Xarelto® rivaroxaban tablets

UPDATED 2023 ACC/AHA/ACCP/HRS GUIDELINE RECOMMENDATIONS

2023 ACC/AHA/ACCP/HRS Guidelines Recommend XARELTO® as an Option for Eligible Patients With AF,* With No Age Limitations for Older Adults[1]

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE†	RECOMMENDATIONS FOR ANTITHROMBOTIC THERAPY
I (Strong)	A (High-quality)	For patients with AF and an estimated annual thromboembolic risk of ≥2%/year (eg, CHA_2DS_2-VASc score of ≥2 in men and ≥3 in women), anticoagulation is recommended to prevent stroke and systemic thromboembolism.
I (Strong)	A (High-quality)	In patients with AF who do not have a history of moderate to severe rheumatic mitral stenosis or a mechanical heart valve, and who are candidates for anticoagulation, DOACs are recommended over warfarin to reduce the risk of mortality, stroke, systemic embolism, and ICH.
2a (Moderate)	A (High-quality)	For patients with AF and an estimated annual thromboembolic risk of ≥1% but <2%/year (equivalent to CHA_2DS_2-VASc score of 1 in men and 2 in women), anticoagulation is reasonable to prevent stroke and systemic thromboembolism.
3: Harm (Strong)	B-R (Randomized)	In patients with AF who are candidates for anticoagulation and without an indication for antiplatelet therapy, aspirin either alone or in combination with clopidogrel as an alternative to anticoagulation is not recommended to reduce stroke risk.
3: No Benefit (Moderate)	B-NR (Nonrandomized)	In patients with AF without risk factors for stroke, aspirin monotherapy for prevention of thromboembolic events is of no benefit.

NOTE: COR and LOE are determined independently (any COR may be paired with any LOE). This table represents select COR and LOE that are used in this table. Select COR: Class 1, Benefit >>> Risk; Class 2a, Benefit >> Risk; Class 3: No Benefit, Benefit = Risk; Class 3: Harm, Risk > Benefit. Select LOE: A recommendation with LOE A indicates high-quality evidence from more than 1 RCT, meta-analyses of high-quality RCTs, OR one or more RCTs corroborated by high-quality registry studies. A recommendation with LOE B-R (Randomized) indicates moderate-quality evidence from 1 or more RCTs OR meta-analyses of moderate-quality RCTs. A recommendation with LOE B-NR (Nonrandomized) indicates moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies OR meta-analyses of such studies.

*XARELTO® is indicated to reduce the risk of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation. The use of XARELTO® is not recommended in patients with prosthetic heart valves. While no longer using the "valvular" and "nonvalvular" classifications of AF and concluding that those terms are obsolete, the 2023 Guideline for the Diagnosis and Management of Atrial Fibrillation notes that DOACs are currently recommended as first-line therapy over warfarin in patients with AF (except moderate to severe mitral stenosis or mechanical heart valve recipients).

†The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

ACC = American College of Cardiology; ACCP = American College of Clinical Pharmacy; AF = atrial fibrillation; AHA = American Heart Association; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65 to 74 years, Sex category; COR = Class of Recommendation; DOAC = direct oral anticoagulant; HRS = Heart Rhythm Society; ICH = intracranial hemorrhage; LOE = Level of Evidence; NVAF = nonvalvular atrial fibrillation; RCT = randomized clinical trial; TIA = transient ischemic attack.

XARELTO® IS THE #1 PRESCRIBED DOAC AMONG ONCE-DAILY‡ DOSING BRANDS INDICATED FOR ADULT PATIENTS WITH NVAF[2]

‡XARELTO® must be taken with the evening meal.

INDICATION

XARELTO® (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF).

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.

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.

Guideline-Recommended Doses of Currently Approved DOACs According to Renal Function[1]*

DOAC	CrCl (mL/min)				
	>95 mL/min	51-95	31-50	15-30	<15 or on dialysis
Apixaban	5 or 2.5 mg twice daily†	5 or 2.5 mg twice daily†	5 or 2.5 mg twice daily†	5 or 2.5 mg twice daily†	5 or 2.5 mg twice daily†
Dabigatran	150 mg twice daily	150 mg twice daily	150 mg twice daily	75 mg twice daily	Contraindicated
Edoxaban	Contraindicated	60 mg once daily	30 mg once daily	30 mg once daily	Contraindicated
Rivaroxaban	**20 mg once daily**	**20 mg once daily**	**15 mg once daily**	**15 mg once daily**	**15 mg once daily‡**

NOTE: Other, nonrenal considerations such as drug interactions may also apply. The gray area indicates doses not studied in the pivotal clinical trials of these agents.

Use in Patients With Renal Impairment[3]

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 of XARELTO® in patients who develop any renal failure while on XARELTO®.

Patients With End-Stage Renal Disease on Dialysis[3]

Clinical efficacy and safety studies with XARELTO® did not enroll patients with CrCl <30 mL/min or ESRD on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO® 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis, as was seen in ROCKET AF.

*Refer to section 8.6 of Prescribing Information for all DOACs regarding use in patients with renal impairment.
†If at least 2 of the following are present: serum creatinine ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg, the recommended dose is 2.5 mg twice daily. The ARISTOTLE trial excluded patients with either a creatinine of >2.5 mg/dL or a calculated CrCl <25 mL/min.
‡Rivaroxaban is not recommended for other indications in patients with a CrCl <15 mL/min, but such a recommendation is not made for the AF indication. However, pharmacokinetic data are limited.
CrCl = creatinine clearance; ESRD = end-stage renal disease.

IMPORTANT SAFETY INFORMATION (cont'd)

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, *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.

DOACs Are Recommended for Eligible Adult Patients With AF and Class III Obesity[1]*

Recommendations for Anticoagulation Considerations in Patients With Class III Obesity

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE†	RECOMMENDATION
2a (Moderate)	B-NR (Nonrandomized)	In patients with AF and class III obesity (BMI ≥40 kg/m^2), DOACs are reasonable to choose over warfarin for stroke risk reduction.
2b (Weak)	C-LD (Limited Data)	In patients with AF who have undergone bariatric surgery, warfarin may be reasonable to choose over DOACs for stroke risk reduction in view of concerns about DOAC drug absorption.

NOTE: COR and LOE are determined independently (any COR may be paired with any LOE). Select COR: Class 2a, Benefit >> Risk; Class 2b, Benefit greater than or equal to Risk. Select LOE: A recommendation with LOE B-NR (Nonrandomized) indicates moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies and the meta-analyses of such studies. A recommendation with LOE C-LD (Limited Data) indicates randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, and physiological or mechanistic studies in human subjects. A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Class III obesity is defined as BMI ≥40 kg/m^2.
†The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.
BMI = body mass index.

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 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).

Xarelto® rivaroxaban tablets

UPDATED 2023 ACC/AHA/ACCP/HRS GUIDELINE RECOMMENDATIONS

Consider These Guideline Recommendations When Prescribing XARELTO® to Eligible Patients With NVAF, Including[1]:

- **Older adults, with no age limitations**
- **Patients with a CrCl ≤50 mL/min**
- **Patients diagnosed with class III obesity***

Use in Patients With Renal Impairment[3]
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 of XARELTO® in patients who develop any renal failure while on XARELTO®.

Patients With End-Stage Renal Disease on Dialysis[3]
Clinical efficacy and safety studies with XARELTO® did not enroll patients with CrCl <30 mL/min or ESRD on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO® 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis, as was seen in ROCKET AF.

*Class III obesity is defined as BMI ≥40 kg/m².

365
FEWER PILLS PER YEAR

ONCE-DAILY† XARELTO®
CARRIES A LOWER PILL BURDEN THAN ELIQUIS®[3,4]

†Taken with the evening meal.

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS (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.

- **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. To reduce the potential risk of bleeding associated with concurrent use of XARELTO® and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. 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®. The next 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. Monitor frequently to detect signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), or bowel and/or bladder dysfunction. Instruct patients to immediately report 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®.

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.
  - **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 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.
  - **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.
- **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).
- **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.

WARNINGS AND PRECAUTIONS (cont'd)

- **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.

USE IN SPECIFIC POPULATIONS (cont'd)

- **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.

- **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.

cp-62551v9

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

REFERENCES: 1. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* Published online November 23, 2023. doi:10.1016/j.jacc.2023.08.017 **2.** Data on file. Janssen Pharmaceuticals, Inc. Data was sourced from IQVIA® NPA Weekly Data (data period of July 2011–November 2023). **3.** XARELTO® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **4.** Eliquis® [prescribing information]. Princeton, NJ and New York, NY: Bristol-Myers Squibb Company and Pfizer, Inc.; 2021.