RIVAROXABAN - rivaroxaban tablet, film coated
RIVAROXABAN- rivaroxaban
Alembic Pharmaceuticals Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RIVAROXABAN TABLETS safely and effectively. See full prescribing information for RIVAROXABAN TABLETS.

RIVAROXABAN tablets, for oral use
Initial U.S. Approval: 2011

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

See full prescribing information for complete boxed warning.

(A) Premature discontinuation of rivaroxaban tablets increases the risk of thrombotic events
Premature discontinuation of any oral anticoagulant, including rivaroxaban tablets, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if rivaroxaban tablets are discontinued for a reason other than pathological bleeding or completion of a course of therapy. (2.2,2.3, 5.1, 14.1)
(B) Spinal/epidural hematoma
Epidural or spinal hematomas have occurred in patients treated with rivaroxaban tablets who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. (5.2, 5.3, 6.2)
Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated. (5.3)

INDICATIONS AND USAGE

Rivaroxaban tablet is a factor Xa inhibitor indicated:
• to reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation (1.1)
• for treatment of deep vein thrombosis (DVT) (1.2)
• for treatment of pulmonary embolism (PE) (1.3)
• for reduction in the risk of recurrence of DVT or PE (1.4)
• for prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery (1.5)
• for prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients (1.6)
• to reduce the risk of major cardiovascular events in patients with coronary artery disease (CAD) (1.7)
• to reduce the risk of major thrombotic vascular events in patients with peripheral artery disease (PAD), including patients after recent lower extremity revascularization due to symptomatic PAD (1.8)
• for treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years (1.9) (1)
• for thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure (1.10) (1)

DOSAGE AND ADMINISTRATION

• Nonvalvular Atrial Fibrillation: 15 or 20 mg, once daily with food (2.1)
• Treatment of DVT and/or PE: 15 mg orally twice daily with food for the first 21 days followed by 20 mg orally once daily with food for the remaining treatment (2.1)
• Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE: 10 mg once daily with or without food, after at least 6 months of standard anticoagulant treatment (2.1)
• Prophylaxis of DVT Following Hip or Knee Replacement Surgery: 10 mg orally once daily with or without food (2.1)
• Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding: 10 mg once daily, with or without food, in hospital and after hospital discharge for a total recommended duration of 31 to 39 days (2.1)
• CAD or PAD: 2.5 mg orally twice daily with or without food, in combination with aspirin (75 to 100 mg) once daily (2.1)
• Pediatric Patients: See dosing recommendations in the Full Prescribing Information (2.2) (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 2.5 mg, 10 mg, 15 mg, and 20 mg (3) (3)

CONTRAINDICATIONS

- Active pathological bleeding (4) (4)
- Severe hypersensitivity reaction to rivaroxaban tablets (4) (4)

WARNINGS AND PRECAUTIONS

- Risk of bleeding: Rivaroxaban tablets can cause serious and fatal bleeding. An agent to reverse the activity of rivaroxaban is available. (5.2)
- Pregnancy-related hemorrhage: Use rivaroxaban tablets with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery.(5.7, 8.1)
- Prosthetic heart valves: Rivaroxaban tablets use not recommended. (5.8)
- Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome: Rivaroxaban tablets use not recommended. (5.10)

ADVERSE REACTIONS

• The most common adverse reaction (>5%) in adult patients was bleeding. (6.1)
• The most common adverse reactions (>10%) in pediatric patients were bleeding, cough, vomiting, and gastroenteritis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

- Avoid combined P-gp and strong CYP3A inhibitors and inducers (7.2, 7.3)
- Anticoagulants: Avoid concomitant use (7.4)

USE IN SPECIFIC POPULATIONS

- Renal impairment: Avoid or adjust dose (8.6)
- Hepatic impairment: Avoid use in Child-Pugh B and C hepatic impairment or hepatic disease associated with coagulopathy (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation
1.2 Treatment of Deep Vein Thrombosis
1.3 Treatment of Pulmonary Embolism
1.4 Reduction in the Risk of Recurrence of Deep Vein Thrombosis and/or Pulmonary Embolism
1.5 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
1.6 Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding
1.7 Reduction of Risk of Major Cardiovascular Events in Patients with Coronary Artery Disease (CAD)
1.8 Reduction of Risk of Major Thrombotic Vascular Events in Patients with Peripheral Artery Disease (PAD), Including Patients after Lower Extremity Revascularization due to Symptomatic PAD
1.9 Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients
1.10 Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Adults
2.2 Recommended Dosage in Pediatric Patients
2.3 Switching to and from Rivaroxaban Tablets
2.4 Discontinuation for Surgery and other Interventions

2.5 Missed Dose
2.6 Administration Options
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Risk of Thrombotic Events after Premature Discontinuation
5.2 Risk of Bleeding
5.3 Spinal/Epidural Anesthesia or Puncture
5.4 Use in Patients with Renal Impairment
5.5 Use in Patients with Hepatic Impairment
5.6 Use with P-gp and Strong CYP3A Inhibitors or Inducers
5.7 Risk of Pregnancy-Related Hemorrhage
5.8 Patients with Prosthetic Heart Valves
5.9 Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy
5.10 Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 General Inhibition and Induction Properties
7.2 Drugs that Inhibit Cytochrome P450 3A Enzymes and Drug Transport Systems
7.3 Drugs that Induce Cytochrome P450 3A Enzymes and Drug Transport Systems
7.4 Anticoagulants and NSAIDs/Aspirin
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.6 QT/QTc Prolongation
13 NON-CLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Stroke Prevention in Nonvalvular Atrial Fibrillation
14.2 Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)
14.3 Reduction in the Risk of Recurrence of DVT and/or PE
14.4 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
14.5 Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding
14.6 Reduction of Risk of Major Cardiovascular Events in Patients with CAD
14.7 Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients after Lower Extremity Revascularization due to Symptomatic PAD
14.8 Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients
14.9 Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the

Fontan Procedure

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

A. Premature discontinuation of rivaroxaban tablets increases the risk of thrombotic events
Premature discontinuation of any oral anticoagulant, including rivaroxaban tablets, increases the risk of thrombotic events. If anticoagulation with rivaroxaban tablets are discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.3, 2.4), Warnings and Precautions (5.1), and Clinical Studies (14.1)].*

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

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

[see Warnings and Precautions (5.2, 5.3) and Adverse Reactions (6.2)].

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)].*

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions (5.3)].*

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

Rivaroxaban tablets are indicated to reduce the risk of stroke and systemic embolism in

adult patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of rivaroxaban tablets and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1)].*

1.2 Treatment of Deep Vein Thrombosis

Rivaroxaban tablets are indicated for the treatment of deep vein thrombosis (DVT).

1.3 Treatment of Pulmonary Embolism

Rivaroxaban tablets are indicated for the treatment of pulmonary embolism (PE).

1.4 Reduction in the Risk of Recurrence of Deep Vein Thrombosis and/or Pulmonary Embolism

Rivaroxaban tablets are indicated for the reduction in the risk of recurrence of DVT and/or PE in adult patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

1.5 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

Rivaroxaban tablets are indicated for the prophylaxis of DVT, which may lead to PE in adult patients undergoing knee or hip replacement surgery.

1.6 Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

Rivaroxaban tablets are indicated for the prophylaxis of venous thromboembolism (VTE) and VTE related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE and not at high risk of bleeding *[see Warnings and Precautions (5.2) and Clinical Studies (14.5)].*

1.7 Reduction of Risk of Major Cardiovascular Events in Patients with Coronary Artery Disease (CAD)

Rivaroxaban tablets, in combination with aspirin, is indicated to reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction and stroke) in adult patients with coronary artery disease.

1.8 Reduction of Risk of Major Thrombotic Vascular Events in Patients with Peripheral Artery Disease (PAD), Including Patients after Lower Extremity Revascularization due to Symptomatic PAD

Rivaroxaban tablets, in combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in adult patients with PAD, including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.

1.9 Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients

Rivaroxaban tablets are indicated for the treatment of venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment.

1.10 Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure

Rivaroxaban tablets are indicated for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Adults

Table 1: Recommended Dosage in Adults

Indication	**Renal Considerations***	**Dosage**	**Food/Timing†**
Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation	CrCl >50 mL/min	20 mg once daily	Take with evening meal
	CrCl ≤50 mL/min‡	15 mg once daily	Take with evening meal
Treatment of DVT and /or PE	CrCl ≥ 15 mL/min‡	15 mg twice daily **▼after 21 days, transition to ▼** 20 mg once daily	Take with food, at the same time each day
	CrCl < 15 mL/min	Avoid Use	
Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE	CrCl ≥ 15 mL/min‡	10 mg once daily, after at least 6 months of standard anticoagulant treatment	Take with or without food
	CrCl < 15 mL/min	Avoid Use	
Prophylaxis of DVT Following:			
- **Hip Replacement Surgery§**	CrCl ≥ 15 mL/min‡	10 mg once daily for 35 days, 6 to10 hours after surgery once hemostasis has been established	Take with or without food
	CrCl < 15 mL/min	Avoid Use	
- **Knee replacement Surgery§**	CrCl ≥ 15 mL/min‡	10 mg once daily for 12 days, 6 to10 hours after surgery once hemostasis has been established	Take with or without food
	CrCl < 15 mL/min	Avoid Use	
Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding	CrCl ≥ 15 mL/min‡	10 mg once daily, in hospital and after hospital discharge, for a total recommended duration of 31 to 39 days	Take with or without food
	CrCl < 15 mL/min	Avoid Use	

Reduction of Risk of Major Cardiovascular Events (CV Death, MI, and Stroke) in CAD	No dose adjustment needed based on CrCl	2.5 mg twice daily, plus aspirin (75 to 100 mg) once daily	Take with or without food
Reduction of Risk of Major Thrombotic Vascular Events in PAD, Including Patients after Lower Extremity Revascularization due to Symptomatic PAD	No dose adjustment needed based on CrCl	2.5 mg twice daily, plus aspirin (75 to 100 mg) once daily. When starting therapy after a successful lower extremity revascularization procedure, initiate once hemostasis has been established.	Take with or without food

*Calculate CrCl based on actual weight. *[See Warnings and Precautions (5.4) and Use in Specific Populations (8.6)]*

†*See Clinical Pharmacology (12.3)*

‡ Patients with CrCl <30 mL/min were not studied, but administration of rivaroxaban tablets are expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Use in Specific Populations (8.6)]*

§*See Dosage and Administration (2.4)*

2.2 Recommended Dosage in Pediatric Patients

Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients

Table 2: Recommended Dosage in Pediatric Patients Birth to Less than 18 Years for Treatment of and Reduction in Risk of Recurrent VTE*,†

Dosage Form	Body Weight	Dosage	Total Daily Dose‡
		Once a Day§	
Tablets	30 kg to 49.9 kg	15 mg	15 mg
	≥50 kg	20 mg	20 mg

* Initiate rivaroxaban tablets treatment following at least 5 days of initial parenteral anticoagulation therapy.
† Patients <6 months of age should meet the following criteria: at birth were at least 37 weeks of gestation, have had at least 10 days of oral feeding, and weigh ≥2.6 kg at the time of dosing.

‡ All doses should be taken with feeding or with food since exposures match that of 20 mg daily dose in adults.
§ Once a day: approximately 24 hours apart; 2 times a day: approximately 12 hours apart; 3 times a day: approximately 8 hours apart

Dosing of rivaroxaban tablets was not studied and therefore dosing cannot be reliably determined in the following patient populations. Its use is therefore not recommended in children less than 6 months of age with any of the following:

- Less than 37 weeks of gestation at birth
- Less than 10 days of oral feeding
- Body weight of less than 2.6 kg.

To increase absorption, all doses should be taken with feeding or with food.

Monitor the child's weight and review the dose regularly, especially for children below 12 kg. This is to ensure a therapeutic dose is maintained.

All pediatric patients (except <2 years old with catheter-related thrombosis): Therapy with rivaroxaban tablets should be continued for at least 3 months in children with thrombosis. Treatment can be extended up to 12 months when clinically necessary. The benefit of continued therapy beyond 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential risk of bleeding.

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

Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure

Table 3: Recommended Dosage for Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease

Dosage Form	Body Weight	Dosage	Total Daily Dose*
		Once a Day†	
Tablets	≥50 kg	10 mg	10 mg

* All doses can be taken with or without food since exposures match that of 10 mg daily dose in adults.
† Once a day: approximately 24 hours apart; 2 times a day: approximately 12 hours apart.

Administration in Pediatric Patients

Food Effect:

For the treatment of VTE in children, the dose should be taken with food to increase absorption. For thromboprophylaxis after Fontan procedure, the dose can be taken with or without food.

Vomit or Spit up: If the patient vomits or spits up the dose within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose is taken, the dose should not be re-administered and the next dose should be taken as scheduled. If the patient vomits or spits up the dose repeatedly, the caregiver should contact the child's doctor right away.

Tablets: Rivaroxaban tablet must not be split in an attempt to provide a fraction of a tablet dose.

For children unable to swallow 10, 15, or 20 mg whole tablets, rivaroxaban oral suspension should be used. Rivaroxaban 2.5 mg tablets are not recommended for use in pediatric patients *[see Use in Specific Populations (8.4)].*

Use in Renal Impairment in Pediatric Patients

Patients 1 Year of Age or Older

- Mild renal impairment (eGFR: 50 to ≤ 80 mL/min/1.73 m^2): No dose adjustment is required.
- Moderate or severe renal impairment (eGFR: <50 mL/min/1.73 m^2): avoid use, as limited clinical data are available.

Estimated glomerular filtration rate (eGFR) can be done using the updated Schwartz formula, eGFR (Schwartz) = (0.413 x height in cm)/serum creatinine in mg/dL, if serum creatinine (SCr) is measured by an enzymatic creatinine method that has been calibrated to be traceable to isotope dilution mass spectrometry (IDMS).

If SCr is measured with routine methods that have not been recalibrated to be traceable to IDMS (e.g., the traditional Jaffé reaction), the eGFR should be obtained from the original Schwartz formula: eGFR (mL/min/1.73 m^2) = k * height (cm)/SCr (mg/dL), where k is proportionality constant:

k = 0.55 in children 1 year to 13 years
k = 0.55 in girls > 13 and < 18 years
k = 0.7 in boys > 13 and < 18 years

Patients Less than 1 Year of Age

Determine renal function using serum creatinine. Avoid use of rivaroxaban tablets in pediatric patients younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available.

Table 4: Reference Values of Serum Creatinine in Pediatric Patients <1 Year of Age

Age	97.5th Percentile of Creatinine (mg/dL)	97.5th Percentile of Creatinine (µmol/L)
Week 2	0.52	46
Week 3	0.46	41
Week 4	0.42	37
Month 2	0.37	33
Month 3	0.34	30

Month 4 to 6	0.34	30
Month 7 to 9	0.34	30
Month 10 to 12	0.36	32

2.3 Switching to and from Rivaroxaban Tablets

Switching from Warfarin to Rivaroxaban Tablets - When switching patients from warfarin to rivaroxaban tablets, discontinue warfarin and start rivaroxaban tablets as soon as the International Normalized Ratio (INR) is below 3 in adults and below 2.5 in pediatric patients to avoid periods of inadequate anticoagulation.

Switching from Rivaroxaban Tablets to Warfarin

- Adults:

No clinical trial data are available to guide converting patients from rivaroxaban tablets to warfarin. Rivaroxaban tablets affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue rivaroxaban tablets and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban tablets would have been taken.

• Pediatric Patients:
To ensure adequate anticoagulation during the transition from rivaroxaban tablets to warfarin, continue rivaroxaban tablets for at least 2 days after the first dose of warfarin. After 2 days of co-administration, an INR should be obtained prior to the next scheduled dose of rivaroxaban tablets. Co-administration of rivaroxaban tablets and warfarin is advised to continue until the INR is ≥ 2.

Once rivaroxaban tablet is discontinued, INR testing may be done reliably 24 hours after the last dose.

Switching from Rivaroxaban tablets to Anticoagulants other than Warfarin - For adult and pediatric patients currently taking rivaroxaban tablets and transitioning to an anticoagulant with rapid onset, discontinue rivaroxaban tablets and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next rivaroxaban tablets dose would have been taken *[see Drug Interactions (7.4)]*.

Switching from Anticoagulants other than Warfarin to Rivaroxaban tablets- For adult and pediatric patients currently receiving an anticoagulant other than warfarin, start rivaroxaban tablets 0 to 2 hours prior to the next scheduled administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop the infusion and start rivaroxaban tablets at the same time.

2.4 Discontinuation for Surgery and other Interventions

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, rivaroxaban tablets should be stopped at least 24 hours before the procedure to reduce the risk of bleeding *[see Warnings and Precautions (5.2)]*. In deciding whether a procedure should be delayed until 24 hours after the last dose of rivaroxaban tablets, the increased risk of bleeding should be weighed against the urgency of intervention. Rivaroxaban tablets should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short *[see Warnings and Precautions (5.1)]*. If oral medication cannot be taken during or after surgical intervention, consider administering

a parenteral anticoagulant.

2.5 Missed Dose

Adults

- For patients receiving 2.5 mg twice daily: if a dose is missed, the patient should take a single 2.5 mg rivaroxaban tablets dose as recommended at the next scheduled time.
- For patients receiving 15 mg twice daily: The patient should take rivaroxaban tablets immediately to ensure intake of 30 mg rivaroxaban tablets per day. Two 15 mg tablets may be taken at once.
- For patients receiving 20 mg, 15 mg or 10 mg once daily: The patient should take the missed rivaroxaban tablets dose immediately. The dose should not be doubled within the same day to make up for a missed dose.

Pediatric Patients

- If rivaroxaban tablets are taken once a day, the patient should take the missed dose as soon as possible once 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.
- If rivaroxaban tablets are taken two times a day, the patient should take the missed morning dose as soon as possible once it is noticed. A missed morning dose may be taken together with the evening dose. A missed evening dose can only be taken in the same evening.
- If rivaroxaban tablets are taken three times a day, if a dose is missed, the patient should skip the missed dose and go back to the regular dosing schedule at the usual time without compensating for the missed dose.

On the following day, the patient should continue with their regular regimen.

2.6 Administration Options

For adult patients who are unable to swallow whole tablets, rivaroxaban tablets (all strengths) may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed rivaroxaban tablets 15 mg or 20 mg tablet, the dose should be immediately followed by food. Administration with food is not required for the 2.5 mg or 10 mg tablets *[see Clinical Pharmacology (12.3)].*

Administration of rivaroxaban tablets via nasogastric (NG) tube or gastric feeding tube: After confirming gastric placement of the tube, rivaroxaban tablets (all strengths) may be crushed and suspended in 50 mL of water and administered via an NG tube or gastric feeding tube. Since rivaroxaban absorption is dependent on the site of drug release, avoid administration of rivaroxaban tablets distal to the stomach which can result in reduced absorption and thereby, reduced drug exposure. After the administration of a crushed rivaroxaban tablets 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding. Enteral feeding is not required following administration of the 2.5 mg or 10 mg tablets *[see Clinical Pharmacology (12.3)].*

Crushed rivaroxaban tablets (all strengths) are stable in water and in applesauce for up to 4 hours. 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.

3 DOSAGE FORMS AND STRENGTHS

- 2.5 mg tablets: Light yellow to yellow round biconvex film-coated tablets debossed

with “9” on one side and “C” on other side.
• 10 mg tablets: Round, pink, biconvex film-coated tablets debossed with “L” on one side and “10” on the other side.
• 15 mg tablets: Round, brown, film-coated biconvex tablets debossed with‘504’ on one side and plain on the other side.
• 20 mg tablets: Triangle shaped, brown, film-coated tablets debossed with ‘505’ on one side and plain on the other side.

4 CONTRAINDICATIONS

Rivaroxaban tablets are contraindicated in patients with:

· active pathological bleeding *[see Warnings and Precautions (5.2)]*

· severe hypersensitivity reaction to rivaroxaban tablets (e.g., anaphylactic reactions) *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including rivaroxaban tablets, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from rivaroxaban tablets to warfarin in clinical trials in atrial fibrillation patients. If rivaroxaban tablets are discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.3, 2.4) and Clinical Studies (14.1)]*.

5.2 Risk of Bleeding

Rivaroxaban tablets increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe rivaroxaban tablets to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue rivaroxaban tablets in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.4)],* selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors.

Concomitant use of drugs that are known combined P-gp and strong CYP3A inhibitors increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions (7.2)]*.

<u>Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding</u>

Acutely ill medical patients with the following conditions are at increased risk of bleeding with the use of rivaroxaban tablets for primary VTE prophylaxis: history of

bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage, active cancer (i.e., undergoing acute, in-hospital cancer treatment), active gastroduodenal ulcer in the three months prior to treatment, history of bleeding in the three months prior to treatment, or dual antiplatelet therapy. Rivaroxaban tablets are not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

Reversal of Anticoagulant Effect

An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable *[see Clinical Pharmacology (12.3)]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical efficacy and safety studies. Monitoring for the anticoagulation effect of rivaroxaban using a clotting test (PT, INR or aPTT) or anti-factor Xa (FXa) activity is not recommended.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban tablets and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban tablets *[see Clinical Pharmacology (12.3)]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban tablets is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (i.e., 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of rivaroxaban tablets *[see Clinical Pharmacology (12.3)]*. The next rivaroxaban tablets dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of rivaroxaban tablets for 24 hours.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

5.4 Use in Patients with Renal Impairment

Nonvalvular Atrial Fibrillation

Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly *[see Dosage and*

Administration (2.1)]. Consider dose adjustment or discontinuation of rivaroxaban tablets in patients who develop acute renal failure while on rivaroxaban tablets *[see Use in Specific Populations (8.6)].*

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE

In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of rivaroxaban tablets in these patients.

Discontinue rivaroxaban tablets in patients who develop acute renal failure while on treatment *[see Use in Specific Populations (8.6)]*.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of rivaroxaban tablets in these patients.

Discontinue rivaroxaban tablets in patients who develop acute renal failure while on treatment *[see Use in Specific Populations (8.6)].*

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of rivaroxaban tablets in these patients.

Discontinue rivaroxaban tablets in patients who develop acute renal failure while on treatment *[see Usein Specific Populations (8.6)].*

Pediatric Patients
There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2); therefore, avoid the use of rivaroxaban tablets in these patients.

There are no clinical data in pediatric patients younger than 1 year with serum creatinine results above 97.5th percentile; therefore, avoid the use of rivaroxaban tablets in these patients *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

5.5 Use in Patients with Hepatic Impairment

No clinical data are available for adult patients with severe hepatic impairment.

Avoid use of rivaroxaban tablets in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased *[see Use in Specific Populations (8.7)]*.

No clinical data are available in pediatric patients with hepatic impairment.

5.6 Use with P-gp and Strong CYP3A Inhibitors or Inducers

Avoid concomitant use of rivaroxaban tablets with known combined P-gp and strong CYP3A inhibitors *[see Drug Interactions (7.2)]*.

Avoid concomitant use of rivaroxaban tablets with drugs that are known combined P-gp and strong CYP3A inducers *[see Drug Interactions (7.3)]*.

5.7 Risk of Pregnancy-Related Hemorrhage

In pregnant women, rivaroxaban tablets should be used only if the potential benefit justifies the potential risk to the mother and fetus. Rivaroxaban tablets dosing in pregnancy has not been studied. The anticoagulant effect of rivaroxaban tablets cannot be monitored with standard laboratory testing. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress) *[see Warnings and Precautions (5.2) and Use in Specific Population (8.1)].*

5.8 Patients with Prosthetic Heart Valves

On the basis of the GALILEO study, use of rivaroxaban tablets is not recommended in patients who have had transcatheter aortic valve replacement (TAVR) because patients randomized to rivaroxaban tablets experienced higher rates of death and bleeding compared to those randomized to an anti-platelet regimen. The safety and efficacy of rivaroxaban tablets have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of rivaroxaban tablets is not recommended in patients with prosthetic heart valves.

5.9 Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy

Initiation of rivaroxaban tablets are not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

5.10 Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

Direct-acting oral anticoagulants (DOACs), including rivaroxaban tablets, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are also discussed in other sections of the labeling:

· Increased Risk of Stroke After Discontinuation in Nonvalvular Atrial Fibrillation *[see Boxed Warning* and *Warnings and Precautions (5.1)]*

· Bleeding Risk *[see Warnings and Precautions (5.2, 5.4, 5.5, 5.6, 5.7)]*

· Spinal/Epidural Hematoma *[see Boxed Warning* and *Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development for the approved indications, 34,947 adult patients were exposed to rivaroxaban tablets.

Hemorrhage

The most common adverse reactions with rivaroxaban tablets were bleeding complications *[see Warnings and Precautions (5.2)]*.

Nonvalvular Atrial Fibrillation

In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for rivaroxaban tablets vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Table 5 shows the number of patients experiencing various types of bleeding events in the ROCKET AF trial.

Table 5: Bleeding Events in ROCKET AF* - On Treatment Plus 2 Days

Parameter	**Rivaroxaban Tablets N = 7111 n (%/year)**	**Warfarin N = 7125 n (%/year)**	**Rivaroxaban Tablets vs. Warfarin HR (95% CI)**
Major Bleeding†	395 (3.6)	386 (3.5)	1.04 (0.9, 1.2)
Intracranial Hemorrhage (ICH) ‡	55 (0.5)	84 (0.7)	0.67 (0.47, 0.93)
Hemorrhagic Stroke§	36 (0.3)	58 (0.5)	0.63 (0.42, 0.96)
Other ICH	19 (0.2)	26 (0.2)	0.74 (0.41, 1.34)
Gastrointestinal (GI)¶	221 (2)	140 (1.2)	1.61 (1.3, 1.99)
Fatal Bleeding#	27 (0.2)	55 (0.5)	0.5 (0.31, 0.79)
ICH	24 (0.2)	42 (0.4)	0.58 (0.35, 0.96)
Non-intracranial	3 (0)	13 (0.1)	0.23 (0.07, 0.82)

Abbreviations: HR = Hazard Ratio, CI = Confidence interval, CRNM = Clinically Relevant Non-Major.

* Major bleeding events within each subcategory were counted once per patient, but

patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.

‡ Intracranial bleeding events included intraparenchymal, intraventricular, subdural, subarachnoid and/or epidural hematoma.

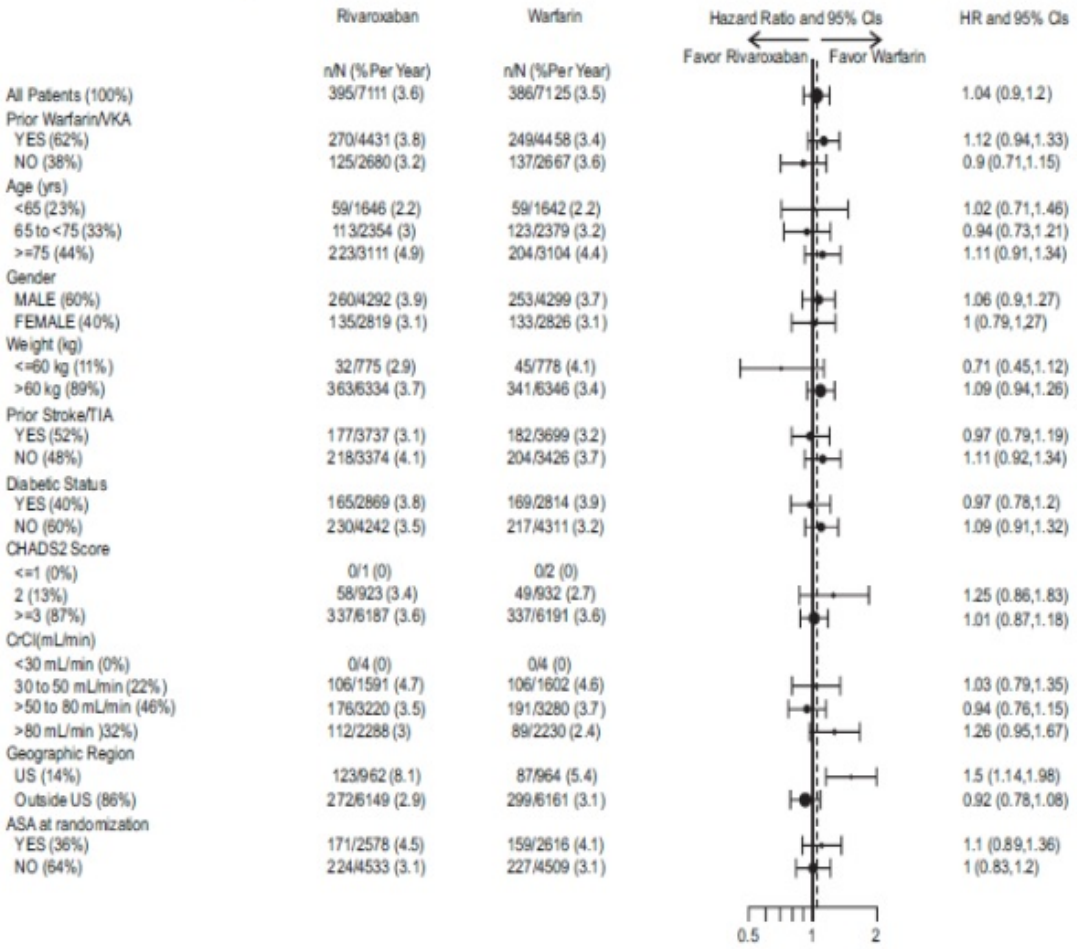
§ Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.

¶ Gastrointestinal bleeding events included upper GI, lower GI, and rectal bleeding.

Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

Figure 1 shows the risk of major bleeding events across major subgroups.

Figure 1: Risk of Major Bleeding Events by Baseline Characteristics in ROCKET AF – On Treatment Plus 2 Days



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted._

Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

EINSTEIN DVT and EINSTEIN PE Studies

In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with rivaroxaban tablets vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean duration of treatment was 208 days for rivaroxaban-treated patients and 204 days for enoxaparin/VKA-treated patients.

Table 6 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

Table 6: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies

Parameter	**Rivaroxaban Tablets† N = 4130 n (%)**	**Enoxaparin/ VKA† N = 4116 n (%)**
Major bleeding event	40 (1)	72 (1.7)
Fatal bleeding	3 (<0.1)	8 (0.2)
Intracranial	2 (<0.1)	4 (<0.1)
Non-fatal critical organ bleeding	10 (0.2)	29 (0.7)
Intracranial‡	3 (<0.1)	10 (0.2)
Retroperitoneal‡	1 (<0.1)	8 (0.2)
Intraocular‡	3 (<0.1)	2 (<0.1)
Intra-articular‡	0	4 (<0.1)
Non-fatal non-critical organ bleeding§	27 (0.7)	37 (0.9)
Decrease in Hb ≥ 2g/dL	28 (0.7)	42 (1)
Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant non-major bleeding	357 (8.6)	357 (8.7)
Any bleeding	1169 (28.3)	1153 (28)

* Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: Rivaroxaban tablets 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2 to 3)]

‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥ 2 g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells

Reduction in the Risk of Recurrence of DVT and/or PE

EINSTEIN CHOICE Study

In the EINSTEIN CHOICE clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1% for rivaroxaban tablets 10 mg, 2% for rivaroxaban tablets 20 mg, and 1% for acetylsalicylic acid (aspirin) 100 mg. The mean duration of treatment was 293 days for rivaroxaban tablets 10 mg-treated patients and 286 days for aspirin 100 mg-treated patients.

.

Table 7 shows the number of patients experiencing bleeding events in the EINSTEIN CHOICE study.

Table 7: Bleeding Events* in EINSTEIN CHOICE

Parameter	**Rivaroxaban Tablets†** **10 mg** **N=1127** **n (%)**	**Acetylsalicylic Acid (aspirin)†100 mg** **N=1131** **n (%)**
Major bleeding event	5 (0.4)	3 (0.3)
Fatal bleeding	0	1 (<0.1)
Non-fatal critical organ bleeding	2 (0.2)	1 (<0.1)
Non-fatal non-critical organ bleeding ‡	3 (0.3)	1 (<0.1)
Clinically relevant non-major (CRNM) bleeding §	22 (2)	20 (1.8)
Any bleeding	151 (13.4)	138 (12.2)

* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

†Treatment schedule: Rivaroxaban tablets 10 mg once daily or aspirin 100 mg once daily.

‡ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥ 2g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells.

§ Bleeding which was clinically overt, did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life._

In the EINSTEIN CHOICE study, there was an increased incidence of bleeding, including major and CRNM bleeding in the rivaroxaban tablets 20 mg group compared to the rivaroxaban tablets 10 mg or aspirin 100 mg groups._

*Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery_*

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with rivaroxaban tablets.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 8.

Table 8: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1 to 3)

	Rivaroxaban Tablets 10 mg	**Enoxaparin†**
Total treated patients	**N = 4487** **n (%)**	**N = 4524** **n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N = 3281** **n (%)**	**N = 3298** **n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	**N = 1206** **n (%)**	**N = 1226** **n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.

† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg

once daily (RECORD 1 to 3)

‡ Includes major bleeding events

Following rivaroxaban tablets treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

In the MAGELLAN study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events. Cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed. Patients with bronchiectasis/pulmonary cavitation, active cancer (i.e., undergoing acute, in-hospital cancer treatment), dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months all had an excess of bleeding with rivaroxaban tablets compared with enoxaparin/placebo and are excluded from all MAGELLAN data presented in Table 9. The incidence of bleeding leading to drug discontinuation was 2.5% for rivaroxaban tablets vs. 1.4% for enoxaparin/placebo.

Table 9 shows the number of patients experiencing various types of bleeding events in the MAGELLAN study.

Table 9: Bleeding Events in MAGELLAN* Study-Safety Analysis Set - On Treatment Plus 2 Days

MAGELLAN Study¶	**Rivaroxaban Tablets 10 mg N=3218 n (%)**	**Enoxaparin 40 mg/placebo N=3229 n (%)**
Major bleeding‡†	22 (0.7)	15 (0.5)
Critical site bleeding	7 (0.2)	4 (0.1)
Fatal bleeding§	3 (<0.1)	1 (<0.1)
Clinically relevant non-major bleeding events (CRNM)	93 (2.9)	34 (1.1)

* Patients at high risk of bleeding (i.e. bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal

ulcer or any bleeding in the previous three months) were excluded.

† Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

‡ Defined as clinically overt bleeding associated with a drop in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.

§ Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

¶ Patients received either rivaroxaban tablets or placebo once daily for 35 ±4 days starting in hospital and continuing post hospital discharge or received enoxaparin or placebo once daily for 10 ±4 days in the hospital.

Reduction of Risk of Major Cardiovascular Events in Patients with CAD

In the COMPASS trial overall, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 2.7% for rivaroxaban tablets 2.5 mg twice daily vs. 1.2% for placebo on background therapy for all patients with aspirin 100 mg once daily. The incidences of important bleeding events in the CAD and PAD populations in COMPASS were similar.

Table 10 shows the number of patients experiencing various types of major bleeding events in the COMPASS trial.

Table 10: Major Bleeding Events in COMPASS - On Treatment Plus 2 Days*

Parameter	**Rivaroxaban Tablets† N=9134 n (%/year)**	**Placebo† N=9107 n (%/year)**	**Rivaroxaban Tablets vs. Placebo HR (95 % CI)**
Modified ISTH Major Bleeding‡	263 (1.6)	144 (0.9)	1.8 (1.5, 2.3)
- Fatal bleeding event Intracranial hemorrhage (ICH) Non-intracranial	12 (<0.1) 6 (<0.1) 6 (<0.1)	8 (<0.1) 3 (<0.1) 5 (<0.1)	1.5 (0.6, 3.7) 2 (0.5, 8) 1.2 (0.4, 4)
- Symptomatic bleeding in critical organ (non-fatal) ICH (fatal and non-fatal) Hemorrhagic Stroke Other ICH	58 (0.3) 23 (0.1) 18 (0.1) 6 (<0.1)	43 (0.3) 21 (0.1) 13 (<0.1) 9 (<0.1)	1.4 (0.9, 2) 1.1 (0.6, 2) 1.4 (0.7, 2.8) 0.7 (0.2, 1.9)
- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)	7 (<0.1)	6 (<0.1)	1.2 (0.4, 3.5)
- Bleeding leading to hospitalization (non-fatal, not in critical organ, not requiring reoperation)	188 (1.1)	91 (0.5)	2.1 (1.6, 2.7)
Major GI bleeding	117 (0.7)	49 (0.3)	2.4 (1.7, 3.4)

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment in the safety analysis set in COMPASS patients.

† Treatment schedule: Rivaroxaban tablets 2.5 mg twice daily or placebo. All patients received background therapy with aspirin 100 mg once daily.

‡ Defined as i) fatal bleeding, or ii) symptomatic bleeding in a critical area or organ, such as intraarticular, intramuscular with compartment syndrome, intraspinal, intracranial, intraocular, respiratory, pericardial, liver, pancreas, retroperitoneal, adrenal gland or kidney; or iii) bleeding into the surgical site requiring reoperation, or iv) bleeding leading to hospitalization.

CI: confidence interval; HR: hazard ratio; ISTH: International Society on Thrombosis and Hemostasis

Reduction of Risk of Major Thrombotic Vascular Events in Patients with Peripheral Artery Disease (PAD), Including Patients after Lower Extremity Revascularization due to Symptomatic PAD
The incidence of premature permanent discontinuation due to bleeding events for rivaroxaban tablets 2.5 mg twice daily vs. placebo on background therapy with aspirin 100 mg once daily in VOYAGER was 4.1% vs. 1.6% and in COMPASS PAD was 2.7% vs. 1.3%, respectively.

Table 11 shows the number of patients experiencing various types of TIMI (Thrombolysis in Myocardial Infarction) major bleeding events in the VOYAGER trial. The most common site of bleeding was gastrointestinal.

Table 11: Major Bleeding Events* in VOYAGER-On Treatment Plus 2 Days

	Rivaroxaban Tablets† N=3256		**Placebo† N=3248**		**Rivaroxaban Tablets vs. Placebo HR (95 % CI)**
Parameter	**n (%)**	**Event rate %/year**	**n (%)**	**Event rate %/year**	
TIMI Major Bleeding (CABG/non-CABG)	62 (1.9)	0.96	44 (1.4)	0.67	1.4 (1, 2.1)
Fatal bleeding	6 (0.2)	0.09	6 (0.2)	0.09	1 (0.3, 3.2)
Intracranial bleeding	13 (0.4)	0.2	17 (0.5)	0.26	0.8 (0.4, 1.6)
Clinically overt signs of hemorrhage associated with a drop in haemoglobin of ≥5 g/dL or drop in hematocrit of ≥15%	46 (1.4)	0.71	24 (0.7)	0.36	1.9 (1.2, 3.2)

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories.
† Treatment schedule: Rivaroxaban tablets 2.5 mg twice daily or placebo. All patients received background therapy with aspirin 100 mg once daily.
CABG: Coronary artery bypass graft; CI: confidence interval; HR: hazard ratio; TIMI: Thrombolysis in Myocardial Infarction Bleeding Criteria

Other Adverse Reactions

Non-hemorrhagic adverse reactions reported in ≥1% of rivaroxaban tablets-treated patients in the EINSTEIN DVT and EINSTEIN PE studies are shown in Table 12.

Table 12: Other Adverse Reactions* Reported by ≥1% of Rivaroxaban Tablets-Treated Patients in EINSTEIN DVT and EINSTEIN PE Studies

Body System Adverse Reaction		
EINSTEIN DVT Study	**Rivaroxaban Tablets 20 mg N=1718 n (%)**	**Enoxaparin/ VKA N=1711 n (%)**
Gastrointestinal disorders		
Abdominal pain	46 (2.7)	25 (1.5)
General disorders and administration site conditions		
Fatigue	24 (1.4)	15 (0.9)
Musculoskeletal and connective tissue disorders		
Back pain	50 (2.9)	31 (1.8)
Muscle spasm	23 (1.3)	13 (0.8)
Nervous system disorders		
Dizziness	38 (2.2)	22 (1.3)
Psychiatric disorders		
Anxiety	24 (1.4)	11 (0.6)
Depression	20 (1.2)	10 (0.6)
Insomnia	28 (1.6)	18 (1.1)
EINSTEIN PE Study	**Rivaroxaban 20 mg N=2412 n (%)**	**Enoxaparin/ VKA N=2405 n (%)**
Skin and subcutaneous tissue disorders		
Pruritus	53 (2.2)	27 (1.1)

* Adverse reaction with Relative Risk >1.5 for rivaroxaban tablets versus comparator

Non-hemorrhagic adverse reactions reported in ≥1% of rivaroxaban tablets-treated patients in RECORD 1 to 3 studies are shown in Table 13.

Table 13: Other Adverse Drug Reactions* Reported by ≥1% of Rivaroxaban Tablets-Treated Patients in RECORD 1 to 3 Studies

Body System Adverse Reaction	**Rivaroxaban Tablets 10 mg N = 4487 n (%)**	**Enoxaparin† N = 4524 n (%)**
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue		

disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication

† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1 to 3)

Pediatric Patients

Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients
The safety assessment is based on data from the EINSTEIN Junior Phase 3 study in 491 patients from birth to less than 18 years of age. Patients were randomized 2:1 to receive body weight- adjusted doses of rivaroxaban tablets or comparator (unfractionated heparin, low molecular weight heparin, fondaparinux or VKA).

Discontinuation due to bleeding events occurred in 6 (1.8%) patients in the rivaroxaban tablets group and 3 (1.9%) patients in the comparator group.

Table 14 shows the number of patients experiencing bleeding events in the EINSTEIN Junior study. In female patients who had experienced menarche, ages 12 to <18 years of age, menorrhagia occurred in 23 (27%) female patients in the rivaroxaban tablets group and 5 (10%) female patients in the comparator group.

Table 14: Bleeding Events in EINSTEIN Junior Study – Safety Analysis Set - Main Treatment Period*

Parameter	**Rivaroxaban Tablets† N=329 n (%)**	**Comparator Group‡ N=162 n (%)**
Major bleeding§	0	2 (1.2)
Clinically relevant non-major bleeding¶	10 (3)	1 (0.6)
Trivial bleeding	113 (34.3)	44 (27.2)
Any bleeding	119 (36.2)	45 (27.8)

* These events occurred after randomization until 3 months of treatment (1 month for patients <2 years with central venous catheter-related VTE (CVC-VTE). Patients may have more than one event.
† Treatment schedule: body weight-adjusted doses of rivaroxaban tablets; randomized 2:1 (Rivaroxaban tablets: Comparator).
‡ Unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux or

VKA.
§ Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.
¶ Defined as clinically overt bleeding, which did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

Non-bleeding adverse reactions reported in ≥5% of rivaroxaban-treated patients are shown in Table 15.

Table 15: Other Adverse Reactions* Reported in Rivaroxaban Tablets-Treated Patients by ≥5% in EINSTEIN Junior Study

Adverse Reaction	**Rivaroxaban Tablets N=329 n (%)**	**Comparator Group N=162 n (%)**
Pain in extremity	23 (7)	7 (4.3)
Fatigue†	23 (7)	7 (4.3)

* Adverse reaction with Relative Risk >1.5 for rivaroxaban tablets versus comparator.
† The following terms were combined: fatigue, asthenia.

A clinically relevant adverse reaction in rivaroxaban tablets-treated patients was vomiting (10.6% in the rivaroxaban tablets group vs 8% in the comparator group).

Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease (CHD) after the Fontan Procedure

The data below are based on Part B of the UNIVERSE study which was designed to evaluate the safety and efficacy of rivaroxaban tablets for thromboprophylaxis in 98 children with CHD after the Fontan procedure who took at least one dose of study drug. Patients in Part B were randomized 2:1 to receive either body weight-adjusted doses of rivaroxaban tablets or aspirin (approximately 5 mg/kg).

Discontinuation due to bleeding events occurred in 1 (1.6%) patient in the rivaroxaban tablets group and no patients in the aspirin group.

Table 16 shows the number of patients experiencing bleeding events in the UNIVERSE study.

Table 16: Bleeding Events in UNIVERSE Study - Safety Analysis Set - On Treatment Plus 2 Days

Parameter	**Rivaroxaban Tablets* N=64 n (%)**	**Aspirin* N=34 n (%)**

Major Bleeding†	1 (1.6)	0
Epistaxis leading to transfusion	1 (1.6)	0
Clinically relevant non-major (CRNM) bleeding§	4 (6.3)	3 (8.8)
Trivial bleeding	21 (32.8)	12 (35.3)
Any bleeding	23 (35.9)	14 (41.2)

* Treatment schedule: body weight-adjusted doses of rivaroxaban tablets or aspirin (approximately 5 mg/kg); randomized 2:1 (Rivaroxaban tablets: Aspirin).
†Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, a transfusion of the equivalent of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.
§ Defined as clinically overt bleeding, which did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

Non-bleeding adverse reactions reported in ≥5% of rivaroxaban tablets-treated patients are shown in Table 17.

Table 17: Other Adverse Reactions* Reported by ≥ 5% of Rivaroxaban Tablets-Treated Patients in UNIVERSE Study (Part B)

Adverse Reaction	**Rivaroxaban Tablets N=64 n (%)**	**Aspirin N=34 n (%)**
Cough	10 (15.6)	3 (8.8)
Vomiting	9 (14.1)	3 (8.8)
Gastroenteritis†	8 (12.5)	1 (2.9)
Rash†	6 (9.4)	2 (5.9)

* Adverse reaction with Relative Risk >1.5 for rivaroxaban tablets versus aspirin.
† The following terms were combined:
Gastroenteritis: gastroenteritis, gastroenteritis viral
Rash: rash, rash maculo-papular, viral rash

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rivaroxaban tablets. 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 lymphatic system disorders: agranulocytosis, thrombocytopenia

Hepatobiliary disorders: jaundice, cholestasis, hepatitis (including hepatocellular injury)

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

Nervous system disorders: hemiparesis

Renal 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)

7 DRUG INTERACTIONS

7.1 General Inhibition and Induction Properties

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding. Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events.

7.2 Drugs that Inhibit Cytochrome P450 3A Enzymes and Drug Transport Systems

Interaction with Combined P-gp and Strong CYP3A Inhibitors

Avoid concomitant administration of rivaroxaban tablets with known combined P-gp and strong CYP3A inhibitors (e.g., ketoconazole and ritonavir) *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

Although clarithromycin is a combined P-gp and strong CYP3A inhibitor, pharmacokinetic data suggests that no precautions are necessary with concomitant administration with rivaroxaban tablets as the change in exposure is unlikely to affect the bleeding risk *[see Clinical Pharmacology (12.3)]*.

Interaction with Combined P-gp and Moderate CYP3A Inhibitors in Patients with Renal Impairment

Rivaroxaban tablets should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (e.g., erythromycin) unless the potential benefit justifies the potential risk *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

7.3 Drugs that Induce Cytochrome P450 3A Enzymes and Drug Transport Systems

Avoid concomitant use of rivaroxaban tablets with drugs that are combined P-gp and strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort) *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

7.4 Anticoagulants and NSAIDs/Aspirin

Coadministration of enoxaparin, warfarin, aspirin clopidogrel and chronic NSAID use may increase the risk of bleeding *[see Clinical Pharmacology (12.3)].*

Avoid concurrent use of rivaroxaban tablets with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation

inhibitors, or NSAIDs *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on rivaroxaban tablets in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use rivaroxaban tablets with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery. The anticoagulant effect of rivaroxaban tablets cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of rivaroxaban tablets for the mother and possible risks to the fetus when prescribing rivaroxaban tablets to a pregnant woman *[see Warnings and Precautions (5.2, 5.7)]*.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnancy is a risk factor for venous thromboembolism and that risk is increased in women with inherited or acquired thrombophilias. Pregnant women with thromboembolic disease have an increased risk of maternal complications including pre-eclampsia. Maternal thromboembolic disease increases the risk for intrauterine growth restriction, placental abruption and early and late pregnancy loss.

Fetal/Neonatal Adverse Reactions

Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.

Labor or Delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding and this risk may be increased during labor or delivery *[see Warnings and Precautions (5.7)].* The risk of bleeding should be balanced with the risk of thrombotic events when considering the use of rivaroxaban tablets in this setting.

Data

Human Data

There are no adequate or well-controlled studies of rivaroxaban tablets in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage. In an *in vitro* placenta perfusion model, unbound rivaroxaban was rapidly transferred across the human placenta.

Animal Data

Rivaroxaban crosses the placenta in animals. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body

weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg during the period of organogenesis. This dose corresponds to about 14 times the human exposure of unbound drug. In rats, peripartal maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

8.2 Lactation

Risk Summary

Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. Rivaroxaban and/or its metabolites were present in the milk of rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for rivaroxaban tablets and any potential adverse effects on the breastfed infant from rivaroxaban tablets or from the underlying maternal condition *(see Data)*.

Data

Animal Data

Following a single oral administration of 3 mg/kg of radioactive [^{14}C]-rivaroxaban to lactating rats between Day 8 to 10 postpartum, the concentration of total radioactivity was determined in milk samples collected up to 32 hours post-dose. The estimated amount of radioactivity excreted with milk within 32 hours after administration was 2.1% of the maternal dose.

8.3 Females and Males of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including rivaroxaban tablets should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

8.4 Pediatric Use

The safety and effectiveness of rivaroxaban tablets have been established in pediatric patients from birth to less than 18 years for the treatment of VTE and the reduction in risk of recurrent VTE. Use of rivaroxaban tablets are supported in these age groups by evidence from adequate and well-controlled studies of rivaroxaban tablets in adults with additional pharmacokinetic, safety and efficacy data from a multicenter, prospective, open-label, active-controlled randomized study in 500 pediatric patients from birth to less than 18 years of age. Rivaroxaban tablets was not studied and therefore dosing cannot be reliably determined or recommended in children less than 6 months who were less than 37 weeks of gestation at birth; had less than 10 days of oral feeding, or had a body weight of less than 2.6 kg *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.8)].*

The safety and effectiveness of rivaroxaban tablets have been established for use in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure. Use of rivaroxaban tablets are supported in these age

groups by evidence from adequate and well-controlled studies of rivaroxaban tablets in adults with additional data from a multicenter, prospective, open-label, active controlled study in 112 pediatric patients to evaluate the single- and multiple-dose pharmacokinetic properties of rivaroxaban tablets and the safety and efficacy of rivaroxaban tablets when used for thromboprophylaxis for 12 months in children with single ventricle physiology who had the Fontan procedure *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.9)].*

Clinical studies that evaluated safety, efficacy, pharmacokinetic and pharmacodynamic data support the use of rivaroxaban tablets 10 mg, 15 mg, and 20 mg tablets in pediatric patients. For the rivaroxaban tablets 2.5 mg tablets, there are no safety, efficacy, pharmacokinetic and pharmacodynamic data to support the use in pediatric patients. Therefore, rivaroxaban tablets 2.5 mg tablets are not recommended for use in pediatric patients.

Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents.

8.5 Geriatric Use

Of the total number of adult patients in clinical trials for the approved indications of rivaroxaban tablets (N=64,943 patients), 64 percent were 65 years and over, with 27 percent 75 years and over. In clinical trials the efficacy of rivaroxaban tablets in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

8.6 Renal Impairment

In pharmacokinetic studies, compared to healthy adult subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in adult subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Clinical Pharmacology (12.3)]*.

<u>Nonvalvular Atrial Fibrillation</u>

Patients with Chronic Kidney Disease not on Dialysis

In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered rivaroxaban tablets 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered rivaroxaban tablets 20 mg once daily. Patients with CrCl <30 mL/min were not studied, but administration of rivaroxaban tablets 15 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment *[see Clinical Pharmacology (12.3)]*.

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with rivaroxaban tablets did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of rivaroxaban tablets 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study *[see Clinical Pharmacology (12.2, 12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF.

<u>Treatment of DVT and/or PE and Reduction in the Risk of Recurrence of DVT and/or PE</u>

In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies, but administration of rivaroxaban tablets is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3)].* Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of rivaroxaban tablets in patients with CrCl <15.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery

The combined analysis of the RECORD 1 to 3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. In the RECORD 1 to 3 trials, patients with CrCl values <30 mL/min at screening were excluded from the studies, but administration of rivaroxaban tablets 10 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3)].* Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of rivaroxaban tablets in patients with CrCl <15 mL/min.

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

Patients with CrCl values <30 mL/min at screening were excluded from the MAGELLAN study. In patients with CrCl <30 mL/min a dose of rivaroxaban tablets 10 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3)].* Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid use of rivaroxaban tablets in patients with CrCl <15 mL/min.

Reduction of Risk of Major Cardiovascular Events in Patients with CAD and Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients After Recent Lower Extremity Revascularization due to Symptomatic PAD

Patients with Chronic Kidney Disease not on Dialysis

Patients with a CrCl <15 mL/min at screening were excluded from COMPASS and VOYAGER, limited data are available for patients with a CrCl of 15 to 30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg rivaroxaban tablets twice daily is expected to give an exposure similar to that in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3)]*, whose efficacy and safety outcomes were similar to those with preserved renal function.

Patients with End-Stage Renal Disease on Dialysis

No clinical outcome data is available for the use of rivaroxaban tablets with aspirin in patients with ESRD on dialysis since these patients were not enrolled in COMPASS or VOYAGER. In patients with ESRD maintained on intermittent hemodialysis, administration of rivaroxaban tablets 2.5 mg twice daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in moderate renal impaired patients in the COMPASS study *[see Clinical Pharmacology (12.2,12.3)]*. It is not known whether these concentrations will lead to similar CV risk reduction and bleeding risk in patients with ESRD on dialysis as was seen in COMPASS.

Pediatric Use

No dosage adjustment is required in patients 1 year of age or older with mild renal impairment (eGFR 50 to ≤ 80 mL/min/1.73 m^2). There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2); therefore, avoid the use of rivaroxaban tablets in these patients.

There are no clinical data in pediatric patients younger than 1 year with serum creatinine results above 97.5^{th} percentile; therefore, avoid the use of rivaroxaban tablets in these patients *[see Dosage and Administration (2.2)]*.

8.7 Hepatic Impairment

In a pharmacokinetic study, compared to healthy adult subjects with normal liver function, AUC increases of 127% were observed in adult subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of rivaroxaban tablets in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology (12.3)]*.

Avoid the use of rivaroxaban tablets in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

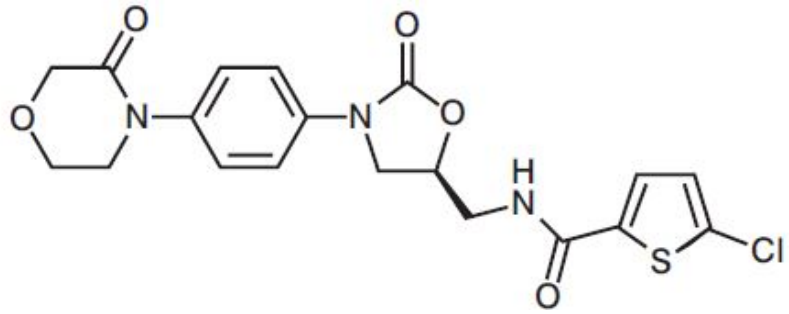
No clinical data are available in pediatric patients with hepatic impairment.

10 OVERDOSAGE

Overdose of rivaroxaban tablets may lead to hemorrhage. Discontinue rivaroxaban tablets and initiate appropriate therapy if bleeding complications associated with overdosage occur. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of rivaroxaban tablets overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*. Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

11 DESCRIPTION

Rivaroxaban, USP, a factor Xa (FXa) inhibitor, is the active ingredient in rivaroxaban tablets, USP with the chemical name 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. The molecular formula of rivaroxaban, USP is $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.88. The structural formula is:



Rivaroxaban, USP is a pure (*S*)-enantiomer. It is an white to yellowish powder. Rivaroxaban, USP is soluble in dimethyl sulfoxide, practically insoluble to very slightly soluble in acetone and water.

Each rivaroxaban tablet, USP contains 2.5 mg, 10 mg, 15 mg or 20 mg of rivaroxaban, USP. The inactive ingredients of rivaroxaban tablets, USP are: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate.
Additionally, the proprietary film coating mixture used for rivaroxaban 2.5 mg tablet is Opadry® Yellow containing D&C yellow #10 aluminium lake, hypromellose, iron oxide red, iron oxide yellow, polyethylene glycol 6000, titanium dioxide, and for rivaroxaban 10 mg tablet is Opadry® Pink containing hypromellose, iron oxide red, polyethylene glycol 6000, talc, titanium dioxide, and for rivaroxaban 15 mg tablet and 20 mg tablet is Opadry® Brown containing hypromellose, iron oxide black, iron oxide red, polyethylene glycol 8000, and titanium dioxide.

FDA approved dissolution test specifications differ from USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rivaroxaban tablets are a selective inhibitor of FXa. It does not require a cofactor (such as Anti-thrombin III) for activity. Rivaroxaban inhibits free FXa and prothrombinase activity. Rivaroxaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, rivaroxaban decreases thrombin generation.

12.2 Pharmacodynamics

Rivaroxaban produces dose-dependent inhibition of FXa activity. Clotting tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest®, are also prolonged dose-dependently. In children treated with rivaroxaban, the correlation between anti-factor Xa to plasma concentrations is linear with a slope close to 1.

Monitoring for anticoagulation effect of rivaroxaban using anti-FXa activity or a clotting test is not recommended.

Specific Populations

Renal Impairment

The relationship between systemic exposure and pharmacodynamic activity of rivaroxaban was altered in adult subjects with renal impairment relative to healthy control subjects *[see Use in Specific Populations (8.6)]*.

Table 18: Percentage Increase in Rivaroxaban PK and PD Measures in Adult Subjects with Renal Impairment Relative to Healthy Subjects from Clinical Pharmacology Studies

		Creatinine Clearance (mL/min)				
					ESRD	**ESRD**

Measure	Parameter	50 to 79	30 to 49	15 to 29	ESRD (on dialysis)*	ESRD (post-dialysis)*
Exposure	AUC	44	52	64	47	56
FXa Inhibition	AUEC	50	86	100	49	33
PT Prolongation	AUEC	33	116	144	112	158

**Separate stand-alone study.*

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the plasma concentration-time curve; AUEC = Area under the effect-time curve

Hepatic Impairment

Anti-Factor Xa activity was similar in adult subjects with normal hepatic function and in mild hepatic impairment (Child-Pugh A class). There is no clear understanding of the impact of hepatic impairment beyond this degree on the coagulation cascade and its relationship to efficacy and safety.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of rivaroxaban is dose-dependent. For the 2.5 mg and 10 mg dose, it is estimated to be 80% to 100% and is not affected by food. Rivaroxaban tablets 2.5 mg and 10 mg tablets can be taken with or without food. Rivaroxaban tablets 20 mg administered in the fasted state has an absolute bioavailability of approximately 66%. Coadministration of rivaroxaban tablets with food increases the bioavailability of the 20 mg dose (mean AUC and C_{max} increasing by 39% and 76% respectively with food). Rivaroxaban tablets 15 mg and 20 mg tablets should be taken with food *[see Dosage and Administration (2.1)]*.

The maximum concentrations (C_{max}) of rivaroxaban appear 2 to 4 hours after tablet intake. The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH. Coadministration of rivaroxaban tablets (30 mg single dose) with the H_2-receptor antagonist ranitidine (150 mg twice daily), the antacid aluminum hydroxide/magnesium hydroxide (10 mL) or rivaroxaban tablets (20 mg single dose) with the PPI omeprazole (40 mg once daily) did not show an effect on the bioavailability and exposure of rivaroxaban (see Figure 4).

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 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 which can result in reduced absorption and related drug exposure.

In a study with 44 healthy subjects, both mean AUC and C_{max} values for 20 mg rivaroxaban administered orally as a crushed tablet mixed in applesauce were comparable to that after the whole tablet. However, for the crushed tablet suspended in water and administered via an NG tube followed by a liquid meal, only mean AUC was comparable to that after the whole tablet, and C_{max} was 18% lower.

Distribution

Protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism

Approximately 51% of an orally administered [^{14}C]-rivaroxaban dose was recovered as inactive metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion

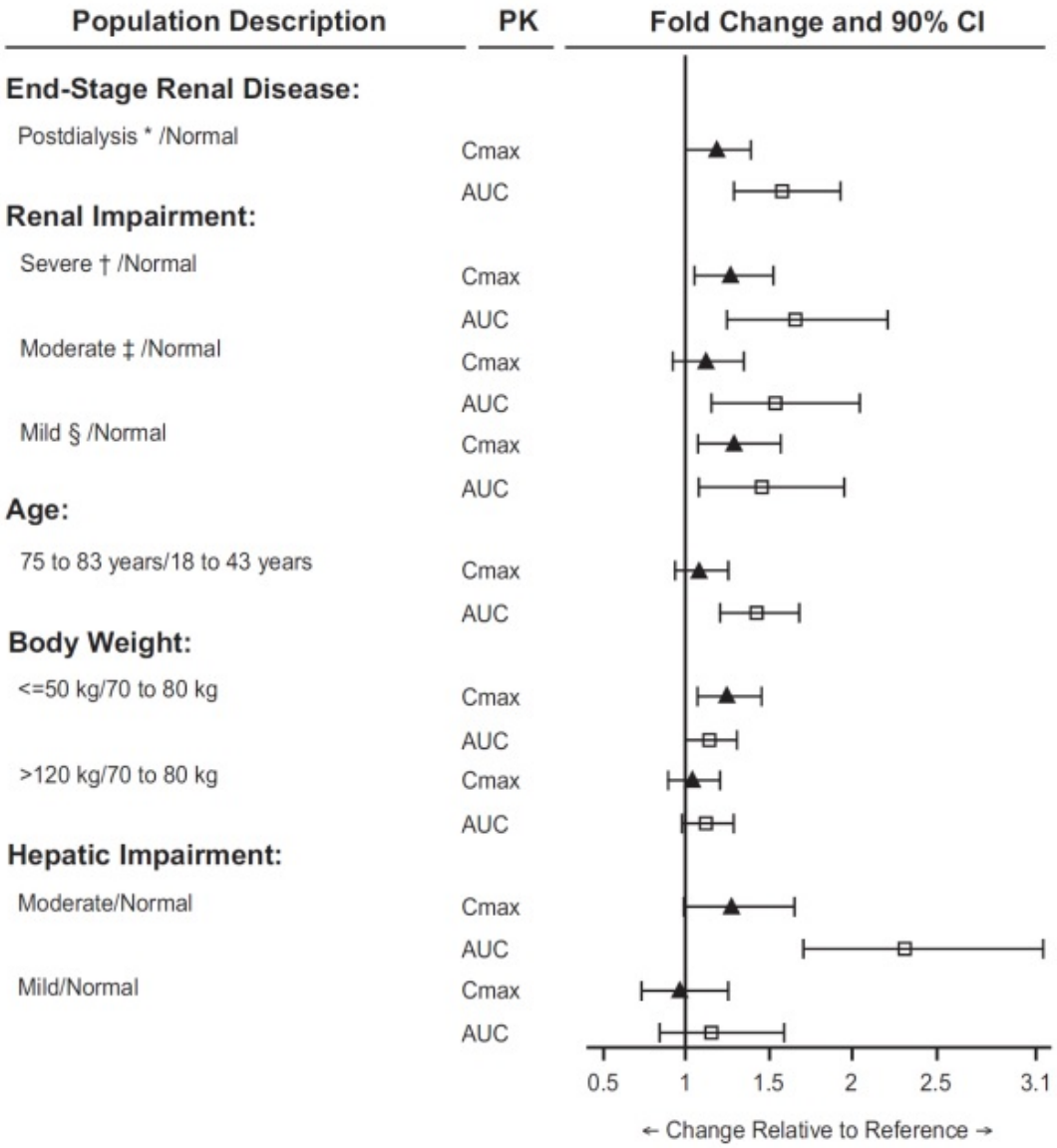
In a Phase 1 study, following the administration of a [^{14}C]-rivaroxaban, approximately one-third (36%) was recovered as unchanged drug in the urine and 7% was recovered as unchanged drug in feces. Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio). Rivaroxaban is a substrate of the efflux transporter proteins P-gp and ABCG2 (also abbreviated BCRP). Rivaroxaban's affinity for influx transporter proteins is unknown.

Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Specific Populations

The effects of level of renal impairment, age, body weight, and level of hepatic impairment on the pharmacokinetics of rivaroxaban are summarized in Figure 2.

Figure 2: Effect of Specific Adult Populations on the Pharmacokinetics of Rivaroxaban



* ESRD subjects maintained with chronic and stable hemodialysis; reported PK findings are following single dose of rivaroxaban post hemodialysis.
† Creatinine clearance 15 to 29 mL/min.
‡ Creatinine clearance 30 to 49 mL/min.
§ Creatinine clearance 50 to 79 mL/min.

[see Dosage and Administration (2.1)]

Gender

Gender did not influence the pharmacokinetics or pharmacodynamics of rivaroxaban tablets.

Race

Healthy Japanese subjects were found to have 20 to 40% on average higher exposures compared to other ethnicities including Chinese. However, these differences in exposure are reduced when values are corrected for body weight.

Elderly

The terminal elimination half-life is 11 to 13 hours in the elderly subjects aged 60 to 76 years *[see Use in Specific Populations (8.5)]*.

Pediatric Patients
The rate and extent of absorption were similar between the tablet and suspension. After repeated administration of rivaroxaban for the treatment of VTE, the C_{max} of rivaroxaban in plasma was observed at median times of 1.5 to 2.2 hours in subjects who ranged from birth to less than 18 years of age.

In children who were 6 months to 9 years of age, *in vitro* plasma protein binding of rivaroxaban is approximately 90%.

The half-life of rivaroxaban in plasma of pediatric patients treated for VTE decreased with decreasing age. Mean half-life values were 4.2 hours in adolescents, 3 hours in children 2 to 12 years of age, 1.9 hours in children 0.5 to <2 years of age, and 1.6 hours in children <0.5 years of age.

An exploratory analysis in pediatric patients treated for VTE did not reveal relevant differences in rivaroxaban exposure based on gender or race.

Renal Impairment

The safety and pharmacokinetics of single-dose rivaroxaban tablets (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 Figure 2). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Use in Specific Populations (8.6)]*.

Hemodialysis in ESRD subjects: Systemic exposure to rivaroxaban administered as a single 15 mg dose in ESRD subjects dosed 3 hours after the completion of a 4-hour hemodialysis session (post-dialysis) is 56% higher when compared to subjects with normal renal function (see Table 18). The systemic exposure to rivaroxaban administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 600 mL/min and a blood flow rate in the range of 320 to 400 mL/min is 47% higher compared to those with normal renal function. The extent of the increase is similar to the increase in patients with CrCl 15 to 50 mL/min taking rivaroxaban tablets 15 mg. Hemodialysis had no significant impact on rivaroxaban exposure. Protein binding was similar (86% to 89%) in healthy controls and ESRD subjects in this study.

Pediatric Patients: Limited clinical data are available in children 1 year or older with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2) or in children younger than 1 year with serum creatinine results above 97.5th percentile *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].*

Hepatic Impairment

The safety and pharmacokinetics of single-dose rivaroxaban tablets (10 mg) were evaluated in a study in healthy adult subjects (n=16) and adult subjects with varying degrees of hepatic impairment (see Figure 2). 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) (see Figure 2). Increases in pharmacodynamic effects were also observed *[see Use in Specific Populations (8.7)]*.

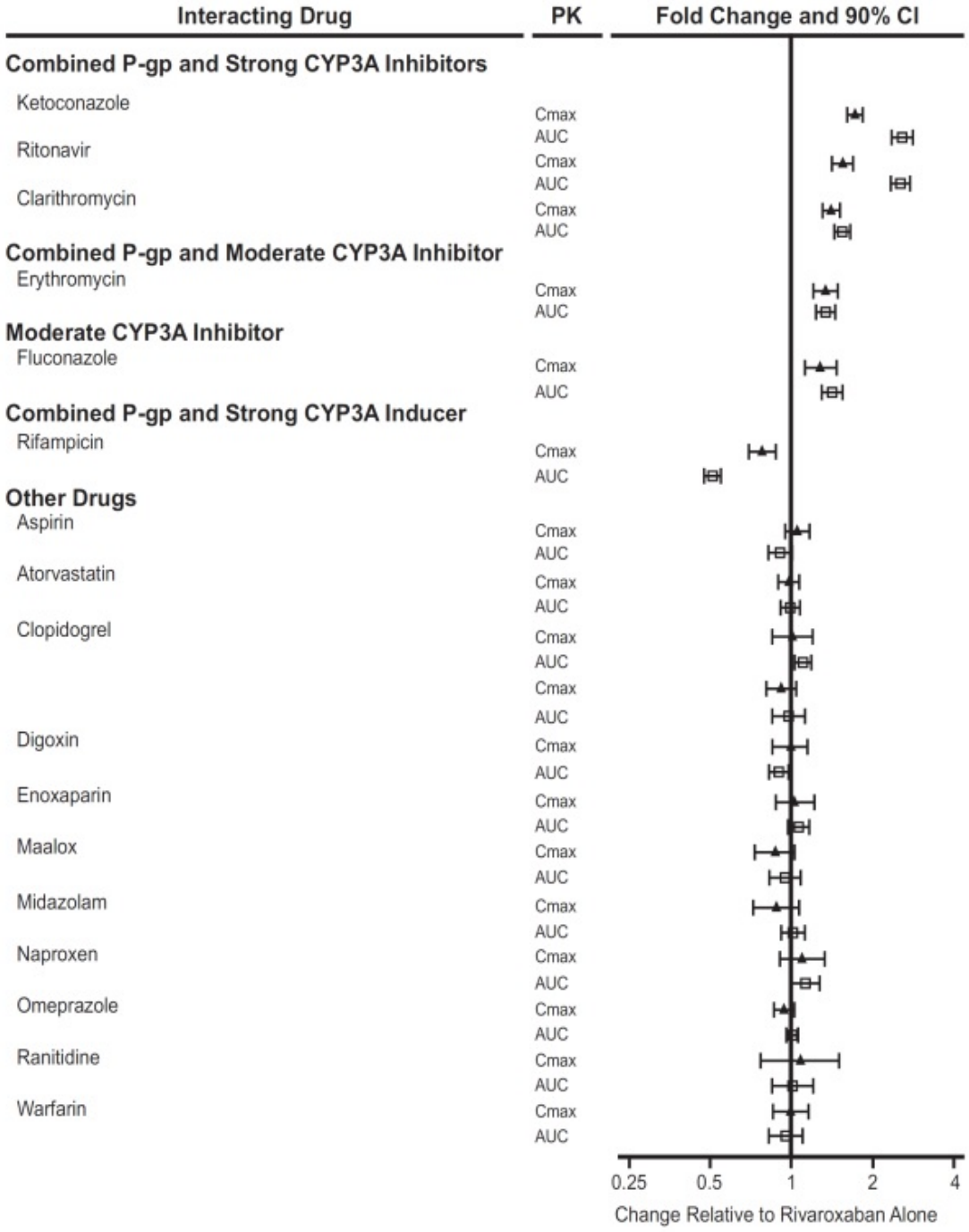
No clinical data are available in pediatric patients with hepatic impairment.

Drug Interactions

In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A nor induces CYP1A2, 2B6, 2C19, or 3A. *In vitro* data also indicates a low rivaroxaban inhibitory potential for P-gp and ABCG2 transporters.

The effects of coadministered drugs on the pharmacokinetics of rivaroxaban exposure are summarized in Figure 3 *[see Drug Interactions (7)]*.

Figure 3: Effect of Coadministered Drugs on the Pharmacokinetics of Rivaroxaban in Adults



Anticoagulants

In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and rivaroxaban tablets (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. In another study, single doses of warfarin (15 mg) and rivaroxaban tablets (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Neither enoxaparin nor warfarin affected the pharmacokinetics of rivaroxaban (see Figure 3).

NSAIDs/Aspirin

In ROCKET AF, concomitant aspirin use (almost exclusively at a dose of 100 mg or less) during the double-blind phase was identified as an independent risk factor for major

bleeding. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with rivaroxaban tablets. Neither naproxen nor aspirin affected the pharmacokinetics of rivaroxaban (see Figure 3).

Clopidogrel

In two drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and rivaroxaban tablets (15 mg single dose) were coadministered in healthy subjects, an increase in bleeding time to 45 minutes was observed in approximately 45% and 30% of subjects in these studies, respectively. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. There was no change in the pharmacokinetics of either drug.

Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A Enzymes and Drug Transport Systems

In a pharmacokinetic trial, rivaroxaban tablets was administered as a single dose in subjects with mild (CrCl = 50 to 79 mL/min) or moderate renal impairment (CrCl = 30 to 49 mL/min) receiving multiple doses of erythromycin (a combined P-gp and moderate CYP3A inhibitor). Compared to rivaroxaban tablets administered alone in subjects with normal renal function (CrCl >80 mL/min), subjects with mild and moderate renal impairment concomitantly receiving erythromycin reported a 76% and 99% increase in AUC_{inf} and a 56% and 64% increase in C_{max}, respectively. Similar trends in pharmacodynamic effects were also observed.

12.6 QT/QTc Prolongation

In a thorough QT study in healthy men and women aged 50 years and older, no QTc prolonging effects were observed for rivaroxaban tablets (15 mg and 45 mg, single-dose).

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rivaroxaban was not carcinogenic when administered by oral gavage to mice or rats for up to 2 years. The systemic exposures (AUCs) of unbound rivaroxaban in male and female mice at the highest dose tested (60 mg/kg/day) were 1- and 2-times, respectively, the human exposure of unbound drug at the human dose of 20 mg/day. Systemic exposures of unbound drug in male and female rats at the highest dose tested (60 mg/kg/day) were 2- and 4-times, respectively, the human exposure.

Rivaroxaban was not mutagenic in bacteria (Ames-Test) or clastogenic in V79 Chinese hamster lung cells *in vitro* or in the mouse micronucleus test *in vivo*.

No impairment of fertility was observed in male or female rats when given up to 200 mg/kg/day of rivaroxaban orally. This dose resulted in exposure levels, based on the unbound AUC, at least 13 times the exposure in humans given 20 mg rivaroxaban daily.

14 CLINICAL STUDIES

14.1 Stroke Prevention in Nonvalvular Atrial Fibrillation

The evidence for the efficacy and safety of rivaroxaban tablets was derived from Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K

antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) [NCT00403767], a multi-national, double-blind study comparing rivaroxaban tablets (at a dose of 20 mg once daily with the evening meal in patients with CrCl >50 mL/min and 15 mg once daily with the evening meal in patients with CrCl 30 to 50 mL/min) to warfarin (titrated to INR 2 to 3) to reduce the risk of stroke and non-central nervous system (CNS) systemic embolism in patients with nonvalvular atrial fibrillation (AF). Patients had to have one or more of the following additional risk factors for stroke:

- a prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or
- 2 or more of the following risk factors:
  - age ≥75 years,
  - hypertension,
  - heart failure or left ventricular ejection fraction ≤35%, or
  - diabetes mellitus

ROCKET AF was a non-inferiority study designed to demonstrate that rivaroxaban tablets preserved more than 50% of warfarin's effect on stroke and non-CNS systemic embolism as established by previous placebo-controlled studies of warfarin in atrial fibrillation.

A total of 14264 patients were randomized and followed on study treatment for a median of 590 days. The mean age was 71 years and the mean CHADS2 score was 3.5. The population was 60% male, 83% Caucasian, 13% Asian and 1.3% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 55% of patients, and 38% of patients had not taken a vitamin K antagonist (VKA) within 6 weeks at time of screening. Concomitant diseases of patients in this study included hypertension 91%, diabetes 40%, congestive heart failure 63%, and prior myocardial infarction 17%. At baseline, 37% of patients were on aspirin (almost exclusively at a dose of 100 mg or less) and few patients were on clopidogrel. Patients were enrolled in Eastern Europe (39%); North America (19%); Asia, Australia, and New Zealand (15%); Western Europe (15%); and Latin America (13%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2 to 3 of 55%, lower during the first few months of the study.

In ROCKET AF, rivaroxaban tablets was demonstrated non-inferior to warfarin for the primary composite endpoint of time to first occurrence of stroke (any type) or non-CNS systemic embolism [HR (95% CI): 0.88 (0.74, 1.03)], but superiority to warfarin was not demonstrated. There is insufficient experience to determine how rivaroxaban tablets and warfarin compare when warfarin therapy is well-controlled.

Table 19 displays the overall results for the primary composite endpoint and its components.

Table 19: Primary Composite Endpoint Results in ROCKET AF Study (Intent-to-Treat population)

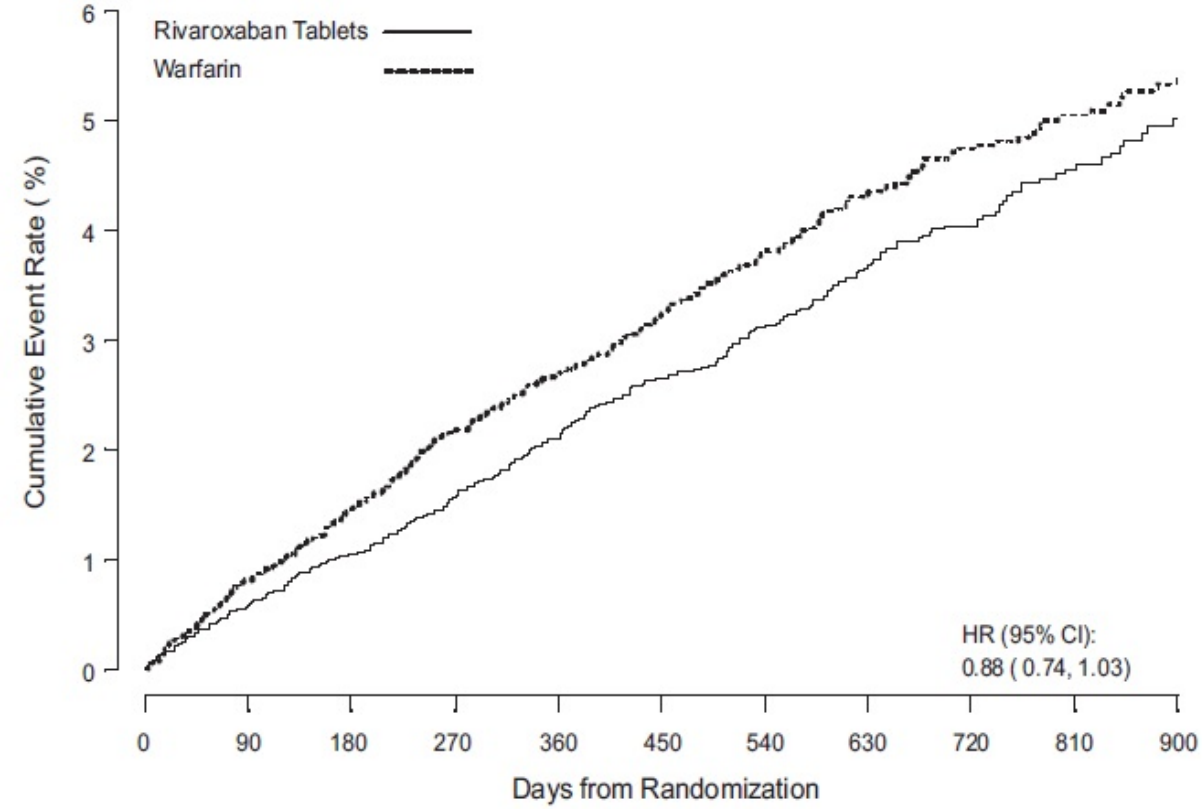
	Rivaroxaban Tablets		**Warfarin**		**Rivaroxaban Tablets vs. Warfarin**
Event	**N = 7081 n (%)**	**Event Rate (per 100 Pt-yrs)**	**N = 7090 n (%)**	**Event Rate (per 100 Pt-yrs)**	**Hazard Ratio (95% CI)**
Primary Composite Endpoint*	269 (3.8)	2.1	306(4.3)	2.4	0.88 (0.74, 1.03)
Stroke	253 (3.6)	2	281 (4)	2.2	

Hemorrhagic Stroke†	33 (0.5)	0.3	57 (0.8)	0.4	
Ischemic Stroke	206 (2.9)	1.6	208 (2.9)	1.6	
Unknown Stroke Type	19 (0.3)	0.2	18 (0.3)	0.1	
Non-CNS Systemic Embolism	20 (0.3)	0.2	27 (0.4)	0.2	

* The primary endpoint was the time to first occurrence of stroke (any type) or non-CNS systemic embolism. Data are shown for all randomized patients followed to site notification that the study would end.
† Defined as primary hemorrhagic strokes confirmed by adjudication in all randomized patients followed up to site notification

Figure 4 is a plot of the time from randomization to the occurrence of the first primary endpoint event in the two treatment arms.

Figure 4: Time to First Occurrence of Stroke (any type) or Non-CNS Systemic Embolism by Treatment Group (Intent-to-Treat population)

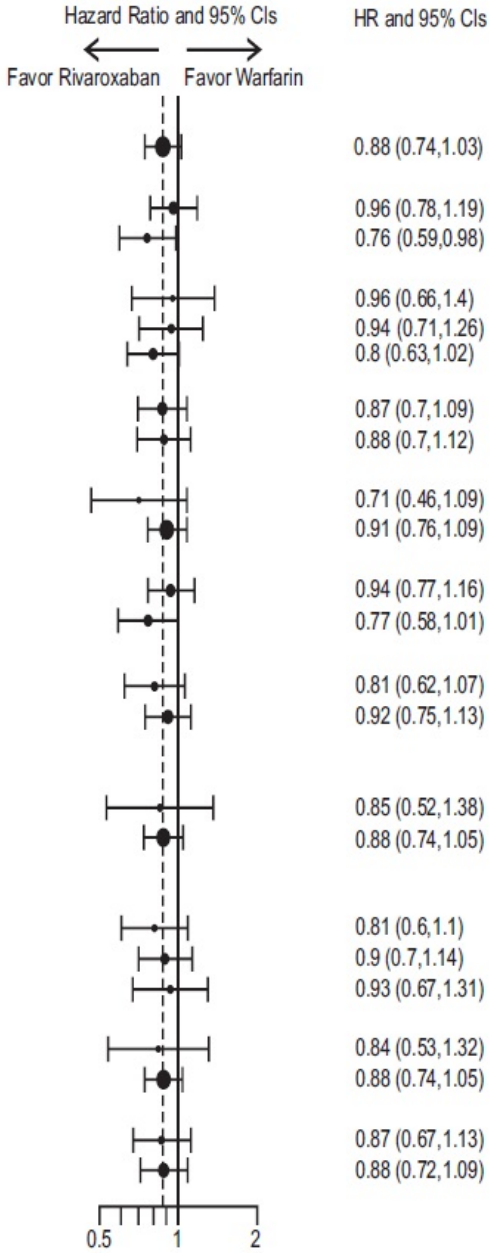


Number of Subjects at Risk:											
Rivaroxaban tablets	7081	6927	6774	6620	6470	5580	4779	3820	2951	2058	1321
Warfarin	7090	6910	6755	6590	6440	5561	4756	3807	2944	2069	1319

Figure 5 shows the risk of stroke or non-CNS systemic embolism across major subgroups.

Figure 5: Risk of Stroke or Non-CNS Systemic Embolism by Baseline Characteristics in ROCKET AF* (Intent-to-Treat Population)

	Rivaroxaban	Warfarin	HR and 95% CIs
	n/N (%Per Year)	n/N (%Per Year)	
All Patients (100%)	269/7081 (2.1)	306/7090 (2.4)	0.88 (0.74,1.03)
Prior Warfarin/VKA			
YES (62%)	168/4413 (2.1)	175/4440 (2.1)	0.96 (0.78,1.19)
NO (38%)	101/2668 (2.2)	131/2650 (3)	0.76 (0.59,0.98)
Age (yrs)			
<65 (23%)	53/1647 (1/8)	55/1637 (1.8)	0.96 (0.66,1.4)
65 to <75 (33%)	91/2352 (2.2)	97/2371 (2.3)	0.94 (0.71,1.26)
>=75 (44%)	125/3082 (2.3)	154/3082 (2.9)	0.8 (0.63,1.02)
Gender			
MALE (60%)	143/4279 (1.9)	164/4287 (2.1)	0.87 (0.7,1.09)
FEMALE (40%)	126/2802 (2.5)	142/2803 (2.9)	0.88 (0.7,1.12)
Weight (kg)			
<=60 kg (11%)	35/777 (2.7)	49/775 (3.8)	0.71 (0.46,1.09)
>60 kg (89%)	234/6302 (2.1)	257/6314 (2.3)	0.91 (0.76,1.09)
Prior Stroke/TIA			
YES (52%)	178/3727 (2.8)	186/3689 (3)	0.94 (0.77,1.16)
NO (48%)	91/3354 (1.5)	120/3401 (1.9)	0.77 (0.58,1.01)
Diabetic Status			
YES (40%)	95/2851 (1.9)	114/2796 (2.3)	0.81 (0.62,1.07)
NO (60%)	174/4230 (2.3)	192/4294 (2.5)	0.92 (0.75,1.13)
CHADS2 Score			
<=1 (0%)	0/1 (0)	0/2 (0)	
2 (13%)	30/924 (1.5)	36/933 (1.7)	0.85 (0.52,1.38)
>=3 (87%)	239/6156 (2.2)	270/6155 (2.6)	0.88 (0.74,1.05)
CrCl(mL/min)			
<30 mL/min (0%)	0/4 (0)	0/4 (0)	
30 to 50 mL/min (22%)	78/1579 (2.9)	96/1584 (3.5)	0.81 (0.6,1.1)
>50 to 80 mL/min (46%)	125/3205 (2.2)	141/3271 (2.4)	0.9 (0.7,1.14)
>80 mL/min (32%)	66/2285 (1.6)	68/2222 (1.7)	0.93 (0.67,1.31)
Geographic Region			
US (14%)	34/965 (1.8)	41/966 (2.1)	0.84 (0.53,1.32)
Outside US (86%)	235/6116 (2.2)	265/6124 (2.5)	0.88 (0.74,1.05)
ASA at randomization			
YES (37%)	105/2575 (2.3)	121/2609 (2.7)	0.87 (0.67,1.13)
NO (63%)	164/4506 (2)	185/4481 (2.3)	0.88 (0.72,1.09)



* Data are shown for all randomized patients followed to site notification that the study would end.
Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

The efficacy of rivaroxaban tablets was generally consistent across major subgroups.

The protocol for ROCKET AF did not stipulate anticoagulation after study drug discontinuation, but warfarin patients who completed the study were generally maintained on warfarin. Rivaroxaban tablets patients were generally switched to warfarin without a period of coadministration of warfarin and rivaroxaban tablets, so that they were not adequately anticoagulated after stopping rivaroxaban tablets until attaining a therapeutic INR. During the 28 days following the end of the study, there were 22 strokes in the 4637 patients taking rivaroxaban tablets vs. 6 in the 4691 patients taking warfarin.

Few patients in ROCKET AF underwent electrical cardioversion for atrial fibrillation. The utility of rivaroxaban tablets for preventing post-cardioversion stroke and systemic embolism is unknown.

14.2 Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

EINSTEIN Deep Vein Thrombosis and EINSTEIN Pulmonary Embolism Studies

Rivaroxaban tablets for the treatment of DVT and/or PE was studied in EINSTEIN DVT [NCT00440193] and EINSTEIN PE [NCT00439777], multi-national, open-label, non-inferiority studies comparing rivaroxaban tablets (at an initial dose of 15 mg twice daily with food for the first three weeks, followed by rivaroxaban tablets 20 mg once daily with food) to enoxaparin 1 mg/kg twice daily for at least five days with VKA and then continued with VKA only after the target INR (2 to 3) was reached. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent and patients with creatinine clearance <30 mL/min, significant liver disease, or active bleeding were excluded from the studies. The intended treatment duration was 3, 6, or 12 months based on investigator's assessment prior to randomization.

A total of 8281 (3449 in EINSTEIN DVT and 4832 in EINSTEIN PE) patients were randomized and followed on study treatment for a mean of 208 days in the rivaroxaban tablets group and 204 days in the enoxaparin/VKA group. The mean age was approximately 57 years. The population was 55% male, 70% Caucasian, 9% Asian and about 3% Black. About 73% and 92% of rivaroxaban tablets-treated patients in the EINSTEIN DVT and EINSTEIN PE studies, respectively, received initial parenteral anticoagulant treatment for a median duration of 2 days. Enoxaparin/VKA-treated patients in the EINSTEIN DVT and EINSTEIN PE studies received initial parenteral anticoagulant treatment for a median duration of 8 days. Aspirin was taken as on treatment concomitant antithrombotic medication by approximately 12% of patients in both treatment groups. Patients randomized to VKA had an unadjusted mean percentage of time in the INR target range of 2 to 3 of 58% in EINSTEIN DVT study and 60% in EINSTEIN PE study, with the lower values occurring during the first month of the study.

In the EINSTEIN DVT and EINSTEIN PE studies, 49% of patients had an idiopathic DVT/PE at baseline. Other risk factors included previous episode of DVT/PE (19%), recent surgery or trauma (18%), immobilization (16%), use of estrogen-containing drug (8%), known thrombophilic conditions (6%), or active cancer (5%).

In the EINSTEIN DVT and EINSTEIN PE studies, rivaroxaban tablets was demonstrated to be non-inferior to enoxaparin/VKA for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE [EINSTEIN DVT HR (95% CI): 0.68 (0.44, 1.04); EINSTEIN PE HR (95% CI): 1.12 (0.75, 1.68)]. In each study the conclusion of non-inferiority was based on the upper limit of the 95% confidence interval for the hazard ratio being less than 2.

Table 20 displays the overall results for the primary composite endpoint and its components for EINSTEIN DVT and EINSTEIN PE studies.

Table 20: Primary Composite Endpoint Results* in EINSTEIN DVT and EINSTEIN PE Studies – Intent-to-Treat Population

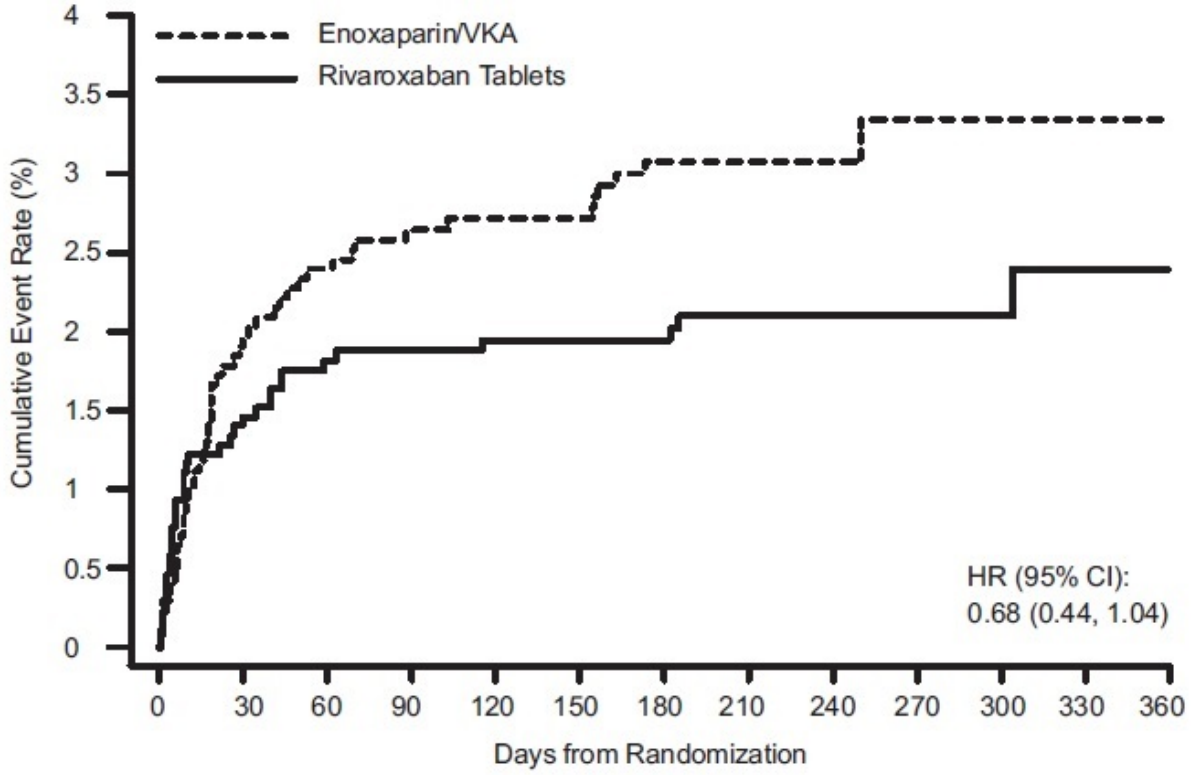
Event	Rivaroxaban Tablets 20 mg†	Enoxaparin/VKA†	Rivaroxaban Tablets vs. Enoxaparin/VKA Hazard Ratio (95% CI)
EINSTEIN DVT Study	**N = 1731 n (%)**	**N = 1718 n (%)**	
Primary Composite Endpoint	36 (2.1)	51 (3)	0.68 (0.44, 1.04)
Death (PE)	1 (<0.1)	0	
Death (PE cannot be excluded)	3 (0.2)	6 (0.3)	
Symptomatic PE and DVT	1 (<0.1)	0	
Symptomatic recurrent PE only	20 (1.2)	18 (1)	
Symptomatic recurrent DVT only	14 (0.8)	28 (1.6)	
EINSTEIN PE Study	**N = 2419 n (%)**	**N = 2413 n (%)**	
Primary Composite Endpoint	50 (2.1)	44 (1.8)	1.12 (0.75, 1.68)
Death (PE)	3 (0.1)	1 (<0.1)	
Death (PE cannot be excluded)	8 (0.3)	6 (0.2)	
Symptomatic PE and DVT	0	2 (<0.1)	
Symptomatic recurrent PE only	23 (1)	20 (0.8)	
Symptomatic recurrent DVT only	18 (0.7)	17 (0.7)	

* For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (3, 6 or 12 months) irrespective of the actual treatment duration. If the same patient had several events, the patient may have been counted for several components.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: Rivaroxaban tablets 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2 to 3)]

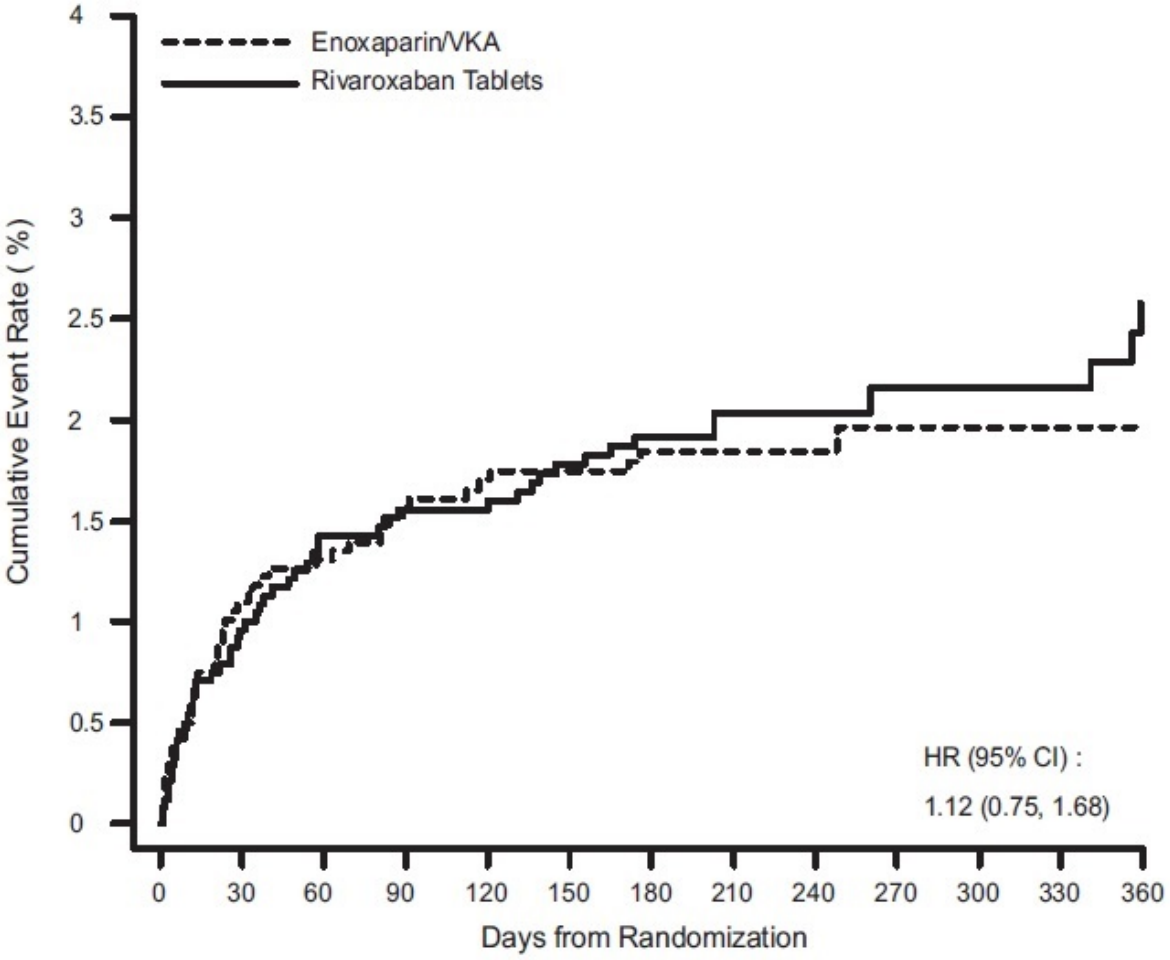
Figures 6 and 7 are plots of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups in EINSTEIN DVT and EINSTEIN PE studies, respectively.

Figure 6: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN DVT Study



Number of Patients at Risk												
Enoxaparin/ VKA (N = 1718)	1616	1581	1565	1368	1358	1301	380	362	342	325	297	264
Rivaroxaban tablets (N = 1731)	1668	1648	1635	1424	1412	1369	400	369	364	345	309	266

Figure 7: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN PE Study



Number of Patients at Risk												
Enoxaparin/ VKA (N = 2413)	2316	2295	2280	2155	2146	2113	835	787	773	746	722	675
Rivaroxaban tablets (N = 2419)	2350	2321	2311	2180	2167	2133	837	794	785	757	725	672

14.3 Reduction in the Risk of Recurrence of DVT and/or PE

EINSTEIN CHOICE Study

Rivaroxaban tablets for reduction in the risk of recurrence of DVT and of PE was evaluated in the EINSTEIN CHOICE study [NCT02064439], a multi-national, double-blind, superiority study comparing rivaroxaban tablets (10 or 20 mg once daily with food) to 100 mg acetylsalicylic acid (aspirin) once daily in patients who had completed 6 to 12 months of anticoagulant treatment for DVT and/or PE following the acute event. The intended treatment duration in the study was up to 12 months. Patients with an indication for continued therapeutic-dose anticoagulation were excluded.

Because the benefit-risk assessment favored the 10 mg dose versus aspirin compared to the 20 mg dose versus aspirin, only the data concerning the 10 mg dose is discussed below.

A total of 2275 patients were randomized and followed on study treatment for a mean of 290 days for the rivaroxaban tablets and aspirin treatment groups. The mean age was approximately 59 years. The population was 56% male, 70% Caucasian, 14% Asian and 3% Black. In the EINSTEIN CHOICE study, 51% of patients had DVT only, 33% had PE only, and 16% had PE and DVT combined. Other risk factors included idiopathic VTE (43%), previous episode of DVT/PE (17%), recent surgery or trauma (12%), prolonged immobilization (10%), use of estrogen containing drugs (5%), known thrombophilic

conditions (6%), Factor V Leiden gene mutation (4%), or active cancer (3%).

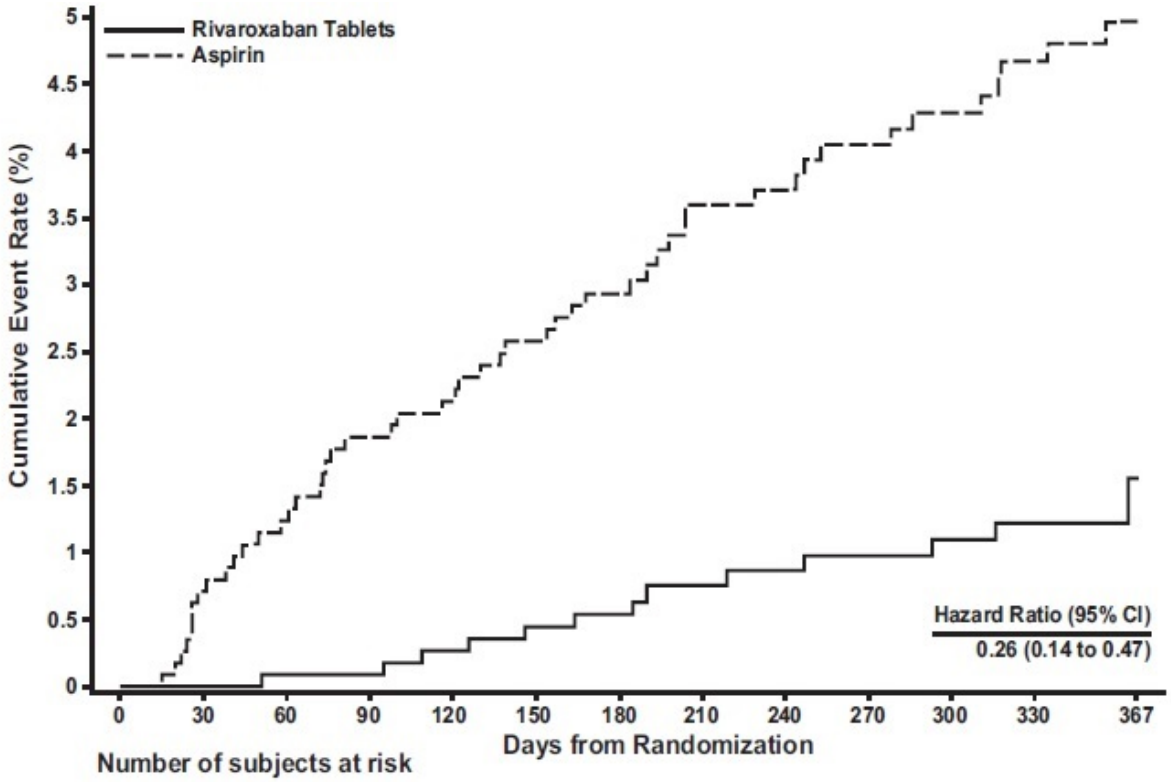
In the EINSTEIN CHOICE study, rivaroxaban tablets 10 mg were demonstrated to be superior to aspirin 100 mg for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE.

Table 21 displays the overall results for the primary composite endpoint and its components.

Table 21: Primary Composite Endpoint and its Components Results* in EINSTEIN CHOICE Study –Full Analysis Set

Event	**Rivaroxaban Tablets 10 mg N=1,127 n (%)**	**Acetylsalicylic Acid (Aspirin) 100 mg N=1,131 n (%)**	**Rivaroxaban Tablets 10 mg vs. Aspirin 100 mg Hazard Ratio (95% CI)**
Primary Composite Endpoint	13 (1.2)	50 (4.4)	0.26 (0.14, 0.47) p<0.0001
Symptomatic recurrent DVT	8 (0.7)	29 (2.6)	
Symptomatic recurrent PE	5 (0.4)	19 (1.7)	
Death (PE)	0	1 (<0.1)	
Death (PE cannot be excluded)	0	1 (<0.1)	

*For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (12 months) irrespective of the actual treatment duration. The individual component of the primary endpoint represents the first occurrence of the event.
Figure 8 is a plot of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups.
Figure 8: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Full Analysis Set) – EINSTEIN CHOICE Study



Number of subjects at risk

Rivaroxaban Tablets	1127	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

14.4 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

Rivaroxaban tablets was studied in 9011 patients (4487 rivaroxaban tablets-treated, 4524 enoxaparin-treated patients) in the REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE, Controlled, Double-blind, Randomized Study of BAY 59-7939 in the Extended Prevention of VTE in Patients Undergoing Elective Total Hip or Knee Replacement (RECORD 1, 2, and 3) [NCT00329628, NCT00332020, NCT00361894] studies.

The two randomized, double-blind, clinical studies (RECORD 1 and 2) in patients undergoing elective total hip replacement surgery compared rivaroxaban tablets 10 mg once daily starting at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin 40 mg once daily started 12 hours preoperatively. In RECORD 1 and 2, a total of 6727 patients were randomized and 6579 received study drug. The mean age [± standard deviation (SD)] was 63 ± 12.2 (range 18 to 93) years with 49% of patients ≥65 years and 55% of patients were female. More than 82% of patients were White, 7% were Asian, and less than 2% were Black. The studies excluded patients undergoing staged bilateral total hip replacement, patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min, or patients with significant liver disease (hepatitis or cirrhosis). In RECORD 1, the mean exposure duration (±SD) to active rivaroxaban tablets and enoxaparin was 33.3 ± 7 and 33.6 ± 8.3 days, respectively. In RECORD 2, the mean exposure duration to active rivaroxaban and enoxaparin was 33.5 ± 6.9 and 12.4 ± 2.9 days, respectively. After Day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration. The efficacy data for RECORD 1 and 2 are provided in Table 22.

Table 22: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery-Modified Intent-to-Treat Population

		RECORD 1			RECORD 2	
Treatment Dosage and Duration	**Rivaroxaban Tablets 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**	**Rivaroxaban Tablets 10 mg once daily**	**Enoxaparin† 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N = 1513**	**N = 1473**		**N = 834**	**N = 835**	
Total VTE	17 (1.1%)	57 (3.9%)	71% (95% CI: 50, 83), p<0.001	17 (2%)	70 (8.4%)	76% (95% CI: 59, 86), p<0.001
Components of Total VTE						
Proximal DVT	1 (0.1%)	31 (2.1%)		5 (0.6%)	40 (4.8%)	
Distal DVT	12 (0.8%)	26 (1.8%)		11 (1.3%)	43 (5.2%)	
Non-fatal PE	3 (0.2%)	1 (0.1%)		1 (0.1%)	4 (0.5%)	
Death (any cause)	4 (0.3%)	4 (0.3%)		2 (0.2%)	4 (0.5%)	
Number of Patients	**N = 1600**	**N = 1587**		**N = 928**	**N = 929**	
Major VTE‡	3 (0.2%)	33 (2.1%)	91% (95% CI: 71, 97), p<0.001	6 (0.7%)	45 (4.8%)	87% (95% CI: 69, 94), p<0.001
Number of Patients	**N = 2103**	**N = 2119**		**N = 1178**	**N = 1179**	
Symptomatic VTE	5 (0.2%)	11 (0.5%)		3 (0.3%)	15 (1.3%)	

* Relative Risk Reduction; CI = confidence interval

† Includes the placebo-controlled period of RECORD 2

‡ Proximal DVT, nonfatal PE or VTE-related death

One randomized, double-blind, clinical study (RECORD 3) in patients undergoing elective total knee replacement surgery compared rivaroxaban tablets 10 mg once daily started at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin. In RECORD 3, the enoxaparin regimen was 40 mg once daily started 12 hours preoperatively. The mean age (±SD) of patients in the study was 68 ± 9 (range 28 to 91) years with 66% of patients ≥65 years. Sixty-eight percent (68%) of patients were female. Eighty-one percent (81%) of patients were White, less than 7% were Asian, and less than 2% were Black. The study excluded patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min or patients with significant liver disease (hepatitis or cirrhosis). The mean exposure duration (±SD) to active rivaroxaban tablets and enoxaparin was 11.9 ± 2.3 and 12.5 ± 3 days, respectively. The efficacy data are provided in Table 23.

Table 23: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Knee Replacement Surgery-Modified Intent-to-Treat Population

		RECORD 3	
Treatment	**Rivaroxaban**	**Enoxaparin 40**	**RRR*,**

Dosage and Duration	Tablets 10 mg once daily	mg once daily	p-value
Number of Patients	**N = 813**	**N = 871**	
Total VTE	79 (9.7%)	164 (18.8%)	48% (95% CI: 34, 60), p<0.001
Components of events contributing to Total VTE			
Proximal DVT	9 (1.1%)	19 (2.2%)	
Distal DVT	74 (9.1%)	154 (17.7%)	
Non-fatal PE	0	4 (0.5%)	
Death (any cause)	0	2 (0.2%)	
Number of Patients	**N = 895**	**N = 917**	
Major VTE†	9 (1%)	23 (2.5%)	60% (95% CI: 14, 81), p = 0.024
Number of Patients	**N = 1206**	**N = 1226**	
Symptomatic VTE	8 (0.7%)	24 (2%)	

* Relative Risk Reduction; CI = confidence interval

† Proximal DVT, nonfatal PE or VTE-related death

14.5 Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

The efficacy and safety of rivaroxaban tablets for prophylaxis of venous thromboembolism in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding was evaluated in the MAGELLAN study (Multicenter, rAndomized, parallel Group Efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically iLL patients comparing rivaroxabaN with enoxaparin [NCT00571649]). MAGELLAN was a multicenter, randomized, double-blind, parallel-group efficacy and safety study comparing rivaroxaban tablets to enoxaparin, in the prevention of VTE in hospitalized acutely ill medical patients during the in-hospital and post-hospital discharge period. Eligible patients included adults who were at least 40 years of age, hospitalized for an acute medical illness, at risk of VTE due to moderate or severe immobility, and had additional risk factors for VTE. The population at risk of VTE was required to have one or more of the following VTE risk factors, i.e. prolonged immobilization, age ≥75 years, history of cancer, history of VTE, history of heart failure, thrombophilia, acute infectious disease contributing to the hospitalization and BMI ≥35 kg/m^2). The causes for hospitalization included heart failure, active cancer, acute ischemic stroke, acute infectious and inflammatory disease and acute respiratory insufficiency. Patients were randomized to receive either rivaroxaban tablets 10 mg once daily for 35±4 days starting in hospital and continuing post hospital discharge (n=4050) or enoxaparin 40 mg once daily for 10±4 days starting in hospital followed by placebo post-discharge (n=4051).

The major efficacy outcome in the MAGELLAN trial was a composite endpoint that included asymptomatic proximal deep venous thrombosis (DVT) in lower extremity, symptomatic proximal or distal DVT in the lower extremity, symptomatic non-fatal pulmonary embolism (PE), and death related to venous thromboembolism (VTE).

A total of 6024 patients were evaluable for the major efficacy outcome analysis (2967 on

rivaroxaban tablets 10 mg once daily and 3057 on enoxaparin/placebo). The mean age was 68.9 years, with 37.1% of the subject population ≥ 75 years. VTE risk factors included severe immobilization at study entry (99.9%), D-dimer > 2X ULN (43.7%), history of heart failure (35.6%), BMI ≥ 35 kg/m 2 (15.2%), chronic venous insufficiency (14.9%), acute infectious disease (13.9%), severe varicosis (12.5%), history of cancer (16.2%), history of VTE (4.5%), hormone replacement therapy (1.1%), and thrombophilia (0.3%), recent major surgery (0.8%) and recent serious trauma (0.2%). The population was 54.7% male, 68.2% White, 20.4% Asian, 1.9% Black and 5.3% Other. Admitting diagnoses for hospitalization were acute infectious diseases (43.8%) followed by congestive heart failure NYHA class III or IV (33.2%), acute respiratory insufficiency (26.4%), acute ischemic stroke (18.5%) and acute inflammatory diseases (3.4%).

Table 24 shows the overall results from the prespecified, modified intent-to-treat (mITT) analysis for the efficacy outcomes and their components. This analysis excludes approximately 25% of the patients mainly due to no ultrasonographic assessment (13.5%), inadequate assessment at day 35 (8.1%), or lack of intake of study medication (1.3%).

Table 24: Efficacy Results at Day 35 (modified Intent-to-Treat) and at Day 10 (per protocol) in the MAGELLAN Study

Events from Day 1 to Day 35, mITT analysis set	**Rivaroxaban Tablets 10 mg N=2967 n (%)**	**Enoxaparin 40 mg/ placebo N=3057 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 35	131 (4.4%)	175 (5.7%)	0.77 (0.62, 0.96)
Symptomatic non-fatal PE	10 (0.3)	14 (0.5)	
Symptomatic DVT in lower extremity	13 (0.4)	15 (0.5)	
Asymptomatic proximal DVT in lower extremity	103 (3.5)	133 (4.4)	
VTE related death	19 (0.6)	30 (1)	
Events from Day 1 to Day 10, PP analysis set	**Rivaroxaban Tablets 10 mg N=2938 n (%)**	**Enoxaparin 40 mg N=2993 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 10	78 (2.7)	82 (2.7)	0.97 (0.71, 1.31)
Symptomatic non-fatal PE	6 (0.2)	2 (<0.1)	
Symptomatic DVT in lower extremity	7 (0.2)	6 (0.2)	
Asymptomatic proximal DVT in lower extremity	71 (2.4)	71 (2.4)	
VTE related death	3 (0.1)	6 (0.2)	
mITT analysis set plus all-cause mortality	**N=3096 n (%)**	**N=3169 n (%)**	**RR (95% CI)**
Other Composite Endpoint at Day 35	266 (8.6)	293 (9.2)	0.93 (0.8, 1.09)
Symptomatic non-fatal PE	10 (0.3)	14 (0.4)	

Symptomatic DVT in lower extremity	13 (0.4)	15 (0.5)	
Asymptomatic proximal DVT in lower extremity	103 (3.3)	133 (4.2)	
All-cause mortality	159 (5.1)	153 (4.8)	

mITT: modified intent-to-treat; PP: per protocol; DVT: Deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism;

CI: Confidence Interval; RR: Relative Risk

Patients with bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months (19.4%) all had an excess of bleeding with rivaroxaban tablets compared with enoxaparin/placebo. Therefore, patients meeting these criteria were excluded from the following analyses presented below.

Table 25 provides the efficacy results for the subgroup of patients not at a high risk of bleeding.

Table 25: Efficacy Results at Day 35 (modified Intent-to-Treat) and at Day 10 (per protocol) in patients not at a high risk of bleeding in the MAGELLAN Study*

Events from Day 1 to Day 35, mITT analysis set	**Rivaroxaban Tablets 10 mg N=2419 n (%)**	**Enoxaparin 40 mg/ placebo N=2506 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 35	94 (3.9)	143 (5.7)	0.68 (0.53, 0.88)
Symptomatic non-fatal PE	7 (0.3)	10 (0.4)	
Symptomatic DVT in lower extremity	9 (0.4)	10 (0.4)	
Asymptomatic proximal DVT in lower extremity	73 (3)	110 (4.4)	
VTE related death	15 (0.6)	26 (1)	
Events from Day 1 to Day 10, PP analysis set	**Rivaroxaban Tablets 10 mg N=2385 n (%)**	**Enoxaparin 40 mg N=2433 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 10	58 (2.4)	72 (3)	0.82 (0.58, 1.15)
Symptomatic non-fatal PE	5 (0.2)	2 (<0.1)	

Symptomatic DVT in lower extremity	6 (0.3)	4 (0.2)	
Asymptomatic proximal DVT in lower extremity	52 (2.2)	62 (2.5)	
VTE related death	2 (<0.1)	6 (0.2)	
mITT analysis set plus all-cause mortality	**N=2504 n (%)**	**N=2583 n (%)**	**RR (95% CI)**
Other Composite Endpoint at Day 35	184 (7.3)	225 (8.7)	0.84 (0.7, 1.02)
Symptomatic non-fatal PE	7 (0.3)	10 (0.4)	
Symptomatic DVT in lower extremity	9 (0.4)	10 (0.4)	
Asymptomatic proximal DVT in lower extremity	73 (2.9)	110 (4.3)	
All-cause mortality	107 (4.3)	112 (4.3)	

* Patients at high risk of bleeding (i.e. bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months) were excluded.

mITT: modified intent-to-treat; PP: per protocol; DVT: Deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism;

CI: Confidence Interval; RR: Relative Risk

14.6 Reduction of Risk of Major Cardiovascular Events in Patients with CAD

The evidence for the efficacy and safety of rivaroxaban tablets for the reduction in the risk of stroke, myocardial infarction, or cardiovascular death in patients with coronary artery disease (CAD) or peripheral artery disease (PAD) was derived from the double-blind, placebo-controlled Cardiovascular OutcoMes for People using Anticoagulation StrategieS trial (COMPASS) [NCT10776424]. A total of 27,395 patients were evenly randomized to rivaroxaban 2.5 mg orally twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg orally twice daily alone, or aspirin 100 mg once daily alone. Because the 5 mg dose alone was not superior to aspirin alone, only the data concerning the 2.5 mg dose plus aspirin are discussed below.

Patients with established CAD or 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). Patients with PAD were either symptomatic with ankle brachial index <0.9 or had asymptomatic carotid artery stenosis ≥50%, a previous carotid revascularization

procedure, or established ischemic disease of one or both lower extremities. Patients were excluded for use of dual antiplatelet, other non-aspirin antiplatelet, or oral anticoagulant therapies, ischemic, non-lacunar stroke within 1 month, hemorrhagic or lacunar stroke at any time, or eGFR <15 mL/min.

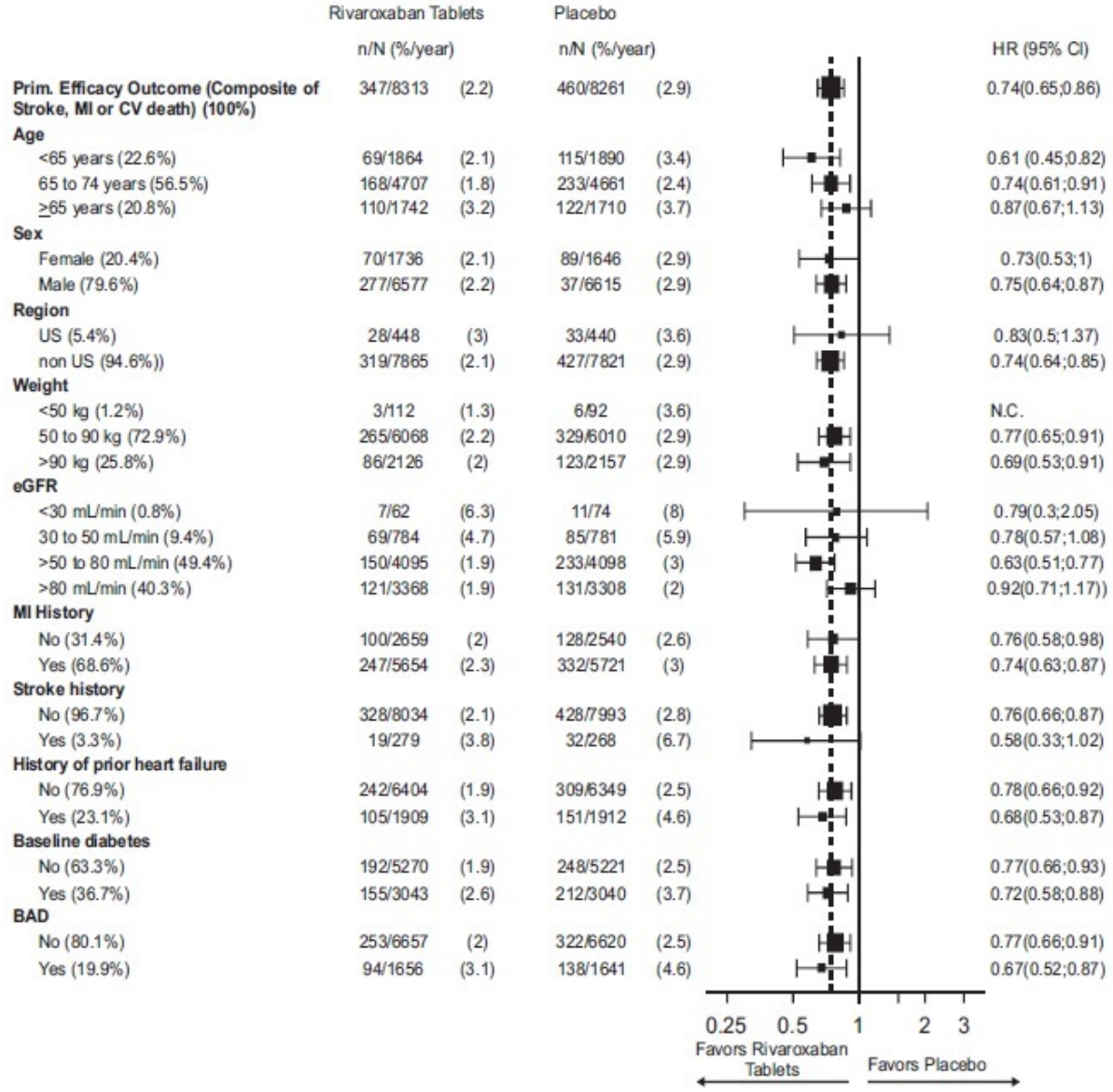
The mean age was 68 years and 21% of the subject population were ≥75 years. Of the included patients, 91% had CAD (and will be referred to as the COMPASS CAD population), 27% had PAD (and will be referred to as the COMPASS PAD population), and 18% had both CAD and PAD. Of the patients with CAD, 69% had prior MI, 60% had prior percutaneous transluminal coronary angioplasty (PTCA)/atherectomy/percutaneous coronary intervention (PCI), and 26% had 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, 26% had asymptomatic carotid artery stenosis > 50%, and 4% had limb or foot amputation for arterial vascular disease.

The mean duration of follow-up was 23 months. Relative to placebo, rivaroxaban tablets reduced the rate of the primary composite outcome of stroke, myocardial infarction or cardiovascular death: HR 0.76 (95% CI: 0.66, 0.86; p=0.00004). In the COMPASS CAD population, the benefit was observed early with a constant treatment effect over the entire treatment period (see Table 26 and Figure 10).

A benefit-risk analysis of the data from COMPASS was performed by comparing the number of CV events (CV deaths, myocardial infarctions and non-hemorrhagic strokes) prevented to the number of fatal or life-threatening bleeding events (fatal bleeds + symptomatic non-fatal bleeds into a critical organ) in the rivaroxaban tablets group versus the placebo group. Compared to placebo, during 10,000 patient-years of treatment, rivaroxaban tablets would be expected to result in 70 fewer CV events and 12 additional life-threatening bleeds, indicating a favorable balance of benefits and risks.

The results in the COMPASS CAD population were consistent across major subgroups (see Figure 9).

Figure 9: Risk of Primary Efficacy Outcome by Baseline Characteristics in the COMPASS CAD Population (Intent-to-Treat Population)*



*All patients received aspirin 100 mg once daily as background therapy.

Table 26: Efficacy results from COMPASS CAD Population*

Event	Rivaroxaban Tablets† N=8313		Placebo† N=8261		Hazard Ratio (95% CI) ‡
	n (%)	Event Rate (%/year)	n (%)	Event Rate (%/year)	
Stroke, MI or CV death	347 (4.2)	2.2	460 (5.6)	2.9	0.74 (0.65, 0.86)
- Stroke	74 (0.9)	0.5	130 (1.6)	0.8	0.56 (0.42, 0.75)

- MI	169 (2)	1.1	195 (2.4)	1.2	0.86 (0.7, 1.05)
- CV death	139 (1.7)	0.9	184 (2.2)	1.1	0.75 (0.6, 0.93)
Coronary heart disease death, MI, ischemic stroke, acute limb ischemia	299 (3.6)	1.9	411 (5)	2.6	0.72 (0.62, 0.83)
- Coronary heart disease death§	80 (1)	0.5	107 (1.3)	0.7	0.74 (0.55, 0.99)
- Ischemic stroke	56 (0.7)	0.3	114 (1.4)	0.7	0.49 (0.35, 0.67)
- Acute limb ischemia#	13 (0.2)	0.1	27 (0.3)	0.2	0.48 (0.25, 0.93)
CV death¶, MI, ischemic stroke, acute limb ischemia	349 (4.2)	2.2	470 (5.7)	3	0.73 (0.64, 0.84)
All-cause mortality	262 (3.2)	1.6	339 (4.1)	2.1	0.77 (0.65, 0.9)

* intention to treat analysis set, primary analyses.

† Treatment schedule: Rivaroxaban tablets 2.5 mg twice daily vs placebo. All patients received aspirin 100 mg once daily as background therapy.

‡ Rivaroxaban tablets vs. placebo.

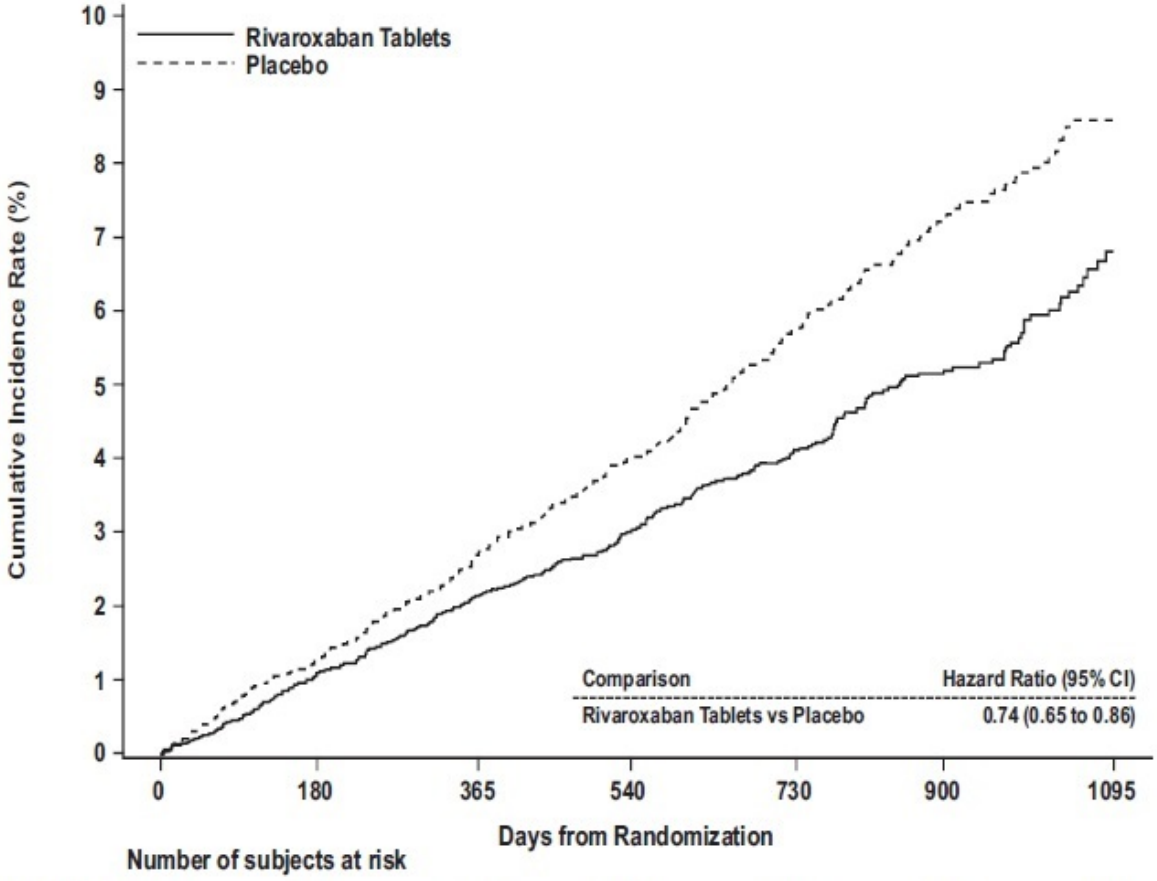
§ Coronary heart disease death: death due to acute MI, sudden cardiac death, or CV procedure.

¶ CV death includes CHD death, or death due to other CV causes or unknown death.

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).

CHD: coronary heart disease, CI: confidence interval; CV: cardiovascular; MI: myocardial infarction

Figure 10: Time to First Occurrence of Primary Efficacy Outcome (Stroke, Myocardial Infarction, Cardiovascular Death) in the COMPASS CAD Population*



Number of subjects at risk							
Rivaroxaban Tablets	8313	8203	7236	5877	3659	2164	639
Placebo	8261	8137	7133	5760	3621	2134	645

*All patients received aspirin 100 mg once daily as background therapy.
CI: confidence interval

14.7 Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients after Lower Extremity Revascularization due to Symptomatic PAD

The efficacy and safety of rivaroxaban tablets 2.5 mg orally twice daily versus placebo on a background of aspirin 100 mg once daily in patients with PAD were evaluated in the COMPASS study (n=4996) and will be referred to as the COMPASS PAD population *[see Clinical Studies (14.6)]*.

The efficacy and safety of rivaroxaban tablets were also evaluated for the reduction in the risk of the composite endpoint of myocardial infarction, ischemic stroke, cardiovascular death, acute limb ischemia (ALI), and major amputation of a vascular etiology in patients undergoing a lower extremity infrainguinal revascularization procedure due to symptomatic peripheral artery disease (PAD) in the double-blinded, placebo-controlled Vascular Outcomes studY of ASA alonG with rivaroxaban in Endovascular or surgical limb Revascularization for peripheral artery disease (PAD) trial (VOYAGER) [NCT02504216]. A total of 6,564 patients were equally randomized to rivaroxaban tablets 2.5 mg orally twice daily vs placebo on a background therapy of aspirin 100 mg once daily.

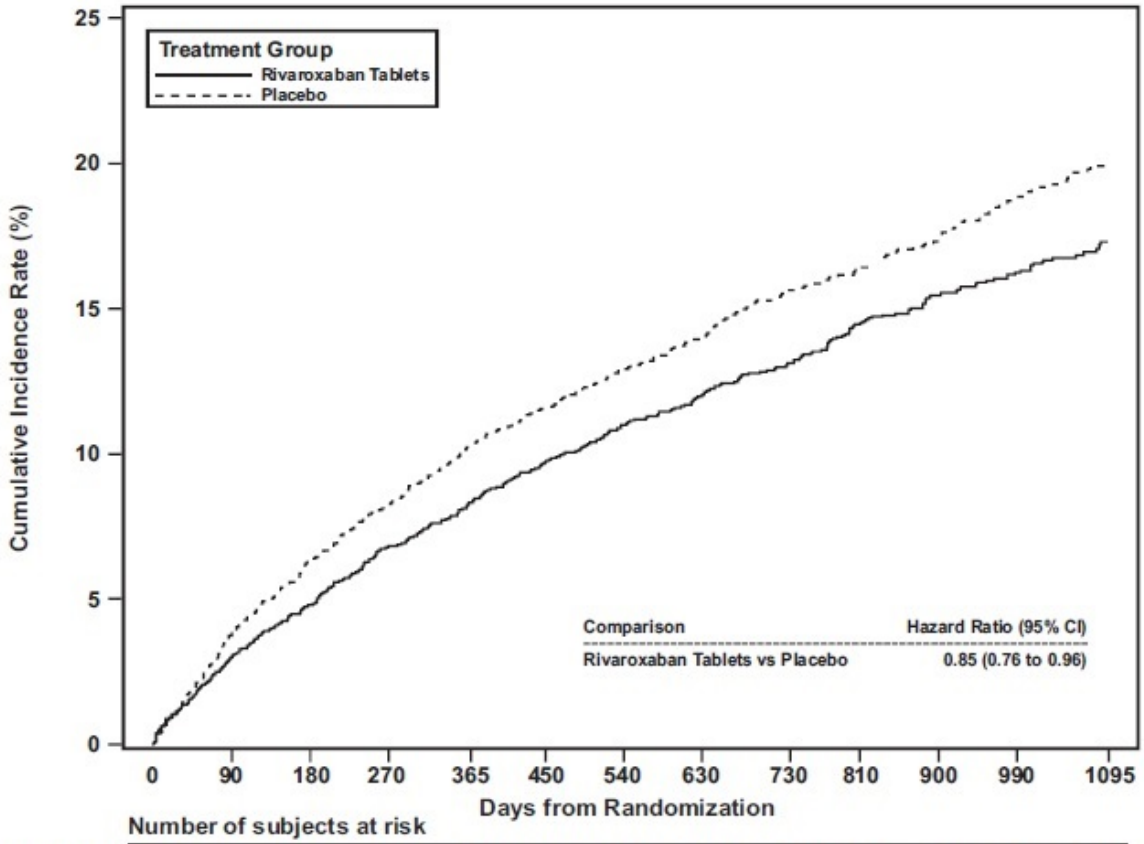
Eligible patients included adults who were at least 50 years of age with documented moderate to severe symptomatic lower extremity atherosclerotic PAD who had a successful peripheral surgical procedure and/or endovascular procedure with or without clopidogrel (up to a maximum of 6 months was allowed; median duration of therapy was

31 days). Patients had either a prior history of limb revascularization with ankle brachial index ≤0.85 or no prior history of limb revascularization with ankle brachial index ≤0.8. Patients in need of dual antiplatelet for >6 months, or any additional antiplatelet other than aspirin and clopidogrel, or oral anticoagulant, as well as patients with a history of intracranial hemorrhage, stroke, or transient ischemic attack (TIA), or patients with eGFR <15 mL/min were excluded.

The mean age was 67 years and 20% of the subject population was ≥75 years. Of the included patients, 35% had surgical revascularization, 47% had endovascular revascularization with clopidogrel, and 18% endovascular revascularization without clopidogrel. The median duration of follow-up was 30.8 months.

Rivaroxaban tablets 2.5 mg twice daily was superior to placebo in reducing the rate of the primary composite outcome of myocardial infarction, ischemic stroke, cardiovascular death, acute limb ischemia (ALI), and major amputation of a vascular etiology. The primary efficacy outcome and its components are provided in Table 27. The Kaplan-Meier plot for the primary efficacy outcome can be seen in Figure 11. The secondary efficacy outcomes were tested for superiority in a prespecified, hierarchical order and the first five of seven endpoints were significantly reduced in the rivaroxaban treatment arm (see Table 27). Compared to placebo during 10,000 patient-years of treatment, rivaroxaban tablets would be expected to result in 181 fewer primary outcome events and 29 more TIMI major bleeding events, indicating a favorable balance of benefits and risks.

Figure 11: Time to First Occurrence of Primary Efficacy Outcome (Myocardial Infarction, Ischemic Stroke, Cardiovascular Death, Acute Limb Ischemia, Major Amputation due to Vascular Origins) in VOYAGER*

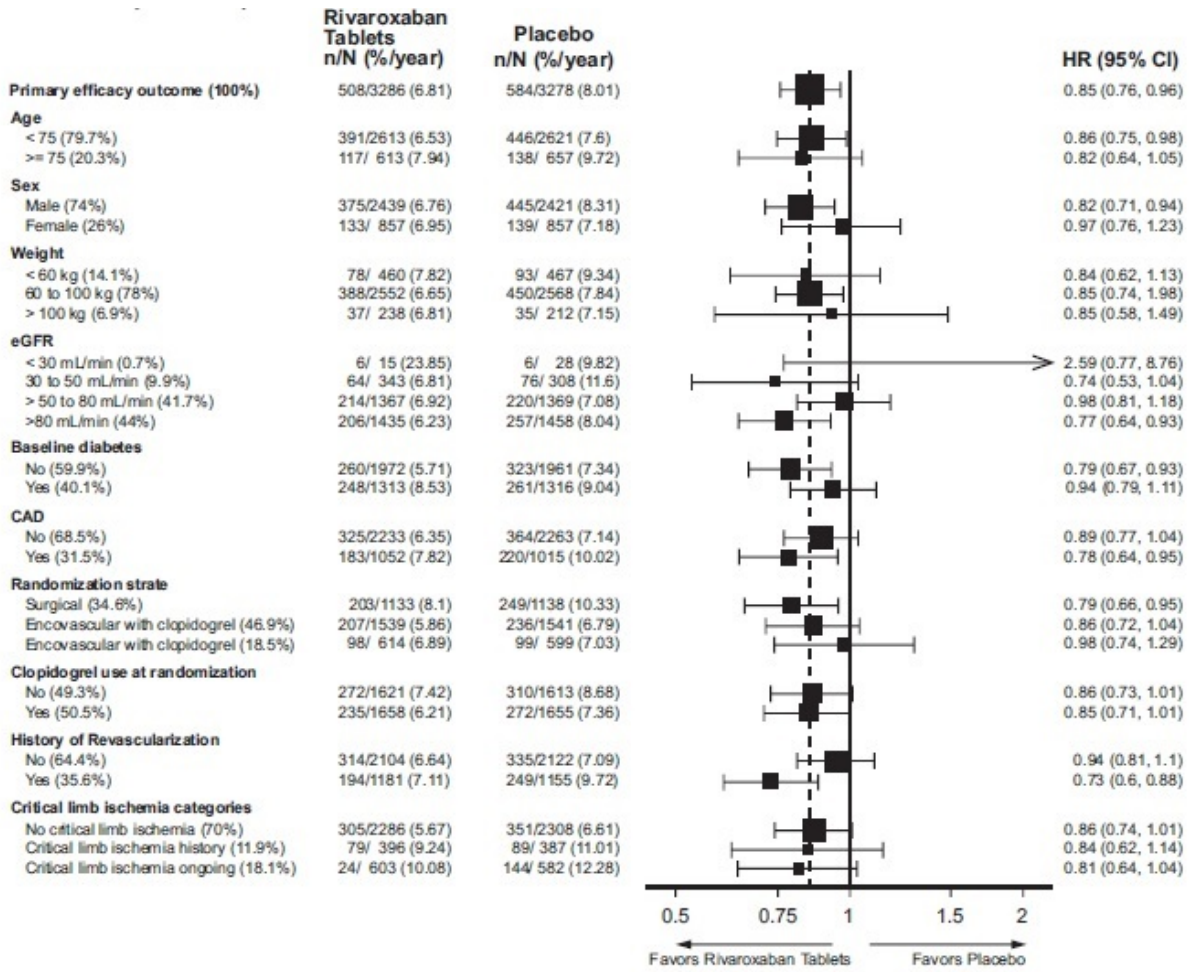


Number of subjects at risk													
Rivaroxaban Tablets	3286	3155	3082	3000	2938	2886	2838	2784	2220	1850	1466	1100	686
Placebo	3278	3127	3032	2957	2881	2830	2775	2721	2152	1804	1408	1048	648

*All patients received aspirin 100 mg once daily as background therapy.

Figure 12 shows the risk of primary efficacy outcome across major subgroups. Subgroup analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. The primary efficacy endpoint generally shows homogeneous results across subgroups.

Figure 12: Risk of Primary Efficacy Outcome by Baseline Characteristics in VOYAGER (Intent-to-Treat Population)*



*All patients received aspirin 100 mg once daily as background therapy.

Table 27 provides the efficacy event rates for the prespecified endpoints in VOYAGER and similar endpoints in the COMPASS PAD population.

Table 27: Efficacy Results in VOYAGER (Intent-to-Treat Population) and COMPASS PAD

	VOYAGER			**COMPASS PAD**		
	Rivaroxaban Tablets N=3286	**Placebo N=3278**	**Hazard Ratio (95% CI)***	**Rivaroxaban Tablets N=2492**	**Placebo N=2504**	**Hazard Ratio (95% CI)***
Outcome Components	**Event Rate (%/year)**		**p-value†**	**Event Rate (%/year)**		
5-Component Outcome (Major thrombotic vascular events)‡	6.8	8	0.85 (0.76, 0.96) p=0.0085	3.4	4.8	0.71 (0.57, 0.87)

MI	1.7	1.9	0.88 (0.7, 1.12)	1.1	1.5	0.76 (0.53, 1.09)
Ischemic Stroke[§]	0.9	1	0.87 (0.63, 1.19)	0.5	0.9	0.55 (0.33, 0.93)
CV death[¶]	2.5	2.2	1.14 (0.93, 1.4)	1.4	1.7	0.82 (0.59, 1.14)
ALI	2	3	0.67 (0.55, 0.82)	0.4	0.8	0.56 (0.32, 0.99)
Major amputation of a vascular etiology[#]	1.3	1.5	0.89 (0.68, 1.16)	0.2	0.6	0.4 (0.2, 0.79)
VOYAGER Secondary Efficacy Outcomes[Þ]						
MI, ischemic stroke, CHD death,[ß] ALI, and major amputation due to vascular etiology	5.8	7.3	0.8 (0.71, 0.91) p=0.0008	2.8	4.2	0.66 (0.53, 0.83)
Unplanned index limb revascularization for recurrent limb ischemia[à]	8.4	9.5	0.88 (0.79, 0.99) p=0.028	N/A	N/A	N/A
Hospitalization for a coronary or peripheral cause of a thrombotic nature[#]	3.5	4.8	0.72 (0.62, 0.85) p<0.0001	1.7	2.9	0.58 (0.44, 0.77)
MI, ischemic stroke, all-cause mortality, ALI, and major amputation due to vascular etiology	8.2	9.3	0.89 (0.79, 0.99) p=0.029	4.8	6	0.8 (0.67, 0.96)
MI, all-cause stroke, CV death, ALI, and major	6.9	8.1	0.86 (0.76, 0.96) p=0.01	3.4	4.9	0.7 (0.57, 0.86)

amputation due to vascular etiology						
All-cause mortality	4	3.7	1.08 (0.92, 1.27)	2.8	3.1	0.91 (0.72, 1.16)
VTE events[è]	0.3	0.5	0.61 (0.37, 1)	0.2	0.3	0.67 (0.3, 1.49)

Efficacy endpoints in COMPASS PAD were analysed according to the pre-specified endpoints in VOYAGER when applicable.
[*] Rivaroxaban tablets vs. placebo.
[†] Two-sided p-values
[‡] Major thrombotic vascular event is the composite of MI, ischemic stroke, CV death, ALI, and major amputation of a vascular etiology.
[§] Ischemic stroke for VOYAGER included stroke of uncertain/unknown etiology whereas COMPASS only included ischemic stroke.
[¶] CV death includes Coronary Heart Disease death, or death due to other CV causes or sudden cardiac arrest and unknown death.
[#] Adjudicated events in VOYAGER and investigator reported events in COMPASS
[Þ] Secondary outcomes for VOYAGER were tested sequentially.
[ß] CHD death includes death due to sudden cardiac death, MI, or coronary revascularization procedure
[à] Unplanned index limb revascularization for recurrent limb ischemia was not captured in COMPASS study.
[è] Investigator reported in VOYAGER and adjudicated events in COMPASS
ALI=acute limb ischemia, CHD=coronary heart disease; CI=confidence interval, CV=cardiovascular; MI=myocardial infarction, VTE=venous thromboembolism.

14.8 Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients

Rivaroxaban tablets for the treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE was evaluated in the EINSTEIN Junior Phase 3 study [NCT02234843], a multicenter, open-label, active-controlled, randomized study in 500 pediatric patients from birth to less than 18 years with confirmed 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. Patients <6 months of age were excluded from enrollment if they were <37 weeks of gestation at birth, or had <10 days of oral feeding, or had a body weight of <2.6 kg.

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE), cerebral vein and sinus thrombosis (CVST), and all other VTE including DVT and PE (non-CVC-VTE).

Patients received initial treatment with therapeutic dosages of unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux for at least 5 days, and were randomized 2:1 to receive either body weight-adjusted doses of rivaroxaban tablets (exposures to match that of 20 mg daily dose in adults) or comparator group (UFH, LMWH, fondaparinux or VKA) for a main study treatment period of 3 months (or 1 month for children <2 years with CVC-VTE). A diagnostic

imaging test was obtained at baseline and at the end of the main study treatment. When clinically necessary, treatment was extended up to 12 months in total (or up to 3 months in total for children <2 years with CVC-VTE).

Table 28 displays the primary and secondary efficacy results.

Table 28: Efficacy Results in EINSTEIN Junior Study – Full Analysis Set

Event	**Rivaroxaban Tablets*** **N=335** **n (%)** **(95% CI)†**	**Comparator Group‡** **N=165** **n (%)** **(95% CI)†**	**Rivaroxaban Tablets vs. Comparator Group Risk Difference (95% CI)§**	**Rivaroxaban Tablets vs. Comparator Group Hazard Ratio (95% CI)**
Primary efficacy outcome: Symptomatic recurrent VTE	4 (1.2) (0.4%, 3%)	5 (3) (1.2%, 6.6%)	-1.8% (-6%, 0.6%)	0.4 (0.11, 1.41)
Secondary efficacy outcome: Symptomatic recurrent VTE or asymptomatic deterioration on repeat imaging	5 (1.5) (0.6%, 3.4%)	6 (3.6) (1.6%, 7.6%)	-2.1% (-6.5%, 0.6%)	

* Treatment schedule: body weight-adjusted doses of rivaroxaban tablets (exposures to match that of 20 mg daily dose in adults); randomized 2:1 (Rivaroxaban tablets: Comparator).
† Confidence intervals for incidence proportion were calculated by applying the method of Blyth-Still-Casella.
‡ Unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux or VKA.
§ Confidence intervals for difference in incidence proportions were calculated by unstratified exact method according to Agresti-Min using the standardized test statistic and inverting a two-sided test.

Complete resolution of thrombus on repeat imaging without recurrent VTE occurred in 128 of 335 children (38.2%, 95% CI 33%, 43.5%) in the rivaroxaban tablets group and 43 of 165 children (26.1%, 95% CI 19.8%, 33%) in the comparator group. Symptomatic recurrent VTE or major bleeding events occurred in 4 of 335 children (1.2%, 95% CI 0.4%, 3%) in the rivaroxaban tablets group and 7 of 165 children (4.2%, 95% CI 2%, 8.4%) in the comparator group.

14.9 Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure

The efficacy and safety of rivaroxaban tablets for thromboprophylaxis in pediatric patients with congenital heart disease who have undergone the Fontan procedure was evaluated in the UNIVERSE Phase 3 study [NCT02846532]. UNIVERSE was a prospective, open-label, active controlled, multicenter, 2-part study, designed to evaluate the single- and multiple-dose pharmacokinetic properties of rivaroxaban tablets (Part A), and to evaluate the safety and efficacy of rivaroxaban tablets when used for thromboprophylaxis for 12 months compared with aspirin (Part B) in children 2 to 8 years of age with single ventricle physiology who had the Fontan procedure. Patients in Part B were randomized 2:1 to receive either body weight-adjusted doses of rivaroxaban tablets (exposures to match that of 10 mg daily dose in adults) or aspirin (approximately 5 mg/kg). Patients with eGFR <30 ml/min/1.73 m^2 were excluded.

The median time between Fontan procedure and the first dose of rivaroxaban tablets was 4 (range: 2 to 61) days in Part A and 34 (range: 2 to 124) days in part B. In comparison, the median time to initiating aspirin was 24 (range 2 to 117) days.

Table 29 displays the primary efficacy results.

Table 29: Efficacy Results in UNIVERSE Study – Full Analysis Set

	Part A*	**Part B†**		
Event	**Rivaroxaban Tablets N=12 n (%) (95% CI)‡**	**Rivaroxaban Tablets§ N=64 n (%) (95% CI)‡**	**Aspirin§ N=34 n (%) (95% CI)‡**	**Rivaroxaban Tablets vs. Aspirin Risk Difference (95% CI)¶**
Primary efficacy outcome: any thrombotic event	1 (8.3) (0.4%, 34.9%)	1 (1.6) (0.1%, 7.8%)	3 (8.8) (2.4%, 22.2%)	-7.3% (-21.7%, 1.1%)
Ischemic stroke	0 (0%, 23.6%)	0 (0%, 5.6%)	1 (2.9) 0.2%, 15.1%)	-2.9% (-16.2%, 2.9%)
Pulmonary embolism	0 (0%, 23.6%)	1 (1.6) (0.1%, 7.8%)	0 (0%, 9%)	1.6% (-9.9%, 8.4%)
Venous thrombosis	1 (8.3) (0.4%, 34.9%)	0 (0%, 5.6%)	2 (5.9) (1.1%, 18.8%)	-5.9% (-20.6%, -0.1%)

* Part A: single arm; not randomized
† Part B: randomized 2:1 (Rivaroxaban tablets: Aspirin)
‡ Confidence intervals for incidence proportion were calculated by applying the method of Blyth-Still-Casella.
§ Treatment schedule: body weight-adjusted doses of rivaroxaban tablets (exposures to match that of 10 mg daily dose in adults) or aspirin (approximately 5 mg/kg)
¶ Confidence intervals for difference in incidence proportions were calculated by unstratified exact method according to Agresti-Min using the standardized test statistic and inverting a two-sided test.

16 HOW SUPPLIED/STORAGE AND HANDLING

Rivaroxaban tablets, USP are available in the strengths and packages listed below:
2.5 mg tablets: Light yellow to yellow round biconvex film-coated tablets debossed with "9" on one side and "C" on other side.

NDC 46708-683-60	Bottle of 60 tablets with child resistant closure
NDC 46708-683-45	Bottle of 180 tablets with child resistant closure
NDC 46708-683-91	Bottle of 1000 tablets
NDC 46708-683-10	100 (10 x 10) tablets unit dose blister pack

10 mg tablets are round, pink, biconvex film-coated tablets debossed with "L" on one side and "10" on the other side. The tablets are supplied in the packages listed:

NDC 46708-346-30	Bottle of 30 tablets with child resistant closure
NDC 46708-346-91	Bottle of 1000 tablets
NDC 46708-346-10	100 (10 x 10) tablets unit dose blister pack

15 mg tablets are round, brown, film-coated biconvex tablets debossed with '504' on one side and plain on the other side. The tablets are supplied in the packages listed:

NDC 46708-347-30	Bottle of 30 tablets with child resistant closure
NDC 46708-347-91	Bottle of 1000 tablets
NDC 46708-347-10	100 (10 x 10) tablets unit dose blister pack

20 mg tablets are triangle shaped, brown, film-coated tablets debossed with '505' on one side and plain on the other side. The tablets are supplied in the packages listed:

NDC 46708-348-30	Bottle of 30 tablets with child resistant closure
NDC 46708-348-91	Bottle of 1000 tablets
NDC 46708-348-10	100 (10 x 10) tablets unit dose blister pack

Starter Pack for treatment of deep vein thrombosis and treatment of pulmonary embolism:
NDC 46708-240-51 30-day starter blister pack containing 51 tablets: 42 tablets of 15 mg and 9 tablets of 20 mg

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Preserve in well-closed containers.
Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

For the tablets, advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Instructions for Patient Use

- Advise patients to take rivaroxaban tablets only as directed.
- Remind patients to not discontinue rivaroxaban tablets without first talking to their healthcare professional.

Adults

- Advise patients with atrial fibrillation to take rivaroxaban tablet once daily with the evening meal.
- Advise patients for initial treatment of DVT and/or PE to take rivaroxaban 15 mg or 20 mg tablets with food at approximately the same time every day *[see Dosage and Administration (2.1)].*
- Advise patients who are at a continued risk of recurrent DVT and/or PE after at least 6 months of initial treatment, to take rivaroxaban tablet 10 mg once daily with or without food *[see Dosage and Administration (2.1)].*

- Advise patients who cannot swallow the tablet whole to crush rivaroxaban tablets and combine with a small amount of applesauce followed by food *[see Dosage and Administration (2.6)].*
- For patients requiring an NG tube or gastric feeding tube, instruct the patient or caregiver to crush the rivaroxaban tablet and mix it with a small amount of water before administering via the tube *[see Dosage and Administration (2.6)].*
- If a dose is missed, advise the patient according to the instructions in the Full Prescribing Information based on their dosing schedule *[see Dosage and Administration (2.5)].*

Pediatric Patients

- The adult caregiver should administer the dose.
- Advise the caregiver whether the dose needs to be taken with food or not *[see Dosage and Administration (2.2)].*
- Advise the caregiver the tablet must not be split in an attempt to provide a fraction of a tablet dose *[see Dosage and Administration (2.2)].*
- If a child vomits or spits up the dose within 30 minutes after receiving the dose, a new dose should be given. However, if the child vomits more than 30 minutes after the dose is taken, the dose should not be re-administered and the next dose should be taken as scheduled. If a child vomits or spits up the dose repeatedly, the caregiver should contact the child's doctor right away *[see Dosage and Administration (2.2)].*
- For children who are unable to swallow whole tablets, rivaroxaban oral suspension may be used.
- If a dose is missed, advise the patient according to the instructions in the Full Prescribing Information based on their dosing schedule *[see Dosage and Administration (2.5)].*

Bleeding Risks

- Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it might take them longer than usual to stop bleeding, and that they may bruise and/or bleed more easily when they are treated with rivaroxaban tablets *[see Warnings and Precautions (5.2)].*
- If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately *[see Boxed Warning].*

Invasive or Surgical Procedures

Instruct patients to inform their healthcare professional that they are taking rivaroxaban tablets before any invasive procedure (including dental procedures) is scheduled.

Concomitant Medication and Herbals

Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions *[see Drug Interactions (7)].*

Pregnancy and Pregnancy-Related Hemorrhage

- Advise patients to inform their physician immediately if they become pregnant or intend to become pregnant during treatment with rivaroxaban tablets *[see Use in Specific Populations (8.1)].*

• Advise pregnant women receiving rivaroxaban tablets to immediately report to their physician any bleeding or symptoms of blood loss *[see Warnings and Precautions (5.7)].*

Lactation
Advise patients to discuss with their physician the benefits and risks of rivaroxaban tablets for the mother and for the child if they are nursing or intend to nurse during anticoagulant treatment *[see Use in Specific Populations (8.2)].*

Females and Males of Reproductive Potential
Advise patients who can become pregnant to discuss pregnancy planning with their physician *[see Use in Specific Populations (8.3)].*

Manufactured by:
Alembic Pharmaceuticals Limited
(Formulation Division),
Village Panelav, P. O. Tajpura,
Near Baska, Taluka-Halol,
Panchmahal 389350, Gujarat, India.

Revised: 01/2025

MEDICATION GUIDE
Rivaroxaban (RIV-a-ROX-a-ban) Tablets

What is the most important information I should know about rivaroxaban tablets?
Rivaroxaban tablets may cause serious side effects, including:
• **Increased risk of blood clots if you stop taking rivaroxaban tablets.** People with atrial fibrillation (a type of irregular heart beat) that is not caused by a heart valve problem (non-valvular) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. Rivaroxaban tablet lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking rivaroxaban tablets, you may have increased risk of forming a clot in your blood.
Do not stop taking rivaroxaban tablets without talking to the doctor who prescribes it for you. Stopping rivaroxaban tablets increases your risk of having a stroke. If you have to stop taking rivaroxaban tablets, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.
• **Increased risk of bleeding.**Rivaroxaban tablets can cause bleeding which can be serious and may lead to death. This is because rivaroxaban tablet is a blood thinner medicine (anticoagulant) that lowers blood clotting. During treatment with rivaroxaban tablets you are likely to bruise more easily, and it may take longer for bleeding to stop. You may have a higher risk of bleeding if you take rivaroxaban tablets and have certain other medical problems.
You may have a higher risk of bleeding if you take rivaroxaban tablets and take other medicines that increase your risk of bleeding, including:
o aspirin or aspirin containing products
o long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
o warfarin sodium (Coumadin®, Jantoven®)
o any medicine that contains heparin

o any medicine that contains heparin
o clopidogrel (Plavix®)
o selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
o other medicines to prevent or treat blood clots

Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

Call your doctor or get medical help right away if you or your child develop any of these signs or symptoms of bleeding:

o unexpected bleeding or bleeding that lasts a long time, such as:
- nose bleeds that happen often
- unusual bleeding from the gums
- menstrual bleeding that is heavier than normal or vaginal bleeding

o bleeding that is severe or you cannot control
o red, pink or brown urine
o bright red or black stools (looks like tar)
o cough up blood or blood clots
o vomit blood or your vomit looks like “coffee grounds”
o headaches, feeling dizzy or weak
o pain, swelling, or new drainage at wound sites

• **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like rivaroxaban tablets, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:

o a thin tube called an epidural catheter is placed in your back to give you certain medicine
o you take NSAIDs or a medicine to prevent blood from clotting
o you have a history of difficult or repeated epidural or spinal punctures
o you have a history of problems with your spine or have had surgery on your spine

If you take rivaroxaban tablets and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots.

Tell your doctor right away if you have:
• back pain
• tingling
• numbness
• muscle weakness (especially in your legs and feet)
• loss of control of the bowels or bladder (incontinence).

Rivaroxaban tablets are not for use in people with artificial heart valves.
Rivaroxaban tablets are not for use in people with antiphospholipid syndrome (APS), especially with positive triple antibody testing.

What is rivaroxaban tablet?

Rivaroxaban tablet is a prescription medicine used to:
• reduce the risk of stroke and blood clots in adults who have a medical condition called atrial fibrillation that is not caused by a heart valve problem. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to the formation of blood clots, which can travel to the brain, causing a stroke, or to other parts of the body.
• treat blood clots in the veins of your legs (deep vein thrombosis or DVT) or lungs (pulmonary embolism or PE)
• reduce the risk of blood clots from happening again in adults who continue to be at risk for DVT or PE after receiving treatment for blood clots for at least 6 months.
• help prevent a blood clot in the legs and lungs of adults who have just had hip or knee replacement surgery.
• help prevent blood clots in certain people hospitalized for an acute illness and after discharge who are at risk of getting blood clots because of the loss of or decreased ability to move around (mobility) and other risks for getting blood clots and who do not

have a high risk of bleeding.

Rivaroxaban tablet is used with low dose aspirin to:
• reduce the risk of serious heart problems, heart attack and stroke in adults with coronary artery disease (a condition where the blood supply to the heart is reduced or blocked).
• reduce the risk of a sudden decrease in blood flow to the legs, major amputation, serious heart problems or stroke in adults with peripheral artery disease (a condition where the blood flow to the legs is reduced) and includes adults who have recently had a procedure to improve blood flow to the legs.
Rivaroxaban are used in children to:
• treat blood clots or reduce the risk of blood clots from happening again in children from birth to less than 18 years, after receiving at least 5 days of treatment with injectable or intravenous medicines used to treat blood clots.
• help prevent blood clots in children 2 years and older with congenital heart disease after the Fontan procedure.
Rivaroxaban was not studied and is not recommended in children less than 6 months of age who:
• were less than 37 weeks of growth (gestation) at birth
• had less than 10 days of oral feeding, **or**
• had a body weight of less than 5.7 pounds (2.6 kg)

Do not take rivaroxaban tablet if you or your child:
• currently have certain types of abnormal bleeding. Talk to your doctor before taking rivaroxaban tablets if you currently have unusual bleeding.
• are allergic to rivaroxaban or any of the ingredients in rivaroxaban tablets. See the end of this Medication Guide for a complete list of ingredients in rivaroxaban tablets.

Before taking rivaroxaban tablets, tell your doctor about all of your medical conditions, including if you or your child:
• have or ever had bleeding problems
• have liver or kidney problems
• have antiphospholipid syndrome (APS)
• are pregnant or plan to become pregnant. It is not known if rivaroxaban tablets will harm your unborn baby.
o **Tell your doctor** right away if you become pregnant during treatment with rivaroxaban tablets. Taking rivaroxaban tablets while you are pregnant may increase the risk of bleeding in you or in your unborn baby.
o Females who are able to become pregnant: Talk with your doctor about pregnancy planning during treatment with rivaroxaban tablets. Talk with your doctor about your risk for severe uterine bleeding if you are treated with blood thinner medicines, including rivaroxaban tablets.
o If you take rivaroxaban tablets during pregnancy **tell your doctor** right away if you have any signs or symptoms of bleeding or blood loss. **See "What is the most important information I should know about rivaroxaban tablets?" for signs and symptoms of bleeding.**
• are breastfeeding or plan to breastfeed. Rivaroxaban can pass into your breast milk. Talk to your doctor about the best way to feed your baby during treatment with rivaroxaban tablets.

Tell all of your doctors and dentists that you or your child are taking rivaroxaban tablets. They should talk to the doctor who prescribed rivaroxaban tablets for you before you have any surgery, medical or dental procedure.

Tell your doctor about all the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some of your other medicines may affect the way rivaroxaban tablets works, causing

side effects. Certain medicines may increase your risk of bleeding. See **“What is the most important information I should know about rivaroxaban tablets?”**

Especially tell your doctor if you or your child take:

- ketoconazole
- ritonavir
- erythromycin
- carbamazepine
- phenytoin
- rifampin
- St. John’s wort

How should I take rivaroxaban tablets?

• Take rivaroxaban tablets exactly as prescribed by your doctor.

• **Do not change your dose or stop taking rivaroxaban tablets unless your doctor tells you to.** Your doctor may change your dose if needed.

• Your doctor will decide how long you should take rivaroxaban tablets.

• Rivaroxaban tablets may need to be stopped for one or more days before any surgery or medical or dental procedure. Your doctor will tell you when to stop taking rivaroxaban tablets and when to start taking rivaroxaban tablets again after your surgery or procedure.

• If you need to stop taking rivaroxaban tablets for any reason, talk to the doctor who prescribed rivaroxaban tablets to you to find out when you should stop taking it. Do not stop taking rivaroxaban tablets without first talking to the doctor who prescribes it to you.

• If you have difficulty swallowing rivaroxaban tablets whole, talk to your doctor about other ways to take rivaroxaban tablets.

• Do not run out of rivaroxaban tablets. Refill your prescription of rivaroxaban tablets before you run out. When leaving the hospital following a hip or knee replacement, be sure that you will have rivaroxaban tablets available to avoid missing any doses.

• If you take too much rivaroxaban tablets, go to the nearest hospital emergency room or call your doctor right away.

If you take rivaroxaban tablets for:

o **Atrial fibrillation that is not caused by a heart valve problem:**

■ Take rivaroxaban tablet **1 time a day with your evening meal.**

■ If you miss a dose of rivaroxaban tablet, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.

o **Blood clots in the veins of your legs or lungs:**

■ Take rivaroxaban tablet **1** or **2 times a day** as prescribed by your doctor.

■ For the **10 mg dose,** take rivaroxaban tablets **with or without food.**

■ For the **15 mg and 20 mg doses**, take rivaroxaban tablets **with food at the same time each day.**

■ If you miss a dose:

► **If you take the 15 mg dose of rivaroxaban tablet 2 times a day (a total of 30 mg of rivaroxaban tablet in 1 day):** Take rivaroxaban tablet as soon as you remember on the same day. You may take 2 doses at the same time to make up for the missed dose. Take your next dose at your regularly scheduled time.

► **If you take rivaroxaban tablet 1 time a day:** Take rivaroxaban tablet as soon as you remember on the same day. Take your next dose at your regularly scheduled time.

o **Hip or knee replacement surgery:**

■ Take rivaroxaban tablet 1 time a day with or without food.

■ If you miss a dose of rivaroxaban tablet, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.

o **Blood clots in people hospitalized for an acute illness:**

■ Take rivaroxaban tablets 1 time a day, with or without food, while you are in the hospital and after you are discharged as prescribed by your doctor.

■ If you miss a dose of rivaroxaban tablet, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.

o **Reducing the risk of serious heart problems, heart attack and stroke in**

coronary artery disease:
- Take rivaroxaban tablets 2.5 mg 2 times a day with or without food.
- If you miss a dose of rivaroxaban tablets, take your next dose at your regularly scheduled time.
- Take aspirin 75 to 100 mg once daily as instructed by your doctor.

o **Reducing the risk of a sudden decrease in blood flow to the legs, major amputation, serious heart problems or stroke in people with peripheral artery disease including those who have recently had a procedure to improve blood flow to the legs:**
- Take rivaroxaban tablets 2.5 mg 2 times a day with or without food.
- If you miss a dose of rivaroxaban tablets, take your next dose at your regularly scheduled time.
- Take aspirin 75 mg to 100 mg 1 time a day as instructed by your doctor.

For children who take rivaroxaban:
- o The dose of rivaroxaban depends on your child's body weight and will be calculated by your child's doctor. Your child's doctor will tell you if rivaroxaban can be given to your child with or without food.
- o The adult caregiver should give the dose.
- o If your child is taking the tablet, the tablet should be taken whole and should not be split in an attempt to provide a lower dose of rivaroxaban tablets.
- o Do not switch between the rivaroxaban oral suspension or tablet without first talking to your doctor.
- o If your child vomits or spits up:
  - if vomiting or spitting up persists, contact your child's doctor right away.
- o If your child misses a dose:
  - If your child is taking rivaroxaban tablets 1 time a day, give the dose as soon as you remember on the same day. If this is not possible, skip this dose and give the next dose at the regularly scheduled time.
  - If your child is taking rivaroxaban tablets 2 times a day, give the missed morning dose as soon as you remember. You may give the missed morning dose together with the evening dose. However, a missed evening dose can only be taken in the same evening.
  - If your child is taking rivaroxaban tablets 3 times a day, skip the missed dose and give the next dose at the regularly scheduled time.

What are the possible side effects of rivaroxaban tablets?
Rivaroxaban tablets may cause serious side effects:
- See **"What is the most important information I should know about rivaroxaban tablets?"**

The most common side effect of rivaroxaban tablets in adults was bleeding.
The most common side effects of rivaroxaban tablets in children include:
- bleeding
- cough
- vomiting
- inflamed stomach and gut

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store rivaroxaban tablets?
- Store rivaroxaban tablets at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Preserve in well-closed containers.
- Bottles of 60's and 180's count of 25 mg strength and bottles of 30's count of 10 mg, 15 mg and 20 mg strengths come in a child-resistant package.
- **Keep rivaroxaban tablets and all medicines out of the reach of children.**

General information about the safe and effective use of rivaroxaban tablets.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use rivaroxaban tablets for a condition for which it was not prescribed. Do not give rivaroxaban tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about rivaroxaban tablets that is written for health professionals.

What are the ingredients in rivaroxaban tablets?
Active ingredient: rivaroxaban
Inactive ingredients tablets:
colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate.
The proprietary film coating mixture used for rivaroxaban 2.5 mg tablet is Opadry® Yellow containing D&C yellow #10 aluminium lake, hypromellose, iron oxide red, iron oxide yellow, polyethylene glycol 6000 and titanium dioxide.
The proprietary film coating mixture used for rivaroxaban 10 mg tablet is Opadry® Pink containing hypromellose, iron oxide red, polyethylene glycol 6000, talc and titanium dioxide.
The proprietary film coating mixture used for rivaroxaban 15 mg tablet and 20 mg tablet is Opadry® Brown containing hypromellose, iron oxide black, iron oxide red, polyethylene glycol 8000 and titanium dioxide.

Trademarks are property of their respective owners.

Manufactured by:
Alembic Pharmaceuticals Limited
(Formulation Division),
Village Panelav, P. O. Tajpura,
Near Baska, Taluka-Halol,
Panchmahal 389350, Gujarat, India.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 01/2025

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 2.5 mg

NDC 46708-683-60
Rivaroxaban
Tablets, USP
2.5 mg
PHARMACIST: Dispense the accompanying
Medication Guide to each patient.
Rx only
60 Tablets
Alembic

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 10 mg

NDC 46708-346-30
Rivaroxaban
Tablets, USP
10 mg
PHARMACIST: Dispense the accompanying
Medication Guide to each patient.
Rx only
30 Tablets
Alembic

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 15 mg

NDC 46708-347-30
Rivaroxaban
Tablets, USP
15 mg
PHARMACIST: Dispense the accompanying
Medication Guide to each patient.
Rx only
30 Tablets
Alembic

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 20 mg

NDC 46708-348-30
Rivaroxaban
Tablets, USP
20 mg
PHARMACIST: Dispense the accompanying
Medication Guide to each patient.
Rx only

30 Tablets
Alembic

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - KIT CARTON

NDC 46708-240-51 Rx only
Rivaroxaban
Tablets, USP
Starter Pack
for treatment of deep vein thrombosis and
treatment of pulmonary embolism
Days 1-21
15 mg per tablet, twice daily
42 tablets
Days 22-30
20 mg per tablet, once daily
9 tablets
Please see full Prescribing Information, including
BOXED WARNINGS, and Medication Guide inside.
First 30-day supply
Alembic

RIVAROXABAN

rivaroxaban tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-346
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVAROXABAN (UNII: 9NDF7JZ4M3) (RIVAROXABAN - UNII:9NDF7JZ4M3)	RIVAROXABAN	10 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
TALC (UNII: 7SEV7J4R1U)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	

Product Characteristics

Color	PINK	**Score**	no score
Shape	ROUND (biconvex)	**Size**	6mm
Flavor		**Imprint Code**	L;10
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-346-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
2	NDC:46708-346-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
3	NDC:46708-346-10	100 in 1 CARTON	05/14/2025	
3		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210301	05/14/2025	

RIVAROXABAN

rivaroxaban tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-347
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVAROXABAN (UNII: 9NDF7JZ4M3) (RIVAROXABAN - UNII:9NDF7JZ4M3)	RIVAROXABAN	15 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	BROWN	**Score**	no score
Shape	ROUND (biconvex)	**Size**	6mm
Flavor		**Imprint Code**	504
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-347-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
2	NDC:46708-347-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
3	NDC:46708-347-10	100 in 1 CARTON	05/21/2025	
3		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210301	05/14/2025	

RIVAROXABAN

rivaroxaban tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-348
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVAROXABAN (UNII: 9NDF7JZ4M3) (RIVAROXABAN - UNII:9NDF7JZ4M3)	RIVAROXABAN	20 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	BROWN	**Score**	no score
Shape	TRIANGLE (biconvex)	**Size**	7mm
Flavor		**Imprint Code**	505
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-348-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
2	NDC:46708-348-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
3	NDC:46708-348-10	100 in 1 CARTON	05/21/2025	
3		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210301	05/14/2025	

RIVAROXABAN

rivaroxaban tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-683
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVAROXABAN (UNII: 9NDF7JZ4M3) (RIVAROXABAN - UNII:9NDF7JZ4M3)	RIVAROXABAN	2.5 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	

FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
D&C YELLOW NO. 10 ALUMINUM LAKE (UNII: CQ3XH3DET6)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics

Color	YELLOW (Light yellow to yellow)	**Score**	no score
Shape	ROUND (biconvex)	**Size**	4mm
Flavor		**Imprint Code**	9;C
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-683-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
2	NDC:46708-683-45	180 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
3	NDC:46708-683-91	1000 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
4	NDC:46708-683-10	100 in 1 CARTON	05/14/2025	
4		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210301	05/14/2025	

RIVAROXABAN

rivaroxaban kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-240

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-240-51	1 in 1 CARTON; Type 0: Not a Combination Product	05/14/2025	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 BLISTER PACK	42
Part 2	1 BLISTER PACK	9

Part 1 of 2

RIVAROXABAN

rivaroxaban tablet, film coated

Product Information

Item Code (Source)	NDC:46708-230
Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVAROXABAN (UNII: 9NDF7JZ4M3) (RIVAROXABAN - UNII:9NDF7JZ4M3)	RIVAROXABAN	15 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	

Product Characteristics

Color	BROWN	**Score**	no score
Shape	ROUND (biconvex)	**Size**	6mm
Flavor		**Imprint Code**	504
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		42 in 1 BLISTER PACK; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210301	05/14/2025	

Part 2 of 2

RIVAROXABAN

rivaroxaban tablet, film coated

Product Information

Item Code (Source)	NDC:46708-231
Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVAROXABAN (UNII: 9NDF7JZ4M3) (RIVAROXABAN - UNII:9NDF7JZ4M3)	RIVAROXABAN	20 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

Color	BROWN	**Score**	no score
Shape	TRIANGLE (biconvex)	**Size**	7mm
Flavor		**Imprint Code**	505
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		9 in 1 BLISTER PACK; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210301	05/14/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210301	05/14/2025	

Labeler - Alembic Pharmaceuticals Limited (650574663)

Establishment

Name	Address	ID/FEI	Business Operations
Alembic Pharmaceuticals Limited		650574671	MANUFACTURE(46708-240, 46708-346, 46708-347, 46708-348, 46708-683)