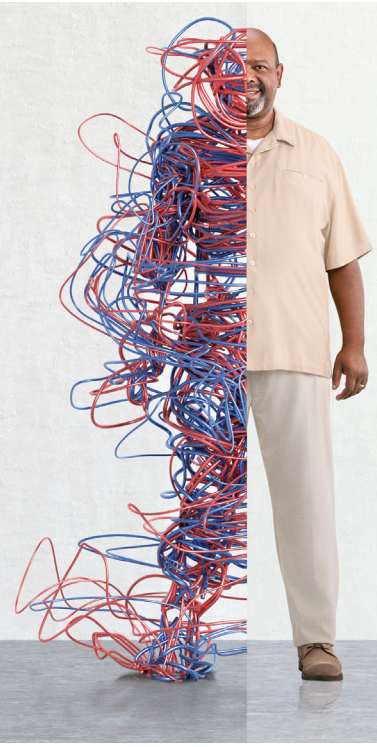
How do you treat your PE patient with obesity?

Xarelto® rivaroxaban tablets



PROFILE
54-year-old with a recent surgery

Presents to ED with shortness of breath

BP, HEART RATE
110/80 mm Hg, 98 bpm

BMI = 30

PaO_2
74 mm Hg on ambient air (88% saturated)

INITIAL DIAGNOSTIC TEST RESULTS
- PE in right lobe involving ~50%

PLAN
Admission for treatment

BMI = body mass index; BP = blood pressure; ED = emergency department; PaO_2 = partial pressure of oxygen in arterial blood; PE = pulmonary embolism.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS

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.

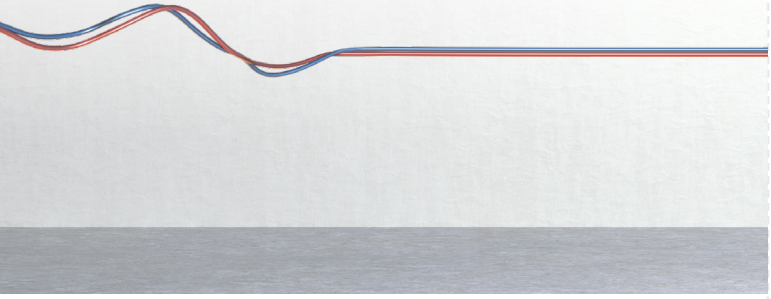
INDICATION

XARELTO® is indicated for the treatment of deep vein thrombosis (DVT).
XARELTO® is indicated for the treatment of pulmonary embolism (PE).
See full Indications on page 20.

Please read additional Important Safety Information on the following pages and full Prescribing Information including Boxed WARNINGS for XARELTO®.

EINSTEIN PE study design[1]

Trial design: Randomized, phase 3, multicenter, open-label, parallel-group, active-controlled, event-driven, noninferiority study with adult patients receiving XARELTO® at an initial dose of 15 mg twice daily with food for the first 3 weeks, followed by XARELTO® 20 mg once daily with food or enoxaparin 1 mg/kg twice daily for at least 5 days with VKA, then VKA only after target INR (2.0-3.0) was reached. Patients were included if they had acute, symptomatic PE with objective confirmation, with or without symptomatic DVT. Patients were treated for 3, 6, or 12 months at HCP discretion.



IMPORTANT SAFETY 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.

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

XARELTO® (rivaroxaban) studied a broad adult patient population for VTE treatment*

KEY CRITERIA†	XARELTO®[2] EINSTEIN DVT/PE[4] N=8282	Eliquis®[3]‡ AMPLIFY[5] N=5395
Treatment duration	3, 6, or 12 months	6 months
Select risk factors for bleeding at baseline		
Recent (<2 months): head trauma, other major trauma, or major surgery	Included§	Excluded
Hemoglobin <9 g/dL	Included	Excluded
Total bilirubin >1.5 times ULN	Included	Excluded
Platelet count <100 x 10^9/L	Included	Excluded
General criteria		
Renal function limitation	<30 mL/min	<25 mL/min
VTE provoked by a transient risk factor	Included	Excluded

*No head-to-head, randomized, controlled trials exist between DOACs.
†Please see protocols for complete list of inclusion and exclusion criteria.
‡Eliquis® (apixaban) is a trademark of Bristol-Myers Squibb Company.
§Patients with active bleeding or at high risk of bleeding were excluded.

DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; HCP = healthcare professional; INR = international normalized ratio; ULN = upper limit of normal; VKA = vitamin K antagonist; VTE = venous thromboembolism.

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, *see* Drug Interactions**
- **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**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

Please read additional Important Safety Information on the following pages and full Prescribing Information including Boxed WARNINGS for XARELTO®.

EINSTEIN PE trial

XARELTO® (rivaroxaban) is the only DOAC with a dedicated PE study, including the largest population studied[1,4-7]

of patients did not experience another DVT or PE*

HR (95% CI): 1.12 (0.75-1.68)†

2.1% (50/2419) with XARELTO® versus 1.8% (44/2413) with enoxaparin and warfarin/VKA

*Patients were followed for an average length of treatment of 208 days in clinical studies.
†RRR calculated using 1 minus the HR.

ARR = absolute risk reduction; CI = confidence interval; CRNMB = clinically relevant nonmajor bleeding; HR = hazard ratio; RRR = relative risk reduction.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO® (eg, anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, 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® to warfarin in clinical trials in atrial fibrillation patients. If XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need

Please read additional Important Safety Information on the following pages and full Prescribing Information including Boxed WARNINGS for XARELTO®.

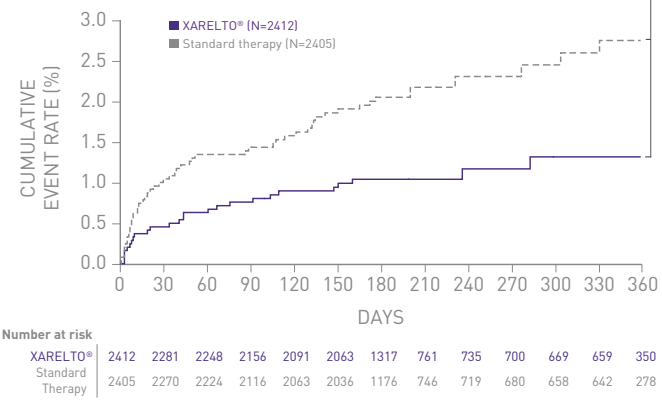
Nearly 3X more PE patients studied in EINSTEIN PE (4832) study vs AMPLIFY (1836)[1,6]

Similar rates of the composite of CRNMB and major bleeding[1‡]: 10.3% (249/2412) with XARELTO® versus 11.4% (274/2405) with enoxaparin and warfarin/VKA
HR (95% CI): 0.90 (0.76-1.07)

Rates of major bleeding

51% RRR† in major bleeding vs enoxaparin and warfarin/VKA

1.1% ARR HR = 0.49 (95% CI: 0.31-0.79)‡



Number at risk

XARELTO®	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Standard Therapy	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

- 1.1% (26/2412) with XARELTO® versus 2.2% (52/2405) with enoxaparin and warfarin/VKA

‡The principal safety outcome was comparable rates of the composite of major bleeding and CRNMB across treatment groups.
§RRR calculated using 1 minus the HR.
‖**Not adjusted for multiplicity.**

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Risk of Bleeding (cont'd):** for blood replacement. Discontinue in patients with active pathological hemorrhage.
  - An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable.
  - Concomitant use of other drugs that impair hemostasis increases risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).

EINSTEIN DVT and EINSTEIN PE pooled analysis[1,8]

Trial design: Randomized, phase 3, multicenter, open-label, parallel-group, active-controlled, event-driven, noninferiority studies (EINSTEIN DVT and EINSTEIN PE) with adult patients receiving XARELTO® at an initial dose of 15 mg twice daily with food for the first 3 weeks, followed by XARELTO® 20 mg once daily with food or enoxaparin 1 mg/kg twice daily for at least 5 days with VKA, then VKA only after target INR (2.0-3.0) was reached. Patients were included in EINSTEIN DVT if they had acute, symptomatic, objectively confirmed proximal DVT, without symptomatic PE, and were included in EINSTEIN PE if they had acute, symptomatic PE with objective confirmation, with or without symptomatic DVT. Patients were treated for 3, 6, or 12 months at HCP discretion.

Primary outcomes: The primary efficacy outcome was symptomatic, recurrent fatal or nonfatal PE or DVT, and the principal safety outcome was clinically relevant bleeding, defined as a composite of major and CRNMB. Bleeding was defined as major if it was clinically overt and associated with a decrease in hemoglobin level of >2 g/dL; if bleeding led to the transfusion of >2 units of red cells; or if bleeding was intracranial or retroperitoneal, occurred in another critical site, or contributed to death. Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with the physician, interruption or discontinuation of the study drug, or discomfort or impairment of activities of daily life.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Risk of Bleeding (cont'd)**
  - 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 XARELTO® for primary VTE prophylaxis: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage; active cancer (ie, undergoing acute, in-hospital cancer treatment); active gastroduodenal ulcer or history of bleeding in the three months prior to treatment; or dual antiplatelet therapy. XARELTO® is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

Consistent efficacy regardless of PE clot burden with XARELTO® (rivaroxaban)[1]*

PE clot burden

VTE event rates

LIMITED†

1.6% (5/309) with XARELTO® versus **1.3%** (4/299) with enoxaparin and warfarin/VKA

INTERMEDIATE†

2.5% (35/1392) with XARELTO® versus **2.2%** (31/1424) with enoxaparin and warfarin/VKA

EXTENSIVE†

1.7% (10/597) with XARELTO® versus **1.4%** (8/576) with enoxaparin and warfarin/VKA

~83% OF PATIENTS
had an intermediate or extensive PE

*Clot burden was defined as limited if a PE was confined to a single lobe involving ≤25% of the vasculature of that lobe and extensive if a PE involved multiple lobes and affected >25% of the entire pulmonary vasculature. All other results for thrombosis and PE were classified as intermediate.

†For illustrative purposes only. Not indicative of location of PEs studied.

Please read additional Important Safety Information on the following pages and full Prescribing Information including Boxed WARNINGS for XARELTO®.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

Please read additional Important Safety Information on the following pages and full Prescribing Information including Boxed WARNINGS for XARELTO®.

Consistent safety profile regardless of clot burden with XARELTO® (rivaroxaban)[4]*

EINSTEIN pooled (DVT/PE) VTE event rates

COMPOSITE OF CRNMB AND MAJOR BLEEDING

LIMITED	INTERMEDIATE	EXTENSIVE
9.2% (73/796) with XARELTO®	**9.7%** (181/1864) with XARELTO®	**9.3%** (126/1359) with XARELTO®
versus	versus	versus
9.3% (76/813) with enoxaparin/VKA	**10.1%** (189/1876) with enoxaparin/VKA	**10.1%** (134/1326) with enoxaparin/VKA
HR (95% CI): 0.97 (0.78-1.34)	HR (95% CI): 0.95 (0.78-1.17)	HR (95% CI): 0.90 (0.78-1.17)

MAJOR BLEEDING†

LIMITED	INTERMEDIATE	EXTENSIVE
1.0% (8/796) with XARELTO®	**1.1%** (20/1864) with XARELTO®	**0.8%** (11/1359) with XARELTO®
versus	versus	versus
1.4% (11/813) with enoxaparin/VKA	**1.7%** (32/1876) with enoxaparin/VKA	**2.1%** (28/1326) with enoxaparin/VKA
HR (95% CI): 0.75 (0.30-1.87)	HR (95% CI): 0.62 (0.36-1.09)	HR (95% CI): 0.36 (0.18-0.73)

*A total of 71 patients in the XARELTO® group and 68 patients in the enoxaparin/VKA group had missing data. 43 patients in the XARELTO® group and 40 patients in the enoxaparin/VKA did not have confirmed DVT and PE.

†Major bleeding was defined as fatal bleeding, critical site bleeding, hemoglobin drop >2 g/dL, or bleeding requiring transfusion >2 units.

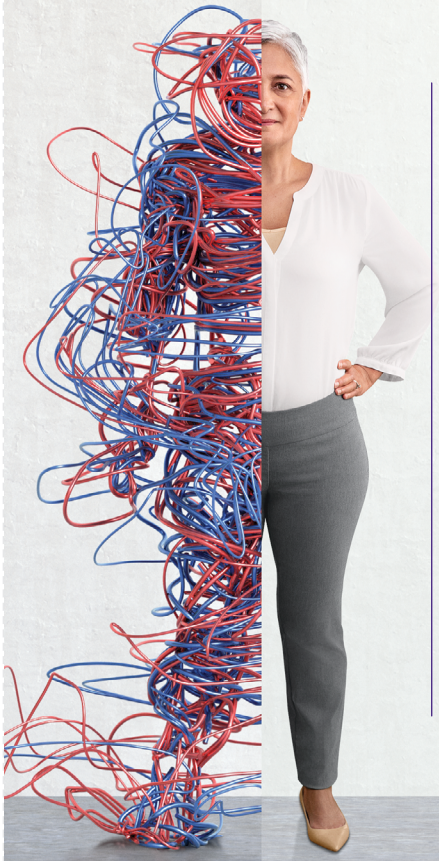
IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Use in Patients with Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation in patients who develop acute renal failure while on XARELTO®. Clinical efficacy and safety studies with XARELTO® did not enroll patients with CrCl <30 mL/min or end-stage renal disease (ESRD) on dialysis.

Patients with VTE are complex.[9-11]

Helping protect them against thrombosis doesn't have to be.



NVAF
Reduce stroke risk

CAD
Reduce the risk of major CV events

PAD
Reduce the risk of major thrombotic vascular events

VTE Prophylaxis
Acutely ill medical patients

DVT/PE
Initial treatment

DVT/PE
Extended treatment

DVT Prophylaxis
After hip/knee replacement surgery

CAD = coronary artery disease; CV = cardiovascular; NVAF = nonvalvular atrial fibrillation; PAD = peripheral artery disease.

XARELTO® is the DOAC that **protects the broadest range** of your patients from VTE events across **Prevention, Treatment, and Extension.**[2]

Please read additional Important Safety Information on the following pages and full Prescribing Information including Boxed WARNINGS for XARELTO®.

Switching adult patients to and from XARELTO® (rivaroxaban)

Switching adult patients to XARELTO®	
From warfarin	Stop warfarin and start XARELTO® when INR is <3.0
From unfractionated heparin	Stop the infusion and start XARELTO® at the same time
From other anticoagulants	Start XARELTO® 0 to 2 hours prior to the next scheduled evening administration of the other anticoagulant

Switching adult patients from XARELTO®	
To warfarin*	One approach is to stop XARELTO® and start parenteral anticoagulant and warfarin at time of next scheduled XARELTO® dose
To other anticoagulants†	Stop XARELTO® and start other anticoagulant when the next dose of XARELTO® would have been given

*No clinical trial data are available to guide converting patients from XARELTO® to warfarin. XARELTO® affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin.
†Oral or parenteral rapid-onset anticoagulants.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Use in Patients with Renal Impairment (cont'd):**
  - **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.
  - **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use

Temporary discontinuation for surgery and other procedures

If XARELTO® must be discontinued for a procedure, follow these guidelines:

Before procedure:

- Stop XARELTO® at least 24 hours before the procedure
- In deciding whether a procedure should be delayed until 24 hours after the last dose of XARELTO®, the increased risk of bleeding should be weighed against the urgency of intervention

After procedure:

- Restart XARELTO® as soon as adequate hemostasis is established
- If oral medication cannot be taken during or after surgical procedures, consider a parenteral anticoagulant

Half-life of XARELTO®	Healthy subjects aged 20 to 45 years	5 to 9 hours
	Elderly subjects aged 60 to 76 years	11 to 13 hours

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Use in Patients with Renal Impairment (cont'd):**

  of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.

  - **Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.

Please read additional Important Safety Information on the following pages and full Prescribing Information including Boxed WARNINGS for XARELTO®.

Distinct pharmacologic profile

Rapid onset of action

- XARELTO® reaches maximum plasma concentrations and inhibits Factor Xa at 2 to 4 hours after the medication is taken[2]*

*Phase 1 randomized, single-blinded, placebo-controlled, dose-escalation study in 108 healthy white males, aged 19 to 45 years. Single doses of rivaroxaban 1.25-, 5-, 10-, 15-, 20-, 30-, 40-, 60-, or 80-mg tablets were tested.

Bioavailability

- A 20-mg dose of XARELTO® has nearly complete bioavailability when taken with food; XARELTO® 15-mg and 20-mg tablets should be taken with food as directed

The clinical significance of this pharmacokinetic information has not been established.

Food considerations

	15 mg	20 mg
Take with food	✓	✓

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Use in Patients with Renal Impairment (cont'd):**
  - **Reduction of Risk of Major Cardiovascular Events in Patients with CAD and Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients after Recent Lower Extremity Revascularization Due to Symptomatic PAD:** For patients with CrCl <15 mL/min, no data are available, and limited data are available for patients with a CrCl of 15 to 30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg XARELTO® twice daily is expected to give an exposure similar to that in patients with moderate renal impairment (CrCl 30 to <50 mL/min), whose efficacy and safety outcomes were similar to those with preserved renal function. Clinical efficacy and safety studies with XARELTO® did not enroll patients with end-stage renal disease (ESRD) on dialysis.
  - **Pediatric Patients:** There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2); therefore, avoid use of XARELTO® 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 XARELTO® in these patients.

XARELTO® (rivaroxaban) has convenient oral dosing for adult patients via crushable administration

Oral administration of crushed XARELTO® tablets for adult patients

Crush XARELTO® tablet	Mix with applesauce	Administer orally immediately	Follow 15-mg and 20-mg doses immediately with food

Administration of XARELTO® via NG or gastric feeding tube for adult patients

Confirm tube placement	Suspend crushed XARELTO® tablet in 50 mL of water	Administer immediately Avoid administration distal to stomach	Follow 15-mg and 20-mg doses immediately by enteral feeding

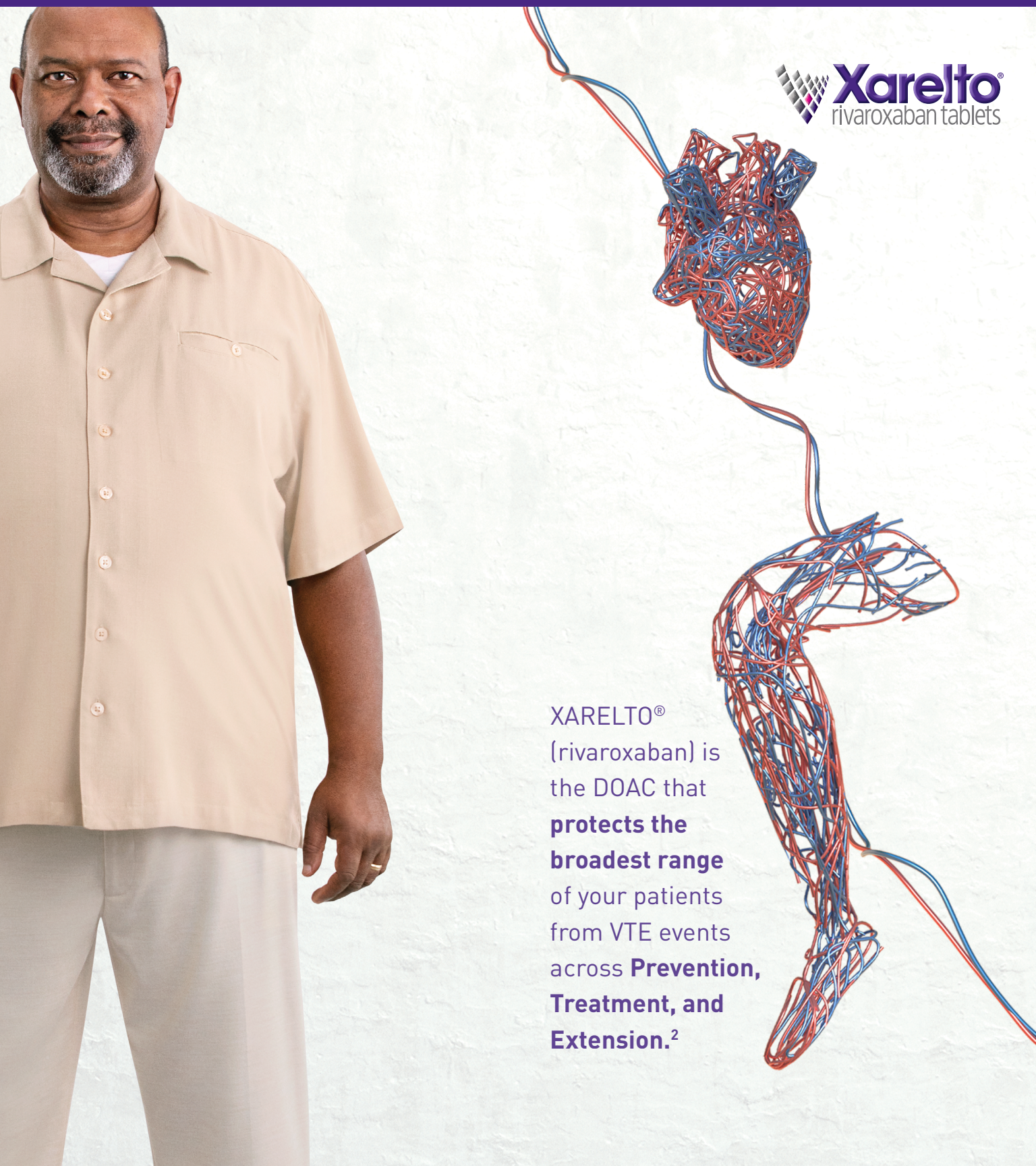
NG = nasogastric.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Use in Patients with Hepatic Impairment:** No clinical data are available for adult patients with severe hepatic impairment. Avoid use 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. No clinical data are available in pediatric patients with hepatic impairment.
- **Use with P-gp and Strong CYP3A Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with known combined P-gp and strong CYP3A inhibitors or inducers.
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO® cannot be monitored with standard laboratory testing. Promptly evaluate signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

Please read additional Important Safety Information on the following pages and full Prescribing Information including Boxed WARNINGS for XARELTO®.



Xarelto®
rivaroxaban tablets

XARELTO® (rivaroxaban) is the DOAC that **protects the broadest range** of your patients from VTE events across **Prevention, Treatment, and Extension.**[2]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Patients with Prosthetic Heart Valves:** Use of XARELTO® is not recommended in patients who have had transcatheter aortic valve replacement (TAVR), based on the results of the GALILEO study, which reported higher rates of death and bleeding in patients randomized to XARELTO® compared to those randomized to an antiplatelet regimen. Safety and efficacy of XARELTO® have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of XARELTO® is not recommended in patients with prosthetic heart valves.
- **Acute PE in Hemodynamically Unstable Patients/Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO® 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.
- **Increased Risk of Thrombosis in Patients with Antiphospholipid Syndrome:** Direct-acting oral anticoagulants (DOACs), including XARELTO®, 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.

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase risk of bleeding.
- Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase risk of thromboembolic events.
- XARELTO® should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (eg, erythromycin) unless the potential benefit justifies the potential risk.
- Coadministration of enoxaparin, warfarin, aspirin, clopidogrel, and chronic NSAID use may increase risk of bleeding.
- Avoid concurrent use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The limited available data on XARELTO® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery.

  The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO® for the mother and possible risks to the fetus when prescribing to a pregnant woman.

  — 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: The risk of bleeding should be balanced with the risk of thrombotic events when considering use in this setting.

  — There are no adequate or well-controlled studies of XARELTO® 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.

- **Lactation:** 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. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for XARELTO® and any potential adverse effects on the breastfed infant from XARELTO® or from the underlying maternal condition.
- **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 XARELTO®, should be assessed in females of reproductive potential and those with abnormal uterine bleeding.
- **Pediatric Use:** XARELTO® 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.

  Clinical studies that evaluated safety, efficacy, and pharmacokinetic/pharmacodynamic data support the use of XARELTO® 10-mg, 15-mg, and 20-mg tablets in pediatric patients. For the XARELTO® 2.5-mg tablets, there are no safety, efficacy, and pharmacokinetic/pharmacodynamic data to support the use in pediatric patients. Therefore, XARELTO® 2.5-mg tablets are not recommended for use in pediatric patients.

  Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents.

Please read additional Important Safety Information on the following page and full Prescribing Information including Boxed WARNINGS for XARELTO®.

IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS (cont'd)

- **Geriatric Use:** In clinical trials the efficacy of XARELTO® 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.

OVERDOSAGE

- Overdose of XARELTO® may lead to hemorrhage. Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

ADVERSE REACTIONS

- Most common adverse reactions in adult patients with XARELTO® were bleeding complications.
- Most common adverse reactions in pediatric patients were bleeding, cough, vomiting, and gastroenteritis.

INDICATIONS

XARELTO® is indicated for the treatment of deep vein thrombosis (DVT). XARELTO® is indicated for the treatment of pulmonary embolism (PE). 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.

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

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.

Please read full Prescribing Information, including Boxed WARNINGS for XARELTO®.

cp-62551v9

References

1. The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297. doi:10.1056/NEJMoa11135 **2.** XARELTO® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **3.** Eliquis® [prescribing information]. Princeton, NJ, New York, NY: Bristol-Myers Squibb Company and Pfizer Inc.; 2021. **4.** Prins MH, Lensing AWA, Bauersachs R, et al; EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis for the EINSTEIN-DVT and PE randomized studies. *Thromb J*. 2013;11(1):21. doi:10.1128/1477-9560-11-21 **5.** Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. doi:10.1056/NEJMoa1302507 **6.** Barco S, Schmidtmann I, Ageno W, et al; HoT-PE Investigators. Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: an international multicentre single-arm clinical trial. *Eur Heart J.* 2020;41(4):509-518. doi:10.1093/eurheartj/ehz367 **7.** Peacock WF, Coleman CI, Diercks DB, et al. Emergency department discharge of pulmonary embolus patients. *Acad Emerg Med.* 2018;25(9):995-1003. doi:10.1111/acem.13451 **8.** The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510. doi:10.1056/NEJMoa1007903 **9.** Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2):e195S-e226S. doi:10.1378/chest.11-2296 **10.** Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693-4738. doi:10.1182/bloodadvances.2020001830 **11.** Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e278S-e325S. doi:10.1378/chest.11-2404

Janssen CarePath

Offering support to help your patients start and stay on therapy

SUPPORT FOR PATIENTS USING COMMERCIAL OR PRIVATE INSURANCE TO PAY FOR MEDICATION

Janssen CarePath Savings Program for XARELTO® (rivaroxaban)

Eligible patients using commercial or private insurance can save on out-of-pocket costs for XARELTO®. Depending on the health insurance plan, savings may apply toward co-pay, co-insurance or deductible. Eligible commercial patients pay $10 for each 30-day to 90-day prescription for XARELTO®, subject to program benefit limits. There is no limit to this benefit for the first 90 days and then a $200 limit for each 30-day supply thereafter. There is a $3,400 maximum program benefit per calendar year. Not valid for patients using Medicare, Medicaid, or other government-funded programs to pay for their medications. Patients prescribed XARELTO® 10 mg because of a recent non-surgical hospital discharge or because they have recently undergone hip or knee replacement surgery are not eligible. Terms expire at the end of each calendar year and may change. There is no income requirement. See full eligibility requirements at **Xarelto.JanssenCarePathSavings.com**.

janssen select

Do your patients pay more than $85 monthly out of pocket for their prescription of XARELTO®? Janssen Select may be able to help.

At Janssen, we know that it can be hard for your patients to stay on treatment when their out-of-pocket costs increase during a coverage gap (eg, commercial high deductibles or the Medicare Part D coverage gap, formerly known as the "Donut hole"). That's why we've created Janssen Select.

Through Janssen Select your patients can:

- Or, pay $85, plus sales tax if applicable, for a 30-day (1-month) supply of XARELTO®.
- Pay $240 for a 90-day (3-month) supply of XARELTO® ($80 per month), plus sales tax if applicable, if the patient and provider choose a 90-day supply.
- Have the same XARELTO® they'd expect delivered directly to their door by Wegmans pharmacy.
- Participate without paying a membership fee or sharing their income information. This program can even help people who may not have qualified for affordability support in the past.
- Register beginning April 1 and get refills until December 31, and they can discontinue anytime.

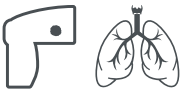
Patients can learn more about the program requirements and register at JanssenSelect.com. For more information, patients can call **888-XARELTO** (888-927-3586), Monday-Friday, 8:00 AM-8:00 PM ET.

Please read full Prescribing Information, including Boxed WARNINGS and Medication Guide for XARELTO®. Provide the Medication Guide to your patients and encourage discussion.

XARELTO® (rivaroxaban) treats and helps protect against DVT/PE wherever your adult patients need it—inpatient and outpatient*

For all DVT/PE dosing below, avoid using XARELTO® in patients with CrCl <15 mL/min†‡

DVT/PE:
Treatment of adult DVT or PE patients



15 mg

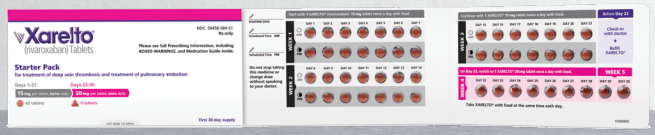
For the first 21 days
Twice daily with food, at approximately the same time each day

20 mg

Starting at day 22
Once daily with food, at approximately the same time each day for remaining treatment

*The decision regarding initiation setting should be based on the prescriber's clinical judgment.
†Calculate CrCl based on actual weight.
‡Patients with CrCl <30 mL/min were not studied, but administration of XARELTO® is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min).
CrCl = creatinine clearance.

Use the 30-day XARELTO® Starter Pack for adult patients for initial treatment of DVT/PE



Please read full Prescribing Information, including Boxed WARNINGS for XARELTO®.

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Xarelto® rivaroxaban tablets

Janssen Pharmaceuticals, Inc.

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