below, ***Renal Impairment***).

Glomerular filtration rate may be estimated by calculating eCrCl, using the Cockroft-Gault formula:

eCrCl (mL/min)=

in males: $\frac{(140\text{-age})\ (\text{years}) \times \text{weight (kg)} \times 1.23}{\text{serum creatinine } (\mu\text{mol/L})}$ or, $\frac{(140\text{-age})\ (\text{yrs}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$

in females: $\frac{(140\text{-age) (years) x weight (kg) x } 1.04}{\text{serum creatinine } (\mu\text{mol/L})}$ or, $\frac{(140\text{-age) (yrs) x weight (kg) x } 0.85}{72 \text{ x serum creatinine (mg/100 mL)}}$

Recommended Dose and Dosage Adjustment

Prevention of VTE after THR or TKR

The recommended dose is one 10 mg tablet once daily. XARELTO 10 mg 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 administration depends on the type of surgery:

- After elective THR surgery, patients should be administered XARELTO for 35 days.
- After elective TKR surgery, patients should be administered XARELTO for 14 days.

Treatment of VTE and Prevention of recurrent DVT and PE

XARELTO is NOT recommended as an alternative to unfractionated heparin in patients with acute pulmonary embolus who are hemodynamically unstable, or who may receive thrombolysis or pulmonary embolectomy, since the safety and efficacy of XARELTO have not been established in these clinical situations (see INDICATIONS AND CLINICAL USE).

The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily (one tablet in the morning and one in the evening) for the first 3 weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (e.g. recent major surgery or trauma). The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

Following completion of at least 6 months treatment for DVT or PE, the recommended dose for prevention of recurrent DVT and PE is 20 mg or 10mg once daily based on an individual assessment of the risk of recurrent DVT and PE against the risk for bleeding. For example, in patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities who are at high risk of VTE recurrence, a dose of 20mg should be considered.

Longer duration of therapy should be considered in patients with DVT or PE provoked by permanent risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

The recommended maximum daily dose is 30 mg during the first 3 weeks of treatment and 20 mg thereafter.

XARELTO 15 mg and 20 mg tablets should be taken with food. XARELTO 10 mg tablets may be taken with or without food.

Treatment of VTE and Prevention of VTE Recurrence in Term Neonates, Infants and Toddlers, Children, and Adolescents Aged Less Than 18 Years

XARELTO is available as a tablet or granules for oral suspension for pediatric use.

Tablet:

Swallow the tablet with liquid.

Granules for oral suspension:

Administer the oral suspension by mouth with the oral dosing syringe. Before administration the granules must be suspended with water into homogenous suspension. Shake the bottle after reconstitution and before each dose. For administration after reconstitution the oral dosing syringe called LDD - Liquid Dosing Device (1 mL, 5 mL or 10 mL) Non-Luer is provided. Complete details on preparation and administration of the oral suspension can be found in the Instructions for Use booklet that is provided with the medicinal product.

Initiation of XARELTO treatment in pediatric patients from 6 months of age to less than 18 years

XARELTO treatment for pediatric patients from 6 months to less than 18 years of age should be initiated following at least 5 days of initial anticoagulation treatment with parenteral heparins. XARELTO is dosed based on body weight using the more appropriate formulation (see Table 13).

Initiation of XARELTO treatment in pediatric patients from term neonates to less than 6 months

XARELTO treatment for pediatric patients from term neonates to less than 6 months of age, who at birth had at least 37 weeks of gestation, weigh at least 2.6 kg, and have had at least 10 days of oral feeding should be initiated following at least 5 days of initial anticoagulation treatment with parenteral heparins (see **WARNINGS AND PRECAUTIONS - Special Populations - *Pediatrics (<18 Years of Age)***). XARELTO is dosed based on body weight using the oral suspension formulation (see Table 13).

Appropriate dosage and dosage form

For pediatric patients with body weight of at least 30 kg, 15 mg or 20 mg XARELTO tablet or oral suspension once daily can be administered. The dose is determined based on body weight.

For pediatric patients with body weight of at least 2.6 kg to less than 30 kg only the oral suspension should be used. The dose and frequency of administration is determined based on body weight. Do not split XARELTO tablets or use XARELTO tablets of lower strength in an attempt to provide doses for children with body weight below 30 kg.

Table 13 - Body weight-adjusted XARELTO dosing schedule for children from birth to less than 18 years of age in mL of suspension and mg of tablets

Pharmaceutical form	Bodyweight (kg)		Regimen [mg] (1 mg=1 mL)			Total daily dose [mg] (1 mg=1 mL)	Suitable blue syringe (oral dosing syringe) for administration
	Min	Max	o.d. once a day	b.i.d. 2 times a day	t.i.d. 3 times a day		
Oral suspension	2.6	< 3			0.8 mg	2.4 mg	1 mL
	3	< 4			0.9 mg	2.7 mg	1 mL
	4	< 5			1.4 mg	4.2 mg	5 mL
	5	< 7			1.6 mg	4.8 mg	5 mL
	7	< 8			1.8 mg	5.4 mg	5 mL
	8	< 9			2.4 mg	7.2 mg	5 mL
	9	< 10			2.8 mg	8.4 mg	5 mL
	10	< 12			3.0 mg	9.0 mg	5 mL
	12	< 30		5 mg		10 mg	5 mL or 10 mL
Tablets or oral suspension	30	< 50	15 mg			15 mg	10 mL
	≥ 50		20 mg			20 mg	10 mL

The weight of a child should be monitored, and the dose reviewed regularly, especially for children weighing below 12 kg. This is to ensure that a therapeutic dose is maintained.

Duration of treatment

Therapy with XARELTO should be continued for at least 3 months in all children, except those aged < 2 years with catheter-related thrombosis. Treatment can be extended up to 12 months when clinically necessary. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

Therapy with XARELTO should be continued for at least 1 month in children aged < 2 years with catheter-related thrombosis. Treatment can be extended up to 3 months when clinically necessary. The benefit-risk of continued therapy after 1 month should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

XARELTO oral suspension or XARELTO 15 mg or 20 mg tablets should be taken with a feeding or with food (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**).

For once daily regimen, XARELTO doses should be taken approximately 24 hours apart.

For twice daily regimen, XARELTO doses should be taken approximately 12 hours apart.

For three times daily regimen, XARELTO doses should be taken approximately 8 hours apart.

Each XARELTO dose should be immediately followed by the intake of one typical serving of liquid. This typical serving may include liquid volume used for feeding. In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be re-administered, and the next dose should be taken as scheduled.

Do not split the XARELTO 15 mg or 20 mg tablet in an attempt to provide a fraction of a tablet dose. For children who are unable to swallow whole 15 mg or 20 mg tablets, XARELTO granules for oral suspension should be used. If the granules for oral suspension are not immediately available, please refer to **DOSAGE AND ADMINISTRATION - Recommended Dose and Dosage Adjustment - *Administration of Crushed Tablets*:**).

XARELTO oral suspension is provided with a 1 mL, 5 mL or a 10 mL blue syringes (oral dosing syringe) with their adapter. To ensure accurate dosing it is recommended to use the blue syringes as follows:

- 1 mL blue syringe (with 0.1 mL graduations) must be used in patients weighing less than 4 kg
- 5 mL blue syringe (with 0.2 mL graduations) may be used in patients weighing 4 kg up to less than 30 kg
- 10 mL blue syringe (with 0.5 mL graduations) should only be used in patients weighing 12 kg or more

For patients weighing 12 kg up to less than 30 kg, either 5 mL or 10 mL blue syringes can be used. Instructions for Use booklet is provided with the XARELTO granules for oral suspension kit. It is recommended that the healthcare professional advises the patient or caregiver which blue syringe to use to ensure that the correct volume is administered.

Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation

The recommended dose is one 20 mg tablet of XARELTO taken once daily with food (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics**, ***Absorption***).

For patients with moderate renal impairment (CrCl 30 – 49 mL/min), the recommended dose is 15 mg once daily with food (see **Renal Impairment** below).

The recommended maximum daily dose is 20 mg.

Prevention of Stroke, Myocardial Infarction, Cardiovascular Death, Acute Limb Ischemia and Mortality in Patients with CAD with or without PAD or prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of major adverse limb events (MALE) or major adverse cardiovascular and cerebrovascular events (MACCE).

The recommended vascular protection regimen for patients with CAD with or without PAD or symptomatic PAD at demonstrated high risk of MALE or MACCE is one tablet of 2.5 mg XARELTO twice daily, one of which in combination with a once daily dose of 75 mg - 100 mg ASA. XARELTO 2.5 mg tablets may be taken with or without food.

Treatment should be continued long term provided the benefit outweighs the risk.

In patients with CAD with or without PAD or symptomatic PAD at demonstrated high risk of MALE or MACCE, XARELTO 2.5 mg twice daily is not indicated in combination with dual antiplatelet therapy.

Administration of Crushed Tablets:

For patients who are unable to swallow whole tablets, XARELTO tablets may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed XARELTO 15 mg or 20 mg tablet, the dose should be immediately followed by food.

A crushed XARELTO tablet may be also administered via nasogastric (NG) tube. After confirming gastric placement of the NG tube, the crushed tablet should be suspended in 50 mL of water and administered via the NG tube after which it should be flushed with water. Because rivaroxaban absorption is dependent on the site of drug release in the GI tract, avoid administration of XARELTO distal to the stomach as this can result in reduced absorption and therefore reduced drug exposure. After the administration of a crushed XARELTO 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding (**ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics, *Absorption***).

An *in vitro* compatibility study indicated that there is no adsorption of rivaroxaban from a water suspension of a crushed XARELTO tablet to PVC or silicone nasogastric (NG) tubing.

No studies were conducted to support the crushing and administration of crushed XARELTO 2.5 mg tablets and crushed ASA tablets together either as a mixture with applesauce or as a mixture administered via NG tube.

Acute myocardial infarction (AMI): Consideration should be given to discontinuing XARELTO in the setting of acute myocardial infarction should the treatment of myocardial infarction involve invasive procedures, such as percutaneous coronary revascularization, or coronary artery bypass surgery. Similar consideration should be given if thrombolytic therapy is to be initiated, because bleeding risk may increase. Patients with acute myocardial infarction should be treated according to current clinical guidelines. In this setting, XARELTO may be resumed, when deemed clinically appropriate, for the prevention of stroke and systemic embolism upon completion of these revascularization procedures.

Concomitant use of ASA or clopidogrel with XARELTO in patients with atrial fibrillation increases the risk of bleeding. Concomitant use of ASA or other antiplatelet agents based on medical need to prevent myocardial infarction should be undertaken with caution. Close clinical surveillance is recommended.

Other situations requiring thrombolytic therapy: XARELTO should be discontinued in situations such as acute ischemic stroke where current clinical practice calls for administering thrombolytic therapy. XARELTO treatment may be subsequently resumed as soon as is deemed clinically appropriate. Measurement of a PT time, in seconds, using the Neoplastin reagent, may inform therapeutic decision-making (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**).

Concomitant use of XARELTO 10 mg, 15 mg and 20 mg with antiplatelet agents: The concomitant use of XARELTO with antiplatelet agents increases the risk of bleeding (see **WARNINGS AND PRECAUTIONS – Bleeding**). If concomitant antiplatelet therapy is contemplated with XARELTO 10 mg, 15 mg, and 20 mg, a careful assessment of the potential risks should be made against potential benefits, weighing risk of increased bleeding against expected benefit.

Patients with nonvalvular atrial fibrillation who undergo PCI with stent placement:
Patients with nonvalvular atrial fibrillation who undergo PCI with stent placement should receive a reduced dose of 15 mg XARELTO once daily (or 10 mg XARELTO once daily for patients with moderate renal impairment [CrCl 30 – 49 mL/min]) in combination with a $P2Y_{12}$ inhibitor (e.g, clopidogrel). This treatment regimen is recommended for a maximum of 12 months after PCI with stent placement (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**, ***Patients with nonvalvular atrial fibrillation who undergo PCI with stent placement***). After completion of the antiplatelet therapy , rivaroxaban dosage should be changed to the standard dose for patients with atrial fibrillation.

Cardioversion:

Patients can be maintained on XARELTO while being cardioverted (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics,** ***Patients undergoing cardioversion***).

Hepatic Impairment

XARELTO is contraindicated in patients with hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and having clinically relevant bleeding risk. Patients with severe hepatic impairment or chronic hepatic disease were excluded from pivotal clinical trials.

The limited clinical data for patients with moderate hepatic impairment indicate a significant increase in the pharmacological activity. XARELTO should be used with caution in these patients (see **CONTRAINDICATIONS** – **WARNINGS AND PRECAUTIONS** – **Hepatic Impairment**, 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.

No clinical data are available in children with hepatic impairment.

Renal Impairment

Table 14 – Dosage and Administration for Adult Patients According to Renal Function

Indication / Creatinine Clearance (CRCL)	Normal >80 mL/min	Mild 50-80 mL/min	Moderate 30-49 mL/min	Severe* 15 - < 30 mL/min	< 15 mL/min
Prevention of VTE After THR or TKR	10 mg od			10 mg od	XARELTO is not recommended
Treatment of VTE and Prevention of Recurrent DVT and PE	15 mg bid for 3 weeks, followed by 20 mg od			15 mg bid for 3 weeks, followed by 20 mg od	
Prevention of recurrent DVT and PE following completion of at least 6 months treatment	10 mg od or 20 mg od			10 mg od or 20 mg od	
Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation	20 mg od		15 mg od	15 mg od	
Prevention of Stroke, CV Death, MI, and Prevention of ALI and Mortality in Patients with CAD with or without PAD or symptomatic PAD at demonstrated high risk of MALE or MACCE	2.5 mg bid + ASA 75 mg - 100 mg od			2.5 mg bid + ASA 75 mg - 100 mg od	

od=once daily, bid=twice daily

*must be used with caution

XARELTO should be used with caution in patients receiving other drugs which increase rivaroxaban plasma concentrations. 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. Renal function should be followed carefully in these patients (see **WARNINGS AND PRECAUTIONS – Renal Impairment** and **DRUG INTERACTIONS – Drug-Drug Interactions**).

In patients with severe renal impairment (CrCl 15 - < 30 mL/min), rivaroxaban plasma levels may be significantly elevated compared to healthy volunteers (1.6-fold on average) which may lead to an increased bleeding risk. Due to limited clinical data, XARELTO must be used with caution in these patients. No clinical data are available for patients with CrCl < 15 mL/min. Use is not recommended in patients with CrCl < 15ml/min. Patients who develop acute renal failure while on XARELTO should discontinue such treatment.

XARELTO 15 mg and 20 mg tablets should be taken with food (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics, *Absorption***).

Renal Impairment (pediatric)

No dose adjustment is required for children 1 year or older with mild renal impairment (glomerular filtration rate: 50 – 80 mL/min/1.73 m^2), based on data in adults and limited data in

pediatric patients (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics - *Renal Insufficiency***).

XARELTO is not recommended in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2), as no clinical data are available (see **WARNINGS AND PRECAUTIONS - Renal Impairment**).

In children younger than 1 year, the renal function should only be determined using serum creatinine. XARELTO is not recommended in children younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available (see **WARNINGS AND PRECAUTIONS - Renal Impairment**).

Table 15 - Reference values of serum creatinine in children younger than 1 year of age (Boer et al, 2010)

Age	97.5th percentile of creatinine (µmol/L)	97.5th percentile of creatinine (mg/dL)
Day 1	81	0.92
Day 2	69	0.78
Day 3	62	0.70
Day 4	58	0.66
Day 5	55	0.62
Day 6	53	0.60
Day 7	51	0.58
Week 2	46	0.52
Week 3	41	0.46
Week 4	37	0.42
Month 2	33	0.37
Month 3	30	0.34
Month 4–6	30	0.34
Month 7–9	30	0.34
Month 10–12	32	0.36

Gender, Race, or Body Weight

No dose adjustment is required for gender or race. (see **ACTION AND CLINICAL PHARMACOLOGY – *Gender*, *Race*, and *Different Weight Categories***)

The pediatric dosage of XARELTO is determined based on body weight (see **DOSAGE AND ADMINISTRATION - *Treatment of VTE and Prevention of VTE Recurrence in Term Neonates, Infants and Toddlers, Children, and Adolescents Aged Less Than 18 Years***).

Geriatrics (>65 years of age)

No dose adjustment is generally required for the elderly. Increasing age may be associated with declining renal function (see **WARNINGS AND PRECAUTIONS –Renal Impairment**, and **DOSAGE AND ADMINISTRATION – Renal Impairment**).

Pediatrics (<18 years of age)

In children less than 18 years of age, the safety and efficacy of XARELTO have not been established for indications other than treatment of venous thromboembolic events (VTE) and

prevention of VTE recurrence. Therefore, XARELTO is not recommended for use in children below 18 years of age for indications other than the treatment of VTE and prevention of VTE recurrence.

The safety and efficacy of XARELTO 2.5 mg and 10 mg film-coated tablets have not been established in children less than 18 years of age; therefore, XARELTO 2.5 mg and 10 mg film-coated tablets are not recommended in this patient population.

Switching from Parenteral Anticoagulants to XARELTO

XARELTO can be started when the infusion of full-dose intravenous heparin is stopped or 0 to 2 hours before the next scheduled injection of full-dose subcutaneous low-molecular-weight heparin (LMWH) or fondaparinux. In patients receiving prophylactic heparin, LMWH or fondaparinux, XARELTO can be started 6 or more hours after the last prophylactic dose.

Switching from XARELTO to Parenteral Anticoagulants

Discontinue XARELTO and give the first dose of parenteral anticoagulant at the time that the next XARELTO dose was scheduled to be taken.

Switching from Vitamin K Antagonists (VKA) to XARELTO

To switch from a VKA to XARELTO, stop the VKA and determine the INR. If the INR is ≤ 2.5, start XARELTO at the usual dose. If the INR is > 2.5, delay the start of XARELTO until the INR is ≤ 2.5 (see ***Considerations for INR Monitoring of VKA Activity during Concomitant XARELTO Therapy***).

Switching from XARELTO to a VKA

As with any short-acting anticoagulant, there is a potential for inadequate anticoagulation when transitioning from XARELTO to a VKA. It is important to maintain an adequate level of anticoagulation when transitioning patients from one anticoagulant to another.

XARELTO should be continued concurrently with the VKA until the INR is ≥ 2.0. For the first 2 days of the conversion period, the VKA can be given in the usual starting doses without INR testing (see ***Considerations for INR Monitoring of VKA Activity during Concomitant XARELTO Therapy***). Children who switch from XARELTO to VKA need to continue XARELTO for 48 hours after the first dose of VKA. Thereafter, while on concomitant therapy, the INR should be tested just prior to the next dose of XARELTO, as appropriate. XARELTO can be discontinued once the INR is > 2.0. Once XARELTO is discontinued, INR testing may be done at least 24 hours after the last dose of XARELTO and should then reliably reflect the anticoagulant effect of the VKA.

Considerations for INR Monitoring of VKA Activity during Concomitant XARELTO Therapy

In general, after starting VKA therapy, the initial anticoagulant effect is not readily apparent for at least 2 days, while the full therapeutic effect is achieved in 5-7 days. Consequently, INR monitoring in the first 2 days after starting a VKA is rarely necessary. Likewise, the INR may remain increased for a number of days after stopping VKA therapy.

Although XARELTO therapy will lead to an elevated INR, depending on the timing of the measurement (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**), the INR is not a valid measure to assess the anticoagulant activity of XARELTO. The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant, including XARELTO.

When switching patients from XARELTO to a VKA, the INR should only be used to assess the anticoagulant effect of the VKA, and not that of XARELTO. Therefore, while patients are concurrently receiving XARELTO and VKA therapy, if the INR is to be tested, it should not be before 24 hours after the previous dose of XARELTO, and should be just prior to the next dose of XARELTO, since at this time the remaining XARELTO concentration in the circulation is too low to have a clinically important effect on the INR. If INR testing is done earlier than just prior to the next dose of XARELTO, the reported INR will not reflect the anticoagulation effect of the VKA only, because XARELTO use may also affect the INR, leading to aberrant readings (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**).

Missed Dose

It is essential to adhere to the dosage schedule provided.

- XARELTO 2.5 mg tablets taken **twice** a day

  If a 2.5 mg twice daily dose is missed the patient should continue with the regular 2.5 mg XARELTO dose as recommended at the next scheduled time.

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

  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 missed tablet.

- XARELTO 15 mg taken **twice** a day:

  If a dose is missed during the 15 mg twice daily treatment phase the patient should take the next dose immediately to ensure the intake of 30 mg total dose per day. In this case two 15 mg tablets may be taken at once. The following day the patient should continue with the regular 15 mg twice daily intake schedule as recommended.

- XARELTO 15 mg or 20 mg tablets taken **once** a day for pediatric patients:

  If rivaroxaban is taken once a day, a missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

- XARELTO oral suspension taken **twice** a day for pediatric patients:

  If rivaroxaban is taken twice a day, a missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken in the same evening.

- XARELTO oral suspension taken **three times** a day for pediatric patients:

  If rivaroxaban is taken three times a day, the three times daily administration schedule with approximately 8-hour intervals should be resumed at the next scheduled dose without compensating for the missed dose.

On the following day, the child should continue with the regular once, twice, or three times daily regimen.

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

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

In adults, rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. There are limited data available in children. No further increase in average plasma exposure is expected due to limited absorption at supratherapeutic doses of 50 mg or above in adults, however, no data are available at supratherapeutic doses in children, because of a solubility ceiling effect.

A specific reversal agent for XARELTO is not available. 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 (see **ACTION AND CLINICAL PHARMACOLOGY** – **Pharmacokinetics**, ***Distribution***).

Management of Bleeding

In the event of hemorrhagic complications in a patient receiving XARELTO, treatment should be temporarily discontinued, and the source of bleeding investigated. XARELTO has a half-life of approximately 5 to 13 hours in adults. The half-life in children estimated using population PK modeling approaches is shorter (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics**). Consideration should be given to the resumption of antithrombotic therapy when clinically appropriate to adequately control risk of underlying thrombosis.

Management of bleeding should be individualised according to the severity and location of the hemorrhage. Appropriate symptomatic treatment should be used as needed, such as mechanical compression (e.g, for severe epistaxis), surgical hemostasis with bleeding control procedures, fluid replacement and hemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anemia or coagulopathy) or platelets.

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

- activated prothrombin complex concentrate (APCC), e.g, FEIBA
- prothrombin complex concentrate (PCC)
- recombinant Factor-VIIa (rFVIIa)

However, there is currently only very limited experience with the use of these products in adults and in children receiving XARELTO.

In a randomized, double-blind, placebo-controlled study, a non-activated prothrombin complex concentrate (PCC) given to 6 healthy male subjects who had previously received XARELTO, completely reversed its anticoagulant effect within 15 minutes, based on coagulation tests. Although this study may have important clinical implications, this effect of PCC has not yet been confirmed in patients with active bleeding who have been previously treated with XARELTO.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of XARELTO. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in adults receiving XARELTO. There is no experience on the use of these agents in children receiving XARELTO. There is neither scientific rationale for benefit or experience with the systemic hemostatic desmopressin in individuals receiving XARELTO.

The prothrombin time (PT), measured in seconds, is influenced by XARELTO in a dose-dependent way with a close correlation to plasma concentrations if the Neoplastin® reagent is used. In patients who are bleeding, measuring the PT (Neoplastin® reagent) may be useful to assist in determining an excess of anticoagulant activity. INR should **NOT** be used to assess the anticoagulant effect of XARELTO (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests** and **ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics**).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

XARELTO (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 (FXa) activity was observed over the complete dose range closely following the pharmacokinetic profiles which provides the 'proof of mechanism' in humans. Inhibition of FXa 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.

  FXa assay tests require calibration and should not be used unless rivaroxaban-specific calibrators and controls are available.

- Prothrombin time (PT), measured in seconds, is influenced by rivaroxaban in a dose-dependent way with a close correlation to plasma concentrations (r = 0.98) if the Neoplastin® reagent is used. Other reagents would provide different results.
  Although XARELTO therapy will lead to an elevated INR, depending on the timing of the measurement, the INR is not a valid measure to assess the anticoagulant activity of XARELTO. The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**).

  In patients who are bleeding, measuring the PT (Neoplastin® reagent) may be useful to assist in determining an excess of anticoagulant activity (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**).

  Figure 1 and Figure 2 below show the relative measured effects of rivaroxaban 20 mg once daily for the PT test using the Neoplastin® reagent (Figure 1) and that expressed by the INR (Figure 2).

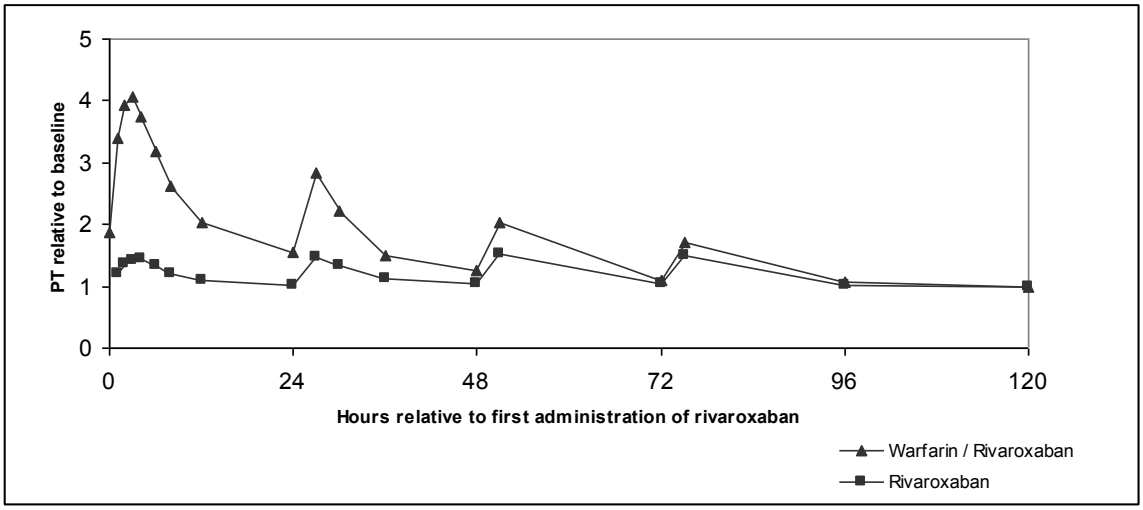


Figure 1: PT Prolongation (Neoplastin® reagent): Relative prolongation expressed as median of ratio to baseline with warfarin / rivaroxaban treatment and rivaroxaban alone, following last day of warfarin (Day -1) and 4 days of 20 mg rivaroxaban od, PD set, n=84

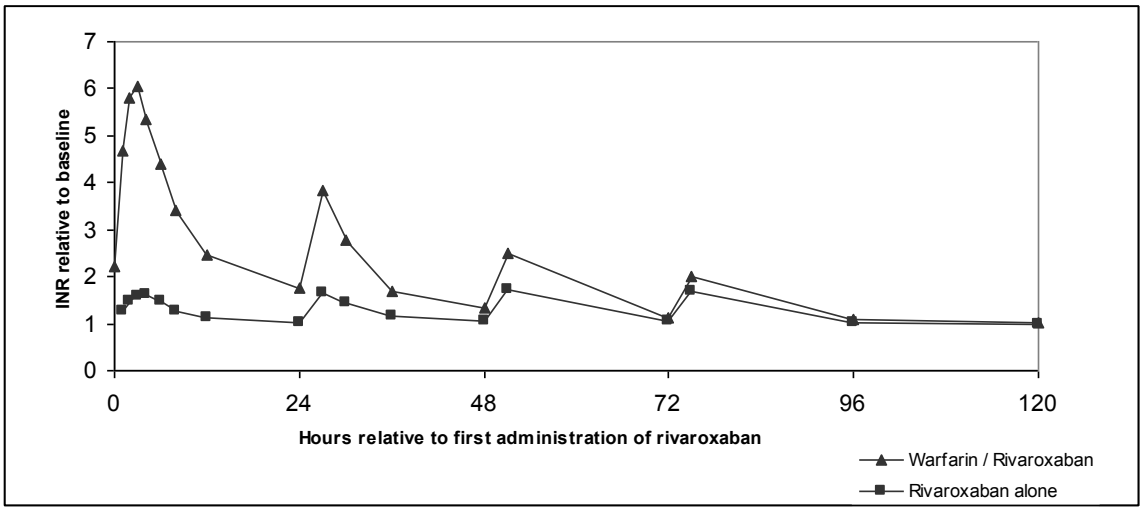


Figure 2: INR prolongation: Relative prolongation expressed as median of ratio to baseline with warfarin/ rivaroxaban treatment and rivaroxaban alone, following last day of warfarin (Day -1) and 4 days of 20 mg rivaroxaban od, PK/PD set, n=84

The usual expected effect of XARELTO on PT when the Neoplastin® reagent is used is shown in Table 16 below. The dose of 2.5 mg XARELTO is expected to only minimally affect PT.

Table 16 – PT (Neoplastin® reagent) by Indication, Following XARELTO Administration

Indication	XARELTO Dosage	Plasma concentration C_{max} (µg/ L)	Plasma concentration C_{trough} (µg/L)	Range of (5/95 percentile) PT (Neoplastin®) C_{max}	Range of (5/95 percentile) PT (Neoplastin®) C_{trough}
Prevention of VTE After THR or TKR	10 mg od	101 (7 – 273)[a]	14 (4 – 51)[c]	13 to 25 seconds[a]	12-17 seconds[c]
Treatment of VTE and Prevention of Recurrent DVT and PE	15 mg bid	---	---	17 to 32 seconds[a]	14–24 seconds[c]
	20 mg od	215 (22– 535)[a]	32 (6–239)[d]	15 to 30 seconds[a]	13–20 seconds[d]
Prevention of Stroke in Patients with Atrial Fibrillation	15 mg od	229 (178 – 313)[b]	57 (18 – 136)[e]	10 to 50 seconds[b]	12–26 seconds[e]
	20 mg od	249 (184 – 343)[b]	44 (12 – 137)[e]	14 to 40 seconds[b]	11–26 seconds[e]

a 2 to 4 hours after drug administration (t_{max})
b 1 to 4 hours after drug administration (t_{max})
c 8 to 16 hours after drug administration (t_{min})
d 18 to 30 hours after drug administration (t_{min})
e 16 to 32 hours after drug administration (t_{min})

- The activated partial thromboplastin time (aPTT) is 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 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.

Pediatric Population

PT (Neoplastin® reagent), aPTT, and anti-factor Xa activity by a calibrated quantitative test) display a close correlation to plasma rivaroxaban concentrations in children. The correlation between anti-factor Xa to plasma concentrations is linear with a slope close to 1. The lower limit of quantifications must be considered when the anti-factor Xa test is used to quantify plasma concentrations of rivaroxaban in children.

QT Prolongation

No QTc prolonging effects were observed in healthy men and women older than 50 years. The treatment difference in QTcF 3 hours post-dose in comparison to placebo as well as QTcF, QTcI and QT analyses at the time of tmax and for post-dose changes in mean and maximum QTcF did not show any dose-related QTcF prolongation at both the 45 mg and the 15 mg dose of rivaroxaban. All changes in LS-means, including their 95% CI, were below 5 milliseconds.

Patients undergoing cardioversion

A prospective, randomized, open-label, multicenter, exploratory study with blinded endpoint evaluation (X-VeRT) was conducted in 1504 patients with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomized 2:1). The rate of stroke occurring within 42 days of cardioversion was low and similar across treatment groups, i.e., rivaroxaban (0.20%) and VKA (0.41%). The rate of major bleeding was also low and similar across treatment groups, i.e., rivaroxaban (0.61%) and VKA (0.80%).

Patients with nonvalvular atrial fibrillation who undergo PCI with stent placement

In a randomized, open label, multicentre study (PIONEER AF-PCI) in patients with nonvalvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease, the 12-month safety of two antithrombotic regimens was compared. One group of 696 patients received rivaroxaban 15 mg o.d. (10 mg o.d. in patients with CrCl 30-49 mL/min) in combination with a P2Y12 inhibitor (e.g, clopidogrel), while a second group of 697 patients received dose-adjusted VKA plus DAPT. Patients with a history of stroke or TIA were excluded from the trial.

The primary safety endpoint, clinically significant bleeding events [a composite of TIMI major bleeding, TIMI minor bleeding and Bleeding Requiring Medical Attention (BRMA)] occurred in 109 patients (15.7%) on the rivaroxaban regimen and in 167 patients (24.0%) on the VKA regimen (HR 0.59; 95% CI 0.47-0.76; $p<0.001$). This difference in bleeding risk was primarily a result of significantly fewer BRMA events in patients on the rivaroxaban regimen. While a consistent treatment effect for all 3 components of the composite was observed, the low number of TIMI major and TIMI minor bleeding events during the trial prevented the demonstration of a significant difference between the two regimens for these endpoints. The secondary endpoint, a composite of CV death, MI or stroke, occurred in 41 patients (5.9%) on rivaroxaban and in 36 patients (5.2%) on VKA; stent thrombosis occurred in 5 patients on rivaroxaban and in 4 patients on VKA. The study was not designed to compare efficacy between the treatment arms, preventing any conclusions regarding efficacy.

Pharmacokinetics

Absorption

The following information is based on the data obtained in adults.

The absolute bioavailability of rivaroxaban is approximately 100% for doses up to10 mg. Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake.

Intake with food does not affect rivaroxaban AUC or C_{max} for doses up to 10 mg. XARELTO 2.5 mg and 10 mg tablets can be taken with or without food. Due to 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.

The bioavailability of rivaroxaban 10 mg, 15 mg and 20 mg tablets under fed conditions, and 2.5 mg and 10 mg tablets under fasted conditions, demonstrated dose-proportionality. XARELTO 15 mg and 20 mg tablets should be taken with food. Bioequivalence was demonstrated for the granules for oral suspension formulation compared to the marketed IR tablet at the 10 mg dose in fasted state as well as for the 20 mg dose in fed state in healthy adult male subjects. (see **DOSAGE AND ADMINISTRATION**, and **DETAILED PHARMACOLOGY - Absorption and Bioavailability**).

Rivaroxaban pharmacokinetic parameters behave in a linear fashion; no evidence of undue accumulation beyond steady-state was seen after multiple doses.

Interindividual variability (CV%) of rivaroxaban pharmacokinetics ranges from 30% to 40%. This may be increased on the day of surgery and on the following day when interindividual variability is 70%.

Table 17 – Summary of PK Parameters After Oral Administration of 10 mg of Rivaroxaban in Humans

	C_{max} [µg/L]	$t_{1/2}$ [h]	AUC [µg*h/L]	Clearance, Urinary Excretion	Volume of Distribution
Healthy (Young) Subjects	~114[a]	5-9	~817	CLsys = ~10 L/h CL_R = 3 – 4 L/h Ae_{ur} = 30% - 40%	V_{ss} = ~50 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

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and C_{max} compared to orally ingested tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of

rivaroxaban distal to the stomach as this can result in reduced absorption and related drug exposure.

In an open-label, randomized, 3-period, 3-treatment crossover comparative bioavailability study conducted in 44 healthy male and female subjects, the bioavailability (AUC_T and C_{max}) of rivaroxaban following a single 20 mg dose as a crushed 20 mg tablet mixed in applesauce and administered orally, or as a crushed 20 mg tablet suspended in water and administered via NG tube was comparable to a whole 20 mg tablet administered orally. Each rivaroxaban treatment was taken with a standardized liquid meal. Given, the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Pediatric population

As in adults, rivaroxaban is readily absorbed after oral administration as IR tablet or granules for oral suspension formulation in children. No PK data following intravenous administration of rivaroxaban to children is available; therefore, the absolute bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food.

Distribution

Plasma protein binding in adults 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.

Pediatric population

In vitro data does not indicate relevant differences in rivaroxaban plasma protein binding in children across different age groups and compared to adults. V_{ss} estimated via population PK modeling in children (age range 0-<18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function. Geometric mean V_{ss} values obtained in the EINSTEIN Junior Phase III study were 93L in children aged 12 to <18 years (median body weight 65 kg), 49L in children aged 6 to <12 years (median body weight 31 kg), 29L in children aged 2-<6 years (median body weight 16 kg) and 14L in children aged birth to <2 years (median body weight 10 kg for 0.5 - <2 years and 4 kg for birth to <0.5 years), respectively.

Metabolism

Rivaroxaban is eliminated by metabolic degradation (approximately 2/3 of the administered dose in adults) as well as by direct renal excretion of unchanged compound (approximately 1/3). Rivaroxaban is metabolized via CYP 3A4, CYP 2J2, and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and ahydrolysis of the amide bonds are the major sites of biotransformation.

Pediatric population

No metabolism data specific to children is available.

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.

CL estimated via population PK modeling in children following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function. Geometric mean CL values obtained in the EINSTEIN Junior Phase III study were 7.3L/h in children aged 12 to <18 years (median body weight 65 kg), 5.0L/h in children aged 6 to <12 years (median body weight 31 kg), 3.4L/h in children aged 2-<6 years (median body weight 16 kg) and 2.7L/h in children aged birth to <2 years (median body weight 10 kg for 0.5 - <2 years and 4 kg for birth to <0.5 years), respectively. The geometric mean values for disposition half-lives ($t_{1/2}$) estimated via population PK modeling decrease with decreasing age and ranged from 4.2h in adolescents to approximately 3h in children aged 2-12 years down to 1.9h and 1.6h in children aged 0.5-<2 years and less than 0.5 years, respectively.

In the EINSTEIN Junior Phase III study, body weight-adjusted dosing in pediatric patients with acute VTE resulted in rivaroxaban exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg once daily. The geometric mean concentrations (95% interval) at sampling time intervals roughly representing maximum and minimum concentrations during the dose interval are summarised in Table 18.

Table 18 – Summary statistics of rivaroxaban steady state plasma concentrations (µg/L) by dosing regimen and age – EINSTEIN Junior Phase III study

Children o.d.	N	12-<18 years	N	6-<12 years				
Day 30 / 2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
Day 90 / 20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
b.i.d	**N**	**6-<12 years**	**N**	**2-<6 years**	**N**	**0.5-<2 years**		
Day 30 / 2.5-4h post	36	145.4 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
Day 90 / 10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c. – n.c.)		
ti.d	**N**	**2-<6 years**	**N**	**Birth-<2 years**	**N**	**0.5-<2 years**	**N**	**Birth - <0.5 years**
Day 30 / 0.5-3h post	5	164.7 (108-283)	25	111.2 (22.9-320)	13	114.3 (22.9-346)	12	108.0 (19.2-320)
Day 30 / 7-8h post	5	33.2 (18.7-99.7)	23	18.7 (10.1-36.5)	12	21.4 (10.5-65.6)	11	16.1 (1.03-33.6)

o.d. = once daily, b.i.d. = twice daily, t.i.d. three times daily, n.c. = not calculated
Values below LLOQ were substituted by 1/2 LLOQ for the calculation of statistics (LLOQ = 0.5 µg/L)
Concentration: geometric mean (5^{th} - 95^{th} percentile)

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 Impairment**, and **DOSAGE AND ADMINISTRATION – *Renal Impairment*)**.

Gender

In adults, there were no clinically relevant differences in pharmacokinetics between male and female patients (see **DETAILED PHARMACOLOGY - *Gender***).

An exploratory analysis did not reveal relevant differences in rivaroxaban exposure between male and female children.

Body Weight

In adults, extremes in body weight (<50 kg vs >120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%) (see **DETAILED PHARMACOLOGY – Body Weight**). In children, XARELTO is dosed based on body weight. An exploratory analysis in children did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure.

Race

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

An exploratory analysis did not reveal relevant interethnic differences in rivaroxaban exposure among Japanese, Chinese or Asian children outside Japan and China compared to the respective overall pediatric population.

Hepatic Insufficiency

No clinical data are available in children with hepatic impairment.

A Phase I study in adults 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 $AUC_{(0\text{-}tn)}$ and 1.2-fold maximal effect (E_{max}). The group difference was statistically significant, both for $AUC_{(0\text{-}tn)}$ ($P < 0.01$) 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 ($AUC_{(0\text{-}tn)}$) and 1.4-fold (E_{max}). A statistically significant group-difference was observed for $AUC_{(0\ tn)}$ ($P < 0.0004$) 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 extrinsic pathway that is comprised of the coagulation Factor-VII, Factor-X, Factor-V, Factor-II, and Factor-I 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 having clinically relevant bleeding risk (see **CONTRAINDICATIONS**, and **WARNINGS AND PRECAUTIONS – Hepatic Impairment**).

Renal Insufficiency

No clinical data are available in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate <50 mL/min/1.73 m2) or in children younger than 1 year with serum creatinine results above 97.5th percentile (see **WARNINGS AND PRECAUTIONS -Renal Impairment**).

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 in adults, 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 ≥ 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 THR or TKR 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.

In Phase II (VTE treatment), rivaroxaban plasma concentrations (AUC) were 1.3- and 1.5-fold in subjects with mild and moderate renal impairment, respectively, compared to subjects with normal renal function. In Phase III subjects (VTE treatment) with mild renal impairment, the peak PT was increased by 1.1-fold, and 1.2-fold for moderate renal impairment compared to subjects with normal renal function.

In patients with atrial fibrillation evaluated in Phase III, the peak PT was increased by 1.2-fold for both mild and moderate renal impairment compared to subjects with normal renal function.

There was no evidence of substantial drug accumulation in patients with mild or moderate renal impairment.

Different Weight Categories

Extremes in body weight (< 50 kg or > 120 kg) of patients taking a 10 mg tablet caused less than a 25% change in the plasma concentration of XARELTO (see **DETAILED PHARMACOLOGY – Body Weight**).

STORAGE AND STABILITY

Store XARELTO film-coated tablets and granules for oral suspension at 15°C to 30°C.

After preparation, the reconstituted XARELTO suspension is stable for 14 days at room temperature (15°C to 30°C) or refrigerated (2°C to 8°C). Do not freeze. If refrigerated, allow the suspension to adjust to room temperature prior to administration. Complete details on preparation and administration of the oral suspension can be found in the Instructions for Use that is provided with the granules for oral suspension kit.

Store in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Excipients (Film-Coated Tablets)

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

Film-coating

Ferric oxide red (10 mg, 15 mg, 20 mg) or ferric oxide yellow (2.5 mg), hypromellose 15 cP, polyethylene glycol, titanium dioxide

2.5 mg Tablets:

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

Each tablet has the Bayer Cross on one side and 2.5 and a triangle on the other side.

XARELTO (rivaroxaban) 2.5 mg tablets are supplied in blisters of 14 (physician sample), and HDPE bottles of 100.

10 mg Tablets:

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 (rivaroxaban) 10 mg tablets are supplied in HDPE bottles of 50.

15 mg Tablets:

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

Each tablet has the Bayer Cross on one side and 15 and a triangle on the other side.

XARELTO tablets 15 mg are supplied in HDPE bottles of 90 and blisters of 7.

20 mg Tablets:

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

Each tablet has the Bayer Cross on one side and 20 and a triangle on the other side.

XARELTO tablets 20 mg are supplied in HDPE bottles of 90 and blisters of 7.

Excipients (1 mg/mL Granules for Oral Suspension):

Granules for oral suspension, white granules.

Citric acid, anhydrous, flavor sweet and creamy, hypromellose 5 cP, mannitol, microcrystalline cellulose and carmellose sodium (syn.: microcrystalline cellulose and carboxymethylcellulose sodium), sodium benzoate, sucralose, xanthan gum

One glass bottle (100 mL) contains 2.625 g white granules, for children weighing < 4 kg, with 51.7 mg of rivaroxaban.

One glass bottle (250 mL) contains 5.25 g white granules, for children weighing ≥ 4 kg, with 103.4 mg of rivaroxaban

Following reconstitution, the oral suspension has a concentration of 1 mg per mL.

To ensure correct dosing, all materials to suspend the granules and administer the resulting oral suspension (syringe, adapter and liquid dosing device) are provided with the medicinal product (except for non-carbonated drinking water).

PART II : SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

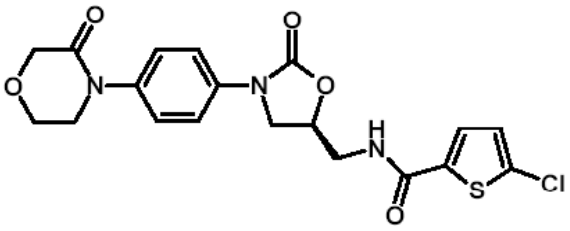
Common Name: Rivaroxaban

Chemical 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: $C_{19}H_{18}ClN_3O_5S$

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)

CLINICAL TRIALS

Prevention of VTE after THR or TKR

The pivotal studies were designed to demonstrate the efficacy of XARELTO (rivaroxaban) for the prevention of venous thromboembolic events , i.e., 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 19. A non-inferiority was adopted with the pre-specification that, if non-inferiority 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 pre-specified 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 19 – Summary of the Pivotal Studies for the Prevention of Venous Thromboembolic Events 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 3029 (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 patients 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; (2) 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 patients 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

The results of the non-inferiority analysis of Total VTE for RECORD 1 and 3 are presented in Table 20. 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 asymptotic two-sided 95% confidence interval was determined. Tests for non-inferiority and superiority were both based on the 95% confidence interval. Non-inferiority was shown if the lower limit of the CI was above the pre-specified non-inferiority margin; -3.5% in RECORD 1 and -4% in RECORD 3.

Table 20 – RECORD 1 (THR) and RECORD 3 (TKR): Non-inferiority 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 od N=1537 n (%)	**Enoxaparin 40 mg od N=1492 n (%)**	**XARELTO 10 mg od N=793 n (%)**	**Enoxaparin 40 mg od 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%; *P* <0.001)		Absolute Risk Reduction[c] 8.7% (5.4% to 12.0%; *P* <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 patients 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 (Non-inferiority was shown if the lower limit of the CI was above the pre-specified non-inferiority 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 od/day (first dose 6 to 8 hours postoperatively) was not inferior to enoxaparin 40 mg/day (first dose 12 to 24 hours preoperatively).

Since non-inferiority was shown, a pre-specified 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 21 and Table 22, respectively.

Table 21 – 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 22 – 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 pre-specified 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 patients treated with XARELTO and 3463 patients treated with enoxaparin in the pivotal studies (RECORD 1 and 3), the results observed for bleeding events have been summarized in Table 23. 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 23 – 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%)	--

Table 23 – 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**
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 (e.g, 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 24 – 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[e]	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 25 – RECORD 2 (THR): 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 (e.g, 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.

Treatment of VTE and prevention of recurrent DVT and PE

The EINSTEIN clinical development program consisted of four Phase III studies. The EINSTEIN DVT and EINSTEIN PE studies evaluated the treatment of VTE and prevention of

recurrent DVT and PE. The EINSTEIN Extension study evaluated the benefit of continued treatment in subjects for whom clinical uncertainty regarding the absolute risk-benefit of extended duration existed.

Patients with VTE who were treated either with rivaroxaban or enoxaparin/VKA for 6 or 12 months in EINSTEIN DVT or EINSTEIN PE, or who were treated for 6 to 14 months with VKA and in whom there was equipoise to continue anticoagulant treatment were eligible for enrollment into EINSTEIN Extension. Subjects considered to have been adequately treated with 6 to 12 months of therapy or those who required more prolonged anticoagulation therapy were not included.

In EINSTEIN CHOICE, patients with confirmed symptomatic VTE who completed 6-12 months of anticoagulant treatment and in whom there was equipoise to continue anticoagulant treatment were eligible for the study. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded.

Table 26 - Summary of the Pivotal Studies for the Treatment of VTE and Prevention of Recurrent DVT and PE

Study	Study Design	Treatment Regimen	Patient Population
EINSTEIN DVT	multicenter, randomized, open-label, event-driven non-inferiority study for efficacy	XARELTO 15 mg bid for 3 weeks followed by 20 mg od 3, 6 or 12 months[a] Standard Therapy Enoxaparin bid bridging to therapeutic VKA 3, 6 or 12 months[a]	Randomized 3449 (1731 XARELTO, 1718 Enox/VKA) Safety Population 3429 (1718 XARELTO, 1711 Enox/VKA) Per Protocol 3096 (1525 XARELTO, 1571 Enox/VKA)
EINSTEIN PE			Randomized 4833, (2420 XARELTO, 2413 Enox/VKA) Safety Population 4817 (2412 XARELTO, 2405 Enox/VKA) Per Protocol 4462 (2224 XARELTO, 2238 Enox/VKA)
EINSTEIN Extension	multicenter, randomized, double-blind, placebo-controlled, event-driven, superiority study for efficacy in subjects with symptomatic proximal DVT or PE	XARELTO 20 mg once daily or placebo for 6 or 12 months[a]	Randomized 1197 (602 XARELTO, 594 placebo)

Table 26 - Summary of the Pivotal Studies for the Treatment of VTE and Prevention of Recurrent DVT and PE

Study	Study Design	Treatment Regimen	Patient Population
EINSTEIN CHOICE	multicenter, randomized, double-blind, double-dummy, active-comparator (ASA), event-driven, superiority study for efficacy in subjects with symptomatic DVT and/or PE	XARELTO 10 mg, or 20 mg or ASA 100 mg once daily[b]	Randomized 3396 (1121 XARELTO 20 mg, 1136 XARELTO 10 mg, 1139 ASA 100 mg)

a Treatment duration as determined by investigator

b Individual (actual) treatment duration depends on the individual randomization date: either 12 months, 9 to <12 months or 6 months

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

bid = twice daily; od = once daily; VKA = vitamin K antagonist; enox = enoxaparin; ASA= acetylsalicylic acid

Duration of administration in EINSTEIN DVT was up to 12 months (i.e., 3, 6 or 12 months) as determined by the investigator, prior to randomization, based on local risk assessment and guidelines. Nearly half of the subjects were treated for 6 to 9 months.

In EINSTEIN DVT, and EINSTEIN PE XARELTO was compared to the standard dual-drug regimen of enoxaparin administered for at least 5 days in combination with VKA until the PT/INR was in therapeutic range (≥ 2.0). VKA alone was then continued, dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

Table 27 – Co-morbid Diseases and Characteristics of Patients in EINSTEIN DVT, EINSTEIN PE and EINSTEIN Extension – ITT Population

	EINSTEIN DVT	EINSTEIN PE	EINSTEIN Extension	EINSTEIN CHOICE
Males (%)	57%	53%	58%	55%
Age, mean (years)	56	58	58	59
Creatinine Clearance (mL/min)				
< 50	7%	8%	7%	5%
50 to < 80	23%	25%	21%	25%
≥ 80	68%	66%	62%	70%
Risk Factors				
Patients with idiopathic DVT/PE	48%	49%	59%	41%
Recent surgery or trauma	19%	17%	4.1%	13%
Immobilization	15%	16%	14%	11%
Previous VTE	19%	19%	16%	18%
Mean TTR, Enox/VKA arm	58%[a]	63%[b]	n/a	n/a
North American subjects	64%	63%	n/a	n/a
Pre-randomization anticoagulation[c]	73%	92%	n/a	n/a
Actual Treatment Duration in XARELTO arm				
≥ 3 months	92%	92%	91%	n/a
≥ 6 months	68%	73%	62%	n/a
≥ 12 months	3%	4%	2%	n/a

a unadjusted Mean TTR. Adjusted Mean TTR is 60%.
b Adjusted mean TTR.
c Pre-randomization anticoagulation was limited to 24 hours in the majority of cases.
n/a=not applicable

Table 28 - Efficacy outcomes in EINSTEIN DVT, EINSTEIN PE and EINSTEIN Extension – ITT population

	EINSTEIN DVT			EINSTEIN PE			EINSTEIN Extension		
	XARELTO N=1731	**Enox/VKA N=1718**	**HR[a] (95% CI) P-value**	**XARELTO N=2419**	**Enox/VKA N=2413**	**HR[a] (95% CI) P-value**	**XARELTO N=602**	**Placebo N=594**	**HR[b] (95% CI) P-value**
Symptomatic Recurrent VTE[b]	36 (2.1%)	51 (3.0%)	0.68 (0.44-1.04) *P*<0.001[a]	50 (2.1%)	44 (1.8%)	1.12 (0.754-1.68) *P*=0.0026[a]	8 (1.3%)	42 (7.1%)	0.18 (0.09-0.39) *P*<0.001
Type of Symptomatic Recurrent VTE									
Fatal PE	1 (<0.1%)	0	-	3 (0.1%)	1	(<0.1%)	0	1 (0.2%)	
Death where PE could not be ruled out	3 (0.2%)	6 (0.3%)	-	8 (0.3%)	6 (0.2%)	-	1 (0.2%)	0	-
Recurrent PE only	20 (1.2%)	18 (1.0%)	-	23 (1.0%)	20 (0.8%)	-	2 (0.3%)	13 (2.2%)	-
Recurrent DVT plus PE	1 (<0.1%)	0	-	0	2 (<0.1%)	-	n.a.	n.a	-
Recurrent DVT only	14 (0.8%)	28 (1.6%)	-	18 (0.7%)	17 (0.7%)	-	5 (0.8%)	31 (5.2%)	-
Symptomatic recurrent VTE and all-cause mortality	69 (4.0%)	87 (5.1%)	0.72 (0.53-0.99) *P* =0.044[c]	97 (4.0%)	82 (3.4%)	1.16 (0.86-1.55) *P* =0.3333[c]	8 (1.3%)	43 (7.2%)	0.18 (0.085-0.38) (P<0.0001)[c]
Net Clinical Benefit	51 (2.9%)	73 (4.2%)	0.67 (0.47-0.95) *P* =0.027[c]	83 (3.4%)	96 (4.0%)	0.85 (0.63-1.14) *P* =0.2752[c]	12 (2.0%)	42 (7.1%)	0.28 (0.15-0.53) *P*<0.0001
All On-Treatment Vascular Events	12 (0.7%)	14 (0.8%)	0.79 (0.36–1.71) *P*=0.55[c]	35 (1.5%)	37 (1.5%)	0.94 0.59-1.49 *P*=0.7780)[c]	3 (0.5)	44 (0.7%)	0.74 (0.17-3.3) *P* =0.69
All-cause Mortality	38 (2.2%)	49 (2.9%)	0.67 (0.44–1.02) (*P*=0.06)[c]	58 (2.4%)	50 (2.1%)	1.13 (0.77-1.65) *P*=0.5260	1 (0.2%)	2 (0.3%)	-

a P-value for non-inferiority (one-sided);
b Some patients had more than one event
c P-value for superiority (two-sided)
n.a.=not assessed

Table 29 - Efficacy outcomes in EINSTEIN CHOICE

	XARELTO 10 mg N=1127	XARELTO 20 mg N=1107	ASA 100 mg N=1137	Rivaroxaban 20 mg vs. ASA 100 mg HR[a] (95% CI) P-value	Rivaroxaban 10 mg vs. ASA 100 mg HR[a] (95% CI) P-value
Symptomatic Recurrent VTE[b]	13 (1.2%)	17 (1.5%)	50 (4.4)	0.34 (0.20-0.59) *P* = 0.0001[c]	0.26 (0.14-0.47) *P* <0.001[c]
Symptomatic recurrent VTE and all-cause mortality	15 (1.3%)	23 (2.1%)	55 (4.9%)	0.42 (0.26-0.68) *P*=0.0005	0.27 (0.15-0.47) *P*<0.0001
Net Clinical Benefit	17 (1.5%)	23 (2.1%)	53 (4.7%)	0.44 (0.27-0.71) *P* = 0.0009[c]	0.32 (0.18-0.55) *P* = <0.0001[c]

a *P*-value for non-inferiority (one-sided);
b Some patients had more than one event
c *P*-value for superiority (two-sided)
FAS =Full Analysis SET

EINSTEIN DVT

EINSTEIN DVT met its principal objective demonstrating that XARELTO was non-inferior to enoxaparin/VKA for the primary outcome of symptomatic recurrent VTE (HR of 0.68 [95% CI = 0.44-1.04], P<0.001) (Table 28 and Figure 3). The results of per-protocol analyses were similar to those of the intention-to-treat analysis. The pre-specified test for superiority was not statistically significant (*P* = 0.0764). The incidence rates for the principal safety outcome (major or clinically relevant non-major bleeding events), as well as the secondary safety outcome (major bleeding events), were similar for both groups (HR of 0.97 [95% CI = 0.76-1.22], *P* = 0.77 and HR of 0.65 [95% CI = 0.33-1.30], *P* = 0.21, respectively). The pre-defined secondary outcome of net clinical benefit, (the composite of the primary efficacy outcome and major bleeding events), was reported with a HR of 0.67 ([95% CI = 0.47-0.95], nominal *P* = 0.03) in favour of XARELTO. The relative efficacy and safety findings were consistent regardless of pre-treatment (none, LMWH, unfractioned heparin or fondaparinux) as well as among the 3, 6 and 12-month durations. In terms of other secondary outcomes, vascular events during study treatment occurred in 12 patients (0.7%) in the XARELTO arm and 14 patients (0.8%) in the enoxaparin/VKA group (HR of 0.79 [95% CI = 0.36-1.71], *P* = 0.55), and total mortality accounted for 38 (2.2%) vs. 49 (2.9%) patients in the XARELTO vs. enoxaparin/VKA arms, respectively, within intended treatment duration (*P* = 0.06).

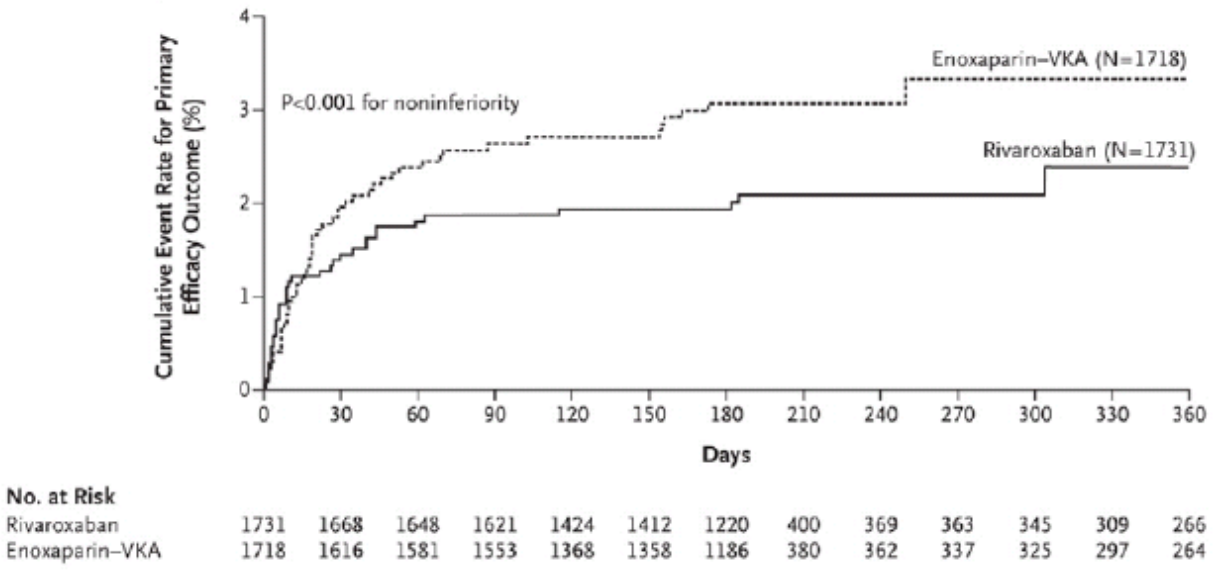
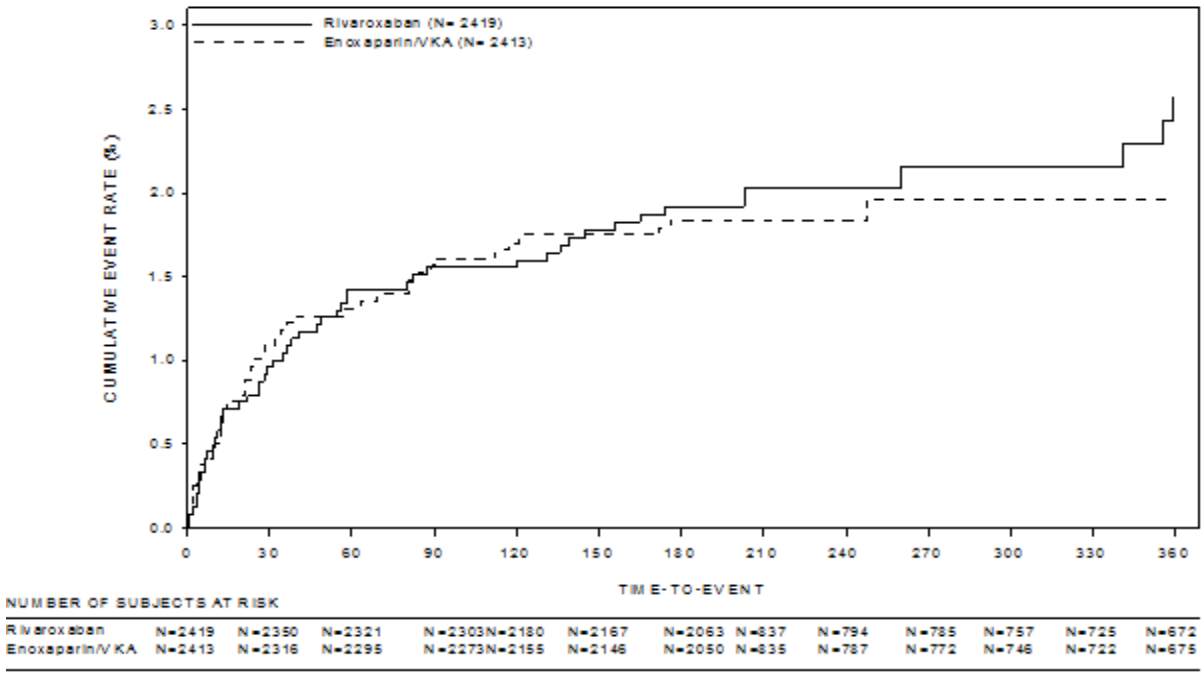


Figure 3: Kaplan-Meier Cumulative Event Rates for the Primary Efficacy Outcome in EINSTEIN-DVT – Intention-to-Treat Population

EINSTEIN PE

EINSTEIN PE met its principal objective demonstrating that XARELTO was non-inferior to enoxaparin/VKA for the primary efficacy outcome of symptomatic recurrent VTE (HR of 1.12 [95% CI: 0.75-1.68], *P=0.0026*) (Table 28 and Figure 4). The results of per-protocol analyses were similar to those of the intention-to-treat analysis. The pre-specified test for superiority was not statistically significant (*P* =0.5737). The incidence rate of the principal safety outcome (major or clinically relevant non-major bleeding events**)** was similar for both groups (HR of 0.90 [95% CI: 0.76 to 1.07] *P=0.2305*). For major bleeding events, the incidence rate was nominally lower in favour of XARELTO treatment group (HR of 0.49 [95% CI: 0.31 – 0.79]*; P*=0.003). The pre-defined secondary outcome of net clinical benefit (the composite of the primary efficacy outcome and major bleeding events) was reported with a HR of 0.85 ([95% CI: 0.63-1.14]; *P*=0.27) in favour of XARELTO. The relative efficacy and safety findings were consistent regardless of pre-treatment (none, LMWH, unfractioned heparin or fondaparinux) as well as among the 3, 6 and 12 month durations. In terms of other secondary outcomes, vascular events during study treatment occurred in 41 patients (1.7%) in the XARELTO arm and 39 patients (1.6%) in the enoxaparin/VKA group (HR of 1.04 [95% CI = 0.67- 1.61], *P* = 0.86), and total mortality accounted for 58 (2.4%) vs. 50 (2.1%) patients in the XARELTO vs. enoxaparin/VKA arms, respectively, within intended treatment duration (*P* = 0.53).

Graphic: Kaplan-Meier Cumulative Rate of the Primary efficacy outcome
Timepoint: Event or censoring up to the intended treatment duration
Population: Intent to treat



NUMBER OF SUBJECTS AT RISK

Rivaroxaban	N=2419	N=2350	N=2321	N=2303	N=2180	N=2167	N=2063	N=837	N=794	N=785	N=757	N=725	N=672
Enoxaparin/VKA	N=2413	N=2316	N=2295	N=2273	N=2155	N=2146	N=2050	N=835	N=787	N=772	N=746	N=722	N=675

Figure 4: Kaplan-Meier analysis: cumulative rate of primary efficacy outcome in study 11702 PE - ITT Population

EINSTEIN Extension

In the EINSTEIN Extension study, XARELTO was superior to placebo for the primary efficacy outcome with a HR of 0.18 [95% CI = 0.09-0.39], *P*<0.001 (i.e, a relative risk reduction of 82%) (Table 28 and Figure 5). For the principal safety outcome (major bleeding events) there was no significant difference between patients treated with XARELTO compared to placebo (*P* = 0.11). The pre-defined secondary outcome of net clinical benefit, defined as the composite of the primary efficacy outcome and major bleeding events, was reported with a HR of 0.28 ([95% CI = 0.15-0.53], *P* < 0.001) in favour of XARELTO. In terms of other secondary outcomes, vascular events occurred in 3 patients in the XARELTO arm and 4 patients in the placebo group (HR of 0.74 [95% CI = 0.17-3.3], *P* = 0.69), and total mortality accounted for 1 (0.2%) vs. 2 (0.3%) of patients in the XARELTO vs. placebo arms, respectively.

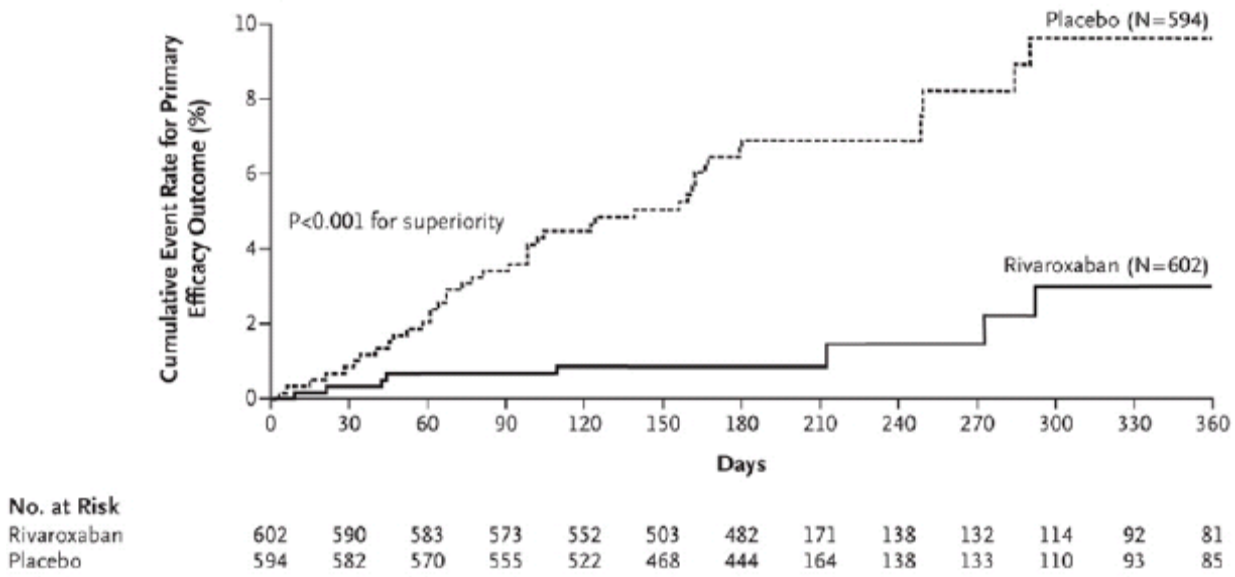


Figure 5: Kaplan-Meier Cumulative Event Rates for the Primary Efficacy Outcome in EINSTEIN Extension

EINSTEIN CHOICE

In EINSTEIN CHOICE 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of therapeutic-dose anticoagulation and who did not have an indication for continued anticoagulation in therapeutic doses, were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT/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. The secondary efficacy outcome was the composite of the primary efficacy outcome, MI, ischemic stroke, or non-CNS systemic embolism.

In the EINSTEIN CHOICE study, the primary efficacy objective for superiority was met for both XARELTO 20 mg and 10 mg versus acetylsalicylic acid 100mg. The secondary efficacy outcome was significantly reduced when comparing XARELTO 20 mg or 10 mg vs. 100 mg acetylsalicylic acid. 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. The secondary safety outcome (non-major bleeding associated with treatment cessation of more than 14 days) was similar when comparing XARELTO 20 mg or 10 mg vs. 100 mg acetylsalicylic acid. Outcomes were consistent across the patients with provoked and unprovoked VTE (see Table 29).

In a prespecified net clinical benefit analysis (NCB) (primary efficacy outcome plus major bleeding events) of EINSTEIN CHOICE , a HR of 0.44 (95% CI 0.27 - 0.71, p = 0.0009) for XARELTO 20 mg once daily vs 100 mg acetylsalicylic acid once daily and a HR of 0.32 (95% CI 0.18 - 0.55, p <0.0001) for XARELTO 10 mg once daily vs 100 mg acetylsalicylic acid once daily were reported.

Kaplan-Meier plot of cumulative rate of the Primary Efficacy Outcome up to the end of individual intended treatment duration (full analysis set)

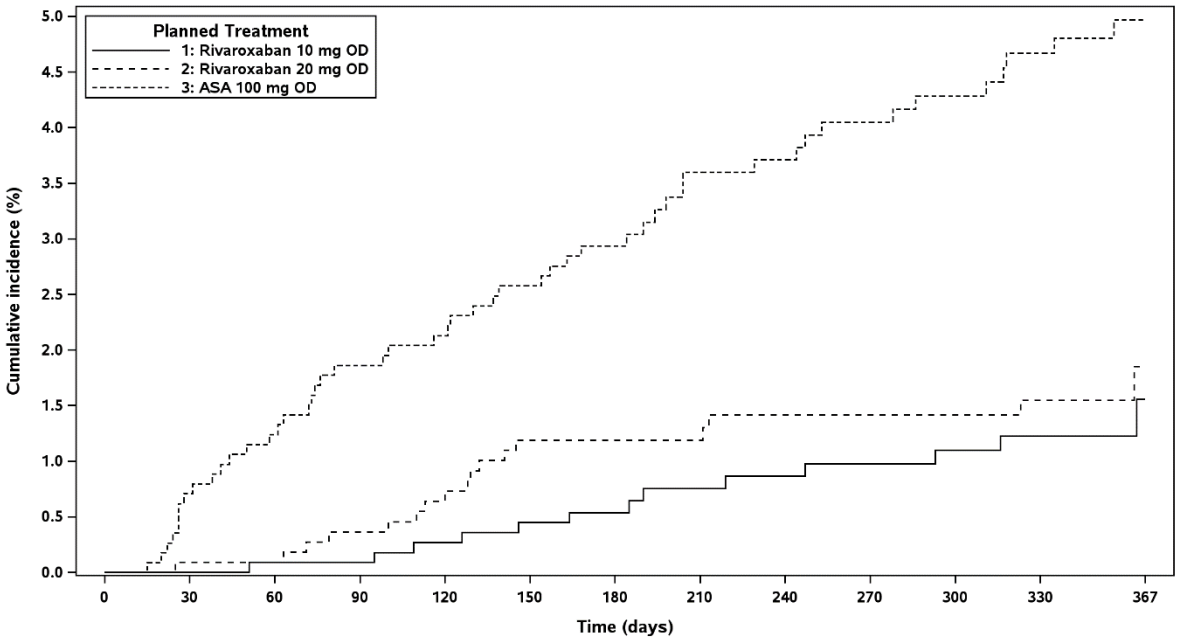


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Figure 6: Kaplan-Meier analysis: cumulative event rates of the primary efficacy outcome until the end of individual intended treatment duration (FAS)

Treatment of VTE and Prevention of VTE Recurrence in Pediatric Patients

A total of 727 children with confirmed acute VTE, of whom 528 received rivaroxaban, were studied in six open-label, multicenter pediatric studies. Body weight-adjusted dosing in patients from birth to <18 years resulted in XARELTO exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg o.d. as confirmed in the EINSTEIN Junior phase III study (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics)

The EINSTEIN Junior Phase III study was a randomized, active-controlled, open-label multicenter clinical study in 500 pediatric patients (aged birth to <18 years) with confirmed acute VTE. There were 276 children aged 12 to < 18 years, 101 children aged 6 to < 12 years, 69 children aged 2 to < 6 years, and 54 children aged < 2 years.

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE), cerebral vein and sinus thrombosis (CVST), or all others including DVT and PE (non-CVC-VTE). The most common presentation of index thrombosis in children aged 12 to < 18 years was non-CVC-VTE (76.4%); in children aged 6 to < 12 years and aged 2 to < 6 years was CVST - (47.5%) and 50.7%, respectively); and in children aged < 2 years was CVC-VTE (68.5%). VTE was provoked by persistent, transient, or both persistent and transient risk factors in 438 (87.6%) children. There were no children < 6 months with CVST in the rivaroxaban group. 22 of the patients with CVST had a central nervous system infection (13 patients in the rivaroxaban group and 9 patients in comparator group).

Patients received initial treatment with therapeutic dosages of UFH, LMWH, or fondaparinux for at least 5 days, and were randomized 2:1 to receive either body weight-adjusted doses of rivaroxaban or comparator group (heparins, VKA) for a main study treatment period of 3 months (1 month for children < 2 years with CVC-VTE). At the end of the main study treatment period, the diagnostic imaging test, which was obtained at baseline, was repeated, if clinically feasible. The study treatment could be stopped at this point, or at the discretion of the Investigator, continued for up to 12 months (for children < 2 years with CVC-VTE up to 3 months) in total.

The primary efficacy outcome was symptomatic recurrent VTE. The principal safety outcome was the composite of major bleeding and clinically relevant non-major bleeding (CRNMB). All key efficacy and safety outcomes were centrally adjudicated by an independent committee blinded for treatment allocation. The key efficacy and safety results are shown in Table 30 and Table 31 below.

At the end of the main treatment period, symptomatic recurrent VTEs occurred in 4 of 335 patients (1.2%) in the XARELTO group and in 5 of 165 patients (3.0%) in the comparator group, hazard ratio (HR) 0.40 (95% CI 0.11 – 1.41). The composite of major bleeding and CRNMB was reported in 10 of 329 patients (3.0%) treated with XARELTO and in 3 of 162 patients (1.9%) in the comparator group with a HR of 1.58 (95% CI 0.51 – 6.27). The prespecified net clinical benefit (symptomatic recurrent VTE plus major bleeding events) was reported in 4 of 335 patients (1.2%) in the XARELTO group and in 7 of 165 patients (4.2%) in the comparator group with a HR of 0.30 (95% CI 0.08 – 0.93). Normalization of the thrombus burden on repeat imaging occurred in 128 of 335 patients (38.2%) with XARELTO treatment and in 43 of 165

patients (26.1%) in the comparator group, with an odds ratio of 1.71 (95% CI 1.124 – 2.59). These findings were generally similar among age groups.

Table 30 - Efficacy results at the end of the main treatment period

Event	XARELTO (N=335*)	Comparator group (N=165*)
Recurrent VTE (primary efficacy outcome)	4 (1.2%)	5 (3.0%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration on repeat imaging	5 (1.5%)	6 (3.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration + no change on repeat imaging	21 (6.3%)	19 (11.5%)
Normalization on repeat imaging	128 (38.2%)	43 (26.1%)
Composite: Symptomatic recurrent VTE + major bleeding (net clinical benefit)	4 (1.2%)	7 (4.2%)
Fatal or non-fatal pulmonary embolism	1 (0.3%)	1 (0.6%)

*FAS= full analysis set, all children who were randomized

Table 31 - Safety results at the end of the main treatment period

	XARELTO (N=329*)	**Comparator group (N=162*)**
Composite: Major bleeding + CRNMB (principal safety outcome)	10 (3.0%)	3 (1.9%)
Major bleeding	0 (0.0%)	2 (1.2%)
Any treatment-emergent bleedings	119 (36.2%)	45 (27.8%)

*SAF= safety analysis set, all children who were randomized and received at least 1 dose of study medication
CRNMB – Clinically Relevant Non-Major Bleeding

The efficacy and safety profile of XARELTO was similar between the pediatric VTE population and the DVT/PE adult population, however, the proportion of subjects with any bleeding was higher in the paediatric VTE population as compared to the DVT/PE adult population.

Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation

Evidence for the effectiveness of XARELTO is derived from the ROCKET AF trial, a prospective, randomized, double-blind, double-dummy, parallel-group, multicenter, pivotal clinical study comparing the efficacy and safety of once daily oral XARELTO with dose-adjusted warfarin in patients with atrial fibrillation at risk of stroke or systemic embolism. In addition to documented atrial fibrillation, patients had prior stroke, TIA or systemic embolism, or 2 or more of the following risk factors without prior stroke:

- clinical heart failure and/or left ventricular ejection fraction ≤35%
- hypertension
- age ≥75 years
- diabetes mellitus

Table 32 – Summary of the ROCKET AF Trial, a Phase III Clinical Trial in Atrial Fibrillation

Study	Study Design	Treatment Regimen	Populations
ROCKET AF	double-blind, double-dummy prospective randomized parallel-group multinational study	**XARELTO** 20 mg od (15 mg od for patients with moderate renal impairment [CrCl 30 – 49 mL/min]) **Warfarin** dose adjusted to an INR of 2.5 (range 2.0 to 3.0)	Randomized 14,264 (7131 XARELTO, 7133 warfarin) Safety Population 14,236 (7111 XARELTO, 7125 warfarin) Per Protocol 14,054 (7008 XARELTO, 7046 warfarin)

Randomized = The randomized / intent-to-treat population represent all uniquely randomized patients.
Safety population = The safety population comprised those patients who received at least 1 dose of study drug.
Per Protocol = The per-protocol population was all intent to-treat patients excluding those who have specific pre-defined major protocol deviations that occur by the time of enrollment into the study or during the trial.
od = once daily

Patients with prosthetic heart valves, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis, were excluded from the ROCKET AF study, and thus were not evaluated. These trial results do not apply to patients these conditions, whether in the presence or absence of atrial fibrillation (see **WARNINGS AND PRECAUTIONS – Cardiovascular, *Patients with valvular disease***).

The primary objective of this study was to demonstrate that XARELTO, a direct Factor-Xa inhibitor, was non-inferior to warfarin in reducing the occurrence of the composite endpoint of stroke and systemic embolism. If non-inferiority was shown, a pre-specified step-wise multiple testing procedure was undertaken to determine whether XARELTO was superior to warfarin in primary and secondary endpoints.

The study design, treatment regimen and patient populations are summarized in Table 33 and Table 34. A total of 14,264 patients were randomized with a mean age of 71 years (range 25 to 97 years) and a mean $CHADS_2$ score of 3.5. Patients were randomized to 20 mg once daily XARELTO (15 mg in patients with moderate renal impairment at screening) or to dose-adjusted warfarin, titrated to an INR of 2.0 to 3.0. ROCKET AF had a mean treatment duration of 572 days of XARELTO given as a fixed dose without routine coagulation monitoring.

ROCKET AF studied patients with significant co-morbidities, e.g, 55% secondary prevention population (prior stroke / TIA / systemic embolism), see Table 33. For patients randomized to warfarin, the time-in-therapeutic range (TTR) of 2.0 to 3.0 was a mean of 55% (cf. 64% in North American patients).

Table 33 – Co-morbid Diseases and Characteristics of Patients in ROCKET AF Trial – ITT Population

Heart failure and/or left ventricular ejection fraction ≤35%	62%
Hypertension	91%
Age ≥ 75 years	44%
Female	40%
Diabetes	40%
Prior Stroke / TIA / Systemic Embolism	55%
Stroke[a]	34%
TIA[a]	22%
Systemic Embolism[a]	4%
Valvular Disease (not meeting exclusion criteria)[b]	14%
Mean $CHADS_2$	3.5
Prior VKA Use	62%
Prior MI	17%

a Some patients may have had more than one event, so sum of individual components do not add up to 55%.
b Patients with prosthetic heart valves, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis were excluded from ROCKET AF. Patient with other valvular disease including aortic stenosis, aortic regurgitation, and/or mitral regurgitation did not meet the exclusion criteria.
ITT Population = 14, 264 patients

At baseline, 36.5% of patients were on chronic ASA, 2.4% on anticoagulants other than VKAs, 8.7% on Class III antiarrhythmics, 54.5% on angiotensin converting enzyme (ACE) inhibitors, 22.7% on angiotensin receptor blockers, 60.0% on diuretics, 24.0% on oral antidiabetics, and 65.5% on beta blockers.

ROCKET AF demonstrated that in patients with atrial fibrillation, XARELTO is non-inferior to warfarin in the primary efficacy endpoint, a composite of prevention of stroke and systemic embolism in the per protocol population, on-treatment analysis (rivaroxaban: 1.71%/year, warfarin 2.16%/year, HR 0.79, 95% CI 0.66-0.96, $P < 0.001$). As non-inferiority was met, XARELTO was tested, as per the pre-specified analysis, for superiority in primary and secondary endpoints. XARELTO demonstrated superiority over warfarin for stroke and systemic embolism in the safety population, on-treatment analysis (HR 0.79, 95% CI 0.65 to 0.95, $P = 0.015$), see Table 34 and Figure 7 below.

Table 34 – ROCKET AF – Time to the First Occurrence of Total Stroke and Systemic Embolism, While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

Parameter	XARELTO (N=7061)		Warfarin (N=7082)		XARELTO vs Warfarin	
	n	%/year	n	%/year	Hazard Ratio (95% CI)	*P*-value for superiority
Total stroke and systemic embolism (Primary Efficacy Outcome)	189	1.70	243	2.15	0.79 (0.65,0.95)	0.015*
Total Stroke	184	1.65	221	1.96	0.85 (0.70,1.03)	0.092
Hemorrhagic Stroke	29	0.26	50	0.44	0.59 (0.37,0.93)	0.024*
Ischemic Stroke	149	1.34	161	1.42	0.94 (0.75,1.17)	0.581
Unknown Stroke Type	7	0.06	11	0.10	0.65 (0.25,1.67)	0.366
Systemic Embolism	5	0.04	22	0.19	0.23 (0.09,0.61)	0.003*
Other Endpoints						
All Cause Death	208	1.87	250	2.21	0.85 (0.70,1.02)	0.073
Vascular Death	170	1.53	193	1.71	0.89 (0.73,1.10)	0.289
Myocardial Infarction	101	0.91	126	1.12	0.81 (0.63,1.06)	0.121

Safety population on-treatment analysis = Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) – Safety Population
Hazard ratio (95% CI) and P-value from Cox proportional hazard model with treatment group as a covariate.
p-value (two-sided) for superiority of XARELTO versus warfarin in hazard ratio
* Statistically significant

While the pre-specified primary analysis for superiority used the on-treatment data set for the safety population, an intention-to treat (ITT) analysis was also conducted. In this analysis, the primary endpoint occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; $P < 0.001$ for non-inferiority; $P = 0.12$ for superiority).

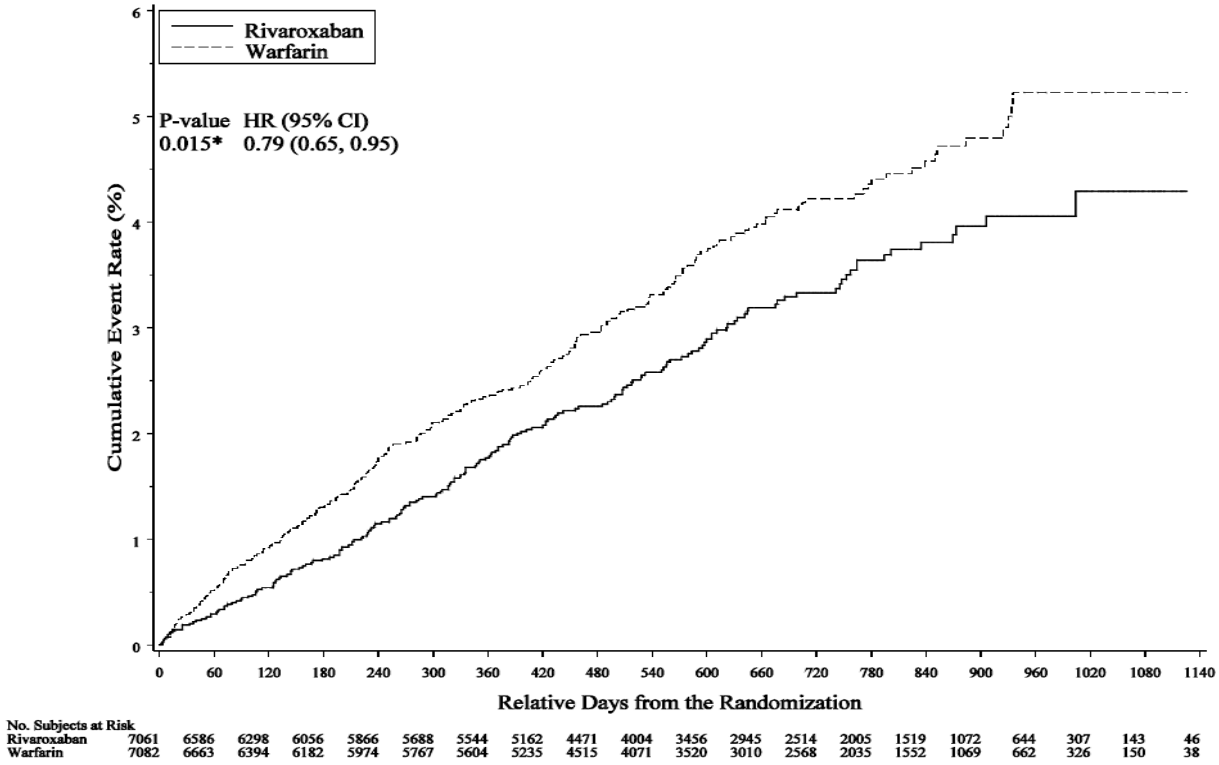


Figure 7: Kaplan-Meier curve of time to first total stroke or systemic embolism in the ROCKET AF trial safety population, on-treatment analysis, includes the 15 mg and 20 mg doses of rivaroxaban

The analysis of the principal safety endpoint demonstrates XARELTO has a similar rate to warfarin for the composite of major and non-major clinically relevant bleeding, see Table 35 below.

Table 35 – ROCKET AF – Time to the First Occurrence of Bleeding Events While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

Parameter	XARELTO (N=7111)		Warfarin (N=7125)		XARELTO vs Warfarin	
	n	%/year	N	%/year	Hazard Ratio (95% CI)	*P*-value
Major and Non-major clinically relevant bleeding event (Principal Safety Endpoint)	1475	14.91	1449	14.52	1.03 (0.96,1.11)	0.442
Major Bleeding	395	3.60	386	3.45	1.04 (0.90,1.20)	0.576
Hemoglobin Drop (2g/dL)	305	2.77	254	2.26	1.22 (1.03,1.44)	0.019*
Transfusion (> 2 units)	183	1.65	149	1.32	1.25 (1.01,1.55)	0.044*
Critical Organ Bleed	91	0.82	133	1.18	0.69 (0.53,0.91)	0.007*
Intracranial Hemorrhage	55	0.49	84	0.74	0.67 (0.47, 0.94)	0.019*
Fatal Bleed	27	0.24	55	0.48	0.50 (0.31,0.79)	0.003*
Non-major Clinically Relevant Bleeding	1185	11.80	1151	11.37	1.04 (0.96,1.13)	0.345

All analysis are based on the time to the first event.
Hemoglobin drop = a fall in hemoglobin of 2 g/dL or more.
Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
Critical organ bleeding are cases where CEC bleeding site=intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal.
Hazard ratio (95% CI) and P-value from Cox proportional hazard model with treatment group as a covariate.
P-value (two-sided) for superiority of XARELTO versus Warfarin in hazard ratio.
* Statistically significant

The incidences of increased liver function tests were low and comparable between the two groups, see Table 36.

Table 36 – ROCKET AF – Incidence of Pre-specified Post-baseline Liver Function Abnormalities – Safety Population

Parameter	XARELTO (N=7111)		Warfarin (N=7125)		XARELTO vs Warfarin
	n/J	%	n/J	%	Hazard Ratio (95% CI)
ALT> 3xULN	203/6979	2.91	203/7008	2.90	1.01 (0.83,1.23)
ALT > 3xULN and TBL > 2xULN	31/6980	0.44	33/7012	0.47	0.95 (0.58,1.55)

ULN = Upper Limit of Normal Range, n = Number of patients with events, N= Number of patients valid for safety population, J = Number of patients with non-missing lab values, TBL: Total Bilirubin
Hazard Ratio (95% CI): time to event analysis using a Cox model with the treatment as the covariate.

The event rates for efficacy and safety outcomes stratified by age groups are presented in Table 37 and Table 38. The event rates for efficacy and safety outcomes stratified by renal function are presented in Table 39 and Table 40.

Table 37 – Efficacy Outcomes by Age Groups in the ROCKET AF Trial, While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

	XARELTO		Warfarin		XARELTO vs Warfarin	
	n/J	Event rate (%/yr)	n/J	Event rate (%/yr)	Hazard Ratio (95% CI)	*P*-value
Total Stroke and Systemic Embolism (Primary Efficacy Outcome)						
All Patients	189/7061	1.70	243/7082	2.15	0.79 (0.65,0.95)	0.015*
< 65 years	43/1642	1.59	42/1636	1.53	1.04 (0.68,1.58)	-
65 to 75 years	77/2767	1.74	98/2768	2.18	0.79 (0.59,1.07)	-
> 75 years	69/2652	1.73	103/2678	2.54	0.68 (0.50,0.92)	-
> 80 years	40/1305	2.17	46/1281	2.39	0.91 (0.60,1.40)	-
≥ 85 years	7/ 321	1.75	9/ 328	1.91	0.92 (0.34,2.47)	-
Total Stroke						
All Patients	184/7061	1.65	221/7082	1.96	0.85 (0.70,1.03)	0.092
< 65 years	42/1642	1.55	36/1636	1.31	1.18 (0.76,1.84)	-
65 to 75 years	75/2767	1.69	90/2768	2.00	0.84 (0.62,1.14)	-
> 75 years	67/2652	1.68	95/2678	2.34	0.72 (0.52,0.98)	-
> 80 years	38/1305	2.06	42/1281	2.18	0.95 (0.61,1.48)	-
Ischemic Stroke						
All Patients	149/7061	1.34	161/7082	1.42	0.94 (0.75,1.17)	0.581
< 65 years	30/1642	1.11	23/1636	0.84	1.32(0.77,2.28)	-
65 to 75 years	68/2767	1.53	66/2768	1.47	1.04 (0.74,1.46)	-
> 75 years	51/2652	1.28	72/2678	1.77	0.72 (0.50,1.03)	-
> 80 years	26/1305	1.41	33/1281	1.71	0.83 (0.50,1.39)	-
Hemorrhagic Stroke						
All Patients	29/7061	0.26	50/7082	0.44	0.59 (0.37,093)	0.024*
< 65 years	9/1642	0.33	12/1636	0.44	0.76 (0.32,1.80)	-
65 to 75 years	4/2767	0.09	19/2768	0.42	0.21 (0.07,0.62)	-
> 75 years	16/2652	0.40	19/2678	0.47	0.86 (0.44,1.67)	-
> 80 years	12/1305	0.65	9/1281	0.47	1.40 (0.59,3.31)	-

Table 37 – Efficacy Outcomes by Age Groups in the ROCKET AF Trial, While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

	XARELTO		Warfarin		XARELTO vs Warfarin	
	n/J	Event rate (%/yr)	n/J	Event rate (%/yr)	Hazard Ratio (95% CI)	*P*-value
Vascular Death						
All Patients	170/7061	1.53	193/7082	1.71	0.89 (0.73,1.10)	0.289
< 65 years	35/1642	1.29	44/1636	1.60	0.81 (0.52,1.26)	-
65 to 75 years	66/2767	1.49	70/2768	1.56	0.95 (0.68,1.33)	-
> 75 years	69/2652	1.73	79/2678	1.94	0.89 (0.64,1.23)	-
> 80 years	34/1305	1.84	35/1281	1.81	1.01 (0.63,1.62)	-
≥ 85 years	15/ 321	3.75	12/ 328	2.54	1.44 (0.67,3.08)	-

Safety population on-treatment analysis = Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) – Safety Population
n=number of patients with events, J=number of patients in each subgroup.
Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
P-value (two-sided) for superiority of XARELTO versus warfarin in hazard ratio
* Statistically significant

Table 38 – Bleeding Endpoints by Age Groups in the ROCKET AF trial, While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

	XARELTO		Warfarin		XARELTO vs. Warfarin	
	n/J	Event rate (%/yr)	n/J	Event rate (%/yr)	Hazard Ratio (95% CI)	*P*-value
Major and Non-major Clinically Relevant Bleeding Event (Principal Safety Endpoint)						
All Patients	1475/7111	14.91	1449/7125	14.52	1.03 (0.96,1.11)	0.442
< 65 years	241/1646	9.73	260/1642	10.41	0.93 (0.78,1.11)	-
65 to 75 years	541/2777	13.59	556/2781	13.95	0.98 (0.87,1.10)	-
> 75 years	693/2688	20.18	633/2702	18.09	1.12(1.00,1.25)	-
> 80 years	362/1320	22.79	313/1298	18.84	1.20 (1.04,1.40)	-
≥85 years	89/ 326	25.46	90/ 335	22.29	1.13 (0.84,1.52)	-
Major Bleeding						
All Patients	395/7111	3.60	386/7125	3.45	1.04 (0.90,1.20)	0.576
< 65 years	59/1646	2.21	59/1642	2.16	1.02 (0.71,1.46)	-
65 to 75 years	133/2777	3.04	148/2781	3.34	0.91 (0.72,1.15)	-
> 75 years	203/2688	5.16	179/2702	4.47	1.15 (0.94,1.41)	-
> 80 years	118/1320	6.50	86/1298	4.50	1.44 (1.09,1.90)	-
≥85 years	28/ 326	7.05	32/ 335	6.91	1.01 (0.61,1.67)	-

Table 38 – Bleeding Endpoints by Age Groups in the ROCKET AF trial, While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

	XARELTO		Warfarin		XARELTO vs. Warfarin	
	n/J	Event rate (%/yr)	n/J	Event rate (%/yr)	Hazard Ratio (95% CI)	*P*-value
Intracranial Hemorrhage						
All Patients	55/7111	0.49	84/7125	0.74	0.67 (0.47,0.93)	0.019*
< 65 years	13/1646	0.48	17/1642	0.62	0.78 (0.38,1.60)	-
65 to 75 years	13/2777	0.29	34/2781	0.75	0.39 (0.20,0.73)	-
> 75 years	29/2688	0.72	33/2702	0.81	0.89 (0.54,1.47)	-
> 80 years	22/1320	1.18	15/1298	0.77	1.54 (0.80,2.96)	-
Fatal Bleeding						
All Patients	27/7111	0.24	55/7125	0.48	0.50 (0.31,0.79)	0.003*
< 65 years	7/1646	0.26	11/1642	0.40	0.65 (0.25,1.66)	-
65 to 75 years	7/2777	0.16	19/2781	0.42	0.37 (0.16,0.89)	-
> 75 years	13/2688	0.32	25/2702	0.61	0.53 (0.27,1.03)	-
> 80 years	10/1320	0.54	12/1298	0.62	0.87 (0.38,2.02)	-
Non-major Clinically Relevant Bleeding						
All Patients	1185/7111	11.80	1151/7125	11.37	1.04 (0.96,1.13)	0.345
< 65 years	191/1646	7.62	210/1642	8.32	0.91 (0.75,1.11)	-
65 to 75 years	444/2777	11.00	445/2781	11.02	1.00 (0.88,1.14)	-
> 75 years	550/2688	15.74	496/2702	13.93	1.13 (1.00,1.28)	-
> 80 years	276/1320	17.06	249/1298	14.74	1.15 (0.97,1.37)	-

Safety population on-treatment analysis = Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) – Safety Population
n=number of patients with events, J=number of patients in each subgroup.
Hazard ratio (95% CI) and P-value from Cox proportional hazard model with treatment group as a covariate.
p-value (two-sided) for superiority of XARELTO versus warfarin in hazard ratio
* Statistically significant

Table 39 – Efficacy Outcomes Stratified by Renal Function at Study Entry in the ROCKET AF Trial, While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

	XARELTO		Warfarin		XARELTO vs Warfarin	
	n/J†	Event rate (%/yr)	n/J†	Event rate (%/yr)	Hazard Ratio (95% CI)	*P*-value
Total Stroke and Systemic Embolism (Primary Efficacy Outcome)						
All Patients	189/7061	1.70	243/7082	2.15	0.79 (0.65,0.95)	0.015*
30 – 49 mL/min	50/1481	2.36	60/1452	2.80	0.84 (0.58,1.22)	-
50 – 80 mL/min	91/3290	1.74	128/3396	2.39	0.73 (0.56,0.96)	-
> 80 mL/min	47/2278	1.25	54/2221	1.43	0.87 (0.59,1.28)	-
Total Stroke						
All Patients	184/7061	1.65	221/7082	1.96	0.85 (0.70,1.03)	0.092
30 – 49 mL/min	49/1481	2.31	52/1452	2.42	0.95 (0.64,1.40)	-
50 – 80 mL/min	88/3290	1.68	120/3396	2.24	0.75 (0.57,0.99)	-
> 80 mL/min	46/2278	1.22	48/2221	1.27	0.95 (0.64,1.43)	-
Ischemic Stroke						
All Patients	149/7061	1.34	161/7082	1.42	0.94 (0.75,1.17)	0.581
30 – 49 mL/min	43/1481	2.03	39/1452	1.82	1.11(0.72,1.72)	-
50 – 80 mL/min	69/3290	1.32	89/3396	1.66	0.80 (0.58,1.09)	-
> 80 mL/min	36/2278	0.95	32/2221	0.85	1.12 (0.70,1.80)	-
Hemorrhagic Stroke						
All Patients	29/7061	0.26	50/7082	0.44	0.59 (0.37,093)	0.024*
30 – 49 mL/min	6/1481	0.28	11/1452	0.51	0.55 (0.20,1.48)	-
50 – 80 mL/min	15/3290	0.29	25/3396	0.47	0.62 (0.33,1.17)	-
> 80 mL/min	8/2278	0.21	14/2221	0.37	0.57 (0.24,1.35)	-
Vascular Death						
All Patients	170/7061	1.53	193/7082	1.71	0.89 (0.73,1.10)	0.289
30 – 49 mL/min	55/1481	2.59	54/1452	2.52	1.02 (0.70,1.49)	-
50 – 80 mL/min	75/3290	1.43	91/3396	1.69	0.85 (0.62,1.15)	-
> 80 mL/min	40/2278	1.06	47/2221	1.24	0.85 (0.56,1.29)	-

Safety population on-treatment analysis = Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

n=number of patients with events, J=number of patients in each subgroup.

†= Patients with CrCl< 30mL/min or missing baseline CrCl are excluded from the rows of CrCl subgroups (30-49 mL/min, 50-80 mL/min, >80 mL/min). The patients are, however, included in the "All Patients" rows.

Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.

P-value (two-sided) for superiority of XARELTO versus warfarin in hazard ratio

* Statistically significant

Table 40 – Bleeding Endpoints Stratified by Renal Function at Study Entry in the ROCKET AF Trial, While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

	XARELTO		Warfarin		XARELTO vs Warfarin	
	n/J[a]	Event rate (%/yr)	n/J[a]	Event rate (%/yr)	Hazard Ratio (95% CI)	p-value
Major and Non-Major Clinically Relevant Bleeding Event (Principal Safety Endpoint)						
All Patients	1475/7111	14.91	1449/7125	14.52	1.03 (0.96,1.11)	0.442
30 – 49 mL/min	336/1498	17.87	341/1472	18.28	0.98 (0.84,1.14)	-
50 – 80 mL/min	725/3313	15.74	719/3410	15.30	1.04 (0.93,1.15)	-
> 80 mL/min	412/2288	12.15	388/2230	11.42	1.06(0.92,1.21)	-
Major Bleeding						
All Patients	395/7111	3.60	386/7125	3.45	1.04 (0.90,1.20)	0.576
30 – 49 mL/min	99/1498	4.72	100/1472	4.72	1.00 (0.76,1.32)	-
50 – 80 mL/min	183/3313	3.54	197/3410	3.72	0.95 (0.78,1.17)	-
> 80 mL/min	112/2288	3.02	89/2230	2.38	1.26 (0.95,1.67)	-
Intracranial Hemorrhage						
All Patients	55/7111	0.49	84/7125	0.74	0.67 (0.47,0.93)	0.019*
30 – 49 mL/min	15/1498	0.70	19/1472	0.88	0.80 (0.41,1.57)	-
50 – 80 mL/min	27/3313	0.51	43/3410	0.80	0.64 (0.40,1.04)	-
> 80 mL/min	13/2288	0.34	22/2230	0.58	0.59 (0.30,1.17)	-
Fatal Bleeding						
All Patients	27/7111	0.24	55/7125	0.48	0.50 (0.31,0.79)	0.003*
30 – 49 mL/min	6/1498	0.28	16/1472	0.74	0.38 (0.15,0.97)	-
50 – 80 mL/min	14/3313	0.27	24/3410	0.45	0.60 (0.31,1.16)	-
> 80 mL/min	7/2288	0.19	15/2230	0.40	0.46 (0.19,1.14)	-
Non-major Clinically Relevant Bleeding						
All Patients	1185/7111	11.80	1151/7125	11.37	1.04 (0.96,1.13)	0.345
30 – 49 mL/min	261/1498	13.67	259/1472	13.61	1.01 (0.85,1.19)	-
50 – 80 mL/min	596/3313	12.77	570/3410	11.94	1.08 (0.96,1.21)	-
> 80 mL/min	327/2288	9.48	321/2230	9.36	1.01 (0.86,1.18)	-

Safety population on-treatment analysis = Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

n=number of patients with events, J=number of patients in each subgroup

a= Patients with CrCl< 30 mL/min or missing baseline CrCl are excluded from the rows of CrCl subgroups (30-49 mL/min, 50-80 mL/min, >80 mL/min). The patients are, however, included in the "All Patients" rows.

Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.

P-value (two-sided) for superiority of XARELTO versus warfarin in hazard ratio

* Statistically significant

Prevention of Stroke, Myocardial Infarction, Cardiovascular Death and Prevention of Acute Limb Ischemia and Mortality in Adult Patients with CAD with or without PAD or prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of MALE or MACCE

The COMPASS study was designed to demonstrate the efficacy and safety of XARELTO 2.5 mg bid in combination with 100 mg ASA or XARELTO 5 mg bid monotherapy, for the prevention of stroke, myocardial infarction (MI) or cardiovascular (CV) death in patients with stable atherosclerotic vascular disease. In the pivotal, double-blind Phase III study 27,395 unique subjects were randomly assigned to antithrombotic study drug. In 2 arms, 18,278 subjects were randomly assigned, in a 1:1 fashion, to XARELTO 2.5 mg bid in combination with ASA 100 mg od, or to ASA 100 mg od (a third study arm with 9,117 participants testing XARELTO 5 mg bid as monotherapy did not show a statistically significant difference in the reduction of stroke, MI or CV death compared to ASA 100 mg od).

Patients with established CAD, PAD or a combination of CAD and PAD were eligible. Patients with CAD who were younger than 65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional cardiovascular risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [eGFR] < 60 ml per minute, heart failure, or non-lacunar ischemic stroke ≥1 month earlier). Certain patients were excluded, such as those patients in need of dual antiplatelet therapy, other non-ASA antiplatelet, or oral anticoagulant therapies, as well as patients with a history of ischemic, non-lacunar stroke within 1 month, any history of hemorrhagic or lacunar stroke, or patients with eGFR < 15 ml/min.

COMPASS was stopped prematurely for superiority of the XARELTO 2.5 mg bid + ASA 100 mg od treatment combination after a mean study drug exposure of 668 days (22 months, 1.83 years).

The mean duration of follow-up was 23 months and the maximum follow-up was 3.9 years. The mean age was 68 years and 21% of the subject population were ≥75 years. Of the patients included, 91% had CAD, 27% had PAD, and 18% had both CAD and PAD. Of the patients with CAD, 69% had prior MI, 60% had prior percutaneous transluminal coronary angioplasty (PTCA)/atherectomy/percutaneous coronary intervention (PCI), and 26% had a history of coronary artery bypass grafting (CABG) prior to study. Of the patients with PAD, 49% had intermittent claudication, 27% had peripheral artery bypass surgery or peripheral percutaneous transluminal angioplasty (PTA), 26% had asymptomatic carotid artery stenosis >50%, and 5% had limb or foot amputation for arterial vascular disease.

Study Results

Relative to ASA 100 mg od, XARELTO 2.5 mg bid in combination with ASA 100 mg od was superior in the reduction of the primary composite outcome of stroke, MI or CV death (hazard ratio [HR] 0.76; 95% CI 0.66;0.86; p = 0.00004). The benefit was observed early with a sustained treatment effect over the entire treatment period (see Table 41 and Figure 8). The composite secondary outcomes (composites of coronary heart disease death, or CV death, with MI, ischemic stroke, and acute limb ischemia (ALI)) as well as all-cause mortality were reduced (see Table 41). Acute limb ischemic events were reduced (HR 0.55; 95% CI 0.32-0.92). There was a numerically lower number of amputations (HR 0.64; 95% CI 0.40-1.00). Sixty-five fewer

subjects died with the combination of XARELTO 2.5 mg bid plus ASA 100 mg od vs. ASA 100 mg od alone (HR 0.82; 95% CI 0.71-0.96; p = 0.01062).

There was a significant increase of the primary safety outcome (modified International Society on Thrombosis and Haemostasis [mISTH] major bleeding events) in patients treated with XARELTO 2.5 mg twice daily in combination with ASA 100 mg once daily compared to patients who received ASA 100 mg (see Table 6). However, the incidence rates for fatal bleeding events, non-fatal symptomatic bleeding into a critical organ as well as intracranial bleeding events did not differ significantly. The prespecified composite outcome for net clinical benefit (CV death, MI, stroke, fatal or symptomatic critical-organ bleeding events) was reduced (see Table 42). The results in patients with CAD with or without PAD or symptomatic PAD at demonstrated high risk of MALE or MACCE were consistent with the overall efficacy and safety results (see Table 42).

In the 3.8% of patients with a history of ischemic, non-lacunar stroke (median time since stroke: 5 years), the reduction of stroke, MI, CV death, and the increase of major bleeding (net clinical benefit HR 0.64; 95% CI 0.4-1.0) were consistent with the overall population (see **WARNINGS AND PRECAUTIONS - Bleeding**).

Table 41 - Efficacy results from the Phase III COMPASS Study

	Overall Study Population[a]		
Treatment and Dosage	**XARELTO 2.5 mg bid plus ASA 100 mg od, N=9152 n (%)**	**ASA 100 mg od N=9126 n (%)**	**Hazard Ratio (95 % CI) p-value[b]**
Primary efficacy outcome: Composite of stroke, MI, CV death	379 (4.1%)	496 (5.4%)	0.76 (0.66;0.86) p = 0.00004[#]
- Stroke*	83 (0.9%)	142 (1.6%)	0.58 (0.44;0.76) p = 0.00006
- MI	178 (1.9%)	205 (2.2%)	0.86 (0.70;1.05) p = 0.14458
- CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64;0.96) p = 0.02053
Secondary efficacy outcomes: Coronary heart disease death, MI, ischemic stroke, acute limb ischemia	329 (3.6%)	450 (4.9%)	0.72 (0.63;0.83) p = 0.00001
- Coronary heart disease death**	86 (0.9%)	117 (1.3%)	0.73 (0.55;0.96) p = 0.02611
- Ischemic stroke	64 (0.7%)	125 (1.4%)	0.51 (0.38;0.69) p = 0.00001
- Acute limb ischemia***	22 (0.2%)	40 (0.4%)	0.55 (0.32;0.92) p = 0.02093

Table 41 - Efficacy results from the Phase III COMPASS Study

	Overall Study Population[a]		
Treatment and Dosage	**XARELTO 2.5 mg bid plus ASA 100 mg od, N=9152 n (%)**	**ASA 100 mg od N=9126 n (%)**	**Hazard Ratio (95 % CI) p-value[b]**
CV death, MI, ischemic stroke, acute limb ischemia	389 (4.3%)	516 (5.7%)	0.74 (0.65;0.85) p = 0.00001
All-cause mortality	313 (3.4%)	378 (4.1%)	0.82 (0.71;0.96) p = 0.01062
Net Clinical Benefit: CV death, MI, stroke, fatal or symptomatic critical-organ bleeding events	431 (4.7%)	534 (5.9%)	0.80 (0.70;0.91) p=0.00052

[a] Intention-to-treat analysis set, primary analyses.
[b] XARELTO 2.5 mg plus ASA 100 mg vs. ASA 100 mg; Log-Rank p-value.
[#] The reduction in the primary efficacy outcome was statistically superior.
* Stroke: includes ischemic stroke, hemorrhagic stroke, and uncertain or unknown stroke
**CHD: coronary heart disease death is defined as death due to acute MI, sudden cardiac death, or CV procedure.
*** Acute limb ischemia is defined as limb-threatening ischemia leading to an acute vascular intervention (i.e., pharmacologic, peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation).
bid: twice daily; od: once daily; CI: confidence interval; MI: myocardial infarction; CV: cardiovascular

Table 42 - Efficacy and safety results from Phase III COMPASS Study - Subgroup analysis[a]

Treatment Dosage	**XARELTO 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (%)**	**ASA 100 mg od N=9126 n (%)**	**Hazard Ratio (95 % CI) p-value[b]**
Patients with CAD*	**N=8313**	**N=8261**	
Primary efficacy outcome: Composite of stroke, MI, or CV death	347 (4.2%)	460 (5.6%)	0.74 (0.65;0.86) p = 0.00003
Primary safety outcome: Modified ISTH major bleeding	263 (3.2%)	158 (1.9%)	1.66 (1.37;2.03) p < 0.00001
Net clinical benefit:** Stroke, MI, CV death, fatal or symptomatic critical organ bleeding	392 (4.7%)	494 (6.0%)	0.78 (0.69;0.90) p = 0.00032

Table 42 - Efficacy and safety results from Phase III COMPASS Study - Subgroup analysis[a]

Treatment Dosage	**XARELTO 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (%)**	**ASA 100 mg od N=9126 n (%)**	**Hazard Ratio (95 % CI) p-value[b]**
CAD patients with PAD	**N=1656**	**N=1641**	
Primary efficacy outcome: Composite of stroke, MI, or CV death	94 (5.7%)	138 (8.4%)	0.67 (0.52;0.87) p = 0.00262
Primary safety outcome: Modified ISTH major bleeding	52 (3.1%)	36 (2.2%)	1.43 (0.93;2.19) p = 0.09819
Net clinical benefit:** Stroke, MI, CV death, fatal or symptomatic critical organ bleeding	101 (6.1%)	145 (8.8%)	0.68 (0.53;0.88) p = 0.00327
CAD patients without PAD	**N=6657**	**N=6620**	
Primary efficacy outcome: Composite of stroke, MI, or CV death	253 (3.8%)	322 (4.9%)	0.77 (0.66;0.91) P = 0.00232
Primary safety outcome: Modified ISTH major bleeding	211 (3.2%)	122 (1.8%)	1.73 (1.38;2.16) P = 0.00000
Net clinical benefit:** Stroke, MI, CV death, fatal or symptomatic critical organ bleeding	291 (4.4%)	349 (5.3%)	0.82 (0.71;0.96) P = 0.01436
Patients with symptomatic PAD*	**N=2492**	**N=2504**	
Primary efficacy outcomes: Composite of stroke, MI or CV death	126 (5.1%)	174 (6.9%)	0.72 (0.57;0.90) p = 0.00466
Primary safety outcome: Modified ISTH major bleeding	77 (3.1%)	48 (1.9%)	1.61 (1.12;2.31) p = 0.00890
Net clinical benefit: Stroke, MI, CV death, fatal or symptomatic critical organ bleeding**	140 (5.6%)	185 (7.4%)	0.75 (0.60;0.94) p = 0.01072
PAD patients without CAD	**N=836**	**N=863**	
Primary efficacy outcomes: Composite of stroke, MI or CV death	32 (3.8%)	36 (4.2%)	0.89 (0.55;1.44) p = 0.63869
Primary safety outcome: Modified ISTH major bleeding	25 (3.0%)	12 (1.4%)	2.19 (1.10;4.36) p = 0.02225
Net clinical benefit: Stroke, MI, CV death, fatal or symptomatic critical organ bleeding**	39 (4.7%)	40 (4.6%)	0.99 (0.64;1.54) p = 0.96349

Table 42 - Efficacy and safety results from Phase III COMPASS Study - Subgroup analysis[a]

Treatment Dosage	XARELTO 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (%)	ASA 100 mg od N=9126 n (%)	Hazard Ratio (95 % CI) p-value[b]

[a] Intention-to-treat analysis set, primary analyses.

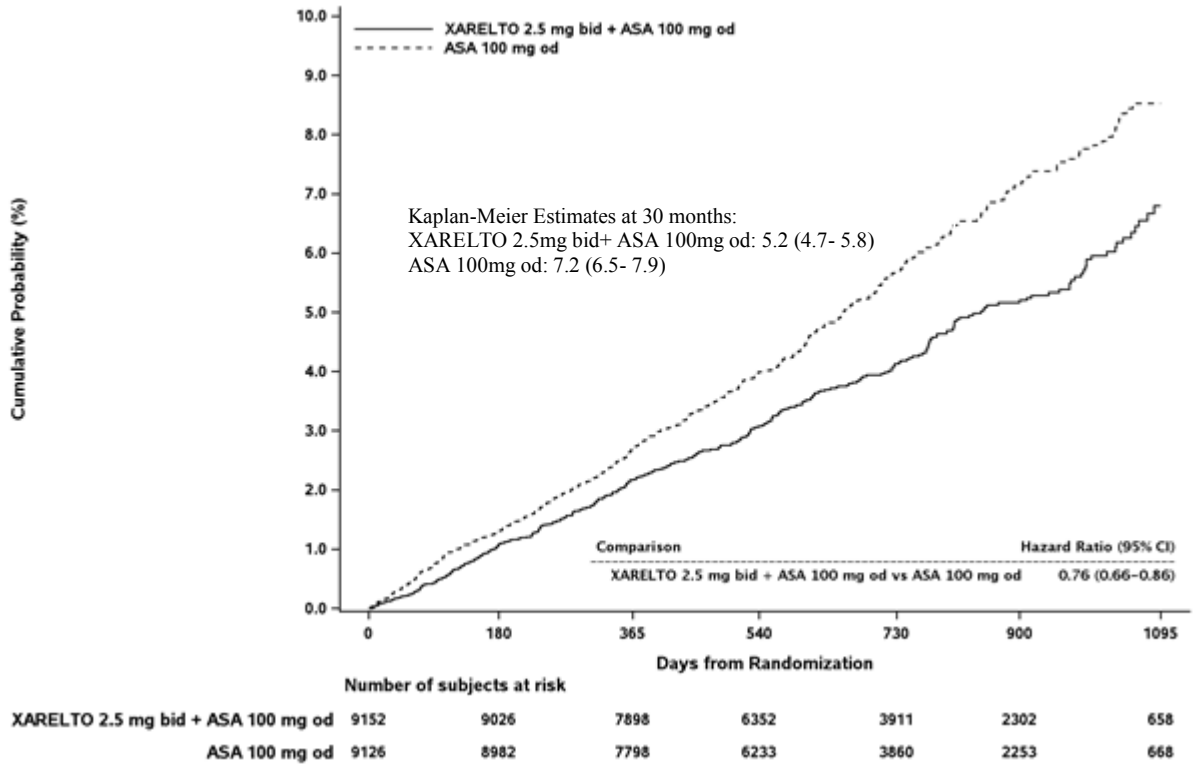
[b] XARELTO 2.5 mg bid plus ASA 100 mg od vs. ASA 100 mg od; Log-Rank p-value.

* **NOTE**: The PAD and CAD subpopulations in the COMPASS trial, and hence in this analysis partly overlap each other. 65.7% of the patients in the PAD subgroup were also diagnosed with CAD; 19.8% of the patients in the CAD subgroup were also diagnosed with PAD.

** Net Clinical Benefit combines the primary composite efficacy endpoint of the COMPASS trial (stroke, MI, CV death) and only the most severe components of the primary safety endpoint: life threatening ISTH bleeding (bleeding death and symptomatic bleeding into a critical organ or site). Bleeding into a surgical site requiring reoperation, or bleeding leading to hospitalization are not part of the Clinical Benefit estimate.

modified ISTH = Modified International Society of Thrombosis and Hemostasis (ISTH) major bleeding is defined as fatal bleeding, symptomatic bleeding into critical area or organ, bleeding into surgical site requiring reoperation or bleeding leading to hospitalization.

bid: twice daily; od: once daily; CI: confidence interval; MI: myocardial infarction, CV: cardiovascular



bid: twice daily; od: once daily; CI: confidence interval

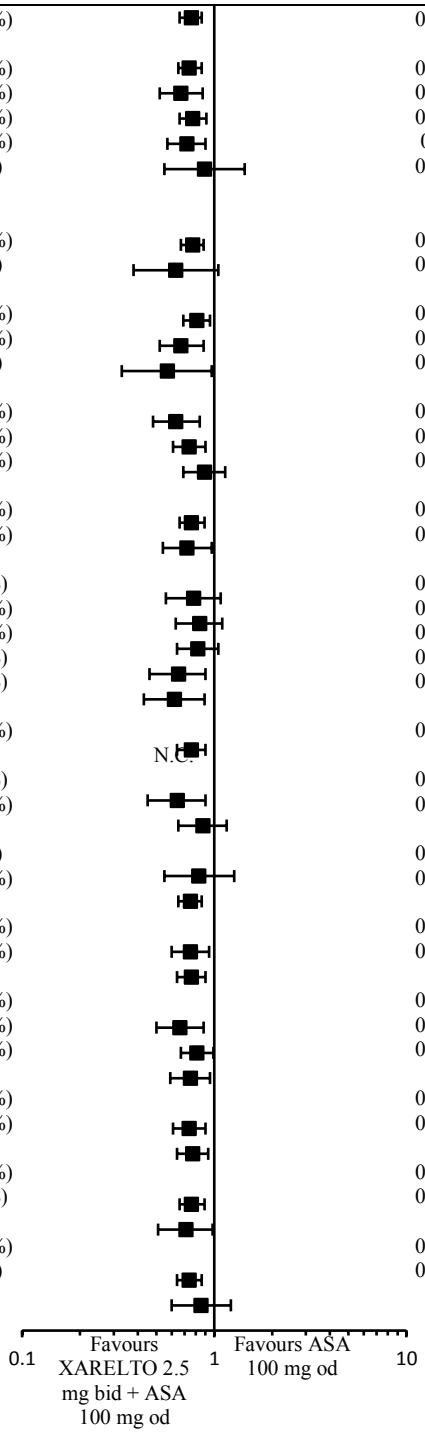
Figure 8: Time to First Occurrence of Primary Efficacy Outcome (Stroke, Myocardial Infarction, Cardiovascular death) in COMPASS

Analysis of Patient Subgroups

The incidences and treatment effect of XARELTO 2.5 mg bid in combination with ASA 100 mg od for the primary efficacy and safety outcome across major subgroups are presented in **Error! Reference source not found.**Table 42 and Table 43 below. The treatment effect was similar with no significant p-value for interaction across major subgroups.

Table 43 - Summary of the Results for the Primary Efficacy Outcome According to Patient Subgroup in the Phase III COMPASS Study

Characteristic	XARELTO 2.5 mg bid + ASA 100 mg od	ASA 100 mg od	HR (95% CI)
	No. of subjects/total no. (%)		
Overall	379/9152 (4.14%)	496/9126 (5.44%)	0.76 (0.66-0.86)
CAD	347/8313 (4.17%)	460/8261 (5.57%)	0.74 (0.65-0.86)
CAD with PAD	94/1656 (5.68%)	138/1641 (8.41%)	0.67 (0.52-0.87)
CAD without PAD	253/6657 (3.80%)	322/6620 (4.86%)	0.77 (0.66-0.91)
Symptomatic PAD	126/2492 (5.06%)	174/2504 (6.95%)	0.72 (0.57-0.9)
PAD without CAD	32/836 (3.83%)	36/863 (4.17%)	0.89 (0.55-1.44)
Asymp. Carotid Artery Stenosis >50%			
No	355/8535 (4.16%)	455/8446 (5.39%)	0.77 (0.67-0.88)
Yes	24/617 (3.89%)	41/680 (6.03%)	0.63 (0.38-1.05)
Polyvascular Disease			
1 Vascular Bed	265/7078 (3.74%)	322/7039 (4.57%)	0.81 (0.69-0.95)
2 Vascular Beds	93/1613 (5.77%)	135/1589 (8.50%)	0.67 (0.52-0.88)
3 Vascular Beds	21/456 (4.58%)	39/497 (7.85%)	0.57 (0.33-0.97)
Age			
<65	79/2150 (3.67%)	126/2184 (5.77%)	0.63 (0.48-0.84)
65-74	179/5087 (3.53%)	238/5045 (4.72%)	0.74 (0.61-0.90)
≥75	121/1924 (6.29%)	132/1897 (6.96%)	0.89 (0.69-1.14)
Sex			
Male	300/7093 (4.23%)	393/7137 (5.51%)	0.76 (0.66-0.89)
Female	79/2059 (3.84%)	103/1989 (5.18%)	0.72 (0.54-0.97)
Region			
North America	63/1304 (4.83%)	80/1309 (6.11%)	0.78 (0.56-1.08)
South America	93/2054 (4.53%)	111/2054 (5.40%)	0.84 (0.63-1.10)
Western Europe*	117/2855 (4.10%)	141/2855 (4.94%)	0.82 (0.64-1.05)
Eastern Europe	59/1607 (3.67%)	90/1604 (5.61%)	0.65 (0.46-0.90)
Asia Pacific	47/1332 (3.53%)	74/1304 (5.67%)	0.62 (0.43-0.89)
Race			
White	235/5673 (4.14%)	306/5682 (5.39%)	0.76 (0.64-0.90)
Black	2/76 (2.63%)	8/92 (8.7%)	N.C.
Asian	54/1451 (3.72%)	81/1397 (5.80%)	0.64 (0.45-0.90)
Other	88/1952 (4.51%)	101/1955 (5.17%)	0.87 (0.65-1.16)
Weight			
≤60kg	41/901 (4.55%)	45/836 (5.38%)	0.83 (0.55-1.27)
>60kg	335/8241 (4.07%)	448/8285 (5.41%)	0.75 (0.65-0.86)
eGFR			
<60mL/min	132/2054 (6.43%)	177/2114 (8.37%)	0.75 (0.60-0.94)
≥60mL/min	247/7094 (3.48%)	319/7012 (4.55%)	0.76 (0.64-0.90)
Tobacco Use History			
Current	80/1944 (4.12%)	122/1972 (6.19%)	0.66 (0.50-0.88)
Former	186/4286 (4.34%)	224/4251 (5.27%)	0.81 (0.67-0.99)
Never	113/2922 (3.87%)	150/2903 (5.17%)	0.75 (0.59-0.95)
Diabetes			
Yes	179/3448 (5.19%)	239/3474 (6.88%)	0.74 (0.61-0.90)
No	200/5704 (3.51%)	257/5652 (4.55%)	0.77 (0.64-0.93)
Hypertension History			
Yes	317/6907 (4.59%)	409/6877 (5.95%)	0.76 (0.66-0.89)
No	62/2245 (2.76%)	87/2249 (3.87%)	0.71 (0.51-0.98)
Lipid Lowering Agent			
Yes	325/8239 (3.94%)	428/8158 (5.25%)	0.74 (0.64-0.86)
No	54/913 (5.91%)	68/968 (7.02%)	0.85 (0.60-1.22)

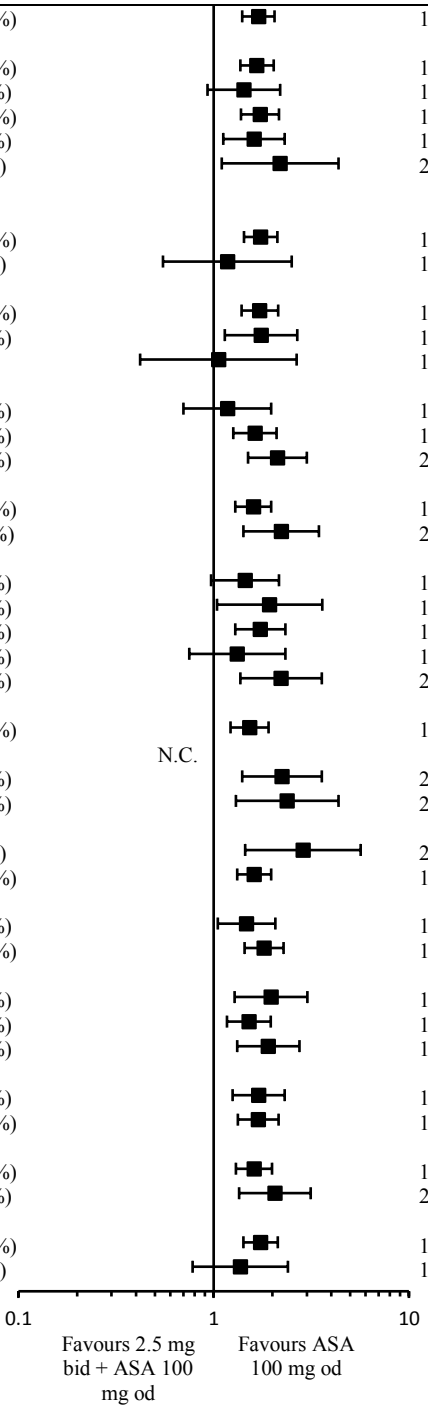


N.C. – Not calculated as minimum number of outcomes were not reached.

*Western Europe also includes AUS/ISR/ZAF.

Table 44 - mISTH Major Bleeding Results According to Patient Subgroup in the Phase III COMPASS Study

Characteristic	XARELTO 2.5 mg bid + ASA 100 mg od	ASA 100 mg od	HR (95% CI)
	No. of subjects/total no. (%)		
Overall	288/9152 (3.15%)	170/9126 (1.86%)	1.70 (1.40-2.05)
CAD	263/8313 (3.16%)	158/8261 (1.91%)	1.66 (1.37-2.03)
CAD with PAD	52/1656 (3.14%)	36/1641 (2.19%)	1.43 (0.93-2.19)
CAD without PAD	211/6657 (3.17%)	122/6620 (1.84%)	1.73 (1.38-2.16)
Symptomatic PAD	77/2492 (3.09%)	48/2504 (1.92%)	1.61 (1.12-2.31)
PAD without CAD	25/836 (2.99%)	12/863 (1.39%)	2.19 (1.10-4.36)
Asymp. Carotid Artery Stenosis >50%			
No	274/8535 (3.21%)	157/8446 (1.86%)	1.74 (1.43-2.12)
Yes	14/617 (2.27%)	13/680 (1.91%)	1.18 (0.55-2.51)
Polyvascular Disease			
1 Vascular Bed	221/7078 (3.12%)	128/7039 (1.82%)	1.72 (1.39-2.14)
2 Vascular Beds	58/1613 (3.6%)	33/1589 (2.08%)	1.75 (1.14-2.68)
3 Vascular Beds	9/459 (1.96%)	9/497 (1.81%)	1.06 (0.42-2.66)
Age			
<65	31/2150 (1.44%)	27/2184 (1.24%)	1.18 (0.70-1.97)
65-74	156/5078 (3.07%)	96/5045 (1.90%)	1.63 (1.26-2.10)
≥75	101/1924 (5.25%)	47/1897 (2.48%)	2.12 (1.50-3.00)
Sex			
Male	224/7093 (3.16%)	142/7137 (1.99%)	1.60 (1.29-1.97)
Female	64/2059 (3.11%)	28/1989 (1. 41%)	2.22 (1.42-3.46)
Region			
North America	59/1304 (4.52%)	41/1309 (3.13%)	1.45 (0.97-2.16)
South America	29/2054 (1.41%)	15/2054 (0.73%)	1.93 (1.04-3.60)
Western Europe*	119/2855 (4.17%)	69/2855 (2.42%)	1.73 (1.29-2.33)
Eastern Europe	28/1607 (1.74%)	21/1604 (1.31%)	1.32 (0.75-2.33)
Asia Pacific	53/1332 (3.98%)	24/1304 (1.84%)	2.21 (1.37-3.58)
Race			
White	194/5673 (3.42%)	127/5682 (2.24%)	1.53 (1.22-1.91)
Black	2/76 (2.63%)	3/92 (3.26%)	N.C.
Asian	57/1451 (3.93%)	25/1397 (1.79%)	2.24 (1.40-3.58)
Other	35/1952 (1.79%)	15/1955 (0.77%)	2.38 (1.30-4.36)
Weight			
≤60kg	34/901 (3.77%)	11/836 (1.32%)	2.87 (1.45-5.66)
>60kg	254/8241 (3.08%)	159/8285 (1.92%)	1.61 (1.32-1.97)
eGFR			
<60mL/min	81/2054 (3.94%)	57/2114 (2.70%)	1.47 (1.05-2.07)
≥60mL/min	206/7094 (2.90%)	113/7012 (1.61%)	1.81 (1.44-2.28)
Tobacco Use History			
Current	61/1944 (3.14%)	32/1972 (1.62%)	1.97 (1.28-3.02)
Former	145/4286 (3.38%)	95/4251 (2.23%)	1.52 (1.17-1.96)
Never	82/2922 (2.81%)	43/2903 (1.48%)	1.90 (1.32-2.75)
Diabetes			
Yes	110/3448 (3.19%)	65/3474 (1.87%)	1.70 (1.25-2.31)
No	178/5704 (3.12%)	105/5652 (1.86%)	1.69 (1.33-2.15)
Hypertension History			
Yes	222/6907 (3.21%)	138/6877 (2.01%)	1.61 (1.30-1.99)
No	66/2245 (2.94%)	32/2249 (1.42%)	2.06 (1.35-3.14)
Lipid Lowering Agent			
Yes	260/8239 (3.16%)	148/8158 (1.81%)	1.74 (1.42-2.13)
No	28/913 (3.07%)	22/968 (2.27%)	1.37 (0.78-2.40)



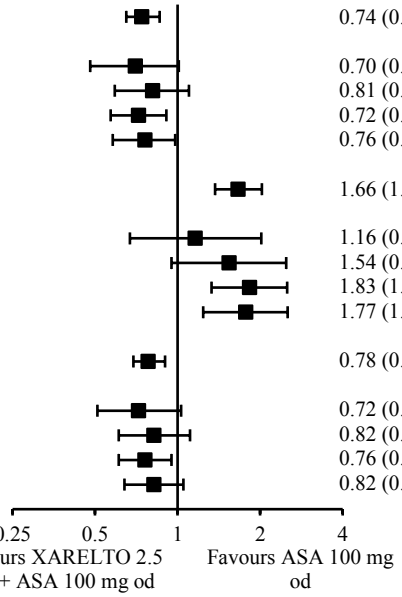
N.C. – Not calculated as minimum number of outcomes were not reached.
*Western Europe also includes AUS/ISR/ZAF.

CAD Subpopulation

The incidences and treatment effect of XARELTO 2.5 mg bid in combination with ASA 100 mg od for the primary efficacy outcome, modified ISTH major bleeding outcome and net clinical benefit are presented for the history of MI subgroups of the CAD sub-population in Table 45.

Table 45 - Primary Efficacy, Primary Safety and Net Clinical Benefit in Patients with CAD[§] from the COMPASS Study

Outcome	CAD Patients	XARELTO 2.5 mg bid + ASA 100 mg od	ASA 100 mg od	HR (95% CI)
		No. of subjects/total no.		
Composite of Stroke, MI or CV Death	All Randomized	347/8313	460/8261	0.74 (0.65-0.86)
	History of MI			
	<2 yrs prior	49/1218	67/1205	0.70 (0.48-1.01)
	2-5 yrs prior	71/1612	91/1667	0.81 (0.59-1.10)
	>5 yrs prior	127/2824	174/2849	0.72 (0.57-0.91)
	No prior MI	100/2659	128/2540	0.76 (0.58-0.98)
Modified ISTH Major Bleeding	All Randomized	263/8313	158/8261	1.66 (1.37-2.03)
	History of MI			
	<2 yrs prior	28/1218	23/1205	1.16 (0.67-2.02)
	2-5 yrs prior	41/1612	28/1667	1.54 (0.95-2.49)
	>5 yrs prior	107/2824	59/2849	1.83 (1.33-2.51)
	No prior MI	87/2659	48/2540	1.77 (1.24-2.52)
Net Clinical Benefit*	All Randomized	392/8313	494/8261	0.78 (0.69-0.90)
	History of MI			
	<2 yrs prior	55/1218	73/1205	0.72 (0.51-1.03)
	2-5 yrs prior	77/1612	97/1667	0.82 (0.61-1.11)
	>5 yrs prior	143/2824	186/2849	0.76 (0.61-0.95)
	No prior MI	117/2659	138/2540	0.82 (0.64-1.05)



[§]**NOTE:** The PAD and CAD subpopulations in the COMPASS trial, and hence in this analysis, partly overlap each other. 65.7% of the patients in the PAD subgroup were also diagnosed with CAD; 19.8% of the patients in the CAD subgroup were also diagnosed with PAD.

*Net Clinical Benefit – Composite of stroke, MI, CV death, fatal bleeding or non-fatal bleeding into a critical organ.

modified ISTH = Modified International Society of Thrombosis and Hemostasis (ISTH) major bleeding is defined as fatal bleeding, symptomatic bleeding into critical area or organ, bleeding into surgical site requiring reoperation or bleeding leading to hospitalization.

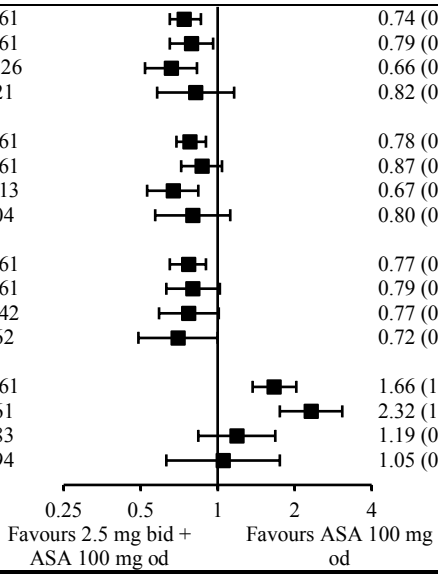
Landmark Analysis

Several pre-specified analyses have been conducted to assess the assumption of time-constant treatment effects on various outcomes of the COMPASS study. In addition, the landmark analyses of the composition of stroke, MI and CV death; modified ISTH major bleeding, net clinical benefit and all-cause mortality were performed in the CAD subgroup of the COMPASS study (Table 46) to assess the treatment effect during year 1, year 2 and beyond year 2 of treatment. In this analysis, patients at risk of the outcome in each of the landmark windows were patients alive at the beginning of the window and who had not previously had the outcome of interest.

Consistent with the pre-specified analyses, this analysis shows that the reduction in the primary efficacy outcome, net clinical benefit and all-cause mortality observed with XARELTO 2.5 mg bid in combination with ASA 100 mg od versus ASA 100 mg od was preserved over time while data suggest that the treatment effect on mISTH bleeding decreases after the first year of treatment; resulting in an improvement in the benefit-risk profile over time.

Table 46- Landmark Analysis of the CAD[§] Sub-Population of the COMPASS Study

Outcome	Time Since Randomization	XARELTO 2.5 mg bid + ASA 100 mg od	ASA 100 mg od	HR (95% CI)
		No. of subjects/total no.		
Composite of Stroke, MI or CV Death	All Randomized	347/8313	460/8261	0.74 (0.65-0.86)
	<1 year	175/8313	220/8261	0.79 (0.65-0.96)
	1-<2 years	114/7230	170/7126	0.66 (0.52-0.84)
	>2 years	58/3658	70/3621	0.82 (0.58-1.16)
Net Clinical Benefit*	All Randomized	392/8313	494/8261	0.78 (0.69-0.90)
	<1 year	206/8313	236/8261	0.87 (0.72-1.04)
	1-<2 years	125/7203	183/7113	0.67 (0.54-0.84)
	>2 years	61/3640	75/3604	0.80 (0.57-1.12)
All-Cause Mortality	All Randomized	262/8313	339/8261	0.77 (0.65-0.90)
	<1 year	116/8313	145/8261	0.79 (0.62-1.01)
	1-<2 years	93/7325	120/7242	0.77 (0.59-1.01)
	>2 years	53/3746	74/3762	0.72 (0.50-1.02)
Modified ISTH Major Bleeding	All Randomized	263/8313	158/8261	1.66 (1.37-2.03)
	<1 year	163/8313	70/8261	2.32 (1.75-3.07)
	1-<2 years	70/7191	59/7183	1.19 (0.84-1.68)
	>2 years	30/3631	29/3694	1.05 (0.63-1.75)



[§]**NOTE**: The PAD and CAD subpopulations in the COMPASS trial partly overlap each other. 65.7% of the patients in the PAD subgroup were also diagnosed with CAD; 19.8% of the patients in the CAD subgroup were also diagnosed with PAD.

*Net Clinical Benefit = Composite of stroke, MI, CV death, fatal bleeding or symptomatic non-fatal bleeding into a critical organ.

modified ISTH = Modified International Society of Thrombosis and Hemostasis (ISTH) major bleeding is defined as fatal bleeding, symptomatic bleeding into critical area or organ, bleeding into surgical site requiring reoperation or bleeding leading to hospitalization.

PAD Subpopulation

The incidences and treatment effect of Xarelto 2.5 mg bid in combination with ASA 100 mg od for the primary efficacy, primary safety, limb and key composite outcomes are presented for the PAD sub-population in Table 47. The analysis demonstrates reductions in the primary efficacy outcome, major adverse limb events (MALE) and the composite of major stroke, MI and cardiovascular events and MALE with XARELTO 2.5 g bid in combination with ASA 100 mg od versus ASA 100 mg od.

Table 47 - Primary Efficacy, Primary Safety, Limb Outcomes and Key Composite Outcomes in Patients with PAD[§] from the COMPASS Study

	XARELTO 2·5 mg bid plus ASA 100 mg od (N=2492)	ASA 100 mg od (N=2504)	Rivaroxaban 2·5 mg bid plus ASA 100 mg od	
Outcome	**n (%)**	**n (%)**	**HR (95% CI)**	**p-value**
Primary efficacy outcome: Stroke, CV Death, MI	126 (5.1%)	174 (6.9%)	0.72 (0.57-0.90)	0.0047
Primary safety outcome Modified ISTH Major Bleeding	77 (3.1%)	48 (1.9%)	1.61 (1.12-2.31)	0.0089
Limb outcomes				
Acute Limb Ischemia	19 (0.8%)	34 (1.4%)	0.56 (0.32-0.99)	0.0422
Chronic Limb Ischemia	16 (0.6%)	24 (1.0%)	0.67 (0.35-1.26)	0.2076
Major Adverse Limb Event (MALE)	30 (1.2%)	56 (2.2%)	0.54 (0.35-0.84)	0.0054
All Vascular Amputations	11 (0.4%)	28 (1.1%)	0.40 (0.20-0.79)	0.0069
Major Amputation	5 (0.2%)	17 (0.7%)	0.30 (0.11-0.80)	0.0112
MALE and Major amputation[a]	32 (1.3%)	60 (2.4%)	0.54 (0.35-0.82)	0.0037
Key Composite Outcomes for PAD				
cardiovascular death, stroke, myocardial infarction or MALE	155 (6.2%)	222 (8.9%)	0.69 (0.56-0.85)	0.0004
cardiovascular death, stroke, myocardial infarction or MALE or Major amputation	157 (6.3%)	225 (9.0%)	0.69 (0.56-0.85)	0.0004

[a] An additional 11 major amputations of a vascular cause were performed not linked to acute or chronic limb ischemia (MALE), 2 in rivaroxaban 2·5 mg twice daily plus ASA, 5 in rivaroxaban 5 mg twice daily, and 4 in ASA alone.

[§]NOTE: The PAD and CAD subpopulations in the COMPASS trial, and hence in this analysis, partly overlap each other. 65.7% of the patients in the PAD subgroup were also diagnosed with CAD; 19.8% of the patients in the CAD subgroup were also diagnosed with PAD.

modified ISTH = Modified International Society of Thrombosis and Hemostasis (ISTH) major bleeding is defined as fatal bleeding, symptomatic bleeding into critical area or organ, bleeding into surgical site requiring reoperation or bleeding leading to hospitalization.

Acute Limb Ischemia = limb threatening ischemia with evidence of acute arterial obstruction by radiologic criteria or a new pulse deficit leading to an intervention (i.e. surgery, thrombolysis, peripheral angioplasty, amputation) within 30 days of symptoms onset.

Chronic Limb Ischemia = severe limb ischemia leading to a vascular intervention.

Major Adverse Limb Event = development of acute or chronic limb ischemia over the course of the trial follow-up, including any additional major amputations due to a vascular event that was not included in acute or chronic limb ischemia.

Major amputation: amputation of a vascular cause above the forefoot, or minor involving the forefoot and digits.

DETAILED PHARMACOLOGY

Animal Pharmacology

In Vitro

XARELTO (rivaroxaban) is a competitive, selective, and direct, antithrombin independent Factor-Xa (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 (80-100%) 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.

Due to reduced extent of absorption, an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food, increases in mean AUC by 39% and mean C_{max} by 76% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability when this dose was taken with food (see **DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment**).

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 gender 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 CYP 3A4/CYP 3A5 and CYP 2J2 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 CYP 3A4/CYP 3A5 accounts for approximately 18% and CYP 2J2 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 gender, accompanied by an increase in C_{max} by 35% in both genders 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)

PT (Neoplastin® reagent), aPTT, and anti-factor Xa activity by a calibrated quantitative test) display a close correlation to rivaroxaban plasma concentrations in children. The lower limit of quantifications must be considered when the anti-factor Xa test is used to quantify plasma concentrations of rivaroxaban in children.

Gender

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, e.g, prothrombin time (PT Neoplastin® reagent), neither age, gender, nor body weight affected the PD parameter/rivaroxaban concentration relationship, i.e, 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

The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects [CrCl ≥80 mL/min (n=8)] and in subjects with varying degrees of renal impairment (see Table 48). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed.

Table 48 - Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Renal Insufficiency from a Dedicated Renal Impairment Study

Parameter		CrCl (mL/min)		
		50 to 79	30 to 49	15 to 29
		N=8	N=8	N=8
Exposure (% increase relative to normal)	**AUC**	**44**	**52**	**64**
	C_{max}	28	12	26
FXa Inhibition (% increase relative to normal)	**AUC**	50	86	100
	E_{max}	9	10	12
PT Prolongation (% increase relative to normal)	**AUC**	33	116	144
	E_{max}	4	17	20

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect; and CrCl = creatinine clearance

In subjects with mild renal impairment, the combined P-gp and moderate CYP 3A4 inhibitor erythromycin (500 mg three times a day) led to a 1.8-fold increase in mean rivaroxaban AUC and 1.6-fold increase in C_{max} when compared to subjects with normal renal function without co-medication. In subjects with moderate renal impairment, erythromycin led to a 2.0-fold increase in mean rivaroxaban AUC and 1.6-fold increase in C_{max} when compared to subjects with normal renal function without co-medication (see **WARNINGS AND PRECAUTIONS – Drug Interactions**). Subjects with either mild or moderate renal impairment had a 1.2- and 1.4-fold increase in Factor Xa inhibition, respectively, and a prolongation of prothrombin time of 1.7- and 1.75-fold in subjects with mild and moderate renal impairment, respectively.

Hepatic Insufficiency

The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects (n=16) and subjects with varying degrees of hepatic impairment (see Table 49). No patients with severe hepatic impairment (Child-Pugh C) were studied. Compared to healthy subjects with normal liver function, significant increases in rivaroxaban exposure were observed in subjects with moderate hepatic impairment (Child-Pugh B). Increases in pharmacodynamic effects were also observed.

Table 49 - Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Hepatic Insufficiency from a Dedicated Hepatic Impairment Study

Parameter		Hepatic Impairment Class (Child-Pugh Class)	
		Mild (Child-Pugh A)	Moderate (Child-Pugh B)
		N=8	N=8
Exposure (% increase relative to normal)	**AUC**	**15**	**127**
	C_{max}	0	27
FXa Inhibition (% increase relative to normal)	**AUC**	8	159
	E_{max}	0	24
PT Prolongation (% increase relative to normal)	**AUC**	6	114
	E_{max}	2	41

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect; and CrCl = creatinine clearance

PHASE IV STUDIES

Two Phase IV clinical studies (XALIA and XANTUS) were done to evaluate the effects of rivaroxaban use under real-world (clinical practice) conditions.

XALIA

In addition to the Phase III EINSTEIN program, a prospective, non-interventional, open-label cohort study (XALIA) investigated the long-term safety of XARELTO under real-world conditions (central outcome adjudication including recurrent VTE, major bleeding and death. In 2619 XARELTO-treated patients, rates of major bleeding, recurrent VTE and all-cause mortality for XARELTO were 0.7%, 1.4% and 0.5%, respectively.

These results are consistent with the established safety profile of XARELTO in this population.

XANTUS

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. 6,785 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism under real-world conditions. The mean CHADS2 score of the population was 2.0. Major bleeding incidence was 2.1 per 100 patient years. Fatal hemorrhage incidence was 0.2 per 100 patient years and intracranial hemorrhage incidence was 0.4 per 100 patient years. Stroke or non-CNS systemic embolism incidence was 0.8 per 100 patient years. These results are consistent with the established safety profile of XARELTO in this population.

TOXICOLOGY

Acute Toxicity

XARELTO (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.

Juvenile Toxicity Data

Rivaroxaban was tested in male and female juvenile rats up to 3-month treatment duration. Treatment started at postnatal day 4 at doses of 6, 20 and 60 mg/kg/day. Rivaroxaban was generally well tolerated except for signs indicating exaggerated pharmacodynamics (increased coagulation time). No evidence of target organ-specific toxicity or toxicity developing organs was seen.

Carcinogenicity

In 2-year carcinogenicity studies, rivaroxaban was tested in mice, up to 60 mg/kg/day (reaching systemic exposure similar to humans) and in rats (up to 3.6-fold higher than in humans) without demonstration of carcinogenic potential.

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.

REFERENCES

1. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. Circulation. 2007;116(2):180-7.
2. Biemond B, Perzborn E, Friederich P, Levi M, Buetehorn U, Bueller H. Prevention and treatment of experimental thrombosis in rabbits with rivaroxaban (BAY 597939) an oral, direct factor Xa inhibitor. Thromb Haemost. 2007;79:471-7.
3. Buller HR, editor. Oral rivaroxaban for the treatment of symptomatic venous thromboembolism: a pooled analysis for the EINSTEIN DVT and EINSTEIN PE Studies. American Society of Hematology Annual Meeting Abstracts; 2012 December 8; Georgia World Congress Center.
4. Buller HR, Prins MH, Lensing AW, Decousus H, Jacobson BF, Minar E ea. Supplementary Appendix to the article Oral Rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):128-97.
5. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287-97.
6. Eriksson BI, Borris L, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. J Thromb Haemost. 2006;4(1):121-8.
7. Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation. 2006;114(22):2374-81.
8. Fisher WD, Eriksson BI, Bauer KA, Borris L, Dahl OE, Gent M, et al. Rivaroxaban for thromboprophylaxis after orthopaedic surgery: pooled analysis of two studies. Thromb Haemost. 2007;97(6):931-7.
9. Geerts W, Bergqvist D, Pineo G, Heit J, Samama C, Lassen M, et al. Prevention of venous thromboembolism. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). CHEST. 2008;133:381S-453S.
10. Gibson CM, Mega JL, Burton P, Goto S, Verheugt F, Bode C, et al. Rationale and design of the Anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome-thrombolysis in myocardial infarction 51 (ATLAS-ACS 2 TIMI 51) trial: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome. Am Heart J. 2011;161(5):815-21 e6.
11. Gibson CM, Mehran R, Bode C, Halperin J, Verheught FW, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med. 2016;375(25):2423-2434.

12. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008;372:31-9.

13. Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939--an oral, direct Factor Xa inhibitor--after multiple dosing in healthy male subjects. Eur J Clin Pharmacol. 2005;61(12):873-80.

14. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol. 2007;47(2):218-26.

15. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358(26):2776-86.

16. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2011;366(1):9-19. Supplementary Appendix. 2011:1-9

17. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19.

18. Moore KT, Vaidyanathan S, Natarajan J, Ariyawansa J, Haskell L, Turner KC. An open-label study to estimate the effect of steady-state erythromycin on the pharmacokinetics, pharmacodynamics, and safety of a single dose of rivaroxaban in subjects with renal impairment and normal renal function. J Clin Pharmacol. 2014;54(12):1407-20.

19. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation and Supplementary Appendix p. 1-23. N Engl J Med. 2011;365(10):883-91.

20. Perzborn E, Strassburger J, Wilmen A, Pohlmann J, Roehrig S, Schlemmer KH, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939--an oral, direct Factor Xa inhibitor. J Thromb Haemost. 2005;3(3):514-21.

21. Turpie AG, Fisher WD, Bauer KA, Kwong LM, Irwin MW, Kalebo P, et al. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. J Thromb Haemost. 2005;3(11):2479-86.

22. Weitz JI, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, et al. Two doses of rivaroxaban versus aspirin for prevention of recurrent venous thromboembolism. Rationale for and design of the EINSTEIN CHOICE study. Thromb Haemost. 2015 Aug 31;114(3):645-50.

23. Kenneth T. Moore, Mark A. Krook, Seema Vaidyanathan1, Troy C. Sarich, C. V. Damaraju, and Larry E. Fields. Rivaroxaban Crushed Tablet Suspension Characteristics and Relative Bioavailability in Healthy Adults When Administered Orally or Via Nasogastric Tube. Clinical Pharmacology in Drug Development. 2014;3(4) 321–327.

24. Ageno W, Mantovani LG, Haas S, Kreutz R, Monje D, Schneider J, van Eickels M, Gebel M, Zell E, Turpie AG. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol 2016; 3: e12–21.

25. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, van Eickels M, Turpie AG; XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J. 2016; Apr 7;37(14):1145-53.

26. Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanas F, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017 Nov 10.

27. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017 Nov 10.

28. Boer DP, de Rijke YB, Hop WC, Cransberg K, Dorresteijn EM. Reference values for serum creatinine in children younger than 1 year of age. Pediatr Nephrol. 2010;25: 2107 - 2113

PART III: CONSUMER INFORMATION

PrXARELTO®

rivaroxaban tablets

rivaroxaban granules for oral suspension

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 10 mg, 15 mg and 20 mg tablets are used for the:

- **Prevention of blood clots after major hip or knee surgery**

  Blood clots could dislodge and travel to the lungs causing serious health risks. Your doctor has prescribed this medication for you because after such an operation you are at an increased risk of getting blood clots.

- **Prevention of blood clots in your brain (stroke) and in other blood vessels in your body if you have atrial fibrillation**

  Your doctor has prescribed this medication for you because you have a form of irregular heart rhythm called atrial fibrillation which can lead to blood clots forming and increases your risk of a stroke.

- **Treatment and prevention of blood clots in the veins of your legs or lungs**

  Your doctor has prescribed this medication for you because you have blood clots in the veins of your legs. This makes you at risk of a blood clot dislodging and traveling to the lungs causing serious health risks.

XARELTO 2.5 mg tablet is used for the:

- **Prevention of stroke, heart attack and severe leg pain or death**

  Your doctor has prescribed this medication for you in combination with acetylsalicylic acid (ASA, ASPIRIN®) if you have:

  - a blockage in the blood vessels to the heart, called coronary artery disease, causing a lack of oxygen in your heart. This may occur with or without the narrowing of limb arteries that causes pain, a circulatory problem called peripheral artery disease; or
  - confirmed peripheral artery disease and are at increased risk for stroke, heart attack or sudden severe blockage of blood flow to your limbs.

XARELTO 1 mg/mL granules for oral suspension is used for the:

- **Treatment and prevention of blood clots in the veins or blood vessels of children's lungs**

  The doctor has prescribed this medication to treat blood clots and prevent re-occurrence of clots in the veins or in the blood vessels of the lungs in full-term newborn babies, infants and toddlers, children and adolescents after at least 5 days of initial treatment with injectable medicines used to treat blood clots.

XARELTO 15mg tablet is used for the:

- **Treatment and prevention of blood clots in the veins or blood vessels of children's lungs**

  The doctor has prescribed this medication to treat blood clots and prevent re-occurrence of clots in the veins or in the blood vessels of the lungs in children and adolescents (aged less than 18 years and weighing from 30kg to 50kg) after at least 5 days of initial treatment with injectable medicines used to treat blood clots.

XARELTO 20mg tablet is used for the:

- **Treatment and prevention of blood clots in the veins or blood vessels of children's lungs**

  The doctor has prescribed this medication to treat blood clots and prevent re-occurrence of clots in the veins or in the blood vessels of the lungs in children and adolescents (aged less than 18 years and weighing more than 50kg) after at least 5 days of initial treatment with injectable medicines used to treat blood clots.

What it does:

XARELTO is an anticoagulant. It helps prevent blood clots from forming by directly blocking the activity of clotting Factor-Xa.

When it should not be used:

If you or the child:

- have severe liver disease which leads to an increased risk of bleeding
- have active bleeding, especially if you are bleeding excessively
- are aware of body wounds or injuries at risk of bleeding, including bleeding in the brain or bleeding in your stomach or gut
- are taking certain oral medications to treat fungal infections or HIV/AIDS, such as NIZORAL®

(ketoconazole), TYBOST® (cobicistat) or NORVIR® (ritonavir)

- are taking dronedarone
- are taking other anticoagulants (blood thinners) such as warfarin, apixaban, dabigatran, edoxaban, heparin or low molecular weight heparin (LMWH) including enoxaparin, dalteparin or heparin derivatives, such as fondaparinux
- are pregnant or are breastfeeding
- 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:

rivaroxaban

What the nonmedicinal ingredients are:

- **Film-coated tablets:**

  cellulose microcrystalline, croscarmellose sodium, ferric oxide red (10 mg, 15 mg, 20 mg), ferric oxide yellow (2.5 mg), hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sodium lauryl sulfate, titanium dioxide

- **Granules for oral suspension:**

  citric acid (anhydrous), sweet and creamy flavor [consisting of flavoring substances, maltodextrin (maize), propylene glycol (E1520), arabic gum (Acacia gum, E414)], hypromellose 5 cP, mannitol, microcrystalline cellulose, carboxymethylcellulose sodium, sodium benzoate, sucralose, xanthan gum

What dosage forms it comes in:

Film-coated tablets, 2.5 mg 10 mg, 15 mg and 20 mg.

Granules for oral suspension, 1 mg/mL:

The granules for oral suspension are white granules in a glass bottle. Two pack sizes are available:

For children weighing less than 4kg

- 1 carton with one bottle (100 mL) containing 2.625 g granules, when reconstituted 51.7 mg rivaroxaban / bottle
- two 1 mL blue oral syringes and adapter
- one 50 mL syringe

For children weighing more than 4kg

- 1 carton with one bottle (250 mL) containing 5.25 g granules, when reconstituted 103.4 mg rivaroxaban / bottle
- two 5 mL blue oral syringes and adapter
- two 10 mL blue oral syringes and adapter
- one 100 mL syringe

After preparation, each mL of suspension contains 1 mg of rivaroxaban.

WARNINGS AND PRECAUTIONS

Do not stop taking XARELTO without first talking to your doctor. If you stop taking XARELTO, blood clots may cause a stroke, heart attack, or other complications. This can be fatal or lead to severe disability.

As with other blood thinners, taking XARELTO may result in serious or life-threatening bleeding from any site, including internal organs.

Take special care when using XARELTO if you or the child:

- have an increased risk of bleeding, as could be the case with conditions such as
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - active ulcer or a recent ulcer of the stomach or bowel
  - a problem with the blood vessels in the back of the eyes (retinopathy)
  - recent bleeding in the brain (stroke, intracranial or intracerebral bleeding)
  - problems with the blood vessels in the brain or spinal column
  - a recent operation on the brain, spinal column or eye
  - a chronic disease of the airways in the lungs causing widening, damage and scarring (bronchiectasis), or a history of bleeding into the lungs
  - are older than 75 years of age
- have a prosthetic heart valve
- if a doctor has told you that you or the child have antiphospholipid syndrome, a disease which can cause blood clots.

For the treatment and prevention of blood clots in the veins of your legs or lungs, XARELTO is not recommended if your doctor determines that:

- you are not able to maintain an adequate blood pressure
- you are taking drugs to break down your blood clots
- you have been scheduled for emergency surgical removal of blood clots from your lung

Talk to the doctor or pharmacist before using XARELTO if any of these apply to you or the child. The doctor may decide to keep you or the child under closer observation.

- If you or the child are having surgery for any reason including an operation that involves a catheter or injection

into the spinal column (e.g, for epidural or spinal anesthesia or pain reduction):

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

You should avoid XARELTO 2.5 mg if you have had a prior stroke with bleeding in the brain (hemorrhagic stroke) or a prior stroke where there was a blockage of the small arteries that provide blood to the brain's deep tissues (lacunar stroke).

You should avoid XARELTO 2.5 mg for at least one month after having a stroke from a blood clot in the brain (ischemic non-lacunar stroke).

Lactose is a nonmedicinal ingredient in XARELTO tablets. Do not take XARELTO if you or the child have one of the following rare hereditary diseases:

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

If you have severe kidney disease or reduced kidney function (for children younger than 1 year), you or the child may not be able to take XARELTO because it may increase the chance of bleeding. The doctor will know how to determine kidney function.

XARELTO is not recommended if you or the child have an artificial heart valve.

XARELTO 2.5 mg and 10 mg film-coated tablets are not recommended in children younger than 18 years old.

XARELTO is not recommended in children younger than 18 years of age for any condition other than the treatment and prevention of blood clots in the veins or blood vessels of children's lungs.

Do not give XARELTO granules for oral suspension to children under 6 months of age who

- at birth had less than 37 weeks of gestation, or
- weigh less than 2.6 kg, or
- had less than 10 days of breast or formula feeding

because dosing of XARELTO cannot be reliably determined and has not been studied in these children.

XARELTO granules for oral suspension contains 1.8 mg sodium benzoate in each mL oral suspension. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old). This medicine contains less than 1 mmol sodium (23 mg) per mL.

Pregnancy and breastfeeding

If there is a chance that you or the child could become pregnant, use a reliable contraceptive while you are taking XARELTO. If you or the child become pregnant while taking XARELTO, immediately tell the doctor, who will decide how to continue treatment.

INTERACTIONS WITH THIS MEDICATION

Tell the doctor or pharmacist if you or the child are taking:

- anticoagulants (blood thinners) such as warfarin, heparin or low molecular weight heparin (LMWH) including enoxaparin, fondaparinux, bivalidrudin, apixaban, dabigatran, edoxaban, or anti-platelet agents, such as clopidogrel, ticlopidine, prasugrel, ticagrelor
- oral medications to treat fungal infections such as ketoconazole, itraconazole, posaconazole
- medications for HIV/AIDS such as ritonavir (NORVIR®), cobicistat (TYBOST®), and lopinavir/ritonavir (KALETRA®)
- are taking dronedarone
- anti-inflammatory and pain relieving medicines including non-steroidal anti-inflammatory drugs (NSAIDs) (e.g, naproxen [NAPROSYN®] or acetylsalicylic acid [ASPIRIN®])
- some antibiotics such as clarithromycin
- rifampicin
- anticonvulsants (to control seizures or fits) such as phenytoin, carbamazepine, phenobarbital
- medicines to treat depression and/or anxiety (selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs))

You or the child are at an increased risk for bleeding if you take XARELTO with:

- NSAIDs
- antiplatelet agents such as ASA or clopidogrel
- antidepressants/anti-anxiety (SSRIs, SNRIs)

Low-dose XARELTO 2.5 mg is prescribed together with low-dose ASA 75 mg – 100 mg. If you need to take another NSAID, your doctor will decide if it is beneficial for you to take it along with your XARELTO / ASA treatment.

The use of XARELTO with prasugrel or ticagrelor is not recommended.

Please tell the doctor or pharmacist if you or the child are taking or have recently taken any other medication, including medications obtained without a prescription as well as vitamins and herbal supplements, such as St. John's Wort. Know the medicines you or the child takes. Keep a list of them and show

it to the doctor and pharmacist when you or the child get a new medicine.

PROPER USE OF THIS MEDICATION

If you or the child are currently taking warfarin (another blood thinner taken by mouth) or receive other anticoagulant treatment given by injection, and the doctor has decided XARELTO is appropriate for you or the child, make sure you ask the doctor exactly when and how best to switch and start taking XARELTO.

Always follow the doctor's instructions. Do not stop taking or giving XARELTO without talking to the doctor first, because XARELTO helps prevent the development of blood clots.

Swallow the tablet preferably with water. Try to take or give the tablet or oral suspension at the same time every day to help you to remember it. The doctor will decide how long you or the child must take XARELTO.

Do not split the tablet in an attempt to provide a fraction of a tablet dose. If you or the child have trouble swallowing the tablet **whole**, talk to the doctor about other ways to take it. The doctor may prescribe XARELTO granules for oral suspension to the child instead of the tablets.

The tablets may be crushed and mixed with applesauce. Take it right away after you have mixed it. A crushed 2.5 mg or 10 mg tablet can be taken with or without food. Eat food right after taking a crushed 15 mg or 20 mg tablet.

The doctor may give you or the child the crushed XARELTO tablet also via a tube.

Prevention of blood clots after major hip or knee surgery

Usual dose: 10 mg once a day 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.

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

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

Prevention of blood clots in your brain (stroke) and in other blood vessels in your body if you have atrial fibrillation

Usual dose: 20 mg once a day with food.

If your kidneys are not working properly, your doctor may prescribe 15 mg once a day with food.

To be sure that you get the full benefit from XARELTO, it is important to take the 15 mg and 20 mg tablets with food.

If you need a procedure to treat blocked blood vessels in your heart (called a percutaneous coronary intervention – PCI with an insertion of a stent), your doctor will reduce your dose to 15 mg once a day (or to 10 mg once a day in case your kidneys are not working properly) in combination with an antiplatelet agent (e.g, clopidogrel).

This is long-term treatment and you should continue to take XARELTO until your physician says otherwise.

The recommended maximum daily dose is 20 mg.

Treatment and prevention of blood clots in the veins of your legs or lungs

Swallow the tablet preferably with water.

Day 1 to 21:

- **15 mg**: Take 1 tablet TWICE a day (in the morning and evening) with food.

Day 22 onwards:

- **20 mg:** Take 1 tablet ONCE a day with food.

After at least 6 months treatment, your doctor may decide to continue treatment with either one 20 mg tablet once a day or one 10 mg tablet once a day.

The 10 mg tablet may be taken with or without food.

This is long-term treatment and you should continue to take XARELTO until your physician says otherwise.

Prevention of stroke, heart attack and severe leg pain or death

Usual dose: 2.5 mg twice a day with or without food. Take XARELTO around the same time every day (for example, one tablet in the morning and one in the evening).

Also take 1 tablet of 75 mg – 100 mg of acetylsalicylic acid (ASA) once a day. Take the ASA tablet at the same time as one of your XARELTO doses.

This is long-term treatment and you should continue to take your treatment until your physician says otherwise.

Treatment and prevention of blood clots in the veins or blood vessels of a child's lungs

This medicine is available for children as granules for oral suspension. Prepare the oral suspension according to the Instructions for Use booklet that is provided with this medicine. Be sure to read and understand the Instructions for Use because it will show you how to prepare and administer the XARELTO oral suspension.

This medicine is also available for children and adolescents weighing 30 kg or more as 15 mg or 20 mg tablets.

Always take or give this medicine to the child exactly as the doctor, pharmacist or nurse has told you. You should check with the doctor, pharmacist or nurse if you are not sure.

Make sure that the correct information on how much and how often to take or give XARELTO is written on the designated field of the carton. If it is not written on the field, ask the pharmacist or doctor to provide the relevant information.

See the Instructions for Use booklet in the carton for how to prepare and administer a dose of XARELTO granules for oral suspension.

How much to take
The dose of XARELTO depends on body weight and will be calculated by the doctor as an amount (volume) in milliliters (mL) of oral suspension or as a tablet (either 15 mg or 20 mg). All materials to prepare and administer the oral suspension are provided with the granules (except for non-carbonated drinking water). The doctor will tell you how much of the oral suspension or which of the tablets (15 mg or 20 mg) you or the child must take.

	Body weight [kg]	Single dose [mL]	Daily frequency of intake	Total daily dose [mg] (1 mL=1 mg)	Blue oral syringe for dose administration
Oral Suspension	2.6 to under 3	0.8	3 times	2.4	1 mL
	3 to under 4	0.9	3 times	2.7	1 mL
	4 to under 5	1.4	3 times	4.2	5 mL
	5 to under 6	1.6	3 times	4.8	5 mL
	6 to under 7	1.6	3 times	4.8	5 mL
	7 to under 8	1.8	3 times	5.4	5 mL
	8 to under 9	2.4	3 times	7.2	5 mL
	9 to under 10	2.8	3 times	8.4	5 mL
	10 to under 12	3.0	3 times	9.0	5 mL
	12 to under 30	5.0	2 times	10.0	5 mL or 10 mL
Tablets or oral suspension	30 to under 50	15.0	once	15.0	10 mL
	50 or more	20.0	once	20.0	10 mL

The child's weight should be monitored and the dose be adjusted by the doctor if necessary, especially for children below 12 kg. This ensures that the correct dose of XARELTO is received.

It is important that the doses of XARELTO are adjusted by the doctor only, never by yourself. Do not switch among the oral suspension, 15 mg tablet or 20 mg tablet without first talking to the doctor, pharmacist or nurse.

Children should keep scheduled doctor's visits because their XARELTO dosage should be adjusted as their weight changes. The doctor may also want to prescribe the tablets if the child is able to swallow them.

Take or give the tablet or oral suspension with feeding or with food.

Each XARELTO dose has to be swallowed along with one typical serving of liquid. This typical serving may include liquid used for feeding.

If the doctor has told you to take or give XARELTO:
- once daily, do this approximately 24 hours apart
- twice daily, do this approximately 12 hours apart
- three times daily, do this approximately 8 hours apart

Try to take or give XARELTO at the same time every day to help you to remember it.

If you or the child spits up the dose or vomits

- less than 30 minutes after taking XARELTO, take or give a new dose
- more than 30 minutes after taking XARELTO, do not take or give a new dose. In this case, take or give the next XARELTO dose at the usual time.

Contact the doctor if you or the child repeatedly spits up the dose or vomits after taking XARELTO.

Overdose

Taking too much XARELTO could increase the risk of bleeding.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose

If you or the child are prescribed XARELTO 10 mg, 15 mg, 20 mg tablets or granules for oral suspension **once** a day and you have missed a dose, take or give it as soon as you remember on the same day. If this is not possible, take or give the next XARELTO dose on the following day at the usual time and then carry on taking or giving a XARELTO dose once a day as normal. Do not take or give a double dose to make up for a forgotten dose.

If you are prescribed XARELTO 15 mg tablets **twice** a day and you have missed a dose, take it as soon as you remember. Do not take more than two 15 mg tablets on one day. If you forget to take a dose you can take two 15 mg tablets at the same time to get a total of two tablets (30 mg) on one day. On the following day you should carry on taking one 15 mg tablet twice a day.

If the child is prescribed XARELTO granules for oral suspension **twice** daily and has missed a dose, take or give the missed morning dose as soon as you remember. You may take or give the forgotten dose together with the evening dose. A missed evening dose can only be taken or given on the same evening.

If the child is prescribed XARELTO granules for oral suspension **three** times a day and they have missed a dose, do not make up for the missed dose. Continue with the next scheduled dose (given every 8 hours).

If you are prescribed XARELTO 2.5 mg **twice** a day and you have missed a dose, take your next XARELTO 2.5 mg tablet as normal.

On the following day, continue as prescribed by the doctor once, twice or three times daily.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

As XARELTO acts on the blood clotting system, most side effects are related to signs of bruising or bleeding. In some cases, bleeding may not be obvious, such as unexplained swelling.

Patients treated with XARELTO may also experience the following side effects:

Nausea, vomiting, stomach ache, constipation, diarrhea, indigestion, and decreased general strength and energy.

In general, the side effects observed in children treated with XARELTO were similar in type to those observed in adults and were primarily mild to moderate in severity.

Side effects that were observed more often in children include:

Very common: headache, fever, nose bleeding, vomiting.

Common: raised heartbeat, blood tests may show an increase in bilirubin, low number of platelets which are cells that help blood to clot, heavy menstrual bleeding observed in girls.

Uncommon: blood tests may show an increase in a subcategory of bilirubin (direct bilirubin).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ Effect		Talk to your healthcare professional		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	Bleeding from the surgical wound, an injury or other medical procedure		✓	
	Unexpected bruising		✓	
	Reduction in red blood cells which can make your skin pale and cause weakness, tiredness, dizziness, headache, breathlessness, unusually fast heartbeat, or chest pain		✓	
	Bleeding into the eye	✓		
	Bleeding from stomach (blood in vomit) or bowel (blood in stools/black stools)		✓	
	Bleeding from hemorrhoids	✓		
	Bleeding under the skin	✓		
	Blood in your urine, (red/pink tinge to urine)		✓	
	Genital bleeding in post menopausal women		✓	
	Increased or more frequent menstrual bleeding	✓		
	Localized swelling		✓	
	Nose bleed lasting more than 5 minutes		✓	
	Pain or swelling in your limbs		✓	
	Low blood pressure (lightheaded-ness, dizziness, and/or fainting)		✓	
	Fever		✓	
	Unusually fast heartbeat		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/ Effect		Talk to your healthcare professional		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
	Itchy skin or rash		✓	
	Bleeding gums for longer than 5 minutes when you brush your teeth		✓	
Un-common	Bleeding into the brain (sudden, severe and unusual headache)			✓
	Coughing up blood		✓	
	Bleeding into a joint (stiff, sore, hot or painful joint)		✓	
	Oozing from the surgical wound		✓	
	Decreased urine output	✓		
Rare	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, and difficulty swallowing or breathing			✓
Unknown	Compartment Syndrome: increased pressure within legs or arms after a bleed, with pain, swelling, numbness or paralysis		✓	
	Agranulocytosis [frequent infection with fever, sore throat, mouth ulcers (sign of decreased white blood cells)]		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/ Effect		Talk to your healthcare professional		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
	Stevens-Johnson syndrome: Severe skin rash with redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			✓

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 XARELTO tablets and granules for oral suspension at room temperature (15°C-30°C).

After preparation, the reconstituted XARELTO suspension can be used for 14 days. Store at room temperature (15°C to 30°C) or in a refrigerator (2°C to 8°C). Do not freeze. If the suspension has been stored in the refrigerator, allow the suspension to adjust to room temperature prior to administration. See the Instructions for Use for complete details on preparation and administration of the oral suspension.

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 throw away medicines you no longer use. These measures will help to protect the environment.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Inc. at 1-800-265-7382.

This document plus the full Product Monograph, prepared for health professionals can be found at: http://www.bayer.ca or by contacting the manufacturer at the above-mentioned phone number.

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