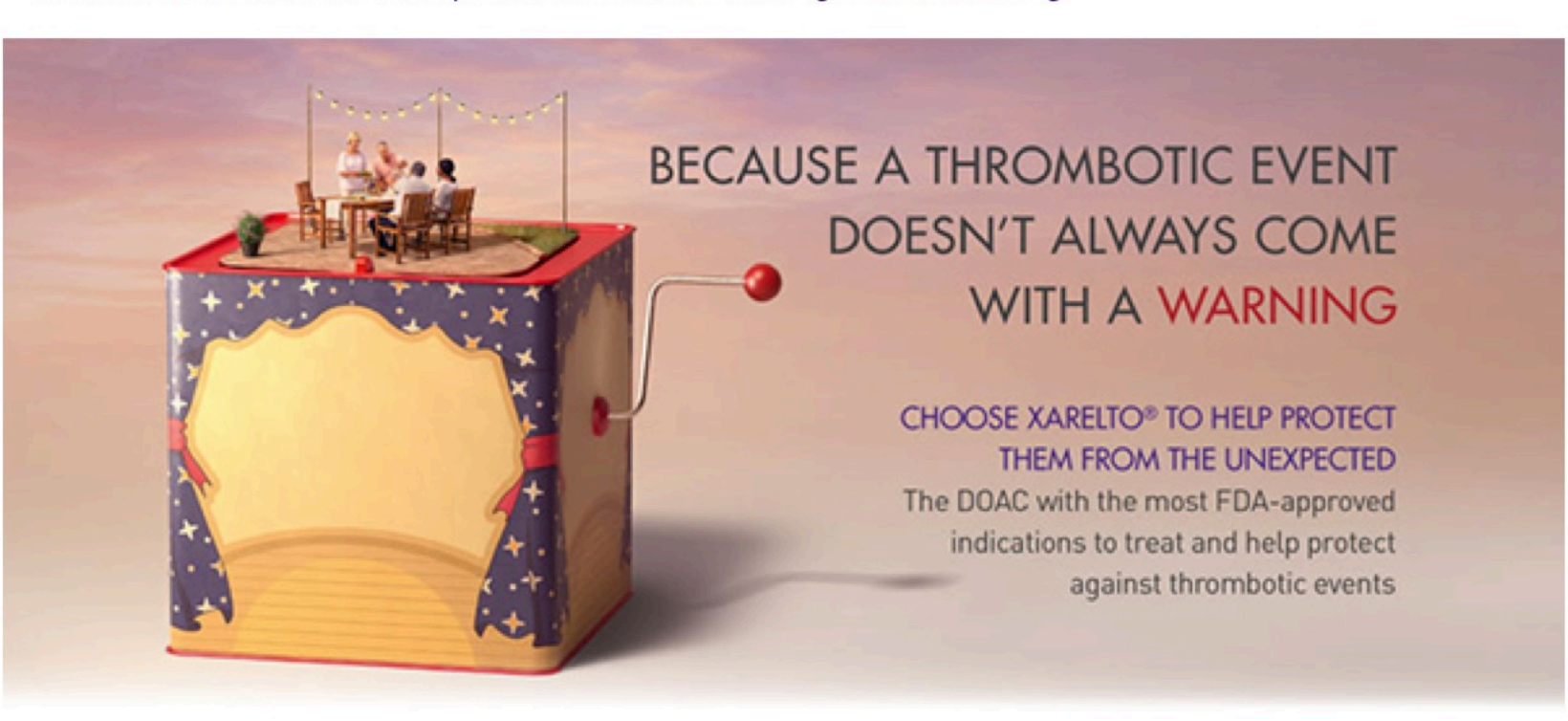
From: [journal email address]
Date: [mm/dd/yy]
To: [HCP]
Subject: A new indication for an established DOAC

IMPORTANT SAFETY INFORMATION
PRESCRIBING INFORMATION

XARELTO® (rivaroxaban) 10-mg dose is **NOW APPROVED** for VTE prophylaxis in acutely ill medical patients at risk for thromboembolic complications who are 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.

SELECT 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.

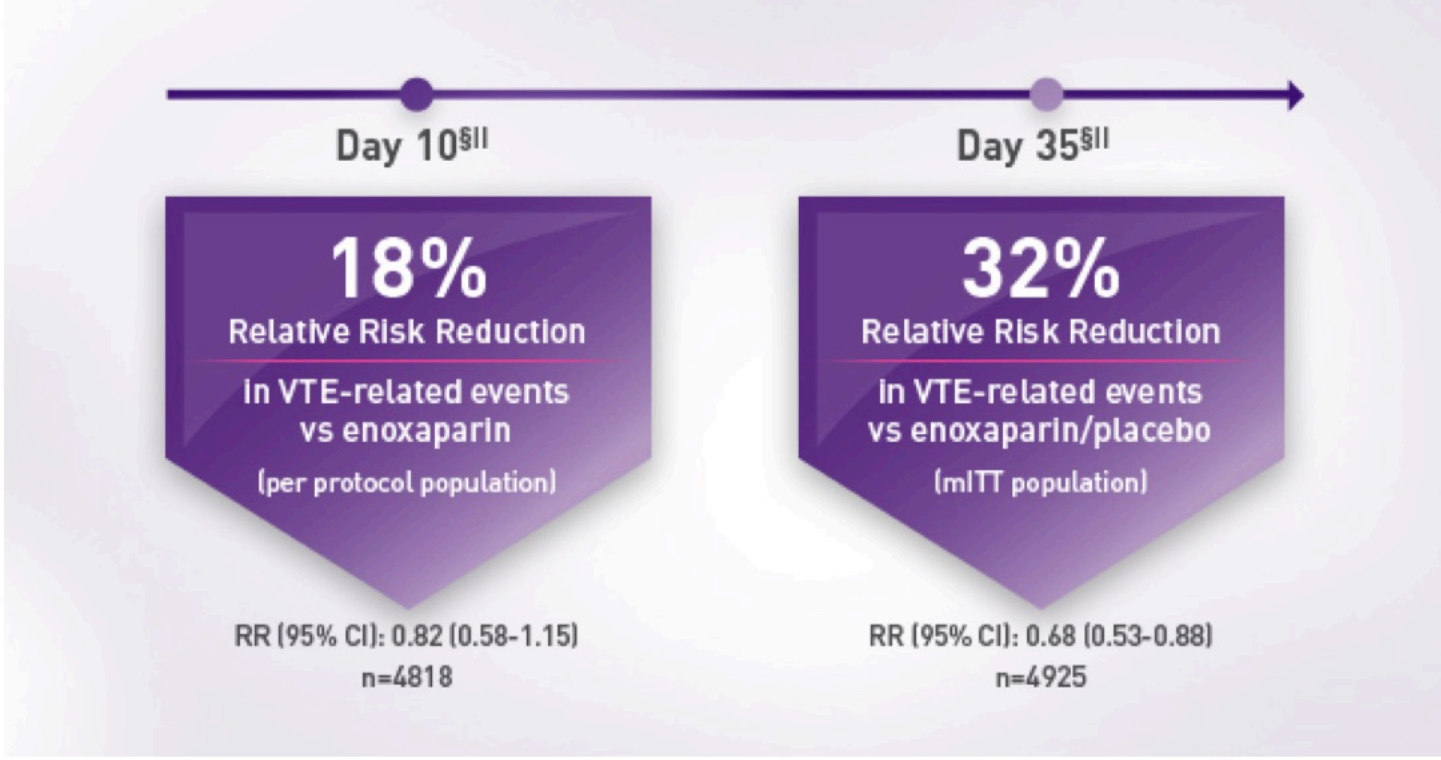
(continued below)

Acutely ill medical patients are at risk of a VTE in the hospital and post-hospital discharge*

Several studies indicate between 50% and 80% of VTE events occur post-hospital discharge.[†1-3]

XARELTO®: Once-daily oral VTE prophylaxis in acutely ill medical patients* both inpatient and outpatient

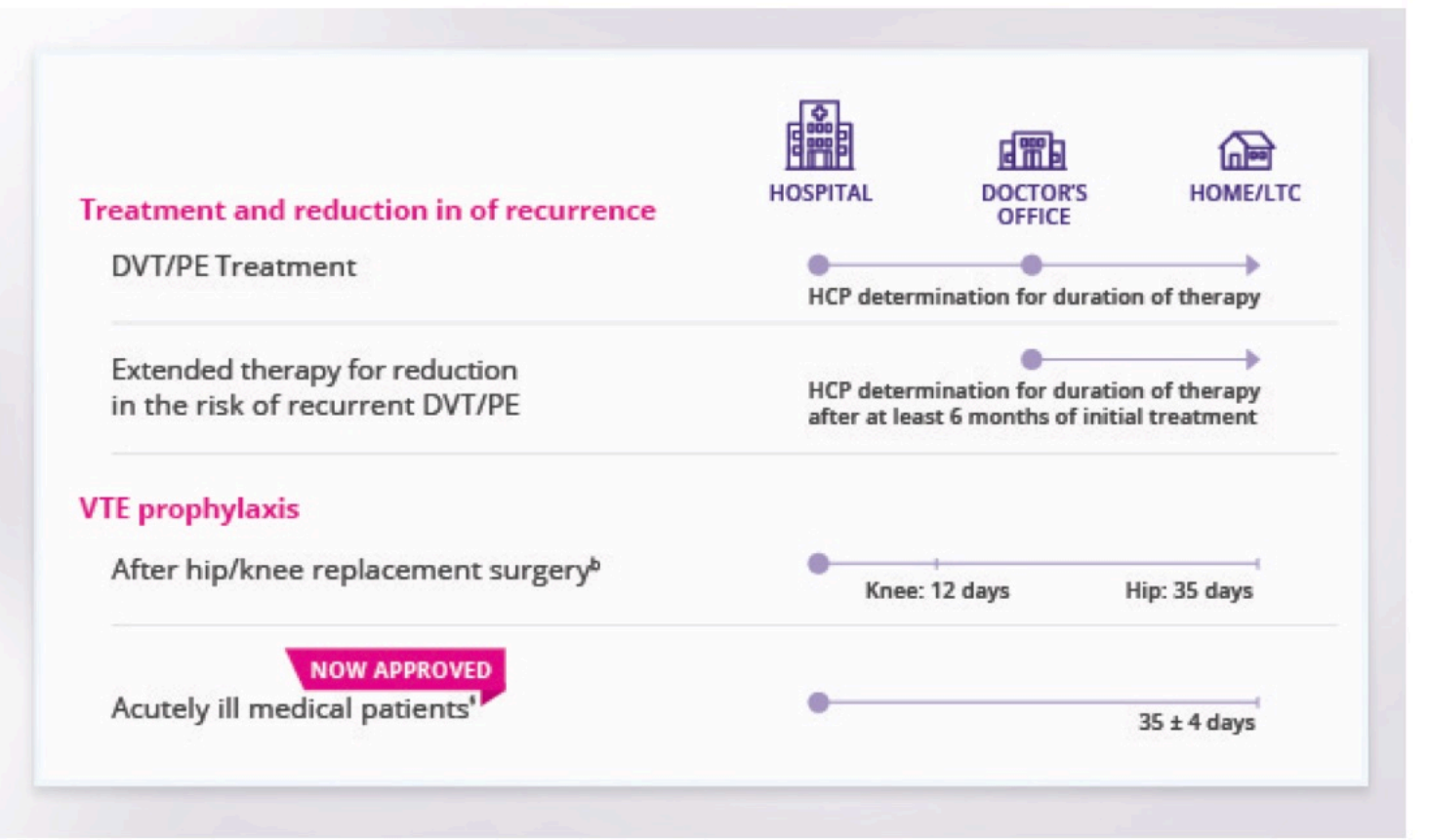
XARELTO® demonstrated a VTE risk reduction in acutely ill medical patients vs standard of care at Day 10 and Day 35 in the MAGELLAN subgroup[*‡]



Bleeding events in the MAGELLAN[||] subgroup at Day 35

Clinical Endpoint	XARELTO® 10 mg %/year	(n/N)	Enoxaparin 40 mg (inpatient)/ Placebo (outpatient) %/year	(n/N)
Major Bleeding[¶#]	0.7	(22/3218)	0.5	(15/3229)
Fatal Bleeding[**]	<0.1	(3/3218)	<0.1	(1/3229)
Critical Site Bleeding[††]	0.2	(7/3218)	0.1	(4/3229)
Clinically Relevant Nonmajor Bleeding[‡‡]	2.9	(93/3218)	1.1	(34/3229)

XARELTO® treats and helps protect against DVT/PE wherever your patients need it—inpatient and outpatient[a4-12]



Condition-specific dosing[c,d,e,f]

TREATMENT AND REDUCTION OF RECURRENCE

DVT/PE Treatment
15 mg twice daily for 21 days, then 20 mg once daily taken with food at the same time each day in patients with CrCl ≥15 mL/min.

Extended Therapy for Reduction in the Risk of Recurrent DVT/PE
10 mg once daily taken with or without food in patients with CrCl ≥15 mL/min after at least 6 months of standard anticoagulant treatment.

VTE PROPHYLAXIS

After Hip/Knee Replacement Surgery[b]
10 mg once daily taken with or without food in patients with CrCl ≥15 mL/min.

Acutely Ill Medical Patients*
10 mg once daily taken with or without food in patients with CrCl ≥15 mL/min.

For all DVT/PE/VTE dosing above, avoid use in CrCl <15 mL/min.

XARELTO®—Reducing the VTE risk for multiple thrombotic indications

In addition to helping protect against a VTE in your acutely ill medical patients, remember that XARELTO® is also indicated to reduce the risk of stroke and SE in patients with NVAF. In combination with aspirin, XARELTO® is also indicated to reduce the risk of major cardiovascular events (CV death, MI, stroke) in patients with chronic CAD or PAD.

CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; HCP = healthcare professional; LTC = long-term care; MI = myocardial infarction; mITT = modified intent-to-treat; NVAF = nonvalvular atrial fibrillation; PAD = peripheral artery disease; PE = pulmonary embolism; RR = relative risk; SE = systemic embolism; VTE = venous thromboembolism.

*For VTE prophylaxis in acutely ill medical patients at risk for thromboembolic complications who are not at high risk of bleeding.

†Results were aggregated across multiple studies. Precise results were dependent on patient characteristics.

‡Patients excluded due to high risk of bleeding: History of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage; active cancer (eg, admitted for chemotherapy or treatment due to active cancer complication); active GI ulcer in the 3 months prior to hospital admission; history of bleeding within the last 3 months prior to hospital admission; or receiving dual antiplatelet therapy.

§Primary efficacy outcomes: The composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or VTE-related death.

||Patients were randomized to receive either XARELTO® 10 mg once daily for 35 ± 4 days starting in hospital and continuing post hospital discharge (n=4050) or enoxaparin 40 mg once daily for 10 ± 4 days starting in hospital followed by placebo post discharge (n=4051).

¶Major bleeding was defined as clinically overt bleeding associated with a drop in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.

#Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

**Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

††Critical site bleeding was defined as bleeding into a critical site such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome.

‡‡Clinically relevant bleeding was a primary safety endpoint of the MAGELLAN study and was a composite of the following data points—major bleeding (including critical site bleeding and fatal bleeding) and clinically relevant nonmajor bleeding. Clinically relevant nonmajor bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, temporary cessation of study treatment, or discomfort for the patient such as pain or impairment of activities of daily life.

aThe decision regarding initiation setting should be based on the prescriber's clinical judgment.

bAdminister 6 to 10 hours after surgery once hemostasis has been established.

cAvoid use in DVT/PE patients with CrCl <30 mL/min.

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

eCalculate CrCl based on actual weight.

fPatients 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)

Want to know more? Please visit our website, XARELTOhcp.com or contact a Janssen representative at 1-800-JANSSEN.

INDICATIONS

XARELTO® is indicated 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.

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 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 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.

XARELTO® is indicated, 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).

IMPORTANT SAFETY INFORMATION

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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.

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).
  - 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.
- **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 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 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 Chronic CAD or 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.
- **Use in Patients with Hepatic Impairment:** No clinical data are available for 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.
- **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:** Safety and efficacy of XARELTO® have not been studied in patients with prosthetic heart valves. 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.
- **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.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

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 IN CLINICAL STUDIES

- Most common adverse reactions with XARELTO® were bleeding complications.

Click here for full Prescribing Information, including Boxed WARNINGS for XARELTO®.

cp-62551v5

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