

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XARELTO® (rivaroxaban) safely and effectively. See full prescribing information for XARELTO.

XARELTO (rivaroxaban) tablets, for oral use
Initial U.S. Approval: 2011

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning.

(A) Premature discontinuation of XARELTO increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy. (2.2, 2.3, 5.1, 14.1)

(B) Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO 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

Indications and Usage (1.6)	10/2018
Dosage and Administration (2.1, 2.4)	10/2018
Warnings and Precautions (5.2)	07/2018

INDICATIONS AND USAGE

XARELTO is a factor Xa inhibitor indicated:

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (1.1)
- for the treatment of deep vein thrombosis (DVT) (1.2)
- for the treatment of pulmonary embolism (PE) (1.3)
- for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months (1.4)
- for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery (1.5)
- in combination with aspirin, to reduce the risk of major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD) (1.6)

DOSAGE AND ADMINISTRATION

- Nonvalvular Atrial Fibrillation:**
 - For patients with CrCl >50 mL/min: 20 mg orally, once daily with the evening meal (2.1)
 - For patients with CrCl ≤50 mL/min: 15 mg orally, once daily with the evening meal (2.1)
- Treatment of DVT and/or PE:** 15 mg orally twice daily with food for the first 21 days followed by 20 mg orally once daily with food for the remaining treatment (2.1)
- Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE:** 10 mg once daily with or without food, after at least 6 months of standard anticoagulant treatment (2.1)
- Prophylaxis of DVT Following Hip or Knee Replacement Surgery:** 10 mg orally once daily with or without food (2.1)
- Reduction of Risk of Major Cardiovascular Events (CV Death, MI, and Stroke) in chronic CAD or PAD:** 2.5 mg orally twice daily, with or without food, in combination with aspirin (75-100 mg) once daily (2.1).

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Active pathological bleeding (4)
- Severe hypersensitivity reaction to XARELTO (4)

WARNINGS AND PRECAUTIONS

- Risk of bleeding: XARELTO can cause serious and fatal bleeding. Promptly evaluate signs and symptoms of blood loss. An agent to reverse the anti-factor Xa activity of rivaroxaban is available. (5.2)
- Pregnancy-related hemorrhage: Use XARELTO with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery. Promptly evaluate signs and symptoms of blood loss. (5.7)
- Prosthetic heart valves: XARELTO use not recommended (5.8)

ADVERSE REACTIONS

The most common adverse reaction (>5%) was bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- Renal impairment: Avoid or adjust dose based on CrCl and Indication (8.6)
- Hepatic impairment: Avoid use in patients with Child-Pugh B and C hepatic impairment or with any degree of hepatic disease associated with coagulopathy (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2019

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- Treatment of Pulmonary Embolism
- Reduction in the Risk of Recurrence of Deep Vein Thrombosis and/or Pulmonary Embolism
- Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

A. Premature discontinuation of XARELTO increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO 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* (2.2, 2.3), *Warnings and Precautions* (5.1), and *Clinical Studies* (14.1)].

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO 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 XARELTO and neuraxial procedures is not known

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

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

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

1 INDICATIONS AND USAGE

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

XARELTO is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

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

1.2 Treatment of Deep Vein Thrombosis

XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

1.3 Treatment of Pulmonary Embolism

XARELTO is indicated for the treatment of pulmonary embolism (PE).

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

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

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

XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

1.6 Reduction of Risk of Major Cardiovascular Events in Patients with Chronic Coronary Artery Disease (CAD) or Peripheral Artery Disease (PAD)

XARELTO, in combination with aspirin, is indicated to reduce the risk of major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Table 1: Recommended Dosage

Indication	Renal Considerations*	Dosage	Food/Timing†
Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation	CrCl >50 mL/min	20 mg once daily	Take with evening meal
	CrCl ≤50 mL/min	15 mg once daily	Take with evening meal
Treatment of DVT and/or PE	CrCl ≥30 mL/min	15 mg <u>twice daily</u> ▼ after 21 days, transition to ▼ 20 mg <u>once daily</u>	Take with food, at the same time each day
	CrCl <30 mL/min	Avoid Use	
Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE	CrCl ≥30 mL/min	10 mg once daily, after at least 6 months of standard anticoagulant treatment	Take with or without food
	CrCl <30 mL/min	Avoid Use	
Prophylaxis of DVT Following:			
- Hip Replacement Surgery‡	CrCl ≥30 mL/min	10 mg once daily for 35 days, 6-10 hours after surgery once hemostasis has been established	Take with or without food
	CrCl <30 mL/min	Avoid Use	
- Knee Replacement Surgery‡	CrCl ≥30 mL/min	10 mg once daily for 12 days, 6-10 hours after surgery once hemostasis has been established	Take with or without food
	CrCl <30 mL/min	Avoid Use	
Reduction of Risk of Major Cardiovascular Events (CV Death, MI, and Stroke) in Chronic CAD or PAD	No dose adjustment needed based on CrCl	2.5 mg <u>twice daily</u> , plus aspirin (75-100 mg) once daily	Take with or without food

* See Use in Specific Populations (8.6)

† See Clinical Pharmacology (12.3)

‡ See Dosage and Administration (2.3)

2.2 Switching to and from XARELTO

Switching from Warfarin to XARELTO - When switching patients from warfarin to XARELTO, discontinue warfarin and start XARELTO as soon as the International Normalized Ratio (INR) is below 3.0 to avoid periods of inadequate anticoagulation.

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