

RIVAROXABAN - rivaroxaban tablet, film coated

Macleods 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)

RECENT MAJOR CHANGES

Warnings and Precautions (5.2)

06/2025

INDICATIONS AND USAGE

Rivaroxaban tablets are a factor Xa inhibitor indicated:

- 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)

DOSAGE AND ADMINISTRATION

- CAD or PAD: 2.5 mg orally twice daily with or without food, in combination with aspirin (75-100 mg) once daily (2.1)

DOSAGE FORMS AND STRENGTHS

- Tablets: 2.5 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)
- Severe hypersensitivity reaction to rivaroxaban tablets (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 contact Macleods Pharma USA, Inc., at 1-888-943-3210 or 1-855-926-3384 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**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 with 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: 8/2025

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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 is 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 & USAGE

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.

2 DOSAGE & ADMINISTRATION

2.1 Recommended Dosage in Adults

Table 1: Recommended Dosage in Adults

Indication	Renal Considerations*	Dosage	Food/Timing†
Reduction of Risk of Major Cardiovascular Events (CV Death, MI, and Stroke) in CAD	No dose adjustment needed based on CrCl	2.5 mg <u>twice daily</u> , plus aspirin (75-100 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 <u>twice daily</u> , plus aspirin (75-100 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)

2.2 Recommended Dosage in Pediatric Patients

Rivaroxaban 2.5 mg tablets are not recommended for use in pediatric patients [see *Use in Specific Populations (8.4)*].

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 3.0 in adults 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.

Once rivaroxaban tablets are 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.

Pediatric Patients

- 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.

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. Administration with food is not required for the 2.5 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. Enteral feeding is not required following administration of the 2.5 mg tablets [see *Clinical Pharmacology (12.3)*].

Crushed rivaroxaban tablets 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 & STRENGTHS

- 2.5 mg tablets are Light yellow colour, circular, biconvex, film coated tablets debossed with “J 7” on one side and plain on the other side.

4 CONTRAINDICATIONS

Rivaroxaban tablets is 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 is 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, including in any organ, 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, P2Y₁₂ 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)*].

Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding

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.

5.5 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 Populations (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.

5.10 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)].

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 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 † N=9134 n (%/year)	Placebo † N=9107 n (%/year)	Rivaroxaban vs. Placebo HR (95 % CI)
Modified ISTH Major Bleeding‡	263 (1.6)	144 (0.9)	1.8 (1.5, 2.3)
- Fatal bleeding event	12 (<0.1)	8 (<0.1)	1.5 (0.6, 3.7)
Intracranial hemorrhage (ICH)	6 (<0.1)	3 (<0.1)	2.0 (0.5, 8.0)
Non-intracranial	6 (<0.1)	5 (<0.1)	1.2 (0.4, 4.0)
-Symptomatic bleeding in critical organ (non-fatal)	58 (0.3)	43 (0.3)	1.4 (0.9, 2.0)
-ICH (fatal and non-fatal)	23 (0.1)	21 (0.1)	1.1 (0.6, 2.0)
Hemorrhagic Stroke Other ICH	18 (0.1)	13 (<0.1)	1.4 (0.7, 2.8)
	6 (<0.1)	9 (<0.1)	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 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 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

Parameter	Rivaroxaban † N=3256		Placebo† N=3248		Rivaroxaban vs. Placebo HR (95 % CI)
	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 (1.0, 2.1)
Fatal bleeding	6 (0.2)	0.09	6 (0.2)	0.09	1.0 (0.3, 3.2)
Intracranial bleeding	13 (0.4)	0.20	17 (0.5)	0.26	0.8 (0.4, 1.6)
Clinically overt	46 (1.4)	0.71	24 (0.7)	0.36	1.9 (1.2, 3.2)

signs of hemorrhage associated with a drop in hemoglobin of ≥ 5 g/dL or drop in hematocrit of $\geq 15\%$					
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* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories.

† Treatment schedule: rivaroxaban 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

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)

Injury, poisoning and procedural complications: Atraumatic splenic rupture

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 2–4% and 15–20%, 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, periparturient 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 [¹⁴C]-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

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)*].

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, and 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 m²). There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m²); 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)*].

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.

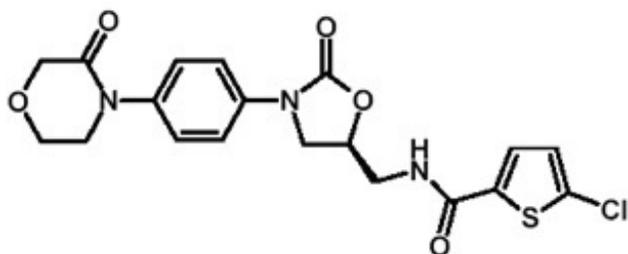
No clinical data are available in pediatric patients with hepatic impairment.

10 OVERDOSAGE

Overdose of Rivaroxaban tablets may lead to hemorrhage. Discontinue rivaroxaban tablets and initiate appropriate therapy if bleeding complications associated with overdose 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, 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 is C₁₉H₁₈ClN₃O₅S and the molecular weight is 435.89. The structural formula is:



Rivaroxaban is a pure (S)-enantiomer. It is an odorless, non-hygroscopic, white to yellowish powder. Rivaroxaban is only slightly soluble in organic solvents (e.g., acetone, polyethylene glycol 400) and is practically insoluble in water and aqueous media.

Each Rivaroxaban tablets, USP contains 2.5 mg of rivaroxaban. The inactive ingredients of Rivaroxaban tablets, USP are: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Additionally, the proprietary film coating mixture used for Rivaroxaban Tablet, USP 2.5 mg is Instacoat@ Yellow and containing Hypromellose, polyethylene glycol, Titanium dioxide, yellow iron oxide.

USP Dissolution test pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rivaroxaban is 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

Measure	Parameter	Creatinine Clearance (mL/min)				
		50-79	30-49	15-29	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 dose, it is estimated to be 80% to 100% and is not affected by food. Rivaroxaban 2.5 mg tablets can be taken with or without 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 (30 mg single dose) with the H₂-receptor antagonist ranitidine (150 mg twice daily), the antacid aluminum hydroxide/magnesium hydroxide (10 mL) or rivaroxaban (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 3).

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.

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 [¹⁴C]-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.

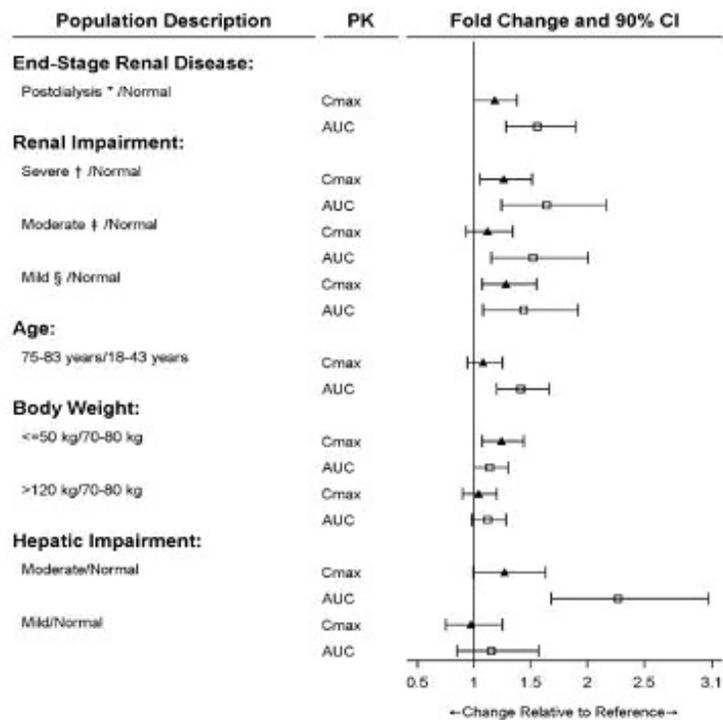
Excretion

In a Phase 1 study, following the administration of [¹⁴C]-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.

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.

Hepatic Impairment

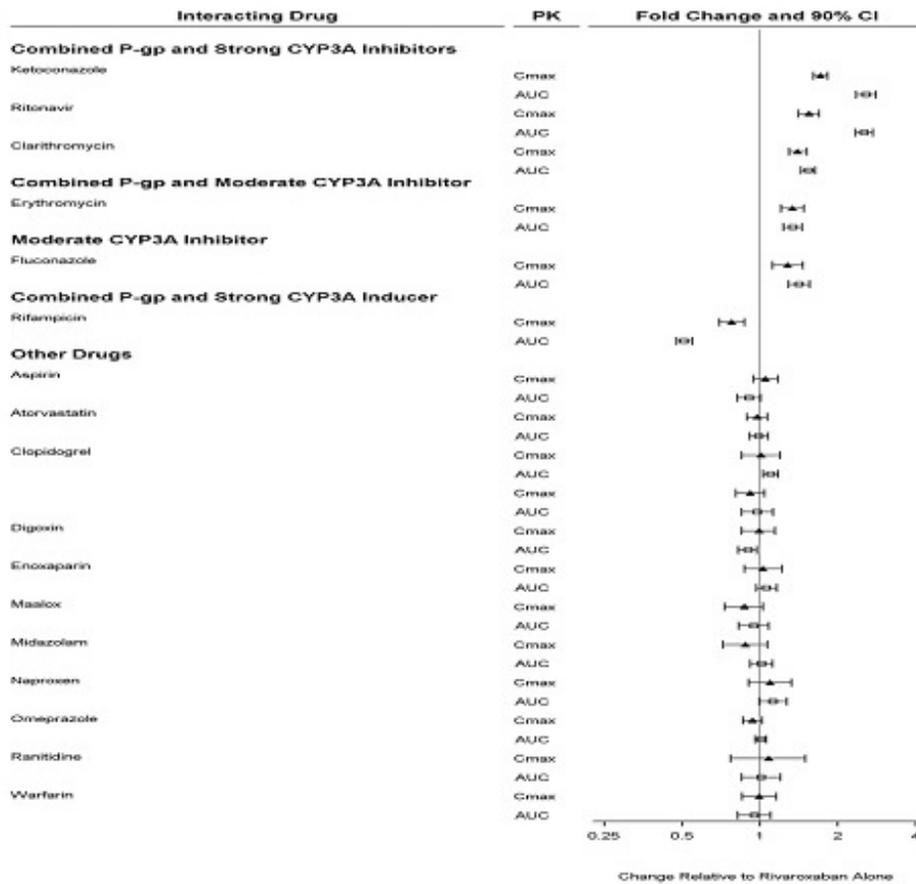
No clinical data are available in pediatric patients with hepatic impairment.

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 another study, single doses of warfarin (15 mg) and rivaroxaban (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. Neither naproxen nor aspirin affected the pharmacokinetics of rivaroxaban (see Figure 3).

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

In a pharmacokinetic trial, rivaroxaban 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 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.

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

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

The evidence for the efficacy and safety of rivaroxaban 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 <0.90 or had asymptomatic carotid artery stenosis $\geq 50\%$, 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

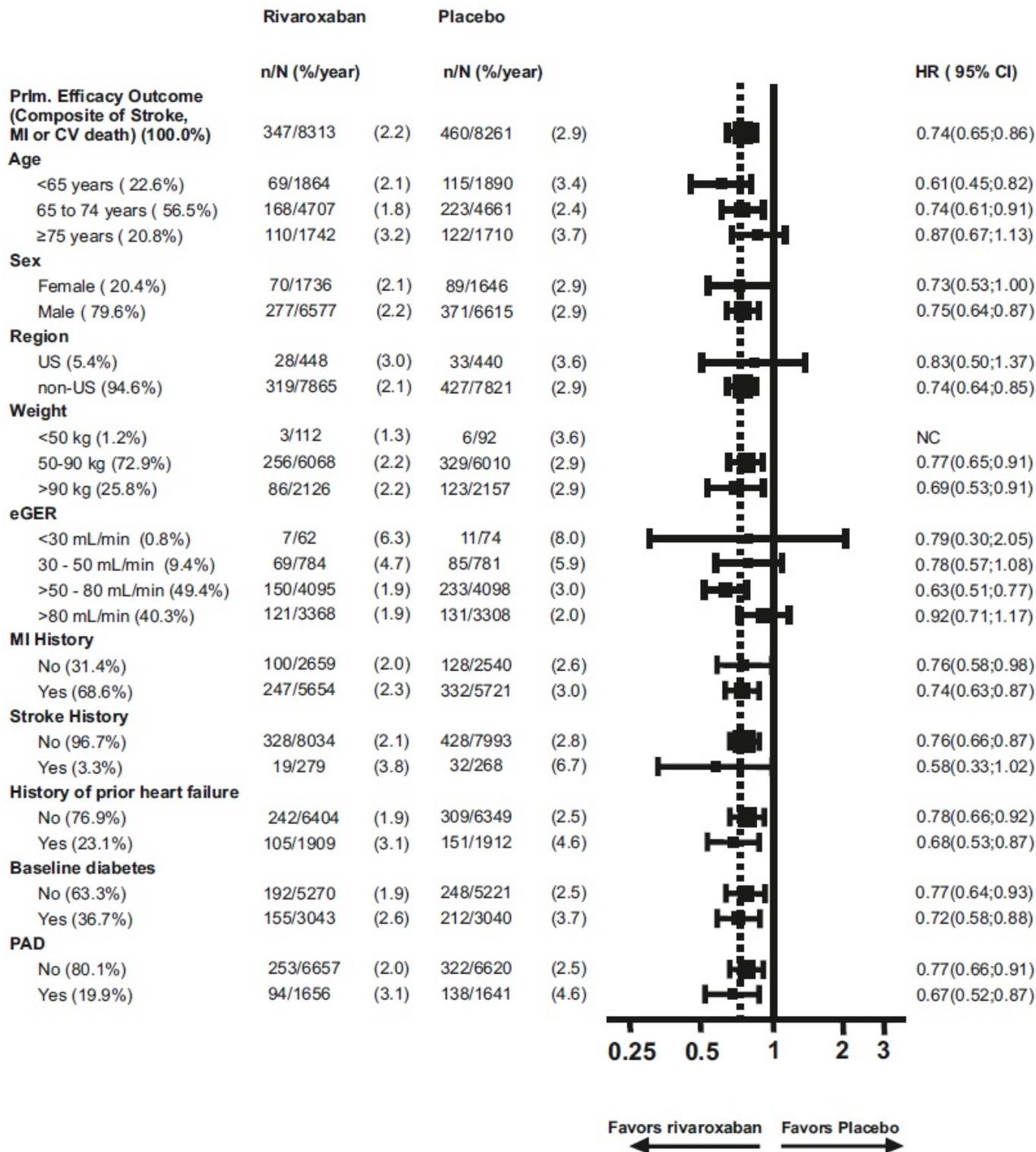
percutaneous transluminal coronary angioplasty (PTCA)/atherectomy/ percutaneous coronary intervention (PCI), and 26% had history of coronary artery bypass grafting (CABG) prior to study. Of the patients with PAD, 49% had intermittent claudication, 27% had peripheral artery bypass surgery or peripheral 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 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 group versus the placebo group. Compared to placebo, during 10,000 patient-years of treatment, rivaroxaban 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 [†] 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 (2.0)	1.1	195 (2.4)	1.2	0.86 (0.70, 1.05)
- CV death	139 (1.7)	0.9	184 (2.2)	1.1	0.75 (0.60, 0.93)
Coronary heart disease death, MI, ischemic stroke, acute limb ischemia	299 (3.6)	1.9	411 (5.0)	2.6	0.72 (0.62, 0.83)
- Coronary heart disease death§	80 (1.0)	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	0.73 (0.64, 0.84)
All-cause mortality	262 (3.2)	1.6	339 (4.1)	2.1	0.77 (0.65, 0.90)

* intention to treat analysis set, primary analyses.

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

‡ rivaroxaban vs. placebo.

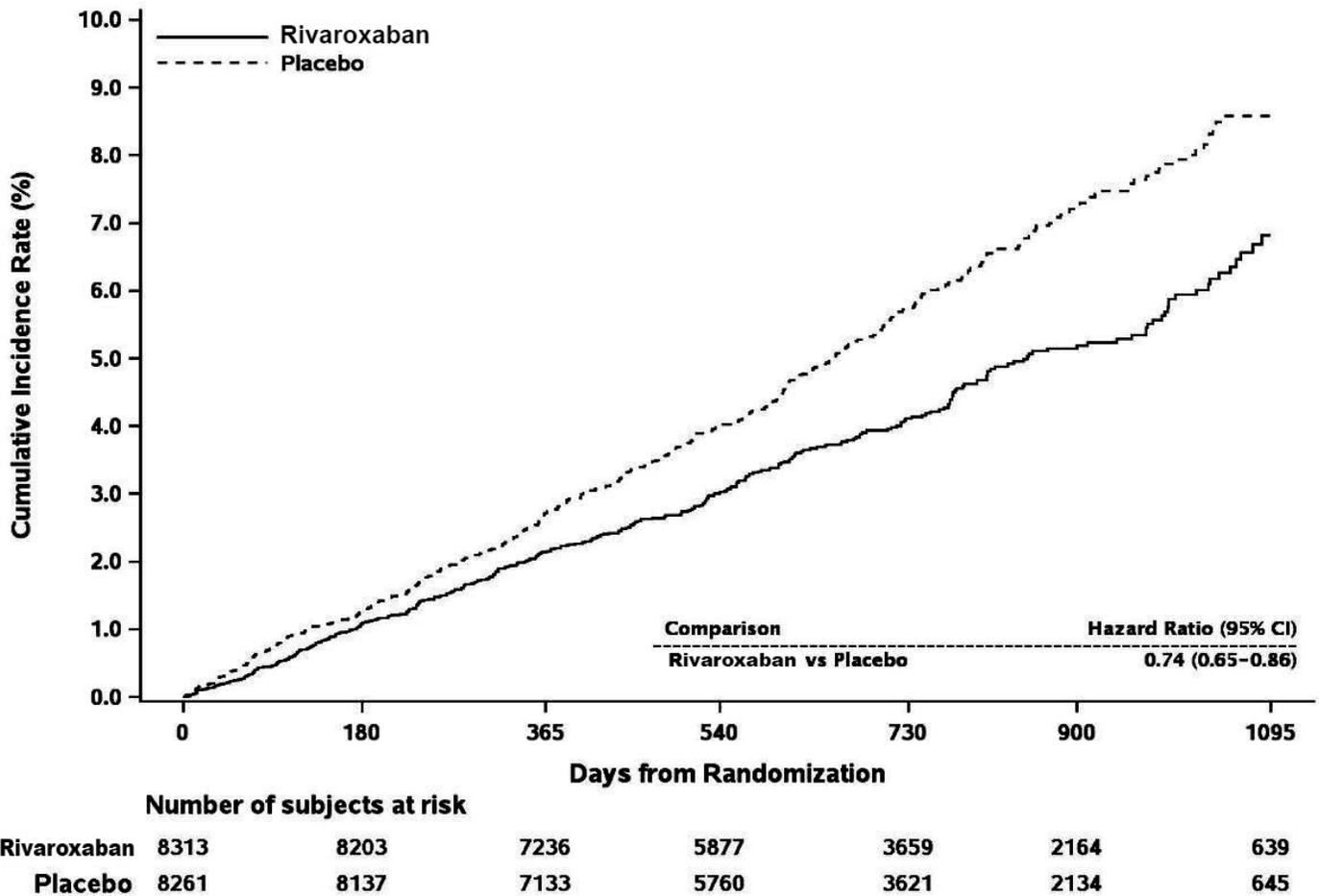
§ Coronary heart disease death: death due to acute MI, sudden cardiac death, or CV procedure.

¶ 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*



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

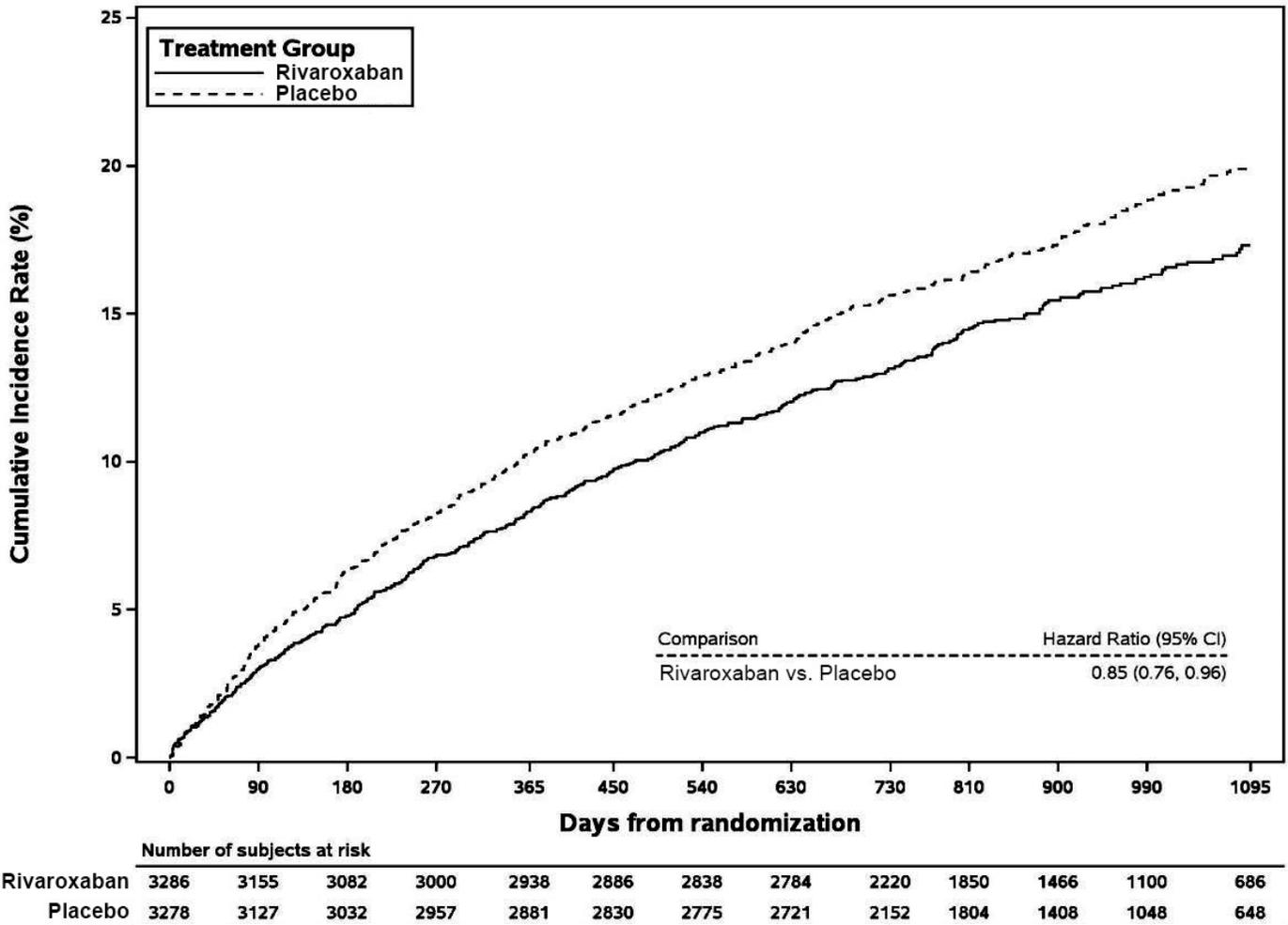
14.7 Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients after Lower Extremity Revascularization due to

Symptomatic PAD

The efficacy and safety of rivaroxaban 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 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 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 ≤ 0.80 . 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 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 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.

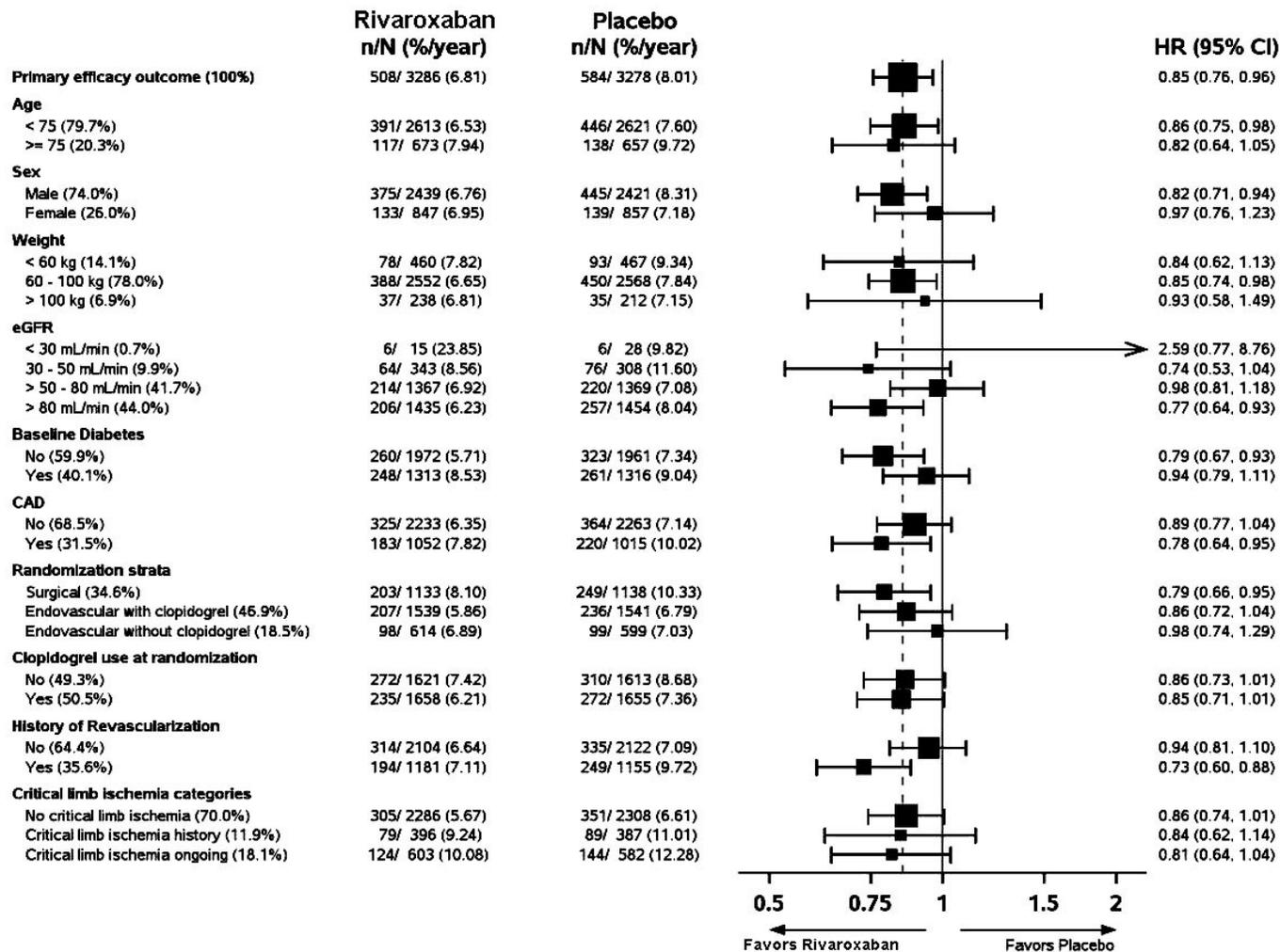
Figure 11: Time to First Occurrence of Primary Efficacy Outcome (Myocardial Infarction, Ischemic Stroke, Cardiovascular Death, Acute Limb Ischemia, Major Amputation due to Vascular Origins) in VOYAGER*



*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

Outcome Components	VOYAGER			COMPASS PAD		
	Rivaroxaban N=3286	Placebo N=3278	Hazard Ratio (95% CI)* p-value†	Rivaroxaban N=2492	Placebo N=2504	Hazard Ratio (95% CI)*
	Event Rate (%/year)			Event Rate (%/year)		
5 Component						

5- Component Outcome (Major thrombotic vascular events)‡	6.8	8.0	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 (0.70, 1.12)	1.1	1.5	0.76 (0.53, 1.09)
Ischemic Stroke§	0.9	1.0	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, 1.40)	1.4	1.7	0.82 (0.59, 1.14)
ALI	2.0	3.0	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	0.40 (0.20, 0.79)
VOYAGER Secondary Efficacy Outcomes ^P						
MI, ischemic stroke, CHD death, ^β ALI, and major amputation due to vascular etiology	5.8	7.3	0.80 (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			0.89			0.80

MI, stroke, CV death, ALI, and major amputation due to vascular etiology	8.2	9.3	(0.79, 0.99) p=0.029	4.8	6.0	(0.67, 0.96)
MI, all-cause stroke, CV death, ALI, and major amputation due to vascular etiology	6.9	8.1	0.86 (0.76, 0.96) p=0.010	3.4	4.9	0.70 (0.57, 0.86)
All-cause mortality	4.0	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, 1.00)	0.2	0.3	0.67 (0.30, 1.49)

Efficacy endpoints in COMPASS PAD were analysed according to the pre-specified endpoints in VOYAGER when applicable.

* Rivaroxaban 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

‡ Secondary outcomes for VOYAGER were tested sequentially.

‡ CHD death includes death due to sudden cardiac death, MI, or coronary revascularization procedure

‡ Unplanned index limb revascularization for recurrent limb ischemia was not captured in COMPASS study.

‡ 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Rivaroxaban Tablets, USP are available in the strengths and packages listed below:

- 2.5 mg tablets are Light yellow colour, circular, biconvex, film coated tablets debossed with "J 7" on one side and plain on the other side. The tablets are supplied in the packages listed:

NDC 33342-488-09	Bottle containing 60 tablets
NDC 33342-488-57	Bottle containing 180 tablets
NDC 33342-488-98	Blister package containing 60 tablets (10 blister cards containing 6 tablets each)

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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).

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 [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 Herbs

Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbs, 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 [see *Use in Specific Populations (8.1)*].
- Advise pregnant women receiving rivaroxaban 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 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)*].

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Macleods Pharma USA, Inc.

Princeton, NJ 08540

Manufactured by :

Macleods Pharmaceuticals Ltd.

Baddi, Himachal Pradesh- 174101, INDIA

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Dispense with Medication Guide available at: www.macleodspharma.com/usa

SPL MEDGUIDE SECTION

MEDICATION GUIDE

Rivaroxaban (RIV a ROX a ban) Tablets

Dispense with Medication Guide available at: www.macleodspharma.com/usa

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 tablets 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 tablets 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 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
- o left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder or diffuse abdominal discomfort (these may be symptoms of rupture of the spleen)

• **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:

<ul style="list-style-type: none">• back pain	<ul style="list-style-type: none">• muscle weakness (especially in your legs and feet)
<ul style="list-style-type: none">• tingling	<ul style="list-style-type: none">• loss of control of the bowels or bladder (incontinence)
<ul style="list-style-type: none">• numbness	

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 are rivaroxaban tablets?

Rivaroxaban tablets 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 adults 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 tablets 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 tablets is 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 tablets 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 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. Talk with your doctor about your risk for severe uterine bleeding if you are treated with blood thinner medicines, including rivaroxaban.

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.

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 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 tablets 1 time a day with your evening meal.

□ If you miss a dose of rivaroxaban tablets, 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 tablets 1 or 2 times a day as prescribed by your doctor.

o Hip or knee replacement surgery:

□ Take rivaroxaban tablets 1 time a day with or without food.

□ If you miss a dose of rivaroxaban tablets, 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 tablets, 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 2.5 mg 2 times a day with or without food.

□ If you miss a dose of rivaroxaban, 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 2.5 mg 2 times a day with or without food.

□ If you miss a dose of rivaroxaban, 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 tablets 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 tablets 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 the rivaroxaban tablet without first talking to your doctor.
- 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:

<ul style="list-style-type: none">• bleeding	<ul style="list-style-type: none">• cough
<ul style="list-style-type: none">• vomiting	<ul style="list-style-type: none">• 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 at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Additionally,

The proprietary film coating mixture used for rivaroxaban tablets 2.5 mg tablets is Instacoat® yellow containing hypromellose, polyethylene glycol, titanium dioxide and red iron oxide

Manufactured for :

Macleods Pharma USA, Inc.

Princeton, NJ 08540

Manufactured by :

Macleods Pharmaceuticals Ltd.

Baddi, Himachal Pradesh- 174101, INDIA

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This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 08/2025

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Rivaroxaban Tablets, 2.5 mg

60's Container Pack

NDC: 33342-488-09

MACLEODS
Pharma USA
NDC 33342-488-09

**Rivaroxaban
Tablets, USP
2.5 mg**

Pharmacist: Dispense the Medication Guide available at www.macleodspharma.com/usa to each patient.

Rx Only 60 Tablets

Each tablet contains:
rivaroxaban 2.5 mg

See package insert for dosing and full Prescribing Information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Keep out of reach of children.

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Code No.: HP/152/07
PMXXXXXX

OPZ AREA

Rivaroxaban Tablets, 2.5 mg

180's Container Pack

NDC: 33342-488-57

 **MACLEODS**
Pharma USA
NDC 33342-488-57

Rivaroxaban Tablets, USP

2.5 mg

Pharmacist: Dispense the Medication Guide available at www.macleodspharma.com/usa to each patient.

Rx Only 180 Tablets

Each tablet contains:
rivaroxaban 2.5 mg

See package insert for dosing and full Prescribing Information.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Keep out of reach of children.

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OPZ AREA
43 x 15 mm

Manufactured by:
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Baddi, Himachal Pradesh-174101 INDIA

Code No.: HP/152/07
PM04337042

Rivaroxaban Tablets, 2.5 mg
60s Blister Pack- Carton
NDC: 33342-488-98

MACLEODS
Pharma USA

NDC 33342-488-98

Rivaroxaban Tablets, USP

2.5 mg per tablet

Pharmacist: Medication Guide available at
www.macleodspharma.com/usa to each patient.
For Hospital Use Only

Rx Only 60 Tablets (10 x 6 unit dose blister cards)

Rivaroxaban Tablets, USP **2.5 mg** per tablet

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Princeton, NJ 08540

Manufactured by:
Macleods Pharmaceuticals Ltd.
Baddi, Himachal Pradesh, INDIA
Code No.: HP/152/07

Batch No. :
Exp. Date:



PM000XXX

60 Tablets (10 x 6 unit dose blister cards) Rx Only

Pharmacist: Medication Guide available at
www.macleodspharma.com/usa to each patient.
For Hospital Use Only

Rivaroxaban Tablets, USP

2.5 mg per tablet

NDC 33342-488-98

MACLEODS
Pharma USA

Rivaroxaban Tablets, USP **2.5 mg** per tablet

Each tablet contains:
rivaroxaban 2.5 mg

See package insert for dosing and
full Prescribing Information.

**This unit dose package is not
child-resistant**

Store at 20° to 25°C (68° to 77°F);
excursions permitted to 15° to 30°C
(59° to 86°F) [see USP Controlled
Room Temperature].

Keep out of reach of children.

RIVAROXABAN

rivaroxaban tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:33342-488
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	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)				
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)				
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
HYPROMELLOSES (UNII: 3NXW29V3WO)				
SODIUM LAURYL SULFATE (UNII: 368GB5141J)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)				
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)				
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)				
Product Characteristics				
Color	YELLOW (Light Yellow)	Score	no score	
Shape	ROUND (circular, biconvex)	Size	6mm	
Flavor		Imprint Code	J;7	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:33342-488-09	60 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
2	NDC:33342-488-57	180 in 1 BOTTLE; Type 0: Not a Combination Product	05/14/2025	
3	NDC:33342-488-98	10 in 1 CARTON	05/14/2025	
3		6 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	ANDA213114	05/14/2025		

Labeler - Macleods Pharmaceuticals Limited (862128535)

Establishment

Name	Address	ID/FEI	Business Operations
Macleods Pharmaceuticals		676260510	ANALYSIS(33342-488) , LABEL(33342-488) , MANUFACTURE(33342-

Limited

070509519

488) , PACK(33342-488)

Revised: 8/2025

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