RIVAROXABAN - rivaroxaban granule, for suspension
Ascend Laboratories, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RIVAROXABAN FOR ORAL SUSPENSION safely and effectively. See full prescribing information for RIVAROXABAN FOR ORAL SUSPENSION.
RIVAROXABAN for oral suspension
Initial U.S. Approval: 2011

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

See full prescribing information for complete boxed warning.

(A) Premature discontinuation of rivaroxaban for oral suspension increases the risk of thrombotic events
Premature discontinuation of any oral anticoagulant, including rivaroxaban for oral suspension, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if rivaroxaban for oral suspension is discontinued for a reason other than pathological bleeding or completion of a course of therapy. (2.2, 2.3, 5.1)

(B) Spinal/epidural hematoma
Epidural or spinal hematomas have occurred in patients treated with rivaroxaban for oral suspension 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 for oral suspension is a factor Xa inhibitor indicated:
- for treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years (1.9)
- for thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure (1.10)

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

- For oral suspension: 1 mg/mL once reconstituted (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)
- Severe hypersensitivity reaction to rivaroxaban for oral suspension (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

- The most common adverse reactions (greater than 10%) in pediatric patients were bleeding, cough, vomiting, and gastroenteritis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ascend Laboratories, LLC at 1-877-272-7901 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.

Revised: 6/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

A. Premature discontinuation of rivaroxaban for oral suspension increases the risk of thrombotic events
Premature discontinuation of any oral anticoagulant, including rivaroxaban for oral suspension, increases the risk of thrombotic events. If anticoagulation with rivaroxaban for oral suspension 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)].

B. Spinal/epidural hematoma
Epidural or spinal hematomas have occurred in patients treated with rivaroxaban for oral suspension 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 for oral suspension 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

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

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

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

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

2 DOSAGE & ADMINISTRATION

2.2 Recommended Dosage in Pediatric Patients

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

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

Dosage Form	Body Weight	1 mg Rivaroxaban for oral suspension = 1 mL Suspension			
		Dosage			Total Daily Dose[‡]
		Once a Day[§]	2 Times a Day[§]	3 Times a Day[§]	
Oral Suspension Only	2.6 kg to 2.9 kg			0.8 mg	2.4 mg
	3 kg to 3.9 kg			0.9 mg	2.7 mg
	4 kg to 4.9 kg			1.4 mg	4.2 mg
	5 kg to 6.9 kg			1.6 mg	4.8 mg
	7 kg to 7.9 kg			1.8 mg	5.4 mg
	8 kg to 8.9 kg			2.4 mg	7.2 mg
	9 kg to 9.9 kg			2.8 mg	8.4 mg
	10 kg to 11.9 kg			3 mg	9 mg

	12 kg to 29.9 kg		5 mg		10 mg
Oral Suspension	30 kg to 49.9 kg	15 mg			15 mg
	≥50 kg	20 mg			20 mg

* Initiate rivaroxaban for oral suspension treatment following at least 5 days of initial parenteral anticoagulation therapy.

† Patients less than 6 months of age should meet the following criteria: at birth were at least 37 weeks of gestation, have had at least 10 days of oral feeding, and weigh ≥2.6 kg at the time of dosing.

‡ All doses should be taken with feeding or with food since exposures match that of 20 mg daily dose in adults.

§ Once a day: approximately 24 hours apart; 2 times a day: approximately 12 hours apart; 3 times a day: approximately 8 hours apart

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

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

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

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

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

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

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

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

Dosage Form	**Body Weight**	**1 mg Rivaroxaban for oral suspension = 1 mL Suspension**		
		Dosage		**Total Daily Dose***
		Once a Day†	**2 Times a Day†**	
Oral Suspension Only	7 kg to 7.9 kg		1.1 mg	2.2 mg
	8 kg to 9.9 kg		1.6 mg	3.2 mg
	10 kg to 11.9 kg		1.7 mg	3.4 mg
	12 kg to 19.9 kg		2 mg	4 mg
	20 kg to 29.9 kg		2.5 mg	5 mg
	30 kg to 49.9 kg	7.5 mg		7.5 mg
Oral Suspension	≥50 kg	10 mg		10 mg

* All doses can be taken with or without food since exposures match that of 10 mg daily dose in adults.

† Once a day: approximately 24 hours apart; 2 times a day: approximately 12 hours apart.

Administration in Pediatric Patients

Food Effect:

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

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

For children unable to swallow 10, 15, or 20 mg whole tablets, rivaroxaban for oral suspension should be used.

Use in Renal Impairment in Pediatric Patients

Patients 1 Year of Age or Older

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

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

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

k = 0.55 in children 1 year to 13 years

k = 0.55 in girls greater than 13 and less than 18 years

k = 0.70 in boys greater than 13 and less than 18 years

Patients Less than 1 Year of Age

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

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

	Age	97.5th Percentile of Creatinine (mg/dL)	97.5th Percentile of Creatinine (µmol/L)
Week 2		0.52	46
Week 3		0.46	41
Week 4		0.42	37
Month 2		0.37	33
Month 3		0.34	30
Month 4 to 6		0.34	30
Month 7 to 9		0.34	30
Month 10 to 12		0.36	32

2.3 Switching to and from Rivaroxaban for oral suspension

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

Switching from Rivaroxaban for oral suspension to Warfarin –

- Pediatric Patients:

To ensure adequate anticoagulation during the transition from rivaroxaban for oral suspension to warfarin, continue rivaroxaban for oral suspension for at least 2 days after the first dose of warfarin. After 2 days of co-administration, an INR should be obtained prior to the next scheduled dose of rivaroxaban for oral suspension. Co-administration of rivaroxaban for oral suspension and warfarin is advised to continue until the INR is ≥ 2.0.

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

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

Switching from Anticoagulants other than Warfarin to Rivaroxaban for oral suspension - For pediatric patients currently receiving an anticoagulant other than warfarin, start rivaroxaban for oral suspension 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 for oral suspension 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 for oral suspension 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 for oral suspension, the increased risk of bleeding should be weighed against the urgency of intervention.

Rivaroxaban for oral suspension 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

Pediatric Patients

- If rivaroxaban for oral suspension is taken once a day, the patient should take the missed dose as soon as possible once it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.
- If rivaroxaban for oral suspension is taken two times a day, the patient should take the missed morning dose as soon as possible once it is noticed. A missed morning dose may be taken together with the evening dose. A missed evening dose can only be taken in the same evening.
- If rivaroxaban for oral suspension is taken three times a day, if a dose is missed, the patient should skip the missed dose and go back to the regular dosing schedule at the usual time without compensating for the missed dose.

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

2.6 Administration Options

Administration of Rivaroxaban suspension via NG tube or gastric feeding tube: Rivaroxaban oral suspension may be given through NG or gastric feeding tube. After the administration, flush the feeding tube with water.

For the treatment or reduction in risk of recurrent VTE in pediatric patients, the dose should then be immediately followed by enteral feeding to increase absorption. For the thromboprophylaxis in pediatric patients with congenital heart disease who have undergone the Fontan

procedure, the dose does not require to be followed by enteral feeding.

An *in vitro* compatibility study indicated that Rivaroxaban suspension can be used with PVC, polyurethane or silicone NG tubing.

2.7 Preparation Instructions for Pharmacy of Rivaroxaban for Oral Suspension

Do not add flavor as product is already flavored (sweet and creamy).

Reconstitute before dispensing:
- Tap the bottle until all granules flow freely.
- Add 150 mL of purified water for reconstitution.
- Shake for 60 seconds. Check that all granules are wetted and the suspension is uniform.
- Push the adaptor into bottleneck and recap bottle.
- The suspension must be used within 60 days.
- Write the "Discard after" date on the bottle and carton. Dispensing Instructions:
- Dispense in the original bottle.
- Dispense the bottle upright with the syringes provided in the original carton.

Store reconstituted suspension at room temperature between 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15ºC to 30ºC (59ºF to 86ºF). Do not freeze.

It is recommended the pharmacist counsel the caregiver on proper use. Alert the patient or caregiver to read the Medication Guide and Instructions for Use.

3 DOSAGE FORMS & STRENGTHS
- For oral suspension: White/off white to yellowish granular powder; once reconstituted, provide flavored white to off-white opaque liquid with a concentration of 1 mg/mL.

4 CONTRAINDICATIONS

Rivaroxaban is contraindicated in patients with:
- active pathological bleeding *[see Warnings and Precautions (5.2)]*
- severe hypersensitivity reaction to rivaroxaban for oral suspension (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, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO tablets to warfarin in clinical trials in another indication in patients. If rivaroxaban 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)]*.

5.2 Risk of Bleeding

Rivaroxaban increases the risk of bleeding, including in any organ, and can cause serious or fatal bleeding. In deciding whether to prescribe rivaroxaban 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 in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

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

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

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 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 is 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 and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban *[see Clinical Pharmacology (12.3)]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban 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 *[see Clinical Pharmacology (12.3)]*. The next rivaroxaban dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of rivaroxaban for 24 hours.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder

dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

5.4 Use in Patients with Renal Impairment

Pediatric Patients

There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR less than 50 mL/min/1.73 m^2); therefore, avoid the use of rivaroxaban 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 in these patients *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

5.5 Use in Patients with Hepatic Impairment

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

Avoid use of rivaroxaban 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 with known combined P-gp and strong CYP3A inhibitors

[see Drug Interactions (7.2)].

Avoid concomitant use of rivaroxaban 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 should be used only if the potential benefit justifies the potential risk to the mother and fetus. Rivaroxaban dosing in pregnancy has not been studied. The anticoagulant effect of rivaroxaban 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 Xarelto tablets is not recommended in patients who have had transcatheter aortic valve replacement (TAVR) because patients randomized to Xarelto tablets experienced higher rates of death and bleeding compared to those randomized to an anti-platelet regimen. The safety and efficacy of rivaroxaban have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of rivaroxaban is not recommended in patients with prosthetic heart valves.

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

Initiation of rivaroxaban 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 embolectomy.

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

Direct-acting oral anticoagulants (DOACs), including rivaroxaban, 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 Another Indication [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.

Pediatric Patients

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

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

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

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

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

Parameter	Rivaroxaban† N=329 n (%)	Comparator Group‡ N=162 n (%)
Major bleeding§	0	2 (1.2)

Clinically relevant non-major bleeding[¶]	10 (3.0)	1 (0.6)
Trivial bleeding	113 (34.3)	44 (27.2)
Any bleeding	119 (36.2)	45 (27.8)

[*] These events occurred after randomization until 3 months of treatment (1 month for patients less than 2 years with central venous catheter-related VTE (CVC-VTE). Patients may have more than one event.

[†] Treatment schedule: body weight-adjusted doses of rivaroxaban; randomized 2:1 (Rivaroxaban: Comparator).

[‡] Unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux or VKA.

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

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

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

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

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

[*] Adverse reaction with Relative Risk greater than 1.5 for rivaroxaban versus comparator.

[†] The following terms were combined: fatigue, asthenia.

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

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

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

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

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

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

Parameter	Rivaroxaban* N=64 n (%)	Aspirin* N=34 n (%)
Major Bleeding[†]	1 (1.6)	0
Epistaxis leading to transfusion	1 (1.6)	0
Clinically relevant non-major (CRNM) bleeding[§]	4 (6.3)	3 (8.8)
Trivial bleeding	21 (32.8)	12 (35.3)
Any bleeding	23 (35.9)	14 (41.2)

[*] Treatment schedule: body weight-adjusted doses of rivaroxaban or aspirin (approximately 5 mg/kg); randomized 2:1 (Rivaroxaban: Aspirin).

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

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

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

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

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

[*] Adverse reaction with Relative Risk greater than 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. 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 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 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 should not be used in patients with CrCl 15 to less than 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 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 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 in pregnant women are insufficient to inform a drug- associated risk of adverse developmental outcomes. Use rivaroxaban with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery. The anticoagulant effect of rivaroxaban cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of rivaroxaban for the mother and possible risks to the fetus when prescribing rivaroxaban to a pregnant woman *[see Warnings and Precautions (5.2,5.7)]*.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Fetal/Neonatal Adverse Reactions

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

Labor or Delivery

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

Data

Human Data

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

Animal Data

Rivaroxaban crosses the placenta in animals. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis.
This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20

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

8.2 Lactation

Risk Summary

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

Data

Animal Data

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

8.3 Females and Males of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including rivaroxaban should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

8.4 Pediatric Use

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

The safety and effectiveness of rivaroxaban have been established for use in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure. Use of rivaroxaban is supported in these age groups by evidence from adequate and well- controlled studies of rivaroxaban in adults with additional data from a multicenter, prospective, open-label, active controlled study in 112 pediatric patients to evaluate the single- and multiple- dose pharmacokinetic properties of rivaroxaban and the safety and efficacy of rivaroxaban when used for thromboprophylaxis for 12 months in children with single ventricle physiology who had the Fontan procedure *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.9)]*.

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 (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 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)]*.

Pediatric Use

No dosage adjustment is required in patients 1 year of age or older with mild renal impairment (eGFR 50 to ≤ 80 mL/min/1.73 m^2). There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR less than 50 mL/min/1.73 m^2); therefore, avoid the use of rivaroxaban 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 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 in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology (12.3)]*.

Avoid the use of rivaroxaban 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.

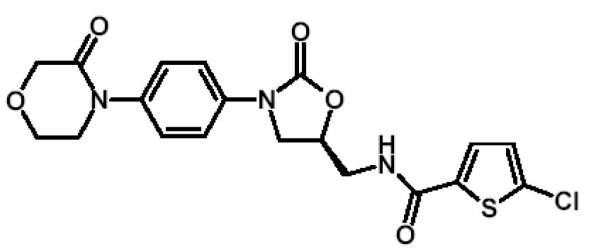
10 OVERDOSAGE

Overdose of rivaroxaban may lead to hemorrhage. Discontinue rivaroxaban and initiate appropriate therapy if bleeding complications associated with overdosage occur. Rivaroxaban systemic exposure is not further increased at single doses less than 50 mg due to limited absorption.
The use of activated charcoal to reduce absorption in case of rivaroxaban 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 for oral suspension 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 $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89. The structural formula is:



Rivaroxaban USP is a pure (*S*)-enantiomer. It is a non-hygroscopic, white to yellowish powder. Rivaroxaban is sparingly soluble in dimethyl formamide and is practically insoluble in water.

Rivaroxaban for oral suspension is supplied as granules in bottles containing 155 mg of rivaroxaban (1 mg of rivaroxaban per mL after reconstitution). The inactive ingredients are: anhydrous citric acid, hypromellose, mannitol, microcrystalline cellulose and carboxymethylcellulose sodium, sodium benzoate, sucralose, cream/vanilla flavor and xanthan gum.

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

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

**Separate stand-alone study.*

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

Hepatic Impairment

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

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of rivaroxaban is dose-dependent. For the 2.5 mg and 10 mg dose, it is estimated to be 80% to 100% and is not affected by food. XARELTO 2.5 mg and 10 mg tablets can be taken with or without food.

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 H_2-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.

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

comparable to that after the whole tablet, and C_{max} was 18% lower.

Distribution

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

Metabolism

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

Excretion

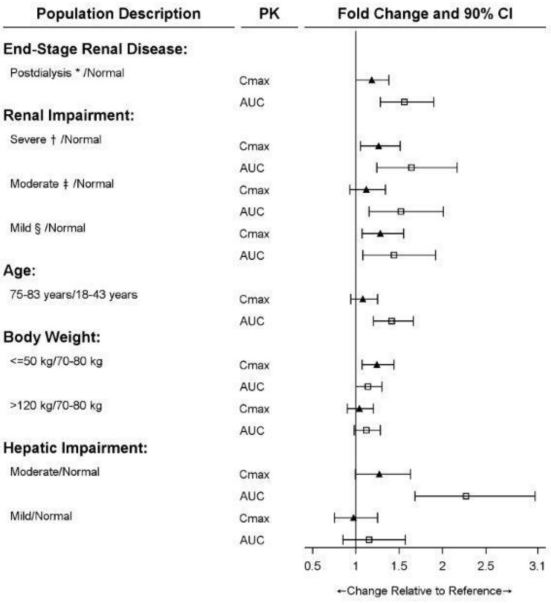
In a Phase 1 study, following the administration of [^{14}C]-rivaroxaban, approximately one-
third (36%) was recovered as unchanged drug in the urine and 7% was recovered as unchanged drug in feces. Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via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

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

Specific Populations

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

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



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

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 less than 2 years of age, and 1.6 hours in children less than 0.5 years of age.

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

Renal Impairment

The safety and pharmacokinetics of single-dose rivaroxaban (10 mg) were evaluated in a study in healthy subjects [CrCl ≥80 mL/min (n=8)] and in subjects with varying degrees of renal impairment (see Figure 2). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Use in Specific Populations (8.6)]*.

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

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

Hepatic Impairment

The safety and pharmacokinetics of single-dose rivaroxaban (10 mg) were evaluated in a study in healthy adult subjects (n=16) and adult subjects with varying degrees of hepatic impairment (see Figure 2). No patients with severe hepatic impairment (Child-Pugh C) were studied. Compared to healthy subjects with normal liver function, significant increases in rivaroxaban exposure were observed in subjects with moderate hepatic impairment (Child-Pugh B) (see Figure 2). Increases in pharmacodynamic effects were also observed *[see Use in Specific Populations (8.7)]*.

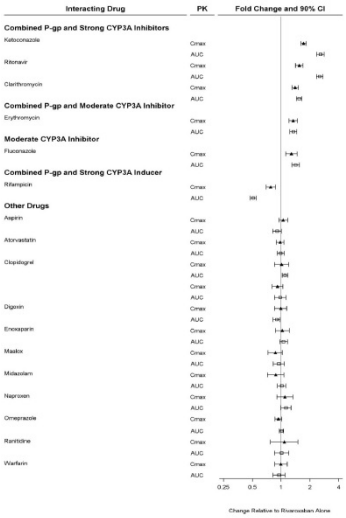
No clinical data are available in pediatric patients with hepatic impairment.

Drug Interactions

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

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

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



Anticoagulants

In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and rivaroxaban (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 (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 a study for another indication, 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).

Clopidogrel

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

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

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

12.6 QT/QTc Prolongation

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

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis & Mutagenesis & Impairment of Fertility

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

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

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

14 CLINICAL STUDIES

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

Rivaroxaban for the treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE was evaluated in the EINSTEIN Junior Phase 3 study [NCT02234843], a multicenter, open-label, active-controlled, randomized study in 500 pediatric patients from birth to less than 18 years with confirmed VTE. There were 276 children aged 12 to less than 18 years, 101 children aged 6 to less than 12 years, 69 children aged 2 to less than 6 years, and 54 children aged less than 2 years. Patients less than 6 months of age were excluded from enrollment if they were less than 37 weeks of gestation at birth, or had less than 10 days of oral feeding, or had a body weight of less than 2.6 kg.

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

Patients received initial treatment with therapeutic dosages of unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux for at least 5 days, and were randomized 2:1 to receive either body weight-adjusted doses of rivaroxaban (exposures to match that of 20 mg daily dose in adults) or comparator group (UFH, LMWH, fondaparinux or VKA) for a main study treatment period of 3 months (or 1 month for children less than 2 years with CVC-VTE). A diagnostic imaging test was obtained at baseline and at the end of the main study treatment. When clinically necessary, treatment was extended up to 12 months in total (or up to 3 months in total for children less than 2 years with CVC-VTE).

Table 28 displays the primary and secondary efficacy results.

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

	Rivaroxaban* N=335	**Comparator Group‡ N=165**	**Rivaroxaban vs. Comparator Group**	**Rivaroxaban vs. Comparator Group**
	n (%)	**n (%)**	**Risk Difference**	**Hazard Ratio**
Event	**(95% CI)†**	**(95% CI)†**	**(95% CI)§**	**(95% CI)**
Primary efficacy outcome: Symptomatic recurrent VTE	4 (1.2) (0.4%, 3.0%)	5 (3.0) (1.2%, 6.6%)	-1.8% (-6.0%, 0.6%)	0.40 (0.11, 1.41)
Secondary efficacy outcome: Symptomatic recurrent VTE or asymptomatic deterioration on repeat imaging	5 (1.5) (0.6%, 3.4%)	6 (3.6) (1.6%, 7.6%)	-2.1% (-6.5%, 0.6%)	

* Treatment schedule: body weight-adjusted doses of Rivaroxaban (exposures to match that of 20 mg daily dose in adults); randomized 2:1 (Rivaroxaban: Comparator).

† Confidence intervals for incidence proportion were calculated by applying the method of Blyth-Still-Casella.

‡ Unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux or VKA.

§ Confidence intervals for difference in incidence proportions were calculated by unstratified exact method according to Agresti-Min using the standardized test statistic and inverting a two-sided test.

Complete resolution of thrombus on repeat imaging without recurrent VTE occurred in 128 of 335 children (38.2%, 95% CI 33.0%, 43.5%) in the rivaroxaban group and 43 of 165 children (26.1%, 95% CI 19.8%, 33.0%) in the comparator group. Symptomatic recurrent VTE or major bleeding events occurred in 4 of 335 children (1.2%, 95% CI 0.4%, 3.0%) in the rivaroxaban group and 7 of 165 children (4.2%, 95% CI 2.0%, 8.4%) in the comparator group.

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

The efficacy and safety of rivaroxaban for thromboprophylaxis in pediatric patients with congenital heart disease who have undergone the Fontan procedure was evaluated in the UNIVERSE Phase 3 study [NCT02846532]. UNIVERSE was a prospective, open-label, active controlled, multicenter, 2-part study, designed to evaluate the single- and multiple-dose pharmacokinetic properties of rivaroxaban (Part A), and to evaluate the safety and efficacy of rivaroxaban when used for thromboprophylaxis for 12 months compared with aspirin (Part B) in children 2 to 8 years of age with single ventricle physiology who had the Fontan procedure. Patients in Part B were randomized 2:1 to receive either body weight-

adjusted doses of rivaroxaban
(exposures to match that of 10 mg daily dose in adults) or aspirin (approximately 5 mg/kg). Patients with eGFR less than 30 ml/min/1.73 m^2 were excluded.

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

Table 29 displays the primary efficacy results.

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

	Part A*	**Part B†**		
	Rivaroxaban	**Rivaroxaban §**	**Aspirin§**	**Rivaroxaban**
	N=12	**N=64**	**N=34**	**vs. Aspirin**
	n (%)	**n (%)**	**n (%)**	**Risk Difference**
Event	**(95% CI)‡**	**(95% CI)‡**	**(95% CI) ‡**	**(95% CI)¶**
Primary efficacy outcome: any thrombotic event	1 (8.3) (0.4%, 34.9%)	1 (1.6) (0.1%, 7.8%)	3 (8.8) (2.4%, 22.2%)	-7.3% (-21.7%, 1.1%)
Ischemic stroke	0 (0.0%, 23.6%)	0 (0.0%, 5.6%)	1 (2.9) 0.2%, 15.1%)	-2.9% (-16.2%, 2.9%)
Pulmonary embolism	0 (0.0%, 23.6%)	1 (1.6) (0.1%, 7.8%)	0 (0.0%, 9.0%)	1.6% (-9.9%, 8.4%)
Venous thrombosis	1 (8.3) (0.4%, 34.9%)	0 (0.0%, 5.6%)	2 (5.9) (1.1%, 18.8%)	-5.9% (-20.6%, -0.1%)

* Part A: single arm; not randomized

† Part B: randomized 2:1 (Rivaroxaban: Aspirin)

‡ Confidence intervals for incidence proportion were calculated by applying the method of Blyth-Still-Casella.

§ Treatment schedule: body weight-adjusted doses of rivaroxaban (exposures to match that of 10 mg daily dose in adults) or aspirin (approximately 5 mg/kg)

¶ Confidence intervals for difference in incidence proportions were calculated by unstratified exact method according to Agresti-Min using the standardized test statistic and inverting a two-sided test.

16 HOW SUPPLIED/STORAGE AND HANDLING

Rivaroxaban for oral suspension is available in the strength and package listed below:

NDC 67877-882-71 Supplied as white to off-white to yellowish granular powder in amber colored glass bottle or amber PET bottle containing 155 mg rivaroxaban packaged with two oral dosing syringes. After reconstitution with 150 mL of purified water, 1 mL of the suspension contains 1 mg rivaroxaban.

Discard reconstituted suspension after "Discard after" date written on the bottle. Storage of granules and reconstituted suspension:

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

Do not freeze the granules or reconstituted suspension. Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

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

Instructions for Patient Use
- Advise patients to take rivaroxaban for oral suspension only as directed.
- Remind patients to not discontinue rivaroxaban for oral suspension without first talking to their healthcare professional.

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

Bleeding Risks
- Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it might take them longer than usual to stop bleeding, and that they may bruise and/or bleed more easily when they are treated with rivaroxaban for oral suspension *[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 for oral suspension before any invasive procedure (including dental procedures) is scheduled. Concomitant Medication and Herbals Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions *[see Drug Interactions (7)]*. Pregnancy and Pregnancy-Related Hemorrhage
- Advise patients to inform their physician immediately if they become pregnant or intend to become pregnant during treatment with rivaroxaban for oral suspension *[see Use in Specific Populations (8.1)]*.
- Advise pregnant women receiving rivaroxaban for oral suspension 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 oral suspension for the mother and for the child if they are nursing or intend to nurse during anticoagulant treatment *[see Use in Specific Populations (8.2)]*.

Females and Males of Reproductive Potential

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

Manufactured by:
Alkem Laboratories Ltd.,
Mumbai - 400 013, INDIA.

Distributed by:
Ascend Laboratories, LLC
Bedminster, NJ 07921

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MEDICATION GUIDE

Rivaroxaban (riv-a-rox-a-ban)
for Oral Suspension

What is the most important information I should know about Rivaroxaban for Oral Suspension?
Rivaroxaban for oral suspension may cause serious side effects, including:

- **Increased risk of blood clots if you stop taking rivaroxaban for oral suspension.** 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 for oral suspension lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking rivaroxaban for oral suspension, you may have increased risk of forming a clot in your blood. **Do not stop taking rivaroxaban for oral suspension without talking to the doctor who prescribes it for you. Stopping rivaroxaban for oral suspension increases your risk of having a stroke.** If you have to stop taking rivaroxaban for oral suspension, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.
- **Increased risk of bleeding.** Rivaroxaban for oral suspension can cause bleeding which can be serious and may lead to death. This is because rivaroxaban for oral suspension is a blood thinner medicine (anticoagulant) that lowers blood clotting. During treatment with rivaroxaban for oral suspension 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 for oral suspension and have certain other medical problems. **You may have a higher risk of bleeding if you take rivaroxaban for oral suspension and take other medicines that increase your risk of bleeding, including:**
  - aspirin or aspirin containing products
  - long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (Coumadin®, Jantoven®)
  - any medicine that contains heparin
  - clopidogrel (Plavix®)
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - 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:
  - 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
  - bleeding that is severe or you cannot control
  - red, pink or brown urine
  - bright red or black stools (looks like tar)
  - cough up blood or blood clots
  - vomit blood or your vomit looks like “coffee grounds”
  - headaches, feeling dizzy or weak
  - pain, swelling, or new drainage at wound sites
  - 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 for oral suspension, 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:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine

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

Tell your doctor right away if you have:
• back pain • muscle weakness (especially in your legs and feet)
• tingling • loss of control of the bowels or bladder (incontinence)
• numbness
Rivaroxaban for oral suspension is not for use in people with artificial heart valves.
Rivaroxaban for oral suspension
is not for use in people with antiphospholipid syndrome (APS), especially with positive triple antibody testing.

What is Rivaroxaban for Oral Suspension?
Rivaroxaban for oral suspension 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 for oral suspension 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 for oral suspension if you or your child:

- currently have certain types of abnormal bleeding. Talk to your doctor before taking rivaroxaban for oral suspension if you currently have unusual bleeding.
- are allergic to rivaroxaban or any of the ingredients in rivaroxaban for oral suspension. See the end of this Medication Guide for a complete list of ingredients in rivaroxaban for oral suspension.

Before taking rivaroxaban for oral suspension, 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 for oral suspension will harm your unborn baby.
  - **Tell your doctor** right away if you become pregnant during treatment with rivaroxaban for oral suspension. Taking rivaroxaban for oral suspension while you are pregnant may increase the risk of bleeding in you or in your unborn baby.
  - Females who are able to become pregnant: Talk with your doctor about pregnancy planning during treatment with rivaroxaban for oral suspension. Talk with your doctor about your risk for severe uterine bleeding if you are treated with blood thinner medicines, including rivaroxaban for oral suspension.
  - If you take rivaroxaban for oral suspension 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 for oral suspension?" for signs and symptoms of bleeding.
- are breastfeeding or plan to breastfeed. Rivaroxaban for oral suspension can pass into your breast milk. Talk to your doctor about the best way to feed your baby during treatment with rivaroxaban for oral suspension.

Tell all of your doctors and dentists that you or your child are taking rivaroxaban for oral suspension. They should talk to the doctor who prescribed rivaroxaban for oral suspension 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 for oral suspension works, causing side effects. Certain medicines may increase your risk of bleeding. See **"What is the most important information I should know about rivaroxaban for oral suspension?"**

Especially tell your doctor if you or your child take:
- ketoconazole
- erythromycin
- phenytoin
- St. John's wort
- ritonavir
- carbamazepine
- rifampin

How should I take rivaroxaban for oral suspension?
- Take rivaroxaban for oral suspension exactly as prescribed by your doctor.
- **Do not change your dose or stop taking rivaroxaban for oral suspension unless your doctor tells you to.** Your doctor may change your dose if needed.
- Your doctor will decide how long you should take rivaroxaban for oral suspension.
- Rivaroxaban for oral suspension 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 for oral suspension and when to start taking rivaroxaban for oral suspension again after your surgery or procedure.
- If you need to stop taking rivaroxaban for oral suspension for any reason, talk to the doctor who prescribed rivaroxaban for oral suspension to you to find out when you should stop taking it. Do not stop taking rivaroxaban for oral suspension without first talking to the doctor who prescribes it to you.
- Do not run out of rivaroxaban for oral suspension. Refill your prescription of rivaroxaban for oral suspension before you run out. When leaving the hospital following a hip or knee replacement, be sure that you will have rivaroxaban for oral suspension available to avoid missing any doses.
- If you take too much rivaroxaban for oral suspension, go to the nearest hospital emergency room or call your doctor right away.

For children who take rivaroxaban for oral suspension:
- The dose of rivaroxaban for oral suspension 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 for oral suspension can be given to your child with or without food.
- The adult caregiver should give the dose.
- If your child is taking the oral suspension, use the syringes provided in the original carton. The suspension will be prepared by the pharmacy. See the **Instructions for Use** included in the carton on how to properly give a dose of rivaroxaban for oral suspension to your child.
- Do not switch between the rivaroxaban for oral suspension or tablet without first talking to your doctor.
- If your child vomits or spits up:
  - right after or within 30 minutes of taking the oral suspension, give a new full dose.
  - more than 30 minutes after taking the oral suspension, do not give the dose again. Give the next dose at the regularly scheduled time.
  - if vomiting or spitting up persists, contact your child's doctor right away.
- If your child misses a dose:
  - If your child is taking rivaroxaban for oral suspension 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 for oral suspension 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 for oral suspension 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 for oral suspension?
Rivaroxaban for oral suspension may cause serious side effects:
- See **"What is the most important information I should know about rivaroxaban for oral suspension?"**

The most common side effects of rivaroxaban for oral suspension in children include:

- bleeding
- cough
- vomiting
- inflamed stomach and gut

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

How should I store rivaroxaban for oral suspension?
- Store rivaroxaban for oral suspension at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Store syringes and bottle upright in the original carton for rivaroxaban for oral suspension.
- **Do not** freeze rivaroxaban for oral suspension.

Keep rivaroxaban for oral suspension and all medicines out of the reach of children.
Discard rivaroxaban for oral suspension after "Discard after" date written on the bottle.

General information about the safe and effective use of rivaroxaban for oral suspension.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use rivaroxaban for oral suspension for a condition for which it was not prescribed. Do not give rivaroxaban for oral suspension 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 for oral suspension that is written for health professionals.

What are the ingredients in rivaroxaban for oral suspension?
Active ingredient: rivaroxaban
Inactive ingredients for oral suspension:
anhydrous citric acid, hypromellose, mannitol, microcrystalline cellulose and carboxymethylcellulose sodium, sodium benzoate, sucralose, cream/vanilla flavor and xanthan gum.

Manufactured by:
Alkem Laboratories Ltd.,
Mumbai - 400 013, INDIA.

Distributed by:
Ascend Laboratories, LLC
Bedminster, NJ 07921

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

Revised: 6/2025

PT 3883-02

INSTRUCTIONS FOR USE

Rivaroxaban

(riv-a-rox-a-ban)

for oral suspension

This Instructions for Use contains information on how to give a dose of rivaroxaban for oral suspension.

Read this Instructions for Use before giving rivaroxaban for oral suspension and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your child's medical condition or treatment.

Important information:

- Rivaroxaban for oral suspension is for oral use only.
- Give rivaroxaban for oral suspension to your child exactly as prescribed by your doctor. The adult caregiver should give the dose. If you have questions, contact your doctor or pharmacist for more information on giving a dose.
- **Only use the oral dosing syringe provided with rivaroxaban for oral suspension.**

Contact your doctor or pharmacist if the oral dosing syringe is missing, lost or damaged.

Storage information

Store rivaroxaban for oral suspension at room temperature between **68°F to 77°F** (20°C to 25°C). **Do not** freeze.

Store the bottle upright with the oral dosing syringes in the original carton.

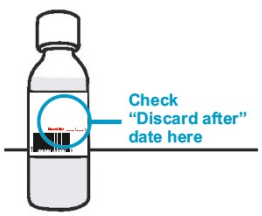
Keep rivaroxaban for oral suspension and all medicines out of reach of children.

Rivaroxaban for oral suspension Oral Dosing Syringe:

Side 1: Dosing in milliliters (mL)	**Side 2: Dosing with color band* (mL)**
	
	*The color band is an aid to withdraw the prescribed dose.

Rivaroxaban for Oral Suspension Bottle

Step 1: Get ready



Check "Discard after" date on the rivaroxaban for oral suspension bottle.

If "Discard after" date has passed, **do not** use and call your doctor or pharmacist.

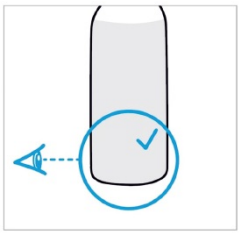
Wash hands.

Wash your hands well with soap and warm water.

Step 2: Prepare rivaroxaban for oral suspension

Shake bottle slowly for 10 seconds before each use.

Do not shake the bottle too fast to avoid foaming. Foaming may lead to giving the wrong dose.



Check rivaroxaban oral suspension.

If there are lumps or granules at the bottom of the bottle, shake the bottle **slowly** again for **10 seconds**.

Step 3: Check the prescribed dose

Find your dose line.

You can use either side of the syringe to set your dose.

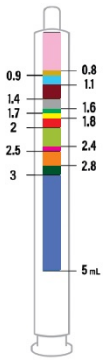
If using mL side of syringe:

Top of the plunger should line up with the prescribed mL.

If using color side of syringe:

Top of the plunger should line up with the prescribed mL dose line at the **bottom of the color band.**

Only use the oral dosing syringe provided with rivaroxaban for oral suspension.

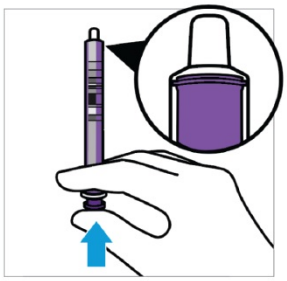


If your dose is more than 5 mL.

You will need to use the same syringe more than one time. Repeat Steps 4 and 5 to complete your dose. Ask your pharmacist if you are not sure.

Dose	Measure
7.5 mL	5 mL + 2.5 mL
10 mL	5 mL + 5 mL
15 mL	5 ml + 5 mL + 5 mL
20 mL	5 mL + 5 mL + 5 mL + 5 mL

Step 4: Set prescribed dose



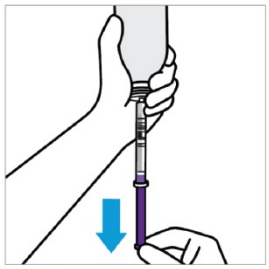
Push plunger all the way in to remove air.

Insert oral dosing syringe into bottle adaptor.

Twist off the cap from the bottle.

Do not remove the bottle adaptor from the bottle.

Insert the syringe tip into the bottle adaptor.



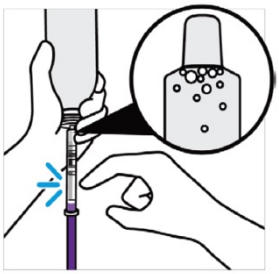
Fill oral dosing syringe.

Turn the bottle upside down, as shown.

Pull the plunger to fill the oral dosing syringe **slightly past your prescribed dose line** to help remove any air bubbles.

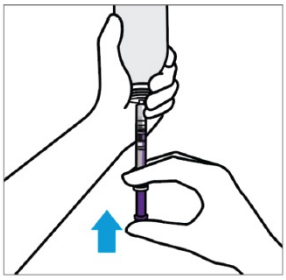
CAUTION:

Make sure you have enough medicine for a full dose. Do not take a partial dose.



Tap syringe to move air bubbles to the top.

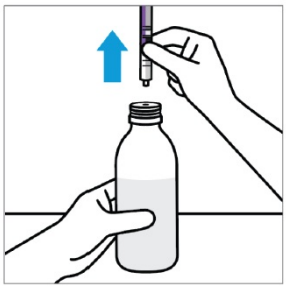
Doing this helps set the correct dose.



Adjust to your prescribed dose.

If using mL side of syringe: Push plunger to align with the prescribed dose line.

If using color side of syringe: Push plunger to align with the prescribed mL dose line at the **bottom of the color band.**



Remove oral dosing syringe.

Place the bottle on a flat surface.

Remove the oral dosing syringe from the bottle.

Step 5: Give the dose

Give the dose.

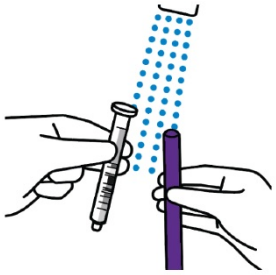
Place the oral dosing syringe gently into the child's mouth with **the tip of the syringe pointing toward the cheek and slowly press the plunger.**

This allows the child to swallow naturally. Make sure the child swallows the full dose.

If your child vomits or spits out the medicine repeatedly, contact your child's doctor right away.

If your dose is **more than 5 mL**, you will need to use the same syringe more than one time. Repeat Steps 4 and 5 to complete your dose.

Step 6: Rinse and store



Close rivaroxaban for oral suspension bottle and rinse oral dosing syringe.

Rinse the oral dosing syringe with tap water and let it air dry.

Do not place the oral dosing syringe in the dishwasher.

Disposing rivaroxaban for oral suspension bottle and syringe

- Throw the rivaroxaban for oral suspension bottle away in your household trash.
- Throw away any used oral dosing syringe with the opening of a new rivaroxaban for oral suspension bottle.
- **Do not pour rivaroxaban for oral suspension down the drain** (for example: sink, toilet, shower or tub).
- **Do not** recycle the bottle.

Dispense with Instructions for Use available at:
www.ascendlaboratories.com/ifu/rivaroxabanfos.pdf

Manufactured by:
Alkem Laboratories Ltd.,
Mumbai - 400 013, INDIA.

Distributed by:
Ascend Laboratories, LLC
Bedminster, NJ 07921

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: June 2025

PT 3884-01

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 67877-882-71

Rivaroxaban for Oral Suspension

1 mg/mL

Carton Pack

Rx Only

RIVAROXABAN
rivaroxaban granule, for suspension

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:67877-882
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RIVAROXABAN (UNII: 9NDF7JZ4M3) (RIVAROXABAN - UNII:9NDF7JZ4M3)	RIVAROXABAN	155 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	
XANTHAN GUM (UNII: TTV12P4NEE)	
VANILLA (UNII: Q74T35078H)	

Product Characteristics

Color	WHITE (Off white to yellowish)	**Score**	
Shape		**Size**	
Flavor	VANILLA (Cream)	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67877-882-71	1 in 1 CARTON	07/07/2025	
1		1 in 1 BOTTLE; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA218502	07/07/2025	

Labeler - Ascend Laboratories, LLC (141250469)

Establishment

Name	Address	ID/FEI	Business Operations
Alkem Laboratories Limited		915628612	ANALYSIS(67877-882) , MANUFACTURE(67877-882) , PACK(67877-882)