

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215859Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XARELTO (rivaroxaban) tablets, for oral use
XARELTO (rivaroxaban) for oral suspension
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 (1.7, 1.8)	08/2021
Indications and Usage (1.9, 1.10)	12/2021
Dosage and Administration (2.1)	08/2021
Dosage and Administration (2.2, 2.3, 2.5, 2.6, 2.7)	12/2021
Warnings and Precautions (5.4, 5.5)	12/2021

INDICATIONS AND USAGE

XARELTO is a factor Xa inhibitor indicated:

- to reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation (1.1)
- for treatment of deep vein thrombosis (DVT) (1.2)
- for treatment of pulmonary embolism (PE) (1.3)
- for reduction in the risk of recurrence of DVT or PE (1.4)
- for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery (1.5)
- for prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients (1.6)
- to reduce the risk of major cardiovascular events in patients with coronary artery disease (CAD) (1.7)
- to reduce the risk of major thrombotic vascular events in patients with peripheral artery disease (PAD), including patients after recent lower extremity revascularization due to symptomatic PAD (1.8)
- for treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years (1.9)
- 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 (2.1)
- Treatment of DVT and/or PE:** 15 mg orally twice daily with food for the first 21 days followed by 20 mg orally once daily with food for the remaining treatment (2.1)
- Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE:** 10 mg once daily with or without food, after at least 6 months of standard anticoagulant treatment (2.1)
- Prophylaxis of DVT Following Hip or Knee Replacement Surgery:** 10 mg orally once daily with or without food (2.1)
- Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding:** 10 mg once daily, with or without food, in hospital and after hospital discharge for a total recommended duration of 31 to 39 days (2.1)
- CAD or PAD:** 2.5 mg orally twice daily with or without food, in combination with aspirin (75-100 mg) once daily (2.1)
- Pediatric Patients:** See dosing recommendations in the Full Prescribing Information (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 2.5 mg, 10 mg, 15 mg, and 20 mg (3)
- For oral suspension: 1 mg/mL once reconstituted (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. An agent to reverse the 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. (5.7, 8.1)
- Prosthetic heart valves: XARELTO use not recommended. (5.8)
- Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome: XARELTO use not recommended. (5.10)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2021

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- Treatment of Deep Vein Thrombosis
- 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
- Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding
- Reduction of Risk of Major Cardiovascular Events in Patients with Coronary Artery Disease (CAD)
- Reduction of Risk of Major Thrombotic Vascular Events in Patients with Peripheral Artery Disease (PAD), Including Patients after Lower Extremity Revascularization due to Symptomatic PAD

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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* (2.3, 2.4), *Warnings and Precautions* (5.1), and *Clinical Studies* (14.1)].

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with 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 adult 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 adult patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

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

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

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

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

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

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

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