XARELTO® DOSING AND TRANSITION MANAGEMENT

XARELTO® DOSING

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<th>Dosing Regimen</th>
<th>Application</th>
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<td><strong>Reduce stroke risk in NONVALVULAR AF</strong></td>
<td>20 mg ONCE DAILY</td>
<td>Patients with CrCl &gt;50 mL/min: with the evening meal OR 15 mg ONCE DAILY</td>
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<tr>
<td><strong>Treatment of DVT and PE</strong></td>
<td>15 mg TWICE DAILY with food for first 21 days</td>
<td><strong>ON DAY 22 TRANSITION TO</strong> 20 mg ONCE DAILY with food, at approximately the same time each day for remaining treatment</td>
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<tr>
<td><strong>Reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE</strong></td>
<td>10 mg ONCE DAILY with or without food, after at least 6 months of standard anticoagulant treatment</td>
<td>KNEE: 12 days HIP: 35 days The initial dose should be taken 6 to 10 hours after surgery provided that hemostasis has been established</td>
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Tablets shown not actual size.

- No routine coagulation monitoring is required.

6 Indications approved by the FDA

- To reduce the risk of stroke and systemic embolism in 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.
- For the treatment of deep vein thrombosis (DVT)
- For the treatment of pulmonary embolism (PE)

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 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.

Renal dosing considerations

- **Nonvalvular AF:** 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 acute renal failure while on XARELTO®.
- **All Other Indications:** Avoid using XARELTO® in patients with CrCl <30 mL/min.

Please see full Prescribing Information for additional dosing considerations.

SWITCHING PATIENTS TO AND FROM XARELTO®

**SWITCHING 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 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.

CrCl = creatinine clearance; INR = international normalized ratio.

- 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
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee replacement surgery
- For the prophylaxis of DVT, which may lead to PE in patients undergoing hip replacement surgery

Important Safety Information continued on next page.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, or visit https://www.xareltohcp.com/PI
CONTRAINDICATIONS

• Concomitant use of other drugs that impair hemostasis increases the risk of bleeding.
• A specific antidote for rivaroxaban is not available. Because rivaroxaban is not expected to be dialyzable.

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 XARELTO® in patients with active pathological hemorrhage.

• A specific antidote for rivaroxaban is not available. Because rivaroxaban is not expected to be dialyzable.

• Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).

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 the 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 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), or 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.

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

• Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE: Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.

• Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO® should discontinue the treatment.

Use in Patients With Hepatic Impairment: No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO® 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.
WARNINGS AND PRECAUTIONS (cont’d)

♦ Use With P-gp and Strong CYP3A4 Inhibitors or Inducers: Avoid concomitant use of XARELTO® with known combined P-gp and strong CYP3A4 inhibitors. Avoid concomitant use of XARELTO® with drugs that are known combined P-gp and strong CYP3A4 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 nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

♦ Patients With Prosthetic Heart Valves: The safety and efficacy of XARELTO® have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO® is not recommended in these patients.

♦ 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.

DRUG INTERACTIONS

♦ Combined P-gp and strong CYP3A4 inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding.

♦ Combined P-gp and strong CYP3A4 inducers decrease exposure to rivaroxaban and may increase the 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 CYP3A4 inhibitors (eg, erythromycin) unless the potential benefit justifies the potential risk.

♦ Coadministration of enoxaparin, warfarin, aspirin, clopidogrel, and chronic NSAID use may increase the risk of bleeding.

♦ Avoid concurrent use of XARELTO® 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.

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 with an anticoagulant that is not readily reversible. 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 XARELTO® 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 the use of XARELTO® 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. The developmental and health benefits of breastfeeding should be considered 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.

♦ Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

OVERDOSE

♦ Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdose occur. A specific antidote for rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of XARELTO® overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable.

ADVERSE REACTIONS IN CLINICAL STUDIES

♦ The most common adverse reactions with XARELTO® were bleeding complications.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, or visit https://www.xareltohcp.com/PI.