Product Monograph

Including Patient Medication Information

[Pr] RIVAROXABAN

Rivaroxaban Tablets

For oral use

2.5 mg, 10 mg, 15 mg and 20 mg

House standard

Anticoagulant

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, Anticoagulant-Related Nephropathy	01/2025
7. Warning and Precautions, Hematologic Bleeding	07/2026

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Part 1: Healthcare Professional Information

1. Indications

RIVAROXABAN (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.

RIVAROXABAN (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).

RIVAROXABAN (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 Administrations).

RIVAROXABAN (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, RIVAROXABAN 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 rivaroxaban have not been established in these clinical situations (see Dosage and Administration).

1.1. Pediatrics

Pediatrics (< 18 years of age): In children less than 18 years of age, the safety and efficacy of rivaroxaban have not been established for indications other than treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence. Therefore, RIVAROXABAN 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 rivaroxaban 2.5 mg and 10 mg film-coated tablets have not been established in children less than 18 years of age; therefore, RIVAROXABAN 2.5 mg and 10 mg film-coated tablets are not recommended in this patient population (see 7.1.3 Pediatrics).

1.2. Geriatrics

Geriatrics (>65 years of age): Clinical studies have included patients with an age > 65 years (see 7 Warnings and Precautions– 7.1.4 Geriatrics and Renal Impairment, and 4 Dosage and Administration– Renal Impairment and Geriatrics (>65 years of age)).

Safety and efficacy data are available (see14 Clinical Trials).

2. 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 7 Warning 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 RIVAROXABAN.
- Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy, and having clinically relevant bleeding risk (see 7 Warning and Precautions – Hepatic Impairment)
- Pregnancy (see 7 Warning and Precautions – 7.1.1 Pregnant Women)
- Nursing women (see 7 Warning and Precautions – 7.1.2 Breast-feeding)
- Hypersensitivity to RIVAROXABAN (rivaroxaban) or to any ingredient in the formulation, (see6 Dosage Forms, Strengths, Composition, and Packaging).

4. Dosage and Precautions

4.1. Dosing Considerations

As for any non-vitamin K antagonist oral anticoagulant (NOAC) drug, before initiating RIVAROXABAN (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 RIVAROXABAN (rivaroxaban), and monitor renal function during RIVAROXABAN 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 RIVAROXABAN (see below, Renal Impairment).

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

eCrCl (mL/min) =

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

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

Switching from Parenteral Anticoagulants to RIVAROXABAN

RIVAROXABAN 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, RIVAROXABAN can be started 6 or more hours after the last prophylactic dose.

Switching from RIVAROXABAN to Parenteral Anticoagulants

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

Switching from Vitamin K Antagonists (VKA) to RIVAROXABAN

To switch from a VKA to RIVAROXABAN, stop the VKA and determine the INR. If the INR is ≤ 2.5, start RIVAROXABAN at the usual dose. If the INR is > 2.5, delay the start of RIVAROXABAN until

the INR is ≤ 2.5 (see Considerations for INR Monitoring of VKA Activity during Concomitant RIVAROXABAN Therapy).

Switching from RIVAROXABAN to a VKA

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

RIVAROXABAN 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 RIVAROXABAN Therapy). Children who switch from RIVAROXABAN to VKA need to continue RIVAROXABAN 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 RIVAROXABAN, as appropriate. RIVAROXABAN can be discontinued once the INR is > 2.0. Once RIVAROXABAN is discontinued, INR testing may be done at least 24 hours after the last dose of RIVAROXABAN and should then reliably reflect the anticoagulant effect of the VKA.

Considerations for INR Monitoring of VKA Activity during Concomitant RIVAROXABAN 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 rivaroxaban therapy will lead to an elevated INR, depending on the timing of the measurement (see 10.2 Pharmacodynamics), the INR is not a valid measure to assess the anticoagulant activity of RIVAROXABAN. The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant, including RIVAROXABAN.

When switching patients from RIVAROXABAN to a VKA, the INR should only be used to assess the anticoagulant effect of the VKA, and not that of RIVAROXABAN. Therefore, while patients are concurrently receiving RIVAROXABAN and VKA therapy, if the INR is to be tested, it should not be before 24 hours after the previous dose of RIVAROXABAN, and should be just prior to the next dose of RIVAROXABAN, since at this time the remaining RIVAROXABAN 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 RIVAROXABAN, the reported INR will not reflect the anticoagulation effect of the VKA only, because RIVAROXABAN use may also affect the INR, leading to aberrant readings (see 10.2 Pharmacodynamics).

4.2. Recommended Dose and Dosage Adjustment

Prevention of VTE after THR or TKR

The recommended dose is one 10 mg tablet once daily. RIVAROXABAN 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 RIVAROXABAN for 35 days.
- After elective TKR surgery, patients should be administered RIVAROXABAN for 14 days.

Treatment of VTE and Prevention of recurrent DVT and PE

RIVAROXABAN 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 rivaroxaban have not been established in these clinical situations (see 1Indications).

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 individualized 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.

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

Treatment of VTE and Prevention of VTE Recurrence in Children and Adolescent Patients Aged Less Than 18 Years Weighing at Least 30 kg

Appropriate dosage
The dose is determined based on body weight.

For pediatric patients with a body weight of at least 30 kg and less than 50 kg, 15 mg RIVAROXABAN tablet once daily can be administered.

For pediatric patients weighing more than 50 kg, 20 mg RIVAROXABAN tablet once daily can be administered.

Initiation of RIVAROXABAN treatment in pediatric patients less than 18 years
RIVAROXABAN treatment for pediatric patients less than 18 years of age should be initiated following at least 5 days of initial anticoagulation treatment with parenteral heparins. RIVAROXABAN is dosed based on body weight (see Table 1).

Table 1 - Body Weight-adjusted RIVAROXABAN Dosing Schedule for Children Less Than 18 Years of Age in mg of Tablets

Pharmaceutical form	Body weight (kg)		Regimen [mg]	Total daily dose [mg]
	Min	Max	o.d. once a day	
Tablets	30	< 50	15 mg	15 mg
	≥ 50		20 mg	20 mg

The weight of a child should be monitored, and the dose reviewed regularly to ensure the therapeutic dose is maintained.

Duration of treatment
Therapy with RIVAROXABAN should be continued for at least 3 months in all children with a body weight of at least 30 kg, 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.

Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation
The recommended dose is one 20 mg tablet of RIVAROXABAN taken once daily with food (see 10.3 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 RIVAROXABAN twice daily, one of which in combination with a once daily dose of 75 mg - 100 mg ASA. RIVAROXABAN 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, RIVAROXABAN 2.5 mg twice daily is not indicated in combination with dual antiplatelet therapy.

Acute myocardial infarction (AMI): Consideration should be given to discontinuing RIVAROXABAN 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, RIVAROXABAN 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 RIVAROXABAN 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: RIVAROXABAN should be discontinued in situations such as acute ischemic stroke where current clinical practice calls for administering thrombolytic therapy.

RIVAROXABAN 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 7 Warnings and Precautions – Monitoring and Laboratory Tests).

Concomitant use of RIVAROXABAN 10 mg, 15 mg and 20 mg with antiplatelet agents: The concomitant use of RIVAROXABAN with antiplatelet agents increases the risk of bleeding (see 7 Warning and Precautions- Bleeding). If concomitant antiplatelet therapy is contemplated with

RIVAROXABAN 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 RIVAROXABAN once daily (or 10 mg RIVAROXABAN once daily for patients with moderate renal impairment [CrCl 30 – 49 mL/min]) in combination with a P2Y12 inhibitor (e.g., clopidogrel). This treatment regimen is recommended for a maximum of 12 months after PCI with stent placement (see 10.2 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 RIVAROXABAN while being cardioverted (see 10.2 Pharmacodynamics, Patients undergoing cardioversion).

Hepatic Impairment

RIVAROXABAN 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. RIVAROXABAN should be used with caution in these patients (see 2 Contraindications, 7 Warnings and Precautions - Hepatic Impairment, and 10.3 Pharmacokinetics – 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 2 – Dosage and Administration for Adult Patients According to Renal Function

Creatinine Clearance (CrCl) / Indication	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	RIVAROXABAN 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

RIVAROXABAN 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 RIVAROXABAN 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 7 Warning and Precautions – Renal Impairment and 9.4 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, RIVAROXABAN 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 RIVAROXABAN should discontinue such treatment.

Renal Impairment (pediatric)
No dose adjustment is required for children with a body weight of at least 30 kg 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 10.3 Pharmacokinetics, Renal Insufficiency).

RIVAROXABAN is not recommended in children with a body weight of at least 30 kg with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2), as no clinical data are available (see 7 Warning and Precautions, Renal Impairment).

Gender, Race, or Body Weight

No dose adjustment is required for gender or race (see 10.3 Pharmacokenics - Sex, Ethnic Origin, and Body Weight).

The pediatric dosage of RIVAROXABAN is determined based on body weight (see 4 Dosage and Administration - Treatment of VTE and Prevention of VTE Recurrence in 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 7 Warnings and Precautions – Renal Impairment, and 4 Dosage and Administration – Renal Impairment).

Pediatrics (<18 years of age)
In children less than 18 years of age, the safety and efficacy of rivaroxaban have not been established for indications other than treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence. Therefore, RIVAROXABAN 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 rivaroxaban 2.5 mg and 10 mg film-coated tablets have not been established in children less than 18 years of age; therefore, RIVAROXABAN 2.5 mg and 10 mg film-coated tablets are not recommended in this patient population.

4.4. Administration

Swallow the tablet with liquid.

RIVAROXABAN 15 mg and 20 mg tablets should be taken with food (see 10.3 Pharmacokinetics, Absorption).

Do not split RIVAROXABAN tablets or use RIVAROXABAN tablets of lower strength in an attempt to provide doses for children with body weight below 30 kg.

For children who are unable to swallow whole 15 mg or 20 mg tablets, please refer to 4 Dosage and Administration - 4.4 Administration - Administration of Crushed Tablets.

Administration of Crushed Tablets:

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

A crushed RIVAROXABAN 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 RIVAROXABAN distal to the stomach as this can result in reduced absorption and therefore reduced drug exposure. After the administration of a crushed RIVAROXABAN 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding (see 10.3 Pharmacokinetics, Absorption).

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

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

4.5. Missed Dose

It is essential to adhere to the dosage schedule provided.

- RIVAROXABAN 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 RIVAROXABAN dose as recommended at the next scheduled time.

- RIVAROXABAN 10 mg, 15 mg, or 20 mg tablets taken **once** a day:
  If a dose is missed, the patient should take RIVAROXABAN 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.

- RIVAROXABAN 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.

- RIVAROXABAN 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.

On the following day, the child should continue with the regular once daily regimen.

5. OVERDOSAGE

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

Overdose following administration of 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 RIVAROXABAN is not available. The use of activated charcoal to reduce absorption in case of RIVAROXABAN overdose may be considered. Administration of activated charcoal up to 8 hours after overdose may reduce the absorption of RIVAROXABAN.

Due to the high plasma protein binding, rivaroxaban is not expected to be removed by dialysis (see 10.3 Pharmacokinetics, Distribution).

Management of Bleeding

In the event of hemorrhagic complications in a patient receiving RIVAROXABAN, treatment should be temporarily discontinued, and the source of bleeding investigated. Rivaroxaban 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 10.3 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 rivaroxaban.

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 rivaroxaban, 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 rivaroxaban.

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

The prothrombin time (PT), measured in seconds, is influenced by rivaroxaban 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 RIVAROXABAN (see 7 WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests and 10.2 Pharmacodynamics).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 3 – Dosage Forms, Strengths, Composition

Route of Administration	Dosage Form / Strength / Composition	Non-Medicinal Ingredients
Oral	Film-coated tablet, 2.5 mg, 10 mg, 15 mg and 20 mg	Microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, sodium lauryl sulphate. The film-coating contains: Hypromellose, Titanium Dioxide, Polyethylene Glycol, FD & C Yellow #5 and Iron Oxide Yellow (2.5 mg), Iron Oxide Red (10 mg, 15 mg and 20 mg).

Description
RIVAROXABAN 2.5 mg Tablets: Yellow, round, coated tablets debossed with "RI" on top and "2.5" below on one side and nothing on the other side.

RIVAROXABAN (rivaroxaban) 10 mg Tablets: Light-red, round, coated tablets debossed with "RI" on top and "10" below on one side and nothing on the other side.

RIVAROXABAN (rivaroxaban) 15 mg Tablets: Red, round, coated tablets debossed with "RI" on top and "15" below on one side and nothing on the other side.

RIVAROXABAN (rivaroxaban) 20 mg Tablets: Brown-red, round, coated tablets debossed with "RI" on top and "20" below on one side and nothing on the other side.

Packaging:
RIVAROXABAN (rivaroxaban) 2.5 mg, 10 mg and 15 mg tablets are supplied in bottles of 100.

RIVAROXABAN (rivaroxaban) 20 mg tablets are supplied in bottles of 100, 250 and 500.

7. Warnings and Precautions

General

Premature discontinuation of any oral anticoagulant, including RIVAROXABAN increases the risk of thrombotic events.

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

Cardiovascular

Patients with valvular disease

RIVAROXABAN 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 rivaroxaban 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 rivaroxaban regimen. A causal relationship between rivaroxaban and all-cause mortality could not be established.

Safety and efficacy of rivaroxaban 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 rivaroxaban provides

adequate anticoagulation in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of RIVAROXABAN is not recommended in this setting.

Of note, in the pivotal Phase III ROCKET AF trial that evaluated rivaroxaban 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

RIVAROXABAN 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 4 Dosage and Administration - Patients with nonvalvular atrial fibrillation who undergo PCI with stent placement; 10.2 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 hemorrhagic or lacunar stroke were not studied. Treatment with RIVAROXABAN 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 RIVAROXABAN 2.5 mg twice daily in combination with ASA should be avoided in the first month after stroke (see 10.3 Pharmacokinetics).

Gastrointestinal

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

Hematologic

The concomitant use of RIVAROXABAN with strong inducers of CYP 3A4, such as rifampicin, and the anticonvulsants, phenytoin, carbamazepine, phenobarbital, reduces rivaroxaban exposure (see 9.4 Drug- Drug Interactions). Combined use of RIVAROXABAN with strong inducers should generally be avoided, since efficacy of rivarobxaban may be compromised resulting in inadequate anticoagulation (see 9.4 Drug-Drug Interactions).

Bleeding

RIVAROXABAN, like other anticoagulants, should be used with caution in patients with an increased bleeding risk. Bleeding can occur at any site during therapy with RIVAROXABAN. 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 RIVAROXABAN (see 2 CONTRAINDICATIONS).

Should severe bleeding occur, treatment with RIVAROXABAN 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 4 below).

Table 4 – 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 9 DRUG INTERACTIONS). Patients on treatment with RIVAROXABAN 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 RIVAROXABAN.

Rivaroxaban 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).

RIVAROXABAN 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 rivaroxaban or warfarin during the ROCKET-AF trial was identified as an independent risk factor for major bleeding (see also 9 DRUG INTERACTIONS).

The antiplatelet agents, prasugrel and ticagrelor, have not been studied with rivaroxaban, 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 4 DOSAGE AND ADMINISTRATION, Other situations requiring thrombolytic therapy).

Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis than patients without malignant disease. In patients with malignant disease who undergo antithrombotic treatment with rivaroxaban, risk of bleeding may increase, in particular in the gastrointestinal, genitourinary tract or respiratory system. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumor location, antineoplastic therapy and stage of disease.

Cases of atraumatic splenic rupture in patients taking direct oral anticoagulants, including rivaroxaban have been reported in the context of a hemorrhagic complication of anticoagulation. Patients receiving rivaroxaban who report left upper abdominal and/or

shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Hepatic/Biliary/Pancreatic
Hepatic Impairment

Patients with significant hepatic disease (e.g, acute clinical hepatitis, chronic active hepatitis, liver cirrhosis) were excluded from clinical trials. Therefore, RIVAROXABAN 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.

Monitoring and Laboratory Tests

The prothrombin time (PT), measured in seconds, is influenced by rivaroxaban 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 4 DOSAGE AND ADMINISTRATION – Considerations for INR Monitoring of VKA Activity during Concomitant RIVAROXABAN Therapy).

Although rivaroxaban therapy will lead to an elevated INR, depending on the timing of the measurement (see 10.2 Pharmacodynamics), the INR is not a valid measure to assess the anticoagulant activity of rivaroxaban. The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant, including RIVAROXABAN.

At recommended doses, RIVAROXABAN affects the measurement of the aPTT and Heptest®. These tests are not recommended for the assessment of the pharmacodynamic effects of rivaroxaban (see 10.2 Pharmacodynamics).

Converting patients from warfarin to RIVAROXABAN, or from RIVAROXABAN 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 10.2 Pharmacodynamics).

Anti-Factor-Xa activity is influenced by rivaroxaban in a dose-dependent fashion. If it is desired to test the pharmacodynamic effects of rivaroxaban 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 RIVAROXABAN requires calibration and should not be done

unless rivaroxaban-specific calibrators and controls are available (see 10.2 Pharmacodynamics).

Although there is no need for routine monitoring of anticoagulation effect of RIVAROXABAN 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.

Perioperative Considerations
As with any anticoagulant, patients on RIVAROXABAN who undergo surgery or invasive procedures are at increased risk for bleeding. In these circumstances, temporary discontinuation of RIVAROXABAN 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 rivaroxaban or any local standard-of-care pharmacological therapy.

Pre-Operative Phase

If an invasive procedure or surgical intervention is required, RIVAROXABAN 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. RIVAROXABAN 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 RIVAROXABAN 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 RIVAROXABAN, 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 RIVAROXABAN should be delayed for 24 hours.

Patients who have undergone epidural puncture and who are receiving RIVAROXABAN 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 RIVAROXABAN 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 RIVAROXABAN. RIVAROXABAN 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 rivaroxaban 15 mg and 20 mg, or rivaroxaban 2.5 mg in combination with ASA in these situations for adults. There is no clinical experience with the use of rivaroxaban 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 rivaroxaban. Discontinue RIVAROXABAN and consider a short acting parenteral anticoagulant in these patients.

Post-Procedural Period

RIVAROXABAN 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

Renal Impairment

Following oral dosing with rivaroxaban, there is a direct relationship between pharmacodynamic effects and the degree of renal impairment (see 10.3 Pharmacokinetics – Renal Insufficiency).

Determine estimated creatinine clearance (eCrCl) in all patients before instituting RIVAROXABAN (see4 Dosage and Administration).

RIVAROXABAN 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 4 Dosage and Administration – Renal Impairment, and 9.4 Drug-Drug Interactions).

Physicians should consider the benefit/risk of anticoagulant therapy before administering RIVAROXABAN 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.

The use of RIVAROXABAN 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.

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, RIVAROXABAN 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 RIVAROXABAN should discontinue such treatment.

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

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

Anticoagulant-Related Nephropathy

There have been post-marketing reports of anticoagulant-related nephropathy (ARN) following rivaroxaban use, presenting as acute kidney injury. In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to

episodes of excessive anticoagulation and hematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with excessive anticoagulation, compromised renal function and hematuria (including microscopic).

7.1. Special Populations

7.1.1. Pregnancy

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

Based on animal data, use of RIVAROXABAN is contraindicated throughout pregnancy (see2 Contraindications, and 16 Non-Clinical Toxicology – Reproductive and Developmental Toxicology).

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

7.1.2. Breastfeeding

No data is available on the use of rivaroxaban in nursing mothers. In rats, rivaroxaban is secreted into breast milk. Therefore, RIVAROXABAN should only be administered after breastfeeding is discontinued (see2 Contraindications, and 16 Non-Clinical Toxicology – Reproductive and Developmental Toxicology).

7.1.3. Pediatrics

Pediatric Use (< 18 years of age): The safety and efficacy of rivaroxaban 2.5 mg and 10 mg film-coated tablets have not been established in children less than 18 years of age. Therefore, RIVAROXABAN 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 rivaroxaban have not been established for indications other than treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence. Therefore, RIVAROXABAN 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 RIVAROXABAN.

RIVAROXABAN is not indicated for child weighing less than 30 kg for the treatment of VTE and prevention of VTE recurrence.

7.1.4. Geriatrics

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 7 Warnings and Precautions – Renal Impairment, and 4 Dosage and administrations – Renal Impairment).

Increasing age may increase hemorrhagic risk. RIVAROXABAN 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 rivaroxaban (see 7 Warnings and Precautions, Drug Interactions, and9 Drug Interactions).

8. Adverse Reactions

8.1. Adverse Reaction Overview

Prevention of VTE after THR or TKR
The safety of 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 rivaroxaban, with 4,571 patients actually receiving rivaroxaban.

In RECORD 1 and 2, a total of 2209 and 1228 THR patients, respectively, were randomized to rivaroxaban 10 mg od. In RECORD 1, the treatment period for both groups was 35±4 days postoperatively. In RECORD 2, patients randomized to rivaroxaban 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 rivaroxaban 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 rivaroxaban has been evaluated in four Phase III trials with 6790 patients treated up to 21 months. Patients were exposed to 15 mg rivaroxaban 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 rivaroxaban 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 rivaroxaban and 4.4% for enoxaparin/VKA (pooled data from EINSTEIN DVT and EINSTEIN PE), 6.5% for rivaroxaban and 3.4% for placebo (EINSTEIN Extension) and 4.5% for rivaroxaban 10 mg, 4.5% for rivaroxaban 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 rivaroxaban 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 rivaroxaban 2.5 mg bid in combination with ASA 100 mg od (9,152), rivaroxaban 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 rivaroxaban 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, rivaroxaban is associated with an increased risk of occult or overt bleeding from any tissue and organ (see 7 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 4). 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 rivaroxaban. 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 rivaroxaban for different indications are not interchangeable, a summary description of major and total bleeding is provided by indication, in Table 5 for VTE prevention in patients undergoing elective THR or TKR surgery, in Table 6 for Treatment of VTE and prevention of recurrent DVT and PE, in Table 7 for stroke prevention in atrial fibrillation, and in Table 8 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 5 – RECORD 1, 2, and 3 (VTE Prevention After THR or TKR) – Treatment-Emergent Bleeding Events (Safety Population with Central Adjudication) in Patients Randomized to Rivaroxaban (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)	Rivaroxaban (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)	Rivaroxaban (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)

		Major Bleeding[a] n (%)	Major Bleeding Including Surgical Site Bleeding Events Associated With Hemoglobin Drops or Transfusions n (%)	Any Bleeding (Major or Nonmajor) n (%)
	P-Value	1.00	0.54	0.273
RECORD 3 (TKR)	Rivaroxaban (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)	Rivaroxaban (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 24 and Table 26 for additional details.

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

Table 6 – 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)

Bleeding event	Pooled EINSTEIN DVT and EINSTEIN PE			EINSTEIN Extension		EINSTEIN CHOICE		
	Rivaroxaban N=4130	Enox/VKA N=4116	HR (95%CI) *P*-value for superiority	20 mg od N=598	Placebo N=590	Rivaroxaban 10 mg N=1127	Rivaroxaban 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)	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)	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 5 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 rivaroxaban group and 6.0 % of subjects in the enoxaparin/VKA group. Major bleeding from a mucosal site was observed in 0.6 % of the rivaroxaban group and 0.7 % of the enoxaparin/VKA group.

Table 7 – 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

	Rivaroxaban		Warfarin		HR (95% CI); *P*-value
	n (%/year)		n (%/year)		
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 5 and Table 6 for definition of other footnotes.
* Statistically significant at nominal 0.05 (two-sided).
See Table 35, Table 37, and Table 38 for additional details.

Mucosal major bleeding was more common in the rivaroxaban 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%) rivaroxaban 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 8- 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	**Rivaroxaban 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
- 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 Rivaroxaban 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).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reaction observed in the clinical trials may not reflect the frequencies observed in clinical practice and should not be compared to the frequencies reported in the clinical trials of another drug.

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 9.

Table 9 – 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])

	Rivaroxaban (N=4571)		Enoxaparin (N=4601)	
	n	(%)	n	(%)
Blood and lymphatic system disorders				
Thrombocytosis (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)
Hematoma	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 (rivaroxaban 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 10.

Table 10- 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		
	Rivaroxaban (N=4130) n (%)	ENOXAPARIN/VK A (N=4116) n (%)	Rivaroxaban (N=598) n (%)	Placebo (N=590) n (%)	Rivaroxaban 10 mg (N=1127) n (%)	Rivaroxaban 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)

	Pooled EINSTEIN DVT and EINSTEIN PE		EINSTEIN Extension		EINSTEIN CHOICE		
	Rivaroxaban (N=4130) n (%)	**ENOXAPARIN/VK A (N=4116) n (%)**	**Rivaroxaban (N=598) n (%)**	**Placebo (N=590) n (%)**	**Rivaroxaban 10 mg (N=1127) n (%)**	**Rivaroxaban 20 mg (N=1107) n (%)**	**ASA 100 mg (N=1131) n (%)**
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)
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 disorder							
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)

	Pooled EINSTEIN DVT and EINSTEIN PE		EINSTEIN Extension		EINSTEIN CHOICE		
	Rivaroxaban (N=4130) n (%)	**ENOXAPARIN/VK A (N=4116) n (%)**	**Rivaroxaban (N=598) n (%)**	**Placebo (N=590) n (%)**	**Rivaroxaban 10 mg (N=1127) n (%)**	**Rivaroxaban 20 mg (N=1107) n (%)**	**ASA 100 mg (N=1131) n (%)**
Hemoptysis	100 (2.42)	98 (2.38)	1 (0.17)	1 (0.17)	0	6 (0.5)	1 (<0.1)
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 11.

Table 11 – Treatment-Emergent Adverse Drug Reactions occurring in ≥1% of Any Treatment Group - EINSTEIN Junior Phase III study (14372) (safety analysis)

	Rivaroxaban (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 hemorrhage	0	0	4	(2.5%)
Injury, poisoning and procedural complications				
Contusion	9	(2.7%)	1	(0.6%)
Subcutaneous hematoma	7	(2.1%)	0	0
Reproductive system and breast disorder				
Menorrhagia	20	(6.1%)	4	(2.5%)
Respiratory, thoracic and mediastinal disorders				
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 12.

Table 12 – 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

	Rivaroxaban (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				
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)

	Rivaroxaban (N=7111)		Warfarin (N=7125)	
	n	(%)	n	(%)
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 13. 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 13 – 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)

	Rivaroxaban 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

8.2.1. 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 rivaroxaban 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.

8.3. Less Common Clinical Trial Adverse 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 hematoma

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 rivaroxaban, 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 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, paresthesia, 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 erythematous, 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: anemia

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

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial 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 rivaroxaban and comparator arms were similar, see Table 9, Table 10, and Table 12 above.

8.5. Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of rivaroxaban. 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, atraumatic splenic rupture, thrombocytopenia

Hepatobiliary Disorders: cholestasis, hepatitis (including hepatocellular injury)

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

Renal and Urinary Disorders: anticoagulant-related nephropathy

Respiratory, Thoracic and Mediastinal Disorders: eosinophilic pneumonia

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

9 Drug Interactions

9.1. Serious Drug Interactions

- Concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein (P- gp), such as cobicistat, ketoconazole, itraconazole, posaconazole, or ritonavir
- 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 RIVAROXABAN.

9.2. Drug Interactions Overview

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 7 Warnings and Precautions - Drug Interactions).

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 7 Warnings and Precautions – Bleeding).

9.4. Drug-Drug Interactions

The use of RIVAROXABAN 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 rivaroxaban 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 (see2 Contraindications, and 7 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 RIVAROXABAN elimination pathways, either CYP 3A4 or P-gp, are expected to increase RIVAROXABAN plasma concentrations to a lesser extent. The expected increase is considered less clinically relevant, see Table 14.

Combined use of rivaroxaban with strong inducers of CYP 3A4 should generally by avoided, since efficacy of rivaroxaban may be compromised.

Table 14 – Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	**Reference**	**Effect**	**Clinical Comment**
Azole antimycotic: ketoconazole	CT	Co-administration of rivaroxaban with the azole-antimycotic ketoconazole (400 mg od) a strong CYP 3A4 and P-gp inhibitor, led to a 2.6-fold increase in mean rivaroxaban steady state AUC and a 1.7-fold increase in mean rivaroxaban C_{max}, with significant increases in its pharmacodynamic effects.	**The use of RIVAROXABAN is contraindicated in patients receiving systemic treatment with ketoconazole (see** 2 Contraindications and 7 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 RIVAROXABAN is contraindicated in patients receiving systemic treatment with cobicistat** (see 2 Contraindications and 7 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 RIVAROXABAN since it may increase exposure of RIVAROXABAN through P-gp and CYP3A4 inhibition, and thereby the risk of bleeding.
fluconazole	CT	Administration of the moderate CYP 3A4 inhibitor fluconazole	No dose adjustment is required.

Concomitant Drug Class: Drug Name	Reference	Effect	Clinical Comment
		(400 mg once daily) led to a 1.4-fold increase in mean rivaroxaban AUC and a 1.3-fold increase in mean C_{max}.	
Protease inhibitor: ritonavir	CT	Co-administration of rivaroxaban with the HIV protease inhibitor ritonavir (600 mg bid), a strong CYP 3A4 and P-gp inhibitor, led to a 2.5-fold increase in mean rivaroxaban AUC and a 1.6-fold increase in mean rivaroxaban C_{max}, with significant increases in its pharmacodynamic effects.	**The use of RIVAROXABAN is contraindicated in patients receiving systemic treatment with ritonavir** (see 2 Contraindicationsand 7 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 rivaroxaban AUC and C_{max}.	No dose adjustment is required. For patients with renal impairment see 7 Warnings and Precautions – Drug Interactions and 10.3 Pharmacokinetics – Special Populations and Conditions – Renal Insufficiency.
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 RIVAROXABAN 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 rivaroxaban with the strong CYP 3A4 and P-gp inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects.	Strong CYP 3A4 inducers should generally be avoided in combination with RIVAROXABAN, as such use can be expected to result in inadequate anticoagulation.
Anticonvulsants: phenytoin carbamazepine phenobarbital	T	The concomitant use of rivaroxaban with strong CYP 3A4 inducers (e.g, phenytoin, carbamazepine, or phenobarbital) may also lead to a decreased rivaroxaban plasma concentration.	Strong CYP 3A4 inducers should generally be avoided in combination with RIVAROXABAN, as such use can be expected to result in inadequate anticoagulation.

Concomitant Drug Class: Drug Name	Reference	Effect	Clinical Comment
Nonsteroidal Anti-inflammatory Drugs (NSAID): naproxen	CT	Co-administration with naproxen did not affect rivaroxaban 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 rivaroxaban 15 mg and naproxen 500 mg in healthy subjects.	Concomitant use with RIVAROXABAN may increase the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss (see 7 Warnings and Precautions – Drug Interactions).
acetylsalicylic acid (ASA)	CT	No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when 500 mg ASA was preadministered 24 hours before concomitant administration of single doses of rivaroxaban 15 mg and ASA 100 mg in healthy subjects.	Concomitant use with rivaroxaban increases the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss (see 7 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 rivaroxaban and warfarin.
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 rivaroxaban 15 mg and clopidogrel 75 mg in healthy subjects. Clopidogrel with or without rivaroxaban 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 rivaroxaban and clopidogrel had maximum bleeding times of up to 45 minutes. Rivaroxaban alone did not lead to a change in	Concomitant use with rivaroxaban increases the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss (see 7 Warnings and Precautions– Drug Interactions).

Concomitant Drug Class: Drug Name	Reference	Effect	Clinical Comment
		bleeding time at 4 hours or 2 days after administration. There was no change in the pharmacokinetics of either drug.	
Antithrombotic: enoxaparin	CT	After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose), an additive effect on anti-Factor-Xa activity was observed, without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the bioavailability and pharmacokinetics of rivaroxaban.	Co-administration of rivaroxaban 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 7 Warnings and Precautions – Drug Interactions).
Selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRIs)	T, CT	When concomitantly used in the rivaroxaban clinical program, numerically higher rates of major or non-major clinically relevant bleeding were observed	As with other anticoagulants, patients on RIVAROXABAN 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 rivaroxaban.

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

Co-administration of the proton pump inhibitor, omeprazole, the H2-receptor antagonist, ranitidine, the antacid, aluminum hydroxide / magnesium hydroxide, or naproxen, clopidogrel, or enoxaparin did not affect rivaroxaban bioavailability or pharmacokinetics.

9.5. Drug-Food Interactions

RIVAROXABAN 2.5 mg and 10 mg may be taken with or without food. RIVAROXABAN 15 mg and 20 mg should be taken with food (see 10.3 Pharmacokinetics).

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

9.6. Drug-Herb Interactions

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

9.7. Drug-Laboratory Test Interactions

Although various clotting parameter tests (PT, aPTT, Heptest®) are affected by the mode of action of rivaroxaban, none of these clotting tests have been demonstrated to reliably assess the anticoagulant activity of rivaroxaban following pmrivaroxaban administration under usual conditions (see 7 Warnings and Precautions – Monitoring and Laboratory Tests, and 10.2 Pharmacodynamics).

The prothrombin time (PT), measured in seconds, is influenced by rivaroxaban 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 7 Warnings and Precautions – Monitoring and Laboratory Tests).

10. Clinical Pharmacology

10.1. Mechanism of Action

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

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

10.2. 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 RIVAROXABAN 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 RIVAROXABAN. The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant (see 7 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 7 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

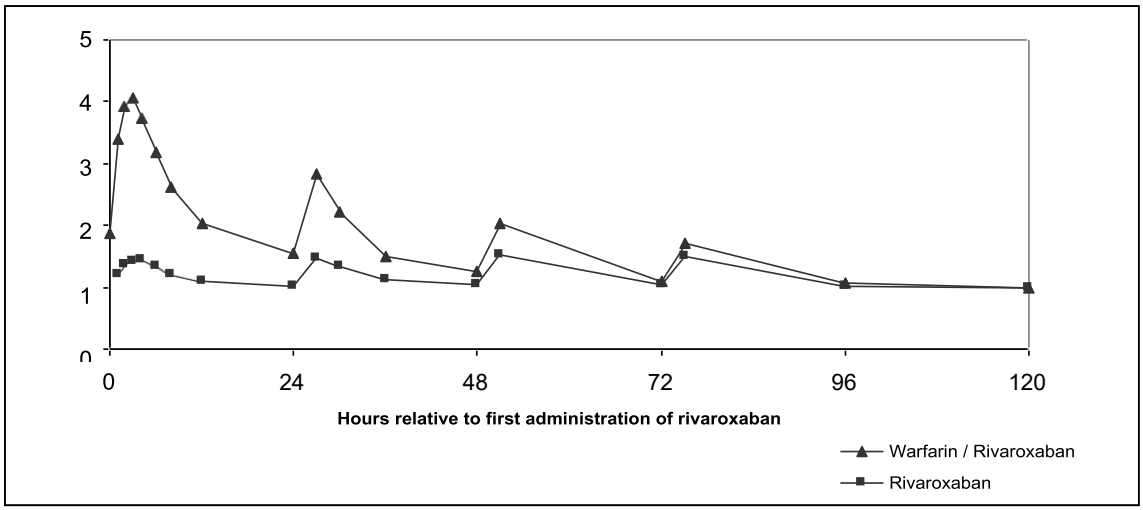
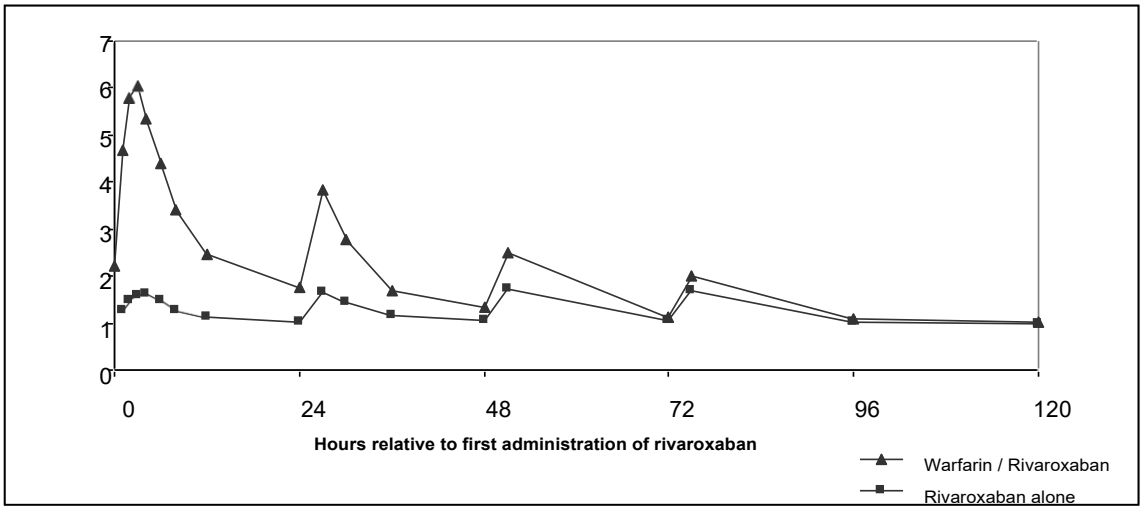


Figure 2: INR prolongation: Relative prolongation expressed as median of ratio to baseline with warfarin/ rivaroxaban treatment and rivaroxaban alone, following last day of warfarin (Day -1) and 4 days of 20 mg rivaroxaban od, PK/PD set, n=84



The usual expected effect of rivaroxaban on PT when the Neoplastin® reagent is used is shown in Table 15 below. The dose of 2.5 mg RIVAROXABAN is expected to only minimally affect PT.

Table 15 – PT (Neoplastin® reagent) by Indication, Following Rivaroxaban Administration

Indication	Rivaroxaban Dosage	Plasma concentration C_{max} (mcg/ L)	Plasma concentration C_{trough} (mcg/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.

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 t_{max} 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.

10.3. 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

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.

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

The absolute bioavailability of rivaroxaban is approximately 100% for doses up to 10 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. RIVAROXABAN 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 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.

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. RIVAROXABAN 15 mg and 20 mg tablets should be taken with food (see4 Dosage and Administration).

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

	C_{max} [mcg/L]	$t_{1/2}$ [h]	AUC [mcg*h/L]	Clearance, Urinary Excretion	Volume of Distribution
Healthy (Young) Subjects	approx. 114[a]	5-9	approx. 817	CL_{sys} = approx. 10 L/h CL_R = 3 – 4 L/h Ae_{ur} = 30% - 40%	V_{ss} = approx. 50 L
Patients	approx. 125	7-11	approx. 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.

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%. The volume of distribution is moderate with V_{ss} being approximately 50 L.

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.

Elimination

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

- **Pediatrics**

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 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.

As in adults, rivaroxaban is readily absorbed after oral administration as IR tablet 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.

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.

No metabolism data specific to children is available.

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 summarized in Table 17.

Table 17 – 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.)		
t.i.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 mcg/L)
Concentration: geometric mean (5^{th} - 95^{th} percentile)

- **Geriatrics**

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 rivaroxaban exposure (approximately 50%) compared to young healthy subjects. This difference may be due to reduced renal function in the elderly (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS – Renal Impairment, and 4 DOSAGE AND ADMINISTRATION – Renal Impairment).

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}.

- **Sex**

There were no relevant differences in pharmacokinetics and pharmacodynamics between male and female subjects, especially when taking into account body weight differences. 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%). In children, RIVAROXABAN is dosed based on body weight. An exploratory analysis in children did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure.

- **Ethnic Origin**

In adults, no clinically relevant interethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding pharmacokinetics and pharmacodynamics.

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.

RIVAROXABAN is contraindicated in patients with hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy, and having clinically relevant bleeding risk (see2 Contraindications, and 7 Warnings and Precautions – Hepatic Impairment).

The safety and pharmacokinetics of single-dose rivaroxaban (10 mg) were evaluated in a study in healthy subjects (n=16) and subjects with varying degrees of hepatic impairment (see Table 18). 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 18 - 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

- **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 m^2) or in children younger than 1 year

with serum creatinine results above 97.5th percentile (see 7 Warning 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.

The safety and pharmacokinetics of single-dose rivaroxaban (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 19). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed.

Table 19 - 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 7 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.

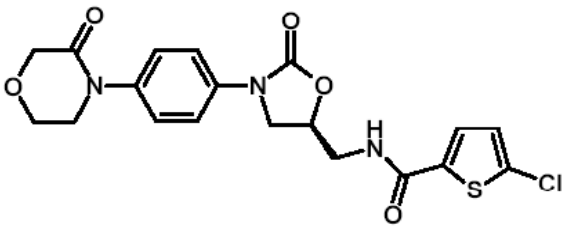
11. Storage, Stability, and Disposal

Store at 15°C to 30°C. Keep out of the reach and sight of children.

Part 2 : Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance:	Rivaroxaban
Chemical Name:	(5-Chloro-N)-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. (S)-5-Chlor-N-{2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-ylmetyl}tiophen-2-carbamid. 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)tiophene-2-carboxamide.
Molecular Formula and molecular mass: :	$C_{19}H_{18}ClN_3O_5S$ and 435.88 g/mol
Structural Formula:	
Physicochemical properties:	
Description:	White to yellowish powder.
Solubility:	Practically insoluble in water (7 mg/L, pure water) and very slightly soluble in acetone. Similarly, the solubility is also seen as being sparingly soluble at pH 1-10.

14. Clinical Trials

14.1. Clinical Trials by Indication

Prevention of VTE after THR or TKR

Table 20 – Summary of the Pivotal Studies for the Prevention of Venous Thromboembolic Events (VTE) in Patients Undergoing Elective Total Hip Replacement (THR) or Total Knee Replacement (TKR) Surgery

Study	Study Design	Treatment Regimen	Patient Populations
RECORD 1[a]	THR patients prospectively randomized to rivaroxaban or enoxaparin; noninferiority, double-blind, double-dummy design; multinational study.	**Rivaroxaban** 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 (2,266 rivaroxaban, 2,275 enoxaparin) Safety Population 4433 (2,209 rivaroxaban, 2,224 enoxaparin) mITT 3153 (1,595 rivaroxaban, 1,558 enoxaparin) mITT (for Major VTE) 3364 (1,686 rivaroxaban, 1,678 enoxaparin) Per Protocol 3029 (1,537 rivaroxaban, 1,492 enoxaparin)
RECORD 3[a]	TKR patients prospectively randomized to rivaroxaban or enoxaparin; noninferiority, double-blind, double-dummy design; multinational study.	**Rivaroxaban** 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 (1,254 rivaroxaban, 1,277 enoxaparin) Safety Population 2459 (1,220 rivaroxaban, 1,239 enoxaparin) mITT 1702 (824 rivaroxaban, 878 enoxaparin) mITT (for Major VTE) 1833 (908 rivaroxaban, 925 enoxaparin) Per Protocol 1631 (793 rivaroxaban, 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 pivotal studies were designed to demonstrate the efficacy of 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 rivaroxaban or to enoxaparin, see Table 20. 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 rivaroxaban 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, rivaroxaban 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 (rivaroxaban 70% and enoxaparin 66%, $P = 0.03$). The reasons for exclusion of patients from various analyses in both studies were also similar.

The results of the non-inferiority analysis of Total VTE for RECORD 1 and 3 are presented in Table 21. For the primary efficacy analysis, the difference between the incidences in the rivaroxaban 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 21 – 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)	
	Rivaroxaban 10 mg od N=1537 n (%)	**Enoxaparin 40 mg od N=1492 n (%)**	**Rivaroxaban 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 rivaroxaban 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 rivaroxaban 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 22 and Table 23, respectively.

Table 22 – 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	Rivaroxaban 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 23– 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	Rivaroxaban 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	166/878	18.9% (16.4% to	9.2% (5.9% to	<0.001	49% (35%-61%)	<0.001
Major VTE	9/908	1.0% (0.5% to	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	0/824	0% (0.0% to 0.5%)	2/878	0.2% (0.0% to 0.8%)	0.2% (-0.2% to	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	20/878	2.3% (1.4% to 3.5%)	1.1% (-0.1% to	0.07	--	--
Distal DVT only	70/824	8.5% (6.7% to	140/878	15.9% (13.6% to	7.3% (4.3% to	<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 fromall 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 abovezero.

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 rivaroxaban 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 rivaroxaban 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 24. In RECORD 1, serious drug-related treatment-emergent adverse events were reported in 26 (1.2%) for rivaroxaban and 23 (1.0%) for enoxaparin. In RECORD 3, serious drug-related treatment-emergent adverse events were reported in 26 (2.1%) for rivaroxaban and 19 (1.5%) for enoxaparin.

Table 24 – RECORD 1 and 3: Detailed Overview of Treatment-Emergent Bleeding Events (Safety Population)[a]

	RECORD 1 (THR)			RECORD 3 (TKR)		
	Rivaroxaban 10 mg od N=2209	**Enoxaparin 40 mg od N=2224**	***P*-Value**	**Rivaroxaban 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%)	--

	RECORD 1 (THR)			RECORD 3 (TKR)		
	Rivaroxaban 10 mg od N=2209	**Enoxaparin 40 mg od N=2224**	***P*-Value**	**Rivaroxaban 10 mg od N=1220**	**Enoxaparin 40 mg od N=1239**	***P*-Value**
	Rivaroxaban 10 mg od N=2209	**Enoxaparin 40 mg od N=2224**	***P*-Value**	**Rivaroxaban 10 mg od N=1220**	**Enoxaparin 40 mg od N=1239**	***P*-Value**
Clinically overt extra-surgical site bleeding leading to transfusion of ≥2 units of blood n (%)	2 (0.1%)	1 (<0.1%)		1 (0.1%)	0 (0.0%)	
Nonmajor Bleeding[d] n (%)	128 (5.8%)	129 (5.8%)	--	53 (4.3%)	54 (4.4%)	--
Clinically relevant nonmajor bleeding n (%)	65 (2.9%)	54 (2.4%)	--	33 (2.7%)	28 (2.3%)	--
Hemorrhagic wound complications[e] n (%)	34 (1.5%)	38 (1.7%)	--	25 (2.0%)	24 (1.9%)	--

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

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

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

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

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

Phase III Supportive Study

RECORD 2 was a randomized, double-blind, double-dummy, prospective study conducted in 2509 randomized patients (safety population = 2457; mITT = 1733) undergoing THR. The aim of RECORD 2 was to assess extended thromboprophylaxis with rivaroxaban 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 rivaroxaban 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 rivaroxaban and enoxaparin.

Table 25 – 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	Rivaroxaban 10 mg od for 35±4 days		Enoxaparin 40 mg for 12±2 days		Absolute Risk Reduction	*P*-Value	Relative Risk Reduction	*P*-Value
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)		% (95% CI)	
Total VTE	17/864	2.0% (1.2% to 3.1%)	81/869	9.3% (7.5% to 11.5%)	7.3% (5.2% to 9.4%)	<0.0001	79% (65% to 87%)	< 0.001
Major VTE	6/961	0.6% (0.2% to 1.4%)	49/962	5.1% (3.8% to 6.7%)	4.5% (3.0% to 6.0%)	<0.0001	88% (71% to 95%)	< 0.001
Death from all causes	2/864	0.2% (<0.1% to 0.8%)	6/869	0.7% (0.3% to 1.5%)	0.5% (-0.2% to 1.3%)	0.29	--	--
Nonfatal PE	1/864	0.1% (<0.1% to 0.6%)	4/869	0.5% (0.1% to 1.2%)	0.3% (-0.2% to 1.1%)	0.37	--	--
DVT (proximal and/or distal)	14/864	1.6% (0.9% to 2.7%)	71/869	8.2% (6.4% to 10.2%)	6.5% (4.5% to 8.5%)	<0.0001	--	--
Proximal DVT	5/864	0.6% (0.2% to 1.3%)	44/869	5.1% (3.7% to 6.7%)	4.5% (2.9% to 6.0%)	<0.0001	--	--
Distal DVT only	9/864	1.0% (0.5% to 2.0%)	27/869	3.1% (2.1% to 4.5%)	2.0% (0.7% to 3.3%)	0.0025	--	--
VTE-related death	0/864	0%	1/869	0.1%	--	--	--	--
Symptomatic VTE[c]	3/1212	0.2% (<0.1% to 0.7%)	15/1207	1.2% (0.7% to 2.0%)	1.0% (0.3% to 1.8%)	0.0040	--	--

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

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

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

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

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 26 – RECORD 2 (THR): Detailed Overview of Treatment-Emergent Bleeding Events (Safety Population)[a]

	Rivaroxaban 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 rivaroxaban 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

Table 27 - 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	Rivaroxaban 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 Rivaroxaban, 1718 Enox/VKA) Safety Population 3429 (1718 Rivaroxaban, 1711 Enox/VKA) Per Protocol 3096 (1525 Rivaroxaban, 1571 Enox/VKA)
EINSTEIN PE			Randomized 4833, (2420 Rivaroxaban, 2413 Enox/VKA) Safety Population 4817 (2412 Rivaroxaban, 2405 Enox/VKA) Per Protocol 4462 (2224 Rivaroxaban, 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	Rivaroxaban 20 mg once daily or placebo for 6 or 12 months[a]	Randomized 1197 (602 Rivaroxaban, 594 placebo)
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	Rivaroxaban 10 mg, or 20 mg or ASA 100 mg once daily[b]	Randomized 3396 (1121 Rivaroxaban 20 mg, 1136 Rivaroxaban 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

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.

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 Rivaroxaban 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 28 – 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 Rivaroxaban 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 29 - Efficacy outcomes in EINSTEIN DVT, EINSTEIN PE and EINSTEIN Extension – ITT population

	EINSTEIN DVT			EINSTEIN PE			EINSTEIN Extension		
	Rivaroxaban N=1731	**Enox/VKA N=1718**	**HR (95% CI) P-value**	**Rivaroxaban N=2419**	**Enox/VKA N=2413**	**HR (95% CI) P-value**	**Rivaroxaban N=602**	**Placebo N=594**	**HR (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 30 – Efficacy outcomes in EINSTEIN CHOICE

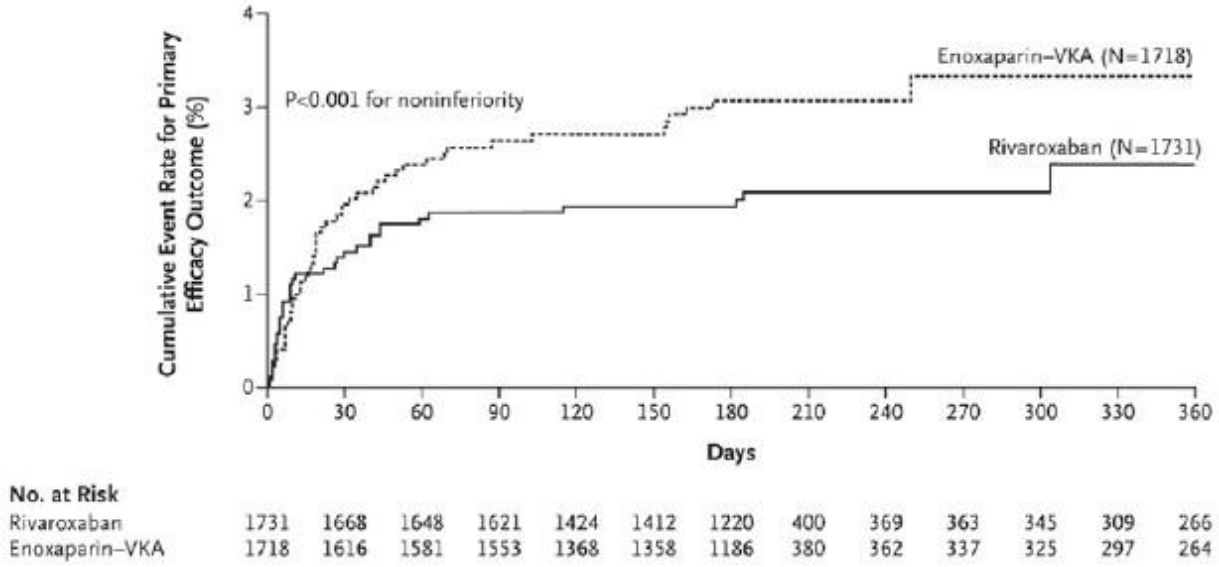
	Rivaroxaban 10 mg N=1127	Rivaroxaban 20 mg N=1107	ASA 100 mg N=1131	Rivaroxaban 20 mg vs. ASA 100 mg HR[a] (95% CI) P-value	Rivaroxaban 10 mg vs. ASA 100 mg HR[a] (95% CI) P-value
Symptomatic Recurrent VTE[b]	13 (1.2%)	17 (1.5%)	50 (4.4%)	0.34 (0.20-0.59) *P* = 0.0001[c]	0.26 (0.14-0.47) *P* <0.001[c]
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 rivaroxaban 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 29 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 rivaroxaban. The relative efficacy and safety findings were consistent regardless of pre-treatment (none, LMWH, unfractionated heparin or fondaparinux) as well as among the 3, 6 and 12-month durations. In terms of other secondary outcomes, vascular events during study treatment occurred in 12 patients (0.7%) in the rivaroxaban 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 rivaroxaban 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

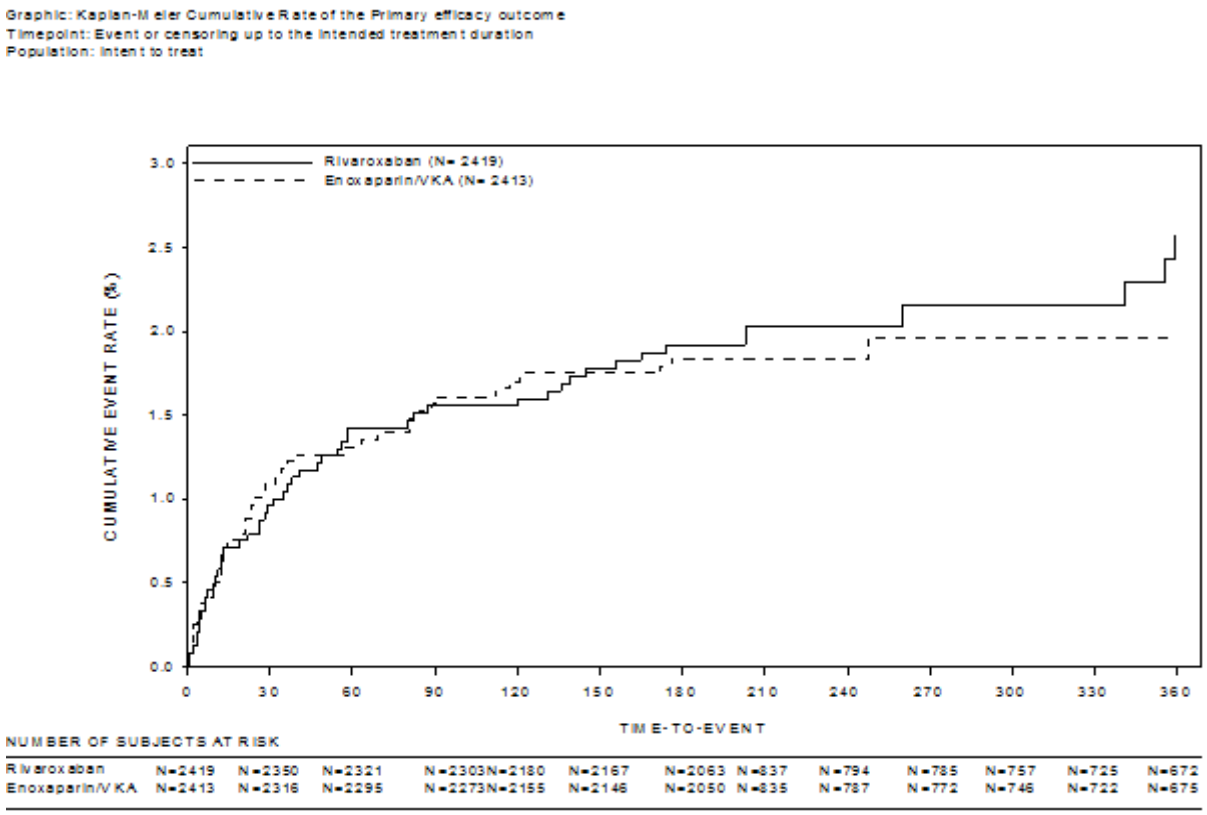


EINSTEIN PE

EINSTEIN PE met its principal objective demonstrating that rivaroxaban 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 29 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 rivaroxaban 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 rivaroxaban. The relative efficacy and safety findings were consistent regardless of pre-treatment (none, LMWH, unfractionated heparin or fondaparinux) as well as among the 3, 6 and 12 month durations. In terms of other secondary outcomes, vascular events during study treatment occurred in 41 patients (1.7%) in the rivaroxaban 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 rivaroxaban vs. enoxaparin/VKA arms, respectively, within intended treatment duration (*P* = 0.53).

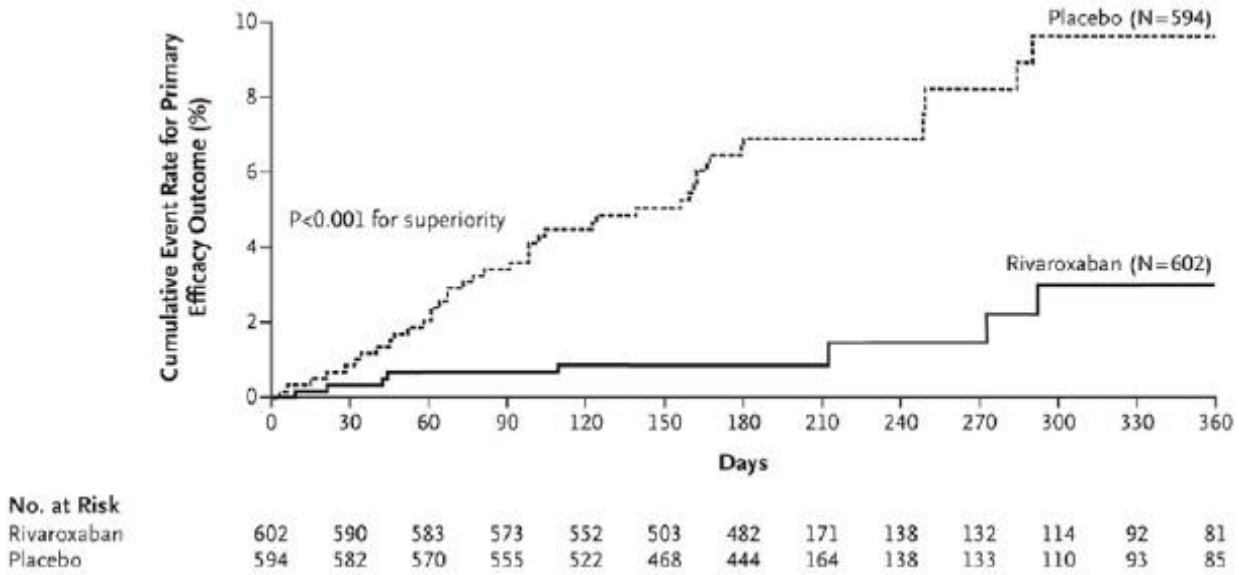
Figure 4: Kaplan-Meier analysis: cumulative rate of primary efficacy outcome in study 11702 PE - ITT Population



EINSTEIN Extension

In the EINSTEIN Extension study, rivaroxaban 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 29 and Figure 5). For the principal safety outcome (major bleeding events) there was no significant difference between patients treated with rivaroxaban 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 rivaroxaban. In terms of other secondary outcomes, vascular events occurred in 3 patients in the rivaroxaban 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 rivaroxaban vs. placebo arms, respectively.

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



EINSTEIN CHOICE

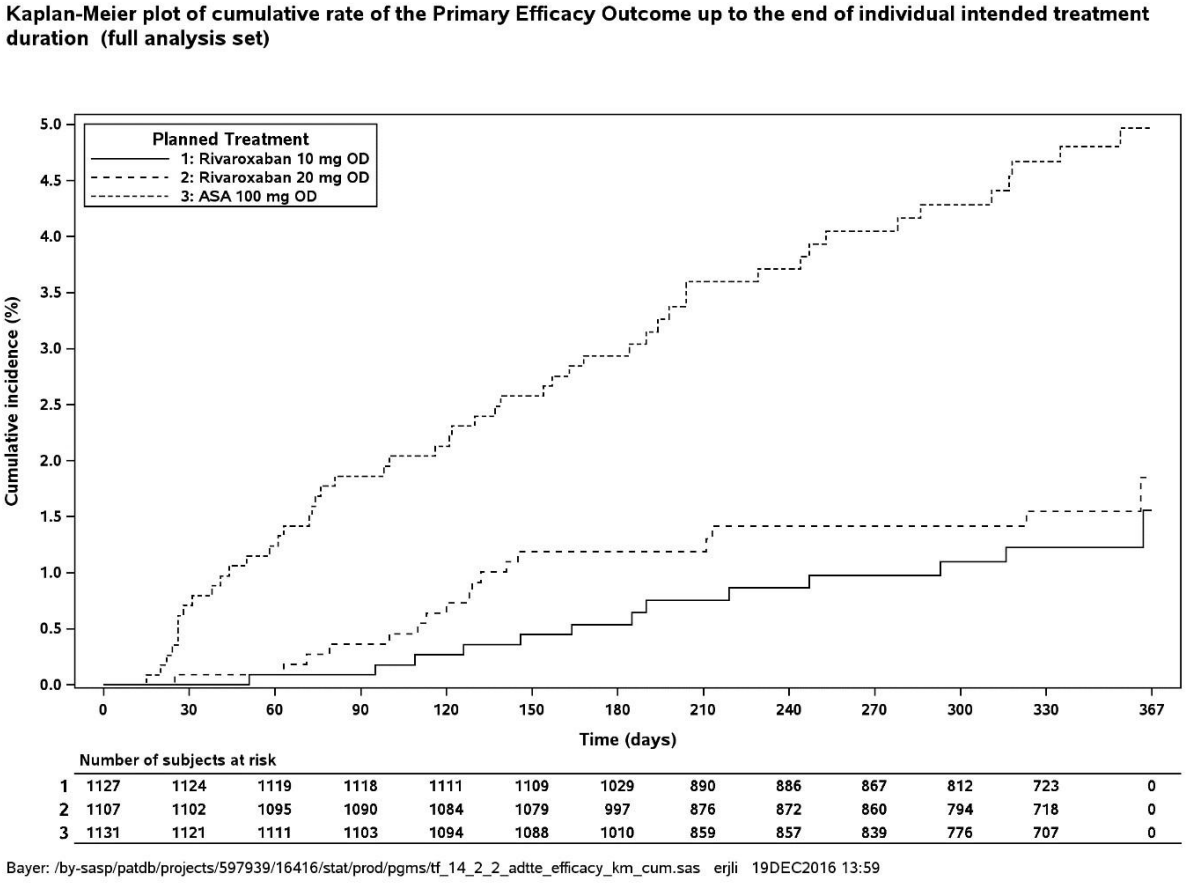
In EINSTEIN CHOICE 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of therapeutic-dose anticoagulation and who did not have an indication for continued anticoagulation in therapeutic doses, were studied for the prevention of fatal PE or non-fatal symptomatic recurrent 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). Rivaroxaban 20 mg once daily and rivaroxaban 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 rivaroxaban 20 mg and 10 mg versus acetylsalicylic acid 100 mg. The secondary efficacy outcome was significantly reduced when comparing rivaroxaban 20 mg or 10 mg vs. 100 mg acetylsalicylic acid. The principal safety outcome (major bleeding events) was similar for patients treated with rivaroxaban 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 rivaroxaban 20 mg or 10 mg vs. 100 mg acetylsalicylic acid. Outcomes were consistent across the patients with provoked and unprovoked VTE (see Table 30).

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 rivaroxaban 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 rivaroxaban 10 mg once daily vs 100 mg acetylsalicylic acid once daily were reported.

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



PHASE IV STUDY

Phase IV clinical studies (XALIA) was 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 rivaroxaban under real-world conditions (central outcome adjudication including recurrent VTE, major bleeding and death. In 2619 rivaroxaban-treated patients, rates of major bleeding, recurrent VTE and all-cause

mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively.

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

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 rivaroxaban 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 10.3 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 31 and Table 32 below.

At the end of the main treatment period, symptomatic recurrent VTEs occurred in 4 of 335 patients (1.2%) in the rivaroxaban 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 rivaroxaban 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 rivaroxaban 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 rivaroxaban 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 31 – Efficacy results at the end of the main treatment period

Event	rivaroxaban (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 32 – Safety results at the end of the main treatment period

Event	rivaroxaban (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 rivaroxaban 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 pediatric VTE population as compared to the DVT/PE adult population.

Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation

Table 33 – 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	**Rivaroxaban** 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 rivaroxaban, 7133 warfarin) Safety Population 14,236 (7111 rivaroxaban, 7125 warfarin) Per Protocol 14,054 (7008 rivaroxaban, 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

Evidence for the effectiveness of rivaroxaban 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 rivaroxaban 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

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 7 Warning and Precautions - Cardiovascular, Patients with valvular disease).

The primary objective of this study was to demonstrate that rivaroxaban, 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 rivaroxaban was superior to warfarin in primary and secondary endpoints.

The study design, treatment regimen and patient populations are summarized in Table 34 and Table 35. A total of 14,264 patients were randomized with a mean age of 71 years (range 25 to 97 years) and a mean CHADS2 score of 3.5. Patients were randomized to 20 mg once daily

rivaroxaban (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 rivaroxaban 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 34. 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 34 – 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, rivaroxaban 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, rivaroxaban was tested, as per the pre-specified analysis, for superiority in primary and secondary endpoints. rivaroxaban 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 35 and Figure 7 below.

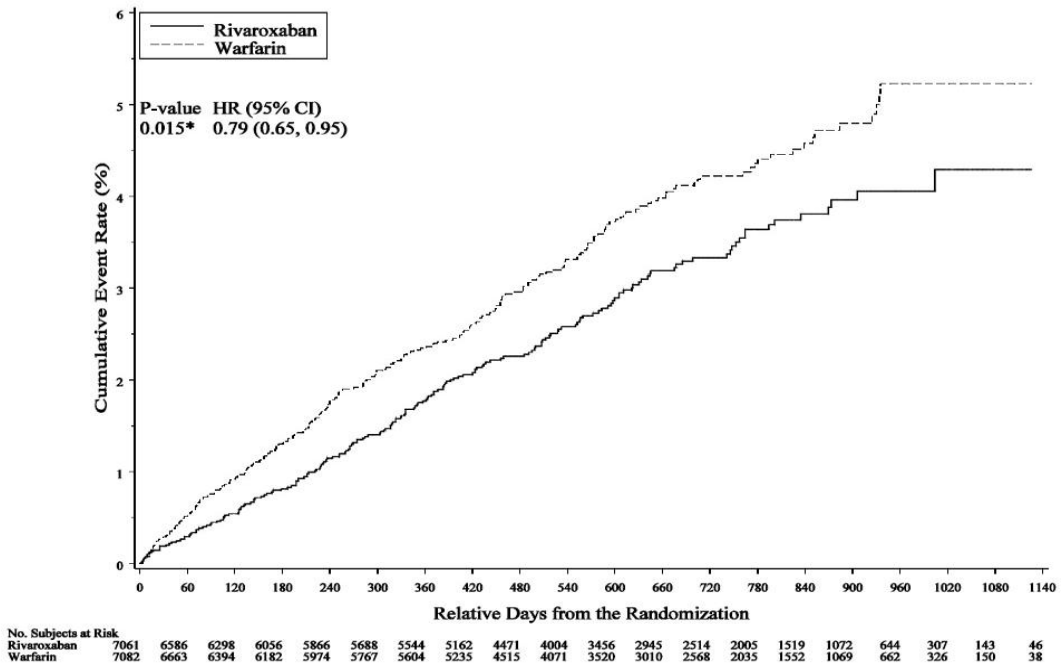
Table 35 – ROCKET AF – Time to the First Occurrence of Total Stroke and Systemic Embolism, While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

Parameter	Rivaroxaban (N=7,061)		Warfarin (N=7,082)		Rivaroxaban 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 rivaroxaban 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 rivaroxaban has a similar rate to warfarin for the composite of major and non-major clinically relevant bleeding, see Table 36 below.

Table 36 – ROCKET AF – Time to the First Occurrence of Bleeding Events While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

Parameter	Rivaroxaban (N=7111)		Warfarin (N=7125)		Rivaroxaban 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*

Parameter	Rivaroxaban (N=7111)		Warfarin (N=7125)		Rivaroxaban vs Warfarin	
	n	%/year	N	%/year	Hazard Ratio (95% CI)	*P*-value
Non-major Clinically Relevant Bleeding	1185	11.80	1151	11.37	1.04 (0.96,1.13)	0.345

All analyses 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 rivaroxaban versus Warfarin in hazard ratio.
* Statistically significant

The incidences of increased liver function tests were low and comparable between the two groups, see Table 37.

Table 37 – ROCKET AF – Incidence of Pre-specified Post-baseline Liver Function Abnormalities – Safety Population

Parameter	Rivaroxaban (N=7111)		Warfarin (N=7125)		Rivaroxaban 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 38 and Table 39. The event rates for efficacy and safety outcomes stratified by renal function are presented in Table 40 and Table 41.

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

	Rivaroxaban		Warfarin		Rivaroxaban 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)	-

	Rivaroxaban		Warfarin		Rivaroxaban vs Warfarin	
	n/J	Event rate (%/yr)	n/J	Event rate (%/yr)	Hazard Ratio (95% CI)	*P*-value
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)	-
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 rivaroxaban versus warfarin in hazard ratio

* Statistically significant

Table 39 – Bleeding Endpoints by Age Groups in the ROCKET AF trial, While on Treatment (up to Last Dose Plus 2 Days) – Safety Population

	Rivaroxaban		Warfarin		Rivaroxaban 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

	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
	n/J	Event rate (%/yr)	n/J	Event rate (%/yr)	Hazard Ratio (95% CI)	*P*-value
< 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)	-
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 rivaroxaban versus warfarin in hazard ratio

* Statistically significant

Table 40 – 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

	Rivaroxaban		Warfarin		Rivaroxaban vs Warfarin	
	n/J[a]	Event rate (%/yr)	n/J[a]	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.

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 rivaroxaban versus warfarin in hazard ratio

* Statistically significant

Table 41 – 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

	Rivaroxaban		Warfarin		Rivaroxaban 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 rivaroxaban versus warfarin in hazard ratio

* Statistically significant

PHASE IV STUDY

Phase IV clinical studies (XANTUS) was done to evaluate the effects of rivaroxaban use under

real-world (clinical practice) conditions.

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. 6,704 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 $CHADS_2$ score of the population was 1.9. 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 rivaroxaban in this population.

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 rivaroxaban 2.5 mg bid in combination with 100 mg ASA or rivaroxaban 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 rivaroxaban 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 rivaroxaban 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 rivaroxaban 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.

Relative to ASA 100 mg od, rivaroxaban 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 42 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 42). 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 rivaroxaban 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 Hemostasis [mISTH] major bleeding events) in patients treated with rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily compared to patients who received ASA 100 mg (see Table 9). 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 43).

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 7 Warnings and Precautions – Bleeding).

Table 42 - Efficacy results from the Phase III COMPASS Study

Treatment and Dosage	Overall Study Population[a]		
	Rivaroxaban 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[c]
- 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
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 Rivaroxaban 2.5 mg plus ASA 100 mg vs. ASA 100 mg; Log-Rank p-value.
c 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

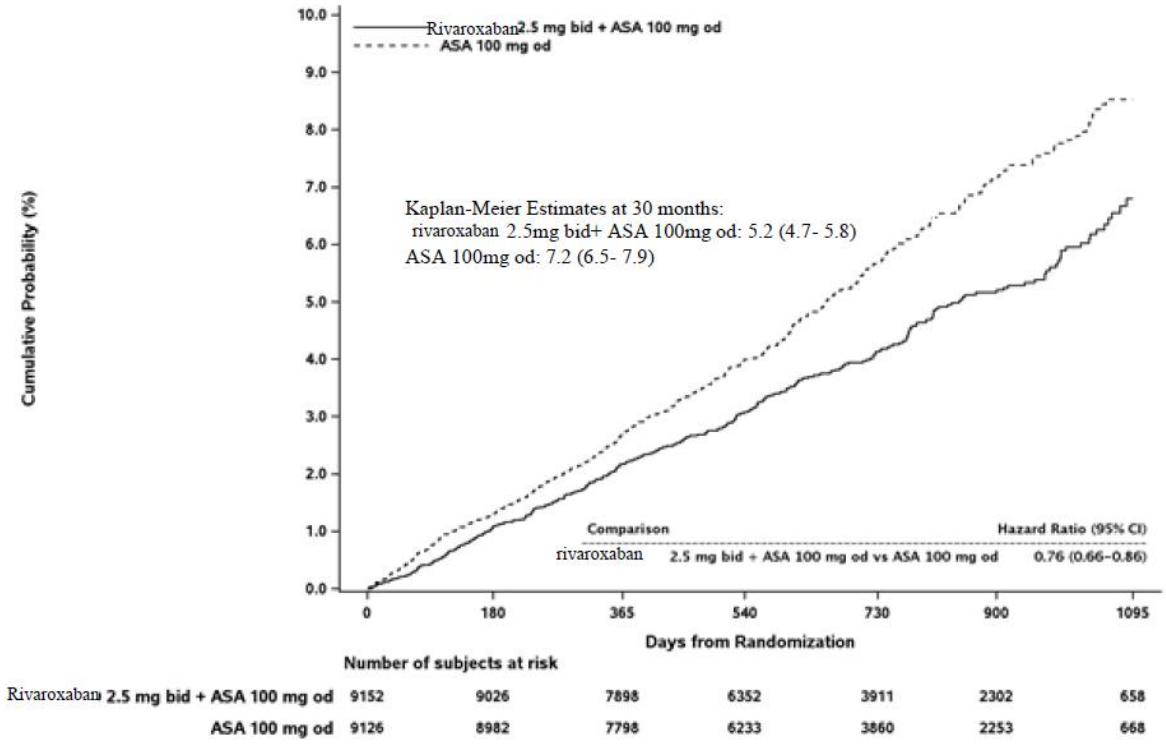
Table 43 - Efficacy and safety results from Phase III COMPASS Study - Subgroup analysis[a]

Treatment Dosage	**Rivaroxaban 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
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

a Intention-to-treat analysis set, primary analyses.
b Rivaroxaban 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

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



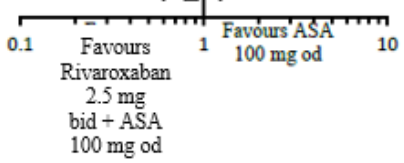
bid: twice daily; od: once daily; CI: confidence interval

Analysis of Patient Subgroups

The incidences and treatment effect of rivaroxaban 2.5 mg bid in combination with ASA 100 mg od for the primary efficacy and safety outcome across major subgroups are presented in Table 43 and Table 44 below. The treatment effect was similar with no significant p-value for interaction across major subgroups.

Table 44 - Summary of the Results for the Primary Efficacy Outcome According to Patient Subgroup in the Phase III COMPASS Study

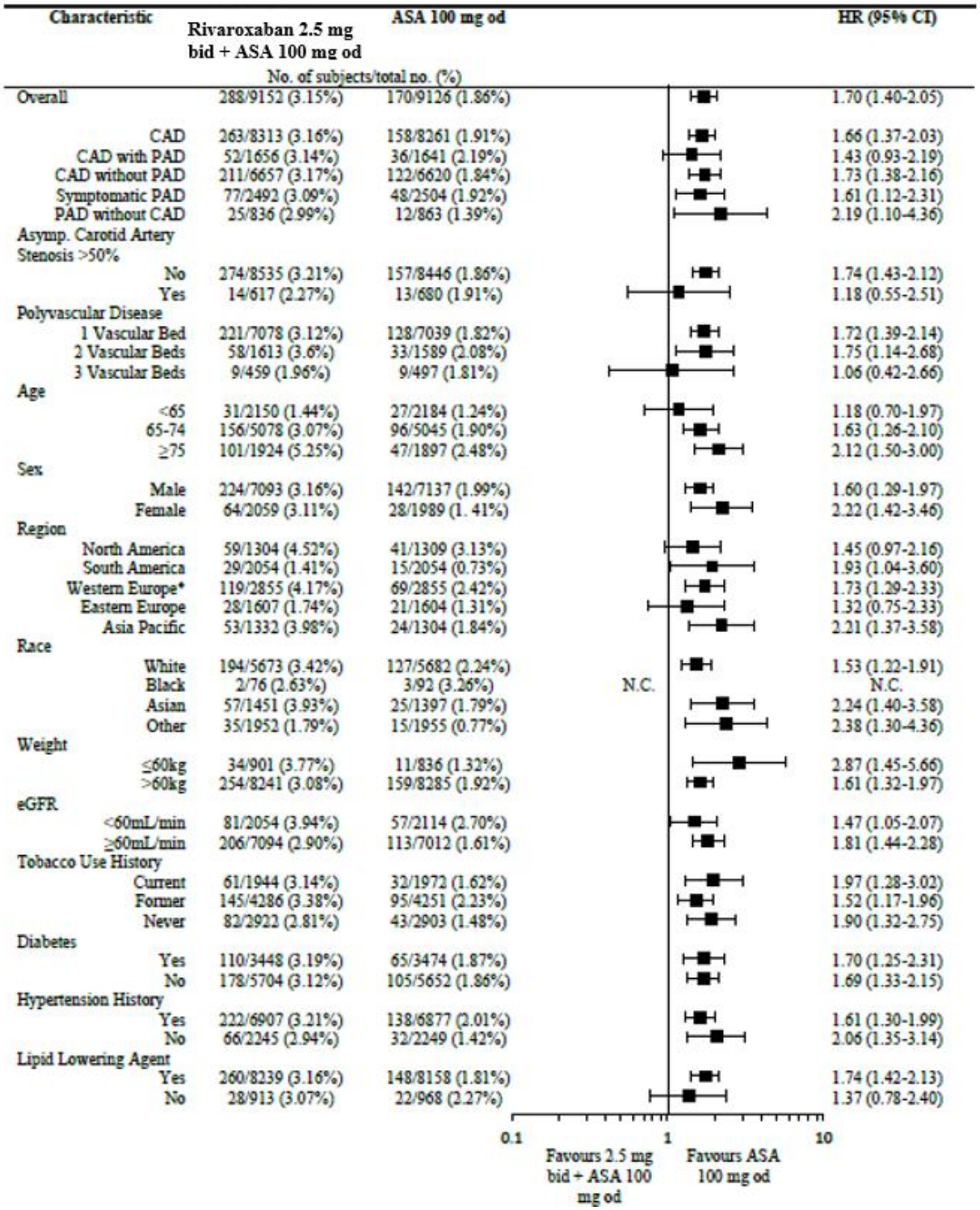
Characteristic	Rivaroxaban 2.5 mg bid + ASA 100 mg od	ASA 100 mg od	HR (95% CI)
	No. of subjects/total no. (%)		
Overall	379/9152 (4.14%)	496/9126 (5.44%)	0.76 (0.66-0.86)
CAD	347/8313 (4.17%)	460/8261 (5.57%)	0.74 (0.65-0.86)
CAD with PAD	94/1656 (5.68%)	138/1641 (8.41%)	0.67 (0.52-0.87)
CAD without 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 45 – mISTH Major Bleeding Results According to Patient Subgroup in the Phase III COMPASS Study



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

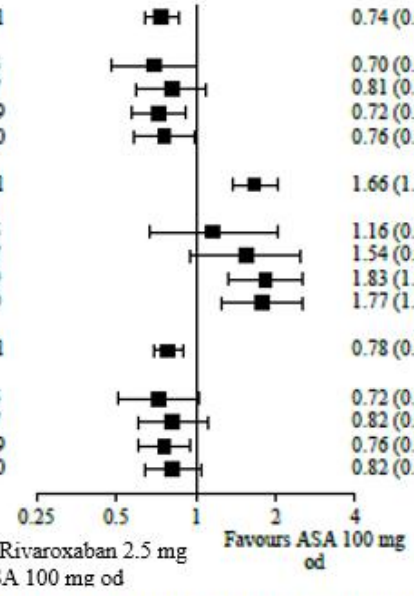
- Western Europe also includes AUS/ISR/ZAF.

CAD Subpopulation

The incidences and treatment effect of rivaroxaban 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 46.

Table 46 – Primary Efficacy, Primary Safety and Net Clinical Benefit in Patients with CAD[§] from the COMPASS Study.

Outcome	CAD Patients	Rivaroxaban 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.

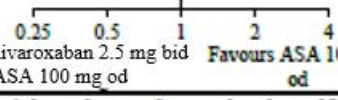
Landmark Analysis

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 47) 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 rivaroxaban 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 47- Landmark Analysis of the CAD§ Sub-Population of the COMPASS Study

Outcome	Time Since Randomization	Rivaroxaban 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 rivaroxaban 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 48. 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 rivaroxaban 2.5 g bid in combination with ASA 100 mg od versus ASA 100 mg od.

Table 48 - Primary Efficacy, Primary Safety, Limb Outcomes and Key Composite Outcomes in Patients with PAD§ from the COMPASS Study

	Rivaroxaban 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.

14.2. Comparative Bioavailability Studies

A randomised, two-treatment, two-sequence, two-period, single 1 x 20 mg dose, crossover bioavailability study of RIVAROXABAN (Rivaroxaban Tablets) 20 mg (Sivem Pharmaceuticals ULC) versus XARELTO® (rivaroxaban tablets) 20 mg (Bayer Inc.) was conducted in 24 healthy Asian adult male subjects under fed (high calorie/high fat) conditions. The results from 19 subjects that completed the study are summarised in the following table.

Table 49– Summary Table of the Comparative Bioavailability Data - Fed

Rivaroxaban (1 x 20 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_t (ng.h/mL)	3320.71 3451.59 (28.32)	3485.21 3614.35 (28.29)	95.2	91.2 - 99.3
AUC_{inf} (ng.h/mL)	3379.16 3507.27 (27.80)	3556.45 3683.67 (28.10)	94.9	90.9 - 99.0
C_{max} (ng/mL)	433.63 443.52 (21.24)	421.17 435.85 (26.20)	102.5	97.7 - 107.5
T_{max}[3] (h)	3.00 (1.50 - 5.50)	3.67 (1.50 - 10.00)		
$T_{½}$[4] (h)	5.43 (21.37)	5.96 (32.16)		

[1] Test: RIVAROXABAN (Rivaroxaban Tablets) 20 mg from Sivem Pharmaceuticals ULC
[2] Reference: Xarelto® (rivaroxaban tablets) 20 mg from Bayer Inc. (purchased in Canada)
[3] Expressed as median (range) only
[4] Expressed as the Arithmetic mean (%CV) only

A randomised, two-treatment, two-sequence, two-period, single 1 x 20 mg dose, crossover bioavailability study of RIVAROXABAN (Rivaroxaban Tablets) 20 mg (Sivem Pharmaceuticals ULC) versus XARELTO® (rivaroxaban tablets) 20 mg (Bayer Inc.) was conducted in 24 healthy Asian adult male subjects under fasting conditions. The results from 23 subjects that completed the study are summarised in the following table.

Table 50– Summary Table of the Comparative Bioavailability Data Fasting

Rivaroxaban (1 x 20 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_t (ng.h/mL)	2723.21 2849.44 (31.69)	2595.36 2749.337 (31.88)	104.9	97.9 - 112.4
AUC_{inf} (ng.h/mL)	2812.54 2957.65 (29.70)	2678.05 2828.05 (30.81)	105.0	97.4 - 113.3
C_{max} (ng/mL)	264.79 282.21 (42.70)	270.15 282.16 (30.46)	98.0	88.0 - 109.2
T_{max}[3] (h)	2.00 (1.00 – 5.00)	2.00 (0.50 – 4.33)		
$T_{½}$[4] (h)	8.91 (83.97)	7.94 (44.42)		

[1] Test: RIVAROXABAN (Rivaroxaban Tablets) 20 mg from Sivem Pharmaceuticals ULC
[2] Reference: Xarelto® (rivaroxaban tablets) 20 mg from Bayer Inc. (purchased in Canada)
[3] Expressed as median (range) only
[4] Expressed as the Arithmetic mean (%CV) only

A randomised, two-treatment, two-sequence, two-period, single 1 x 10 mg dose, crossover bioavailability study of RIVAROXABAN (Rivaroxaban Tablets) 10 mg (Sivem Pharmaceuticals ULC) versus XARELTO® (rivaroxaban tablets) 10 mg (Bayer Inc.) was conducted in 24 healthy Asian adult male subjects under fasting conditions. The results from 24 subjects that completed the study are summarised in the following table.

Table 51– Summary Table of the Comparative Bioavailability Data - Fasting

Rivaroxaban (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_t (ng.h/mL)	1671.70 1726.10 (25.34)	1696.40 1765.75 (28.48)	98.5	93.7 - 103.7
AUC_{inf} (ng.h/mL)	1739.62 1790.29 (24.11)	1768.86 1830.92 (26.61)	98.3	93.7 - 103.3
C_{max} (ng/mL)	190.92 198.29 (25.57)	194.32 201.258 (26.23)	98.3	90.9 - 106.2
T_{max}[3] (h)	2.835 (0.75 - 5.00)	2.67 (0.75 – 4.67)		
$T_{½}$[4] (h)	6.39 (23.08)	6.93 (22.97)		

[1] Test: RIVAROXABAN (Rivaroxaban Tablets) 10 mg from Sivem Pharmaceuticals ULC
[2] Reference: Xarelto® (rivaroxaban tablets) 10 mg from Bayer Inc.(purchased in Canada)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (%CV) only

A double-blind, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover bioavailability Study of RIVAROXABAN (Rivaroxaban Tablets) 2.5 mg (Sivem Pharmaceuticals ULC) versus PrXARELTO® (Rivaroxaban Tablets) 2.5 mg (Bayer Inc.,) was conducted in 32 healthy, adult, subjects under fasting conditions. The results of the 28 subjects who completed the study are summarized as follow:

Table 52– Summary Table of the Comparative Bioavailability Data

Rivaroxaban (1 x 2.5 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng•h/mL)	505.85 533.61 (37.45)	482.26 501.58 (30.56)	106.4	101.7 - 111.3
AUC_I (ng•h/mL)	527.07 555.18 (36.95)	504.92 524.77 (30.45)	105.8	101.3 - 110.6

Rivaroxaban (1 x 2.5 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
C_{max} (ng/mL)	77.43 80.74 (31.06)	75.10 77.05 (23.64)	104.1	98.8 - 109.8
T_{max}[3] (h)	2.67 (0.67 - 5.00)	2.67 (0.67- 4.50)		
$T_{½}$[4] (h)	4.36 (19.90)	4.17 (22.38)		

[1] RIVAROXABAN (Rivaroxaban Tablets), 2.5 mg (Sivem Pharmaceuticals ULC)
[2] PrXARELTO® (Rivaroxaban Tablets), 2.5 mg (Bayer Inc.)
[3] Expressed as the median (range) only
[‡] Expressed as the arithmetic mean (CV%) only.

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General Toxicology (repeat-dose studies)

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

Carcinogenicity

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.

Genotoxicity

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.

Reproductive and Developmental 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 (see2 Contraindications).

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

[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 2 Contraindications).

Juvenile Toxicity
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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. XARELTO® (Tablets, 2.5 mg, 10 mg, 15 mg and 20 mg of rivaroxaban), submission control 297542, Product Monograph, Bayer Inc. (2025-09-23).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] RIVAROXABAN
Rivaroxaban Tablets

This patient medication information is written for the person who will be taking **RIVAROXABAN**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.
This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **RIVAROXABAN**, talk to a healthcare professional.

What RIVAROXABAN is used for:
RIVAROXABAN 10 mg, 15 mg and 20 mg tablets are used in adults to:

- prevent blood clots after major hip or knee surgery
- treat and prevent blood clots in the veins of the legs, arms or lungs
- prevent blood clots in the brain (stroke) and other blood vessels in the body of patients who have atrial fibrillation (irregular heart rhythm)

RIVAROXABAN 2.5 mg tablets are used in combination with acetylsalicylic acid (ASA) in adults to:

- prevent stroke, heart attack or severe leg or arm pain in patients with peripheral artery disease who are at high risk. This is a condition where the blood vessels that carry blood away from the heart to other parts of the body (arteries) are narrowing due to plaque buildup.
- prevent stroke, heart attack, severe leg or arm pain, or death in patients with coronary heart disease. This is a condition where the blood vessels supplying blood to the heart (coronary arteries) become narrow or blocked due to plaque buildup. This causes a lack of oxygen in the heart. These patients may also have peripheral artery disease.

RIVAROXABAN 15 mg and 20 mg tablets are used to treat and prevent blood clots in the veins of the arms or legs, or in the blood vessels of the lungs in:

- children and adolescents below 18 years of age who weigh from 30 kg to 50 kg (15 mg tablets)
- children and adolescents below 18 years of age who weigh more than 50 kg (20 mg tablets)

RIVAROXABAN will be given to your child once they complete at least 5 days of treatment with an injectable blood thinner.

How RIVAROXABAN work:

RIVAROXABAN belongs to a group of medicines called anticoagulants (blood thinners). It helps prevent blood clots from forming by directly blocking the activity of a clotting factor called Factor-Xa.

The ingredients in RIVAROXABAN are:
Medicinal ingredient: rivaroxaban

Non-medicinal ingredients: Microcrystalline Cellulose, Colloidal Silicon Dioxide, Croscarmellose Sodium, Hydroxypropyl Cellulose, Lactose Monohydrate, Magnesium Stearate, Sodium Lauryl Sulphate. The film-

coating contains: FD & C Yellow #5 (for the 2.5 mg), Hypromellose, Iron Oxide Red (for the 10 mg, 15 mg and 20 mg), Iron Oxide Yellow (for the 2.5 mg), Polyethylene Glycol, Titanium Dioxide.

RIVAROXABAN comes in the following dosage forms:

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

Do not use RIVAROXABAN if you or the child:

- are allergic to rivaroxaban or to any other ingredients in RIVAROXABAN. RIVAROXABAN tablets contain lactose.
- are actively bleeding, especially if you are excessively bleeding
- have any injuries or conditions that may increase your risk of bleeding. This includes:
  - active or recent bleeding in the brain
  - active or recent bleeding in the stomach or gut
  - have difficulties to stop bleeding (bleeding disorder)
- take medicines to treat HIV/AIDS, such as cobicistat and ritonavir
- take medicines to treat fungal infections, such as ketoconazole, itraconazole and posaconazole
- take dronedarone, a medicine used to control an abnormal heart rhythm called atrial fibrillation
- take any other medicines used to prevent or treat blood clots. This includes:
  - warfarin, dabigatran, apixaban, edoxaban, heparin
  - low molecular weight heparin (LMWH), such as enoxaparin and dalteparin
  - heparin derivatives, such as fondaparinux
- have severe liver disease, which can lead to an increased risk of bleeding
- are pregnant, think you might be pregnant or plan on becoming pregnant
- are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RIVAROXABAN. Talk about any health conditions or problems you may have, including if you:

- have an increased risk of bleeding. This includes if you:
  - have severe kidney problems or reduced kidney function
  - are taking Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which are used to relieve pain and reduce inflammation, such as ibuprofen, naproxen and celecoxib
  - are taking acetylsalicylic acid (ASA, or ASPIRIN) or any other medicines used to prevent stroke or heart disease, such as clopidogrel, prasugrel and ticagrelor
  - are taking medicines to treat depression or other psychological conditions
  - have low levels of platelets in the blood or your platelets do not work properly
  - have very high blood pressure, not controlled by medical treatment
  - have or have had an ulcer in the stomach or bowel
  - have a problem with the blood vessels in the back of the eyes (retinopathy)
  - have problems with the blood vessels in the brain or spinal column
  - had surgery on the brain, spinal column or eyes
  - have bronchiectasis, which is a chronic disease where the bronchial tubes of the lungs become damaged, widened, and thickened
  - have a history of bleeding into the lungs
  - are older than 75 years of age
  - have been diagnosed with cancer, had a relapse of cancer or have been treated for cancer in the last 6 months

  - have liver problems
  - 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)
- have damaged heart valves or heart valve disease
- have a prosthetic heart valve
- have antiphospholipid syndrome, also known as Hughes syndrome. This is a disorder of the immune system that causes an increased risk of blood clots.
- have a stent, which is a small metal coil inserted into a blocked blood vessel to restore blood flow by keeping it open
- have a history of stroke, with or without bleeding in the brain
- are taking rifampicin, a medicine used to treat bacterial infections, including tuberculosis
- are taking medicines used to prevent epilepsy or seizures, such as phenytoin, carbamazepine and phenobarbital
- are lactose intolerant. RIVAROXABAN tablets contain lactose.

Other warnings you should know about:

Do not stop taking or giving RIVAROXABAN to your child without first talking to your healthcare professional. If you or your child stop taking RIVAROXABAN, blood clots may form and cause a stroke, heart attack, or other serious complications. This can lead to severe disability or even death.

Risk of Bleeding: As with other blood thinners, taking RIVAROXABAN may increase the risk of bleeding from any part of the body, including internal organs. It may be serious or even life-threatening. Tell your healthcare professional **right away** if you or your child have any unusual bleeding or bruising. For examples of bleeding, see the **Serious side effects and what to do about them** table below.

Spinal or epidural blood clots (hematoma): People who take RIVAROXABAN and have medicine injected into their spinal or epidural area, or have a spinal puncture, have a risk of forming a spinal or epidural blood clot. This can cause long-term or permanent loss of the ability to move (paralysis). The risk of developing a spinal or epidural blood clot is higher if:

- A thin tube called an epidural catheter is placed in your/your child's back to give certain medicines
- You/your child take NSAIDs or a medicine to prevent blood from clotting
- You/your child have a history of difficult or repeated epidural or spinal punctures
- You/your child have a history of problems with the spinal column or have had surgery on the spinal column

If you or your child take RIVAROXABAN and receive spinal anesthesia or have a spinal puncture, your healthcare professional will watch you or your child closely for symptoms of spinal or epidural blood clots.

Tell your healthcare professional **right away** if you/your child develops the following symptoms after an epidural or a spinal procedure:

- back pain
- tingling
- numbness
- muscle weakness (especially in your legs and feet)

- or loss of control of the bowels or bladder (incontinence)

Surgery:
- Tell your healthcare professional if you or your child are going to have any surgeries, including dental procedures, while taking RIVAROXABAN. There is an increased risk of bleeding if you or your child take RIVAROXABAN during these procedures. It can be life-threatening.
- Your healthcare professional may ask you or your child to stop taking RIVAROXABAN before the surgery, and to resume taking RIVAROXABAN after the procedure. It is important that you or your child take RIVAROXABAN before and after the procedure exactly at the times the healthcare professional has instructed.

Anticoagulant-Related Nephropathy (ARN):
Some cases were reported in patients taking rivaroxaban. It is a type of serious kidney damage caused by anticoagulant medicines. ARN causes bleeding in the kidneys, sometimes with the presence of blood in the urine. This leads to the kidneys being unable to function properly. Your healthcare professional may monitor the health of your kidneys during your treatment with RIVAROXABAN. If you are experiencing symptoms of ARN during your treatment, tell your healthcare professional right away.

Children and adolescents:

- RIVAROXABAN 2.5 mg and 10 mg tablets are not to be used in children and adolescents under 18 years of age.
- RIVAROXABAN should **not** be used in children and adolescent under 18 years of age for any conditions other than the treatment and prevention of blood clots in the veins of the legs or arms, or blood vessels in the lungs.

Pregnancy:
- RIVAROXABAN should **not** be used during pregnancy. Taking it during pregnancy may harm an unborn baby.
- Your healthcare professional may ask you or your child (depending on their age), to use a highly effective birth control method while taking RIVAROXABAN.
- If you or your child discover that you/they are pregnant while taking RIVAROXABAN, contact your healthcare professional **as soon as possible**.

Breastfeeding: RIVAROXABAN should **not** be used while breastfeeding. It may pass into breast milk and harm a breastfed baby. RIVAROXABAN will only be given to you/your child once you/they have stopped breastfeeding.

Check-ups and testing: Your healthcare professional may:
- evaluate your/your child's risk of bleeding before starting RIVAROXABAN and regularly during treatment. This includes performing blood tests to check the amount of red blood cells in the blood, and monitoring blood pressure.
- do blood tests before you/your child start taking RIVAROXABAN and during treatment to check if your/your child's kidneys are working properly

Depending on the test results, your healthcare professional may discontinue your/your child's treatment with RIVAROXABAN.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions:

Serious drug interactions with RIVAROXABAN include:

- Certain treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein (P-gp), such as
  - medicines used to treat HIV/AIDS, such as cobicistat and ritonavir
  - medicines used to treat fungal infections, such as ketoconazole, itraconazole and posaconazole
- Other anticoagulant medicines to prevent or treat blood clots, 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

The following may interact with RIVAROXABAN:

- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which are used to relieve pain and reduce inflammation, such as ibuprofen, naproxen and celecoxib
- Acetylsalicylic acid (ASA, or ASPIRIN), used to relieve fever and pain
- Medicines used to prevent stroke or heart disease, such as clopidogrel, prasugrel and ticagrelor
- Dronedarone, a medicine used to control an abnormal heart rhythm called atrial fibrillation
- Medicines used to treat bacterial infections, such as clarithromycin and rifampicin
- Medicines used to control epilepsy or seizures, such as phenytoin, carbamazepine and phenobarbital
- Medicines used to treat depression or other psychological conditions, such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
- St. John's Wort (also known as *Hypericum perforatum*), a herbal remedy used to treat depression

RIVAROXABAN 2.5 mg tablets are prescribed with acetylsalicylic acid (ASA). Ask your healthcare professional first before taking any other NSAIDs. They will determine if it is beneficial for you to take it during your treatment with RIVAROXABAN and ASA.

How to take RIVAROXABAN:

- Take or give your child:
  - RIVAROXABAN tablets exactly as your healthcare professional tells you
  - RIVAROXABAN tablets at the same time every day to help you remember it
  - RIVAROXABAN 2.5 mg and 10 mg tablets with or without food
  - RIVAROXABAN 15 mg and 20 mg tablets **with** food
- Swallow tablet whole, preferably with water. Do **not** split tablets.
- Tell your child's healthcare professional if your child has trouble swallowing RIVAROXABAN tablets.

They may prescribe your child another rivaroxaban product.

- RIVAROXABAN tablets may be crushed and mixed with apple sauce. Take the applesauce mixture 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 healthcare professional may give you or the child the crushed RIVAROXABAN tablet also via a tube.
- It is not recommended to crush and mix a 2.5 mg RIVAROXABAN tablet and an acetylsalicylic acid (ASA, or ASPIRIN) tablet together with applesauce.

- Do **not** stop taking or giving RIVAROXABAN to your child without talking to the healthcare professional first.
- **If you or the child spits up the dose or vomits:**
  - less than 30 minutes after taking RIVAROXABAN, take or give a new dose
  - more than 30 minutes after taking RIVAROXABAN, do not take or give a new dose. In this case, take or give the next RIVAROXABAN dose at the usual time.

  Contact the healthcare professional if you or the child repeatedly spits up the dose or vomits after taking RIVAROXABAN.

Usual dose:

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

  Usual adult dose: Take one 10 mg tablet 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 healthcare professional tells you to stop.
  If you have had a major hip operation, you will usually take RIVAROXABAN for 35 days.
  If you have had a major knee operation, you will usually take RIVAROXABAN for 14 days.

- **Treatment and prevention of blood clots in the veins of the legs or arms, or blood vessels of the lungs**

  Adults:

  - **Day 1 to 21**: Take one 15 mg tablet TWICE a day (in the morning and evening) with food.
  - **Day 22 and onwards**: Take one 20 mg tablet ONCE a day with food.

  After at least 6 months treatment, your healthcare professional 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 a long-term treatment and you should continue to take RIVAROXABAN until your healthcare professional says otherwise.

  Children: RIVAROXABAN is available for children as tablets. Your child's healthcare professional will decide the right dose of RIVAROXABAN for your child depending on their body weight.

  Always give RIVAROXABAN to your child exactly as the healthcare professional tells you to. You should check with your child's healthcare professional if you are not sure.

  Children should keep scheduled visits with their healthcare professional. This is because their dose

of RIVAROXABAN should be adjusted as their weight changes.

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

  Usual adult dose: Take one 20 mg tablet once a day with food.

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

  This is a long-term treatment and you should continue to take RIVAROXABAN until your healthcare professional says otherwise.

  The recommended maximum daily dose is 20 mg.

- **Prevention of stroke, heart attack, severe leg or arm pain, or death if you have coronary artery disease and/or peripheral artery disease**

  Usual adult dose: Take one 2.5 mg tablet twice a day with or without food. Take RIVAROXABAN 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, or ASPIRIN) once a day. Take the ASA tablet at the same time as one of your RIVAROXABAN doses.

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

Overdose:
Taking too much RIVAROXABAN may cause excessive bleeding.

If you think you, or a person you are caring for, have taken too much RIVAROXABAN, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

- If you take RIVAROXABAN 2.5 mg tablets twice a day and miss a dose, skip the missed dose and take the next dose as usual.
- If you take RIVAROXABAN 15 mg tablets **twice** a day and miss a dose, take the missed dose as soon as you remember. 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) in one day. Do not take more than two 15 mg tablets in one day. The next day, take RIVAROXABAN as usual.
- If you or your child takes RIVAROXABAN 10 mg, 15 mg or 20 mg tablets **once** a day and miss a dose, take or give your child the missed dose as soon as you remember on the same day. If this is not possible, you or your child should skip the missed dose and take the next dose on the following day as usual. Do not take or give your child a double dose to make up for the one that was missed.

Possible side effects from using RIVAROXABAN:
These are not all the possible side effects you may have when taking RIVAROXABAN. If you experience

any side effects not listed here, tell your healthcare professional.

As RIVAROXABAN 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 RIVAROXABAN 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 RIVAROXABAN 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).

RIVAROXABAN can cause abnormal blood test results. The healthcare professional may perform blood tests before you or your child take RIVAROXABAN and regularly during treatment. They will tell you if the test results are abnormal and if you or your child need treatment to correct these side effects.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the drug and get immediate medical help
	Only if severe	In all cases	
Common			
Anemia (decreased number of red blood cells): pale complexion, weakness, tiredness, dizziness, headache, breathlessness, unusually fast heartbeat, or chest pain		✓	
Bleeding from hemorrhoids	✓		
Bleeding from the surgical wound, an injury or other medical procedure		✓	
Bleeding gums for longer than 5 minutes when you brush your teeth		✓	
Bleeding in the eye	✓		
Bleeding under the skin	✓		
Blood in your urine, (red/pink tinge to urine)		✓	
Fever		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the drug and get immediate medical help
	Only if severe	In all cases	
Gastrointestinal (GI) bleeding (bleeding anywhere along the GI tract between mouth and anus): blood in vomit, black tarry stool, bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness		✓	
Genital bleeding in post-menopausal women		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Increased or more frequent menstrual bleeding	✓		
Itchy skin or rash		✓	
Localized swelling		✓	
Nose bleed lasting more than 5 minutes		✓	
Pain or swelling in your limbs		✓	
Seizure (fit) reported in children: loss of consciousness with uncontrollable shaking			✓
Tachycardia (abnormally fast heartbeat)		✓	
Unexpected bruising		✓	
Uncommon			
Decreased urine output	✓		
Hemarthrosis (bleeding into a joint): joint pain, swelling		✓	
Hemoptysis: coughing up blood		✓	
Intracerebral hemorrhage (bleeding in the brain): sudden, severe headache; confusion; nausea and vomiting; seizures; loss of consciousness			✓
Oozing from the surgical wound		✓	
Seizure (fit) reported in adults: loss of consciousness with uncontrollable shaking			✓
Syncope (fainting): a temporary loss of consciousness due to a sudden drop in blood pressure		✓	
Rare			
Allergic Reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat			✓
Liver Disorder: yellowing of the skin or eyes, dark urine, pale stools abdominal pain, nausea, vomiting, loss of appetite		✓	
Very rare			
Splenic Rupture: left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder		✓	
Unknown			

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the drug and get immediate medical help
	Only if severe	In all cases	
Agranulocytosis (decrease in white blood cells): frequent infection with fever, chills, sore throat		✓	
Anticoagulant-related nephropathy (ARN) (serious kidney damage caused by anticoagulant medicines): bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly		✓	
Compartment Syndrome: increased pressure within legs or arms after a bleed, with pain, swelling, numbness or paralysis		✓	
Eosinophilic Pneumonia (accumulation of a type of white blood cells that cause inflammation in the lung): shortness of breath, cough, wheezing, chest pain, fever, and unintended weight loss		✓	
Stevens-Johnson Syndrome (SJS) (severe skin rash): 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			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Keep RIVAROXABAN tablets at room temperature (15°C - 30°C).
- Keep out of the reach and sight of children.
- Do not use RIVAROXABAN after the expiry date which is stated on the bottle 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.

If you want more information about RIVAROXABAN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), manufacturer's website www.sivem.ca, or by calling 1-855-788-3153.

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