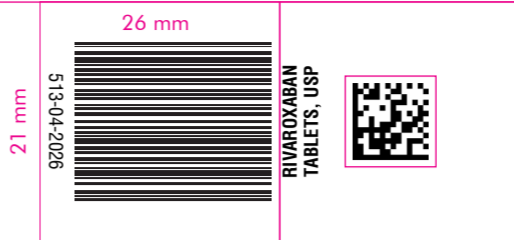


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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RIVAROXABAN TABLETS safely and effectively.

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 is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

RECENT MAJOR CHANGES
Warnings and Precautions (5.2) 03/2026

INDICATIONS AND USAGE
Rivaroxaban Tablets is 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 mg to 100 mg) once daily (2.1)

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
1.7 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

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

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.
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.

- use of indwelling epidural or 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
optimal timing between the administration of Rivaroxaban Tablets and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis

1 INDICATIONS AND 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 AND ADMINISTRATION
2.1 Recommended Dosage in Adults
Table 1: Recommended Dosage in Adults

Table with 4 columns: Indication, Renal Considerations, Dosage, Food/Timing. Rows include Reduction of Risk of Major Cardiovascular Events (CV Death, MI, and Stroke) in CAD and Reduction of Risk of Major Thrombotic Vascular Events in PAD.

* Calculate CrCl based on actual weight.
† 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

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 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.

Switching from Rivaroxaban Tablets to Anticoagulants other than Warfarin – 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.

Switching from Anticoagulants other than Warfarin to Rivaroxaban Tablets – Patients currently receiving an anticoagulant other than warfarin, start Rivaroxaban Tablets 0 hours to 2 hours prior to the next scheduled administration of the drug (e.g., low molecular weight heparin or nonwarfarin oral anticoagulant) and omit administration of the other anticoagulant.

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.

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 (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 ScieGen Pharmaceuticals, Inc. at (1-855-724-3436) 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 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: 4/2026

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

13 NON-CLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
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

16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed.

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.

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.

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.

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: Beige, round, film coated tablets debossed with '513' on one side and plain on the other side.

CONTRAINDICATIONS
Rivaroxaban tablets are contraindicated in patients with:
active pathological bleeding
severe hypersensitivity reaction to Rivaroxaban Tablets (e.g., anaphylactic reactions)

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.

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 years 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), 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.

Reversal of Anticoagulant Effect
A specific agent to reverse the anti-factor Xa activity of rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not dialyzable.

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 longterm or permanent paralysis.

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.

5.4 Use in Patients with Renal Impairment
Discontinue Rivaroxaban Tablets in patients who develop acute renal failure while on treatment.

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.

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.

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.

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.

5.9 Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolotomy
Initiation of Rivaroxaban Tablets is 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 embolotomy.

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).

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
Bleeding Risk
Spinal/Epidural Hematoma

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.

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

7.1 General Inhibition and Induction Properties
Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters, the latter also known as breast cancer resistance protein (BCRP).

7.2 Drugs that Induce Cytochrome P450 3A Enzymes and Drug Transport Systems
Avoid concomitant administration of Rivaroxaban Tablets with known combined P-gp and strong CYP3A inhibitors (e.g., ketoconazole and ritonavir).

7.3 Drugs that Inhibit 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).

7.4 Anticoagulants and NSAIDs/Aspirin
Concomitant administration of enoxaparin, warfarin, aspirin, clopidogrel and chronic NSAID use may increase the risk of bleeding.

7.5 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.

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.

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 2.5 mg tablets, there are no safety, efficacy, pharmacokinetic and pharmacodynamic data to support the use in pediatric patients.

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.

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

8.7 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.

8.8 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.9 Use in Patients with 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.

8.10 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.11 Use in Patients with 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.

8.12 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.13 Use in Patients with 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.

8.14 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.15 Use in Patients with 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.

8.16 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.17 Use in Patients with 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.

8.18 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.19 Use in Patients with 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.

8.20 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.21 Use in Patients with 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.

8.22 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.23 Use in Patients with 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.

8.24 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.25 Use in Patients with 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.

8.26 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.27 Use in Patients with 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.

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

Table with 3 columns: Body System Adverse Reaction, Rivaroxaban Tablets 10 mg N=4487 n (%), Enoxaparin N=4524 n (%). Rows include Injury, poisoning and procedural complications, Musculoskeletal and connective tissue disorders, Nervous system disorders, Skin and subcutaneous tissue disorders.

* 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)

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

Table with 3 columns: Adverse Reaction, Rivaroxaban N=64 n (%), Aspirin N=34 n (%). Rows include Cough, Vomiting, Gastroenteritis, Rash.

* Adverse reaction with Relative Risk >1.5 for Rivaroxaban 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)
Injury, poisoning and procedural complications: Atraumatic splenic rupture

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, the latter also known as breast cancer resistance protein (BCRP).

7.2 Drugs that Induce Cytochrome P450 3A Enzymes and Drug Transport Systems
Avoid concomitant administration of Rivaroxaban Tablets with known combined P-gp and strong CYP3A inhibitors (e.g., ketoconazole and ritonavir).

7.3 Drugs that Inhibit 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).

7.4 Anticoagulants and NSAIDs/Aspirin
Concomitant administration of enoxaparin, warfarin, aspirin, clopidogrel and chronic NSAID use may increase the risk of bleeding.

7.5 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.

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.

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 2.5 mg tablets, there are no safety, efficacy, pharmacokinetic and pharmacodynamic data to support the use in pediatric patients.

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.

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

8.7 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.

8.8 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.9 Use in Patients with 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.

8.10 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.11 Use in Patients with 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.

8.12 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.13 Use in Patients with 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.

8.14 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.15 Use in Patients with 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.

8.16 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.17 Use in Patients with 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.

8.18 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.19 Use in Patients with 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.

8.20 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.21 Use in Patients with 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.

8.22 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.23 Use in Patients with 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.

8.24 Use in Patients with Renal Impairment
No clinical data are available for adult patients with severe hepatic impairment.

8.25 Use in Patients with 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.

16.5" (L)

Width: 15.5" W
Length: 16.5 in" L
Fold: 1.25" x 1.25"

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 mL/min 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.

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.

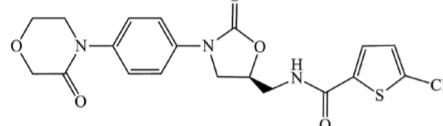
No clinical data are available in pediatric patients with hepatic impairment.

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. A specific agent to reverse the anti-factor Xa activity of rivaroxaban is not 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-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl] thiophene-2-carboxamide. The molecular formula of rivaroxaban is C₂₁H₁₈C₂N₄O₅S and the molecular weight is 435.88. The structural formula is:



Rivaroxaban is a pure (S)-enantiomer. It is an odorless, non-hygroscopic, white to off-white powder. Freely soluble in dimethyl sulfoxide, dimethyl formamide, Slightly soluble in Dichloromethane, Very slightly soluble in acetone, and methanol and practically insoluble in water, anhydrous ethanol and heptane.

Each Rivaroxaban Tablets, USP contains 2.5 mg of rivaroxaban. The inactive ingredients of Rivaroxaban Tablets, USP are: Anhydrous Lactose NF, Croscarmellose Sodium NF, Hypromellose USP, Magnesium Stearate NF, and Sodium Lauryl Sulfate NF. Additionally, the film coating mixture for Rivaroxaban 2.5 mg tablets is Opadry II, Beige, and contains: Polyethylene Glycol, Polyvinyl Alcohol, Red Iron Oxide, Talc, Titanium Dioxide, and Yellow Iron Oxide.

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 concentration 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)*
Exposure	AUC	44	52	64	47
FXa inhibition	AUEC	50	86	100	49
PT	AUEC	33	116	144	112
Prolongation					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.

Cardiac Electrophysiology

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).

12.3 Pharmacokinetics

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 2.5 mg tablets 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 15 mg tablets and 20 mg tablets should be taken with food [see *Dosage and Administration* (2.1)].

The maximum concentrations (C_{max}) of rivaroxaban appear 2 hours 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 H₂-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 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.

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 those after the whole tablet. However, for the crushed tablet suspended in water and administered with 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 [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.

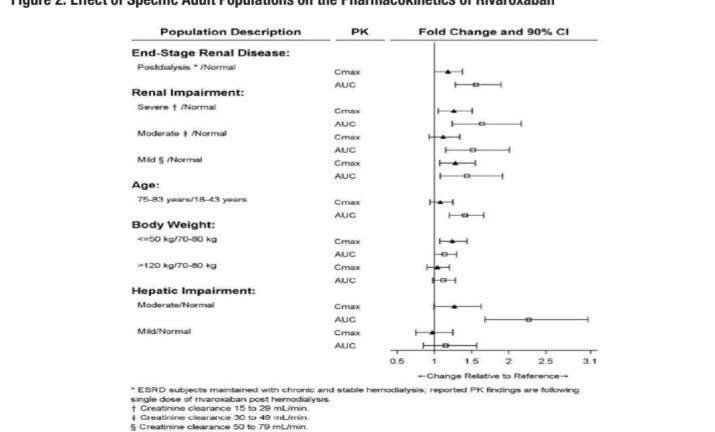
Excretion

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 known as 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 hours to 9 hours in healthy subjects aged 20 years 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



[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 hours to 13 hours in the elderly subjects aged 60 years to 76 years [see *Use in Specific Populations* (8.6)].

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 mL/min 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 mL/min 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.

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)].

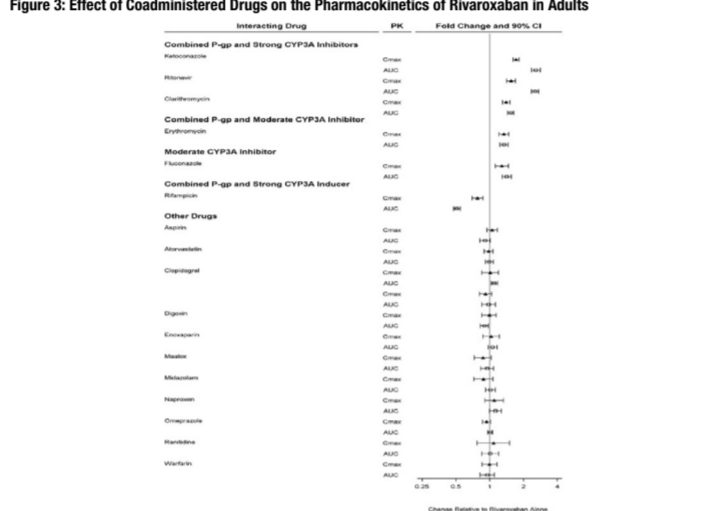
No clinical data are available in pediatric patients with hepatic impairment.

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 latter also known as BCRP.

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 mL/min to 79 mL/min) or moderate renal impairment (CrCl = 30 mL/min to 49 mL/min) receiving multiple doses of erythromycin (a combined P-gp and moderate CYP3A4 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 AUC₀₋₂₄ 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 (AUC) 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

14.8 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) [NCT0176424]. 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 ≥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.

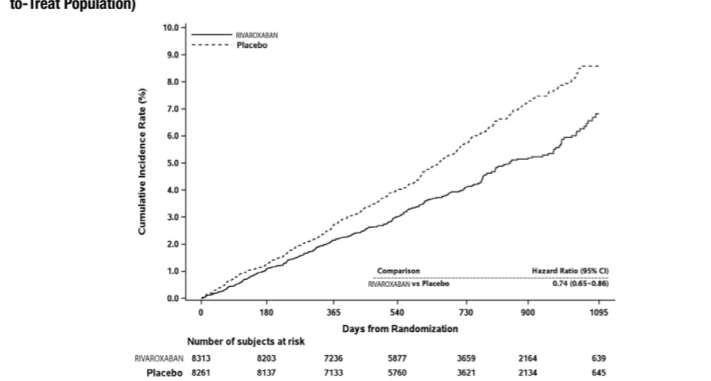
The mean age was 68 years and 21% of the subject population were >75 years. Of the included patients, 91% had CAD (and will be referred to as the COMPASS CAD population), 27% had PAD (and will be referred to as the COMPASS PAD population), and 18% had both CAD and PAD. Of the patients with CAD, 69% had 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 > 30%, 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=0.0004). 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 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 † 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 Tablets 2.5 mg twice daily vs placebo. All patients received aspirin 100 mg once daily as background therapy.

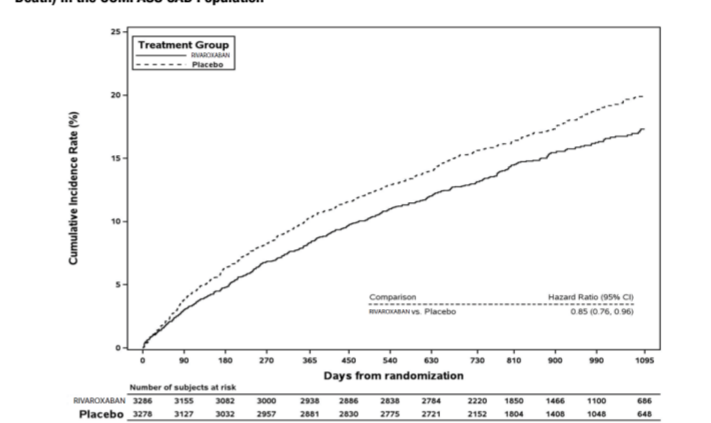
‡ Rivaroxaban vs. placebo.

§ 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 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 infringuinal 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 <0.80. 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 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,

JOB SPECIFICATION FORM

Customer Name:

Artwork #:

Customer Rep:

Job #:

Date Submitted:

JOB INFO

Job Name:

Type: New Design ()

Reprint ()

File Name:

JOB TYPE: () Insert

() Med Guide

() Patient Guide

Rev:

Proof #:

Grain direction:

Manufacture by:

Manufacture for:

Fold Type:

Flat Size:

Final Folded size:

Font Size:

Finishing For Padding:

Customer Item #:

Barcode Reader:

Barcode Type:



Paper Stock:

Ink:

Notes

APPROVED: OK to Print () Approved By:

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