HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XARELTO® (rivaroxaban) tablets, for oral use

Initial U.S. Approval: 2011

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning

(A) Premature discontinuation of XARELTO increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy (2.3, 2.8, 5.1, 14.1).

(B) Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.2, 5.3, 6.2).

Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated (5.3).

RECENT MAJOR CHANGES

- Deep Vein Thrombosis and/or Pulmonary Embolism (1.4) 10/2017
- Dosage and Administration (2.1, 2.6) 10/2017
- Warnings and Precautions (5.2) 06/2018

INDICATIONS AND USAGE

XARELTO is a factor Xa inhibitor indicated:

- for the treatment of deep vein thrombosis (DVT) (1.2)
- for the treatment of pulmonary embolism (PE) (1.3)
- 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 (1.4)
- for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery (1.5)

DOSE FORMS AND STRENGTHS

Tablets: 10 mg, 15 mg, and 20 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)
- Severe hypersensitivity reaction to XARELTO (4)

WARNINGS AND PRECAUTIONS

- Risk of bleeding: XARELTO can cause serious and fatal bleeding. Promptly evaluate signs and symptoms of blood loss. An agent to reverse the anti-factor Xa activity of rivaroxaban is available. (5.2)
- Pregnancy-related hemorrhage: Use XARELTO with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery. Promptly evaluate signs and symptoms of blood loss. (5.7)
- Prosthetic heart valves: XARELTO use not recommended (5.8)

ADVERSE REACTIONS

The most common adverse reaction (>5%) was bleeding. (6.1)

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

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A4 inhibitors and inducers: Avoid concomitant use (7.2, 7.3)
- Anticoagulants: Avoid concomitant use (7.4)

USE IN SPECIFIC POPULATIONS

- Renal impairment: Avoid or adjust dose based on CrCl and Indication (8.6)
- Hepatic impairment: Avoid use in patients with Child-Pugh B and C hepatic impairment or with any degree of hepatic disease associated with coagulopathy (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
XARELTO® (rivaroxaban) tablets

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
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10 OVERDOSAGE

11 DESCRIPTION

11.1 Mechanism of Action
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12.1 Mechanism of Action
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13 NON-CLINICAL TOXICOLOGY

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14 CLINICAL STUDIES

14.1 Stroke Prevention in Nonvalvular Atrial Fibrillation
14.2 Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)
14.3 Reduction in the Risk of Recurrence of DVT and/or PE
14.4 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

15 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. Premature discontinuation of XARELTO increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see Dosage and Administration (2.3, 2.8), Warnings and Precautions (5.1), and Clinical Studies (14.1)].

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

• use of indwelling epidural catheters
• concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
• a history of traumatic or repeated epidural or spinal punctures
• a history of spinal deformity or spinal surgery
• optimal timing between the administration of XARELTO and neuraxial procedures is not known [see Warnings and Precautions (5.2, 5.3) and Adverse Reactions (6.2)]. Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary [see Warnings and Precautions (5.3)]. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [see Warnings and Precautions (5.3)].

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

XARELTO is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled [see Clinical Studies (14.1)].

1.2 Treatment of Deep Vein Thrombosis

XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

1.3 Treatment of Pulmonary Embolism

XARELTO is indicated for the treatment of pulmonary embolism (PE).

1.4 Reduction in the Risk of Recurrence of Deep Vein Thrombosis and/or Pulmonary Embolism

XARELTO is indicated for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation (2.4)</td>
<td>CrCl &lt;50 mL/min: 20 mg once daily with the evening meal</td>
</tr>
<tr>
<td></td>
<td>CrCl 15 to 50 mL/min: 15 mg once daily with the evening meal</td>
</tr>
<tr>
<td>Treatment of DVT (2.5)</td>
<td>15 mg twice daily with food, for first 21 days</td>
</tr>
<tr>
<td></td>
<td>▼ after 21 days, transition to ▼</td>
</tr>
<tr>
<td>Treatment of PE (2.5)</td>
<td>10 mg once daily with or without food, after at least 6 months of standard anticoagulant treatment</td>
</tr>
<tr>
<td>Prophylaxis of DVT Following Hip or Knee Replacement Surgery (2.7)</td>
<td>Hip replacement: 10 mg once daily with or without food for 35 days</td>
</tr>
<tr>
<td></td>
<td>Knee replacement: 10 mg once daily with or without food for 12 days</td>
</tr>
</tbody>
</table>

2.2 Important Food Effect Information

The 15 mg and 20 mg XARELTO tablets should be taken with food, while the 10 mg tablet can be taken with or without food [see Clinical Pharmacology (12.3)].

In the nonvalvular atrial fibrillation efficacy study XARELTO was taken with the evening meal.

2.3 Switching to and from XARELTO

Switching from Warfarin to XARELTO - When switching patients from warfarin to XARELTO, discontinue warfarin and start XARELTO as soon as the International Normalized Ratio (INR) is below 3.0 to avoid periods of inadequate anticoagulation.

Switching from XARELTO to Warfarin - 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. One approach is to discontinue XARELTO and begin both a parenteral anticoagulant and warfarin at the time the next dose of XARELTO would have been taken.

Switching from XARELTO to Anticoagulants other than Warfarin - For patients currently taking XARELTO and transitioning to an anticoagulant with rapid onset, discontinue XARELTO and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next XARELTO dose would have been taken [see Drug Interactions (7.4)].

Switching from Anticoagulants other than Warfarin to XARELTO - For patients currently receiving an anticoagulant other than warfarin, start XARELTO 6 to 2 hours prior to the next scheduled evening administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop the infusion and start XARELTO at the same time.

2.4 Nonvalvular Atrial Fibrillation

For patients with creatinine clearance (CrCl) >50 mL/min, the recommended dose of XARELTO is 20 mg taken orally once daily with the evening meal.

For patients with CrCl 15 to 50 mL/min, the recommended dose is 15 mg once daily with the evening meal [see Use in Specific Populations (8.6)].
XARELTO® (rivaroxaban) tablets

2.5 Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

The recommended dose of XARELTO for the initial treatment of acute DVT and/or PE is 15 mg taken orally twice daily with food for the first 21 days. After this initial treatment period, the recommended dose of XARELTO is 20 mg taken orally once daily with food, at approximately the same time each day [see Clinical Studies (14.2)].

2.6 Reduction in the Risk of Recurrence of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

The recommended dose of XARELTO for the reduction in the risk of recurrence of DVT and/or PE after at least 6 months of standard anticoagulant treatment in patients at continued risk of DVT and/or PE is 10 mg taken orally once daily with or without food [see Clinical Studies (14.3)].

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

The recommended dose of XARELTO is 10 mg taken orally once daily with or without food. The initial dose should be taken 6 to 10 hours after surgery provided that hemostasis has been established [see Dosage and Administration (2.8)].

- For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
- For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

2.8 Discontinuation for Surgery and other Interventions

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, XARELTO should be stopped at least 24 hours before the procedure to reduce the risk of bleeding [see Warnings and Precautions (5.2)]. 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. XARELTO should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short [see Warnings and Precautions (5.1)]. If oral medication cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant.

2.9 Missed Dose

If a dose of XARELTO is not taken at the scheduled time, administer the dose as soon as possible on the same day as follows:

- For patients receiving 15 mg twice daily: The patient should take XARELTO immediately to ensure intake of 30 mg XARELTO per day. In this particular instance, two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
- For patients receiving 20 mg, 15 mg or 10 mg once daily: The patient should take the missed XARELTO dose immediately.

2.10 Administration Options

For patients who are unable to swallow whole tablets, 10 mg, 15 mg or 20 mg XARELTO tablets may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed XARELTO 15 mg or 20 mg tablet, the dose should be immediately followed by food [see Dosage and Administration (2.2), (2.2, 2.4, 2.5) and Clinical Pharmacology (12.3)].

Administration via nasogastric (NG) tube or gastric feeding tube: After confirming gastric placement of the tube, 10 mg, 15 mg or 20 mg XARELTO tablets may be crushed and suspended in 50 mL of water and administered via an NG tube or gastric feeding tube. Since rivaroxaban absorption is dependent on the site of drug release, avoid administration of XARELTO distal to the stomach in which can result in reduced absorption and thereby, reduced drug exposure. After the administration of a crushed XARELTO 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding [see Clinical Pharmacology (12.3)].

Crushed 10 mg, 15 mg or 20 mg XARELTO tablets are stable in water and in applesauce for up to 4 hours. An in vitro compatibility study indicated that there is no adsorption of rivaroxaban from a water suspension of a crushed XARELTO tablet to PVC or silicone nasogastric (NG) tubing.

3 DOSAGE FORMS AND STRENGTHS

- 10 mg tablets: Round, light red, biconvex and film-coated with a triangle pointing down above a “10” marked on one side and “Xa” on the other side
- 15 mg tablets: Round, red, biconvex, and film-coated with a triangle pointing down above a “15” marked on one side and “Xa” on the other side
- 20 mg tablets: Triangle-shaped, dark red, and film-coated with a triangle pointing down above a “20” marked on one side and “Xa” on the other side

4 CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- active pathological bleeding [see Warnings and Precautions (5.2)]
- severe hypersensitivity reaction to XARELTO (e.g., anaphylactic reactions) [see Adverse Reactions (6.2)]

5 WARNINGS AND PRECAUTIONS

5.1 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 [see Dosage and Administration (2.3, 2.8) and Clinical Studies (14.1)].

5.2 Risk of Bleeding

XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of 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. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years. Concurrent use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) [see Drug Interactions (7.4)], selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors. Concomitant use of drugs that are known combined P-gp and strong CYP3A4 inhibitors increases rivaroxaban exposure and may increase bleeding risk [see Drug Interactions (7.2)].

Reversal of Anticoagulant Effect

An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable [see Clinical Pharmacology (12.3)]. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Partial reversal of prothrombin time effects has been demonstrated using an aprotinin product, but this has not been studied for rivaroxaban. Reversal of XARELTO is likely to be effective in situations in which renal function may decline) and adjust dose as clinically indicated [see Dose and Administration (2.3, 2.8) and Clinical Studies (14.1)].

5.3 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, consider the pharmacokinetic profile of XARELTO [see Clinical Pharmacology (12.3)]. 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 (i.e., 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 (12.3)]. 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/analgnesia 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.

5.4 Use in Patients with Renal Impairment

Nonvalvular Atrial Fibrillation

Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly [see Drug Interactions (7.2)]. Consider dose adjustment or discontinuation of XARELTO in patients who develop acute renal failure while on XARELTO [see Use in Specific Populations (8.6)].
**XARELTO® (rivaroxaban) tablets**

**Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reducing the Risk of Recurrence of DVT and/or PE**

Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an increased risk in rivaroxaban exposure and pharmacodynamic effects in this patient population [see Use in Specific Populations (8.6)].

**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 increased risk 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 [see Use in Specific Populations (8.6)].

**5.5 Use in Patients with Haptic 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 [see Use in Specific Populations (8.7)].

**5.6 Use with P-gp and Strong CYP3A4 Inducers or Inhibitors**

Avoid concomitant use of XARELTO with drugs that are known combined P-gp and strong CYP3A4 inducers [see Drug Interactions (7.2)]. Avoid concomitant use of XARELTO with drugs that are known combined P-gp and strong CYP3A4 inducers [see Drug Interactions (7.3)].

**5.7 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 any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress) [see Warnings and Precautions (5.2)].

**5.8 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.

**5.9 Acute PE in Hemodynamically Unstable Patients or 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 require thrombolysis or pulmonary embolectomy.

**6 ADVERSE REACTIONS**

The following adverse reactions are also discussed in other sections of the labeling:

- Increased risk of stroke after discontinuation in nonvalvular atrial fibrillation [see Boxed Warning and Warnings and Precautions (5.1)]
- Bleeding risk [see Warnings and Precautions (5.2, 5.4, 5.5, 5.6, 5.7)]
- Spinal/epidural hematoma [see Boxed Warning and Warnings and Precautions (5.3)]

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development for the approved indications, 18,560 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF); 6962 patients who received XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily to treat DVT or PE (EINSTEIN DVT, EINSTEIN PE), 10 mg or 20 mg orally once daily (EINSTEIN Extension, EINSTEIN CHOICE) to reduce the risk of recurrence of DVT and/or PE; and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

**Hemorrhage**

The most common adverse reactions with XARELTO were bleeding complications [see Warnings and Precautions (5.2)].

**Nonvalvular Atrial Fibrillation**

In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

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**Table 1: Bleeding Events in ROCKET AF – On Treatment Plus 2 Days**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO N=7111 (n/[%/year])</th>
<th>Warfarin N=7125 (n/[%/year])</th>
<th>XARELTO vs. Warfarin HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>395 (3.6)</td>
<td>386 (3.5)</td>
<td>1.04 (0.90, 1.20)</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>55 (0.5)</td>
<td>84 (0.7)</td>
<td>0.67 (0.47, 0.93)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>36 (0.3)</td>
<td>58 (0.6)</td>
<td>0.66 (0.42, 0.96)</td>
</tr>
<tr>
<td>Other ICH</td>
<td>19 (0.2)</td>
<td>26 (0.2)</td>
<td>0.74 (0.41, 1.34)</td>
</tr>
<tr>
<td>Gastrointestinal (GI)</td>
<td>221 (2.0)</td>
<td>140 (1.2)</td>
<td>1.61 (1.30, 1.99)</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>27 (0.2)</td>
<td>55 (0.5)</td>
<td>0.50 (0.31, 0.79)</td>
</tr>
<tr>
<td>ICH</td>
<td>24 (0.2)</td>
<td>42 (0.4)</td>
<td>0.58 (0.35, 0.96)</td>
</tr>
<tr>
<td>Non-intracranial</td>
<td>3 (0.0)</td>
<td>13 (0.1)</td>
<td>0.23 (0.07, 0.82)</td>
</tr>
</tbody>
</table>

Abbreviations: HR = Hazard Ratio, CI = Confidence interval, CRNM = Clinically Relevant Non-Major.

- Major bleeding events within each subgroup were counted once per patient, but patients may have contributed events to multiple subgroups. These events occurred during treatment or within 2 days of stopping treatment.
- Defined as clinically overt bleeding associated with a decrease 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.
- Intracranial bleeding events included intraparenchymal, intraventricular, subdural, subarachnoid and/or epidural hematoma.
- Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.
- Gastrointestinal bleeding events included upper GI, lower GI, and rectal bleeding.
- Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

Figure 1 shows the risk of major bleeding events across major subgroups.

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**Note:** The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

**Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)**

EINSTEIN DVT and EINSTEIN PE Studies

In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively.
XARELTO® (rivaroxaban) tablets

The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients. Table 2 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

Table 2: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® 10 mg n (%)</th>
<th>Enoxaparin/VKA n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>40 (1.0)</td>
<td>72 (1.7)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>3 (&lt;0.1)</td>
<td>8 (0.2)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>2 (&lt;0.1)</td>
<td>4 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal critical organ bleeding</td>
<td>10 (0.2)</td>
<td>29 (0.7)</td>
</tr>
<tr>
<td>Intracranial†</td>
<td>3 (&lt;0.1)</td>
<td>10 (0.2)</td>
</tr>
<tr>
<td>Retroperitoneal‡</td>
<td>1 (&lt;0.1)</td>
<td>8 (0.2)</td>
</tr>
<tr>
<td>Intraocular‡</td>
<td>3 (&lt;0.1)</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Major bleeding event‡</td>
<td>0</td>
<td>4 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal critical organ bleeding</td>
<td>27 (0.7)</td>
<td>37 (0.9)</td>
</tr>
<tr>
<td>Decrease in Hb ≥ 2 g/dL</td>
<td>28 (0.7)</td>
<td>42 (1.0)</td>
</tr>
<tr>
<td>Transfusion of ≥ 2 units of whole blood or packed red blood cells</td>
<td>18 (0.4)</td>
<td>25 (0.6)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>357 (8.6)</td>
<td>357 (8.7)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>1169 (26.3)</td>
<td>1153 (26.0)</td>
</tr>
</tbody>
</table>

* Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.
† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA (enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)).
‡ Includes major bleeding events
§ Includes the placebo-controlled period for RECORD 2, enoxaparin dosing 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA.
¶ Bleeding which is clinically overt, did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

Reduction in the Risk of Recurrence of DVT and/or PE

EINSTEIN CHOICE Study

In the EINSTEIN CHOICE clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1% for XARELTO 10 mg, 2% for XARELTO 20 mg, and 1% for acetylsalicylic acid (aspirin) 100 mg. The mean duration of treatment was 293 days for XARELTO 10 mg-treated patients and 286 days for aspirin 100 mg-treated patients. Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN CHOICE study.

Table 3: Bleeding Events* in EINSTEIN CHOICE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® 10 mg n (%)</th>
<th>Acetylsalicylic Acid (aspirin)† 100 mg n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>5 (0.4)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0</td>
<td>&lt;1 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal critical organ bleeding</td>
<td>2 (0.2)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal non-critical organ bleeding§</td>
<td>3 (0.3)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Clinically relevant non-major (CRNM) bleeding‡</td>
<td>22 (2.0)</td>
<td>20 (1.8)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>151 (13.4)</td>
<td>138 (12.2)</td>
</tr>
</tbody>
</table>

* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.
† Treatment schedule: XARELTO 10 mg once daily or aspirin 100 mg once daily.
‡ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥ 2 g/dL and/or transfusion of ≥ 2 units of whole blood or packed red blood cells.
§ Bleeding which was clinically overt, did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

XARELTO® (rivaroxaban) tablets

In the EINSTEIN CHOICE study, there was an increased incidence of bleeding, including major and CRNM bleeding in the XARELTO 20 mg group compared to the XARELTO 10 mg or aspirin 100 mg groups.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO. The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.

Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® 10 mg n (%)</th>
<th>Enoxaparin n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>14 (0.3)</td>
<td>9 (0.2)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding into a critical organ</td>
<td>2 (&lt;0.1)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Bleeding that required re-operation</td>
<td>7 (0.2)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>Extra-surgical site bleeding requiring transfusion of ≥ 2 units of whole blood or packed cells</td>
<td>4 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Any bleeding event‡</td>
<td>261 (5.8)</td>
<td>251 (5.6)</td>
</tr>
</tbody>
</table>

Hip Surgery Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=3281 n (%)</th>
<th>N=3298 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>7 (0.2)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding into a critical organ</td>
<td>1 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Bleeding that required re-operation</td>
<td>2 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Extra-surgical site bleeding requiring transfusion of ≥ 2 units of whole blood or packed cells</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Any bleeding event‡</td>
<td>201 (6.1)</td>
<td>191 (5.8)</td>
</tr>
</tbody>
</table>

Knee Surgery Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=1326 n (%)</th>
<th>N=1326 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>7 (0.6)</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding into a critical organ</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Bleeding that required re-operation</td>
<td>5 (0.4)</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>Extra-surgical site bleeding requiring transfusion of ≥ 2 units of whole blood or packed cells</td>
<td>4 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Any bleeding event‡</td>
<td>60 (5.0)</td>
<td>60 (4.9)</td>
</tr>
</tbody>
</table>

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.
† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)
‡ Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (>60%) occurred during the first week after surgery. Other Adverse Reactions

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN DVT and EINSTEIN PE studies are shown in Table 5.

Table 5: Non-hemorrhagic Adverse Reactions in XARELTO-Treated Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® 10 mg n (%)</th>
<th>Enoxaparin n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bleeding</td>
<td>1169 (26.3)</td>
<td>1153 (26.0)</td>
</tr>
</tbody>
</table>

Other Adverse Reactions
Table 5: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN DVT and EINSTEIN PE Studies

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>XARELTO 20 mg N=1718 n (%)</th>
<th>Enoxaparin/VKA N=1711 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
<td>46 (2.7)</td>
<td>25 (1.5)</td>
</tr>
<tr>
<td>General disorders and</td>
<td>Fatigue</td>
<td>24 (1.4)</td>
<td>15 (0.9)</td>
</tr>
<tr>
<td>administration site conditions</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>50 (2.9)</td>
</tr>
<tr>
<td></td>
<td>Muscle spasm</td>
<td>23 (1.3)</td>
<td>13 (0.8)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>38 (2.2)</td>
<td>22 (1.3)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Anxiety</td>
<td>24 (1.4)</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>20 (1.2)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>28 (1.6)</td>
<td>18 (1.1)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>53 (2.2)</td>
<td>27 (1.1)</td>
</tr>
</tbody>
</table>

* Adverse reaction with Relative Risk >1.5 for XARELTO versus comparator

Table 6: Other Adverse Drug Reactions† Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>XARELTO 10 mg N=4487 n (%)</th>
<th>Enoxaparin† N=4524 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Wound secretion</td>
<td>125 (2.8)</td>
<td>89 (2.0)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity</td>
<td>74 (1.7)</td>
<td>55 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Muscle spasm</td>
<td>92 (1.2)</td>
<td>32 (0.7)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Syncope</td>
<td>55 (1.2)</td>
<td>32 (0.7)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>96 (2.1)</td>
<td>79 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Blister</td>
<td>63 (1.4)</td>
<td>40 (0.9)</td>
</tr>
</tbody>
</table>

* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication
† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

Other clinical trial experience: In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of XARELTO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis, thrombocytopenia
Gastrointestinal disorders: enterocolitis, ileitis
Hepatobiliary disorders: jaundice, cholestasis, hepatitis (including hepatocellular injury)
Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

7 DRUG INTERACTIONS

7.1 General Inhibition and Induction Properties

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. 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.

7.2 Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

Interaction with Combined P-gp and Strong CYP3A4 Inhibitors

Avoid concomitant administration of XARELTO with known combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) [see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)].

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggests that no precautions are necessary with concomitant administration with XARELTO as the change in exposure is unlikely to affect the bleeding risk [see Clinical Pharmacology (12.3)].

Interaction with Combined P-gp and Moderate CYP3A4 Inhibitors in Patients with Renal Impairment

XARELTO should not be used in patients with CrCl 15 to <30 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (e.g., erythromycin) unless the potential benefit justifies the potential risk [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)].

7.3 Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort) [see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)].

7.4 Anticoagulants and NSAIDs/Aspirin

Coadministration of enoxaparin, warfarin, aspirin, clopidogrel and chronic NSAID use may increase the risk of bleeding [see Clinical Pharmacology (12.3)].

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 [see Warnings and Precautions (5.2)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on XARELTO in pregnant women is insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO with caution in pregnant women 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 XARELTO to a pregnant woman [see Warnings and Precautions (5.2, 5.7)].

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnancy is a risk factor for venous thromboembolism and that risk is increased in women with inherited or acquired thrombophilias. Pregnant women with thromboembolic disease have an increased risk of maternal complications including pre-eclampsia. Maternal thromboembolic disease increases the risk for intrauterine growth restriction, placental abruption and early and late pregnancy loss.

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 or neonate.

Labor or Delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding and this risk may be increased during labor or delivery [see Warnings and Precautions (5.7)]. The risk of bleeding should be balanced with the risk of thrombotic events when considering the use of XARELTO in this setting.

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome
8.2 Lactation

Risk Summary

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. Rivaroxaban and/or its metabolites were present in the milk of rats, dogs, and rabbits. 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 (see Data).

Data

Animal data

Following a single oral administration of 3 mg/kg of radioactive [14C]-rivaroxaban to lactating rats between Day 8 to 10 postpartum, the concentration of total radioactivity was determined in milk samples collected up to 32 hours post-dose. The estimated amount of radioactivity excreted in milk was about 2.1% of the maternal dose.

8.3 Females and Males of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were ≥75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 57% were 65 years and over and about 16% were >75 years. In EINSTEIN CHOE, approximately 39% were 65 years and over and about 12% were >75 years. 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, but the risk-benefit profile was favorable in all age groups (see Clinical Pharmacology [12.3] and Clinical Studies [14]).

8.6 Renal Impairment

In pharmacokinetic studies, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 84% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed (see Clinical Pharmacology [12.3]).

Nonvalvular Atrial Fibrillation

In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban similar to those in patients with normal renal function (see Dosage and Administration [2.4] and Clinical Pharmacology [12.3]).

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with XARELTO did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 15 mg once daily resulted in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study (see Clinical Pharmacology [12.2, 12.3]). 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.

8.7 Hepatic Impairment

In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B). The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated (see Clinical Pharmacology [12.3]). Avoid the 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.

10 OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. 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 (see Warnings and Precautions [5.2] and Clinical Pharmacology [12.3]). Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

11 DESCRIPTION

Rivaroxaban, a factor Xa (FXa) inhibitor, is the active ingredient in XARELTO Tablets with the chemical name 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-pyrrolinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamide. The molecular formula of rivaroxaban is C19H12ClN2O4S and the molecular weight is 435.89. The structural formula is:

Rivaroxaban is a pure (S)-enantiomer. It is an odorless, non-hygroscopic, white to yellowish powder. Rivaroxaban is only slightly soluble in organic solvents (e.g., acetone, polyethylene glycol 400) and is practically insoluble in water and aqueous media.

Each XARELTO tablet contains 10 mg, 15 mg, or 20 mg of rivaroxaban. The active ingredients of XARELTO are: microcrystalline cellulose, hypromellose, lactose monohydrate, magnesium stearate, and titanium dioxide, and for XARELTO 10 mg tablets is Opadry® Pink and for XARELTO 15 mg tablets is Opadry® II Dark Red, containing ferric oxide red, hypromellose, polyethylene glycol 3500, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XARELTO is a selective inhibitor of FXa. It does not require a cofactor (such as Anti-thrombin III) for activity. Rivaroxaban inhibits free FXa and prothrombinase activity. Rivaroxaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, rivaroxaban decreases thrombin generation.

12.2 Pharmacodynamics

Dose-dependent inhibition of FXa activity was observed in humans. Neoplatin® prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® are also prolonged dose-dependently. Anti-factor Xa activity is also influenced by rivaroxaban.

Specific Populations

Renal Impairment

The relationship between systemic exposure and pharmacodynamic activity of rivaroxaban was altered in subjects with renal impairment relative to healthy control subjects (see Use in Specific Populations [8.6]).
Absorption
The absolute bioavailability of rivaroxaban is dose-dependent. For the 10 mg dose, it is estimated to be 80% to 100% and not affected by food. XARELTO 10 mg tablets can be taken with or without food. For the 20 mg dose in the fasted state, the absolute bioavailability is approximately 66%. Co-administration of XARELTO with food increases the bioavailability of the 20 mg dose (mean AUC and Cmax increasing by 39% and 76% respectively with food). XARELTO 15 mg and 20 mg tablets should be taken with food [see Dosage and Administration (2.2)].

The maximum concentrations (Cmax) of rivaroxaban appear 2 to 4 hours after tablet intake. The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH. Co-administration of XARELTO (30 mg single dose) with the H2-receptor antagonist ranitidine (150 mg once daily) did not show an effect on the bioavailability and exposure of rivaroxaban (see Figure 3).

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 25% and 56% decrease in AUC and Cmax compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of rivaroxaban distal to the intestine. Exposure is further reduced when drug is released in the distal small intestine.

Excretion
In a Phase 1 study, following the administration of [14C]-rivaroxaban, approximately 51% of an orally administered [14C]-rivaroxaban dose was recovered as unchanged drug in the urine and 7% was recovered as unchanged drug in feces. Unchanged rivaroxaban was recovered as inactive metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Metabolism
Approximately 51% of an orally administered [14C]-rivaroxaban dose was recovered as inactive metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion
In a Phase 1 study, following the administration of [14C]-rivaroxaban, approximately one-third (36%) was recovered as unchanged drug in the urine and 7% was recovered as unchanged drug in feces. Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate S:1 ratio). Rivaroxaban is a substrate of the efflux transporter proteins P-gp and ABCG2 (also abbreviated Bcrp). Rivaroxaban's affinity for influx transporter proteins is unknown.

Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Specific Populations
The effects of level of renal impairment, age, body weight, and level of hepatic impairment on the pharmacokinetics of rivaroxaban are summarized in Figure 2.

Gender
Gender did not influence the pharmacokinetics or pharmacodynamics of XARELTO.

Race
Healthy Japanese subjects were found to have 20 to 40% on average higher exposures compared to other ethnicities including Chinese. However, these differences in exposure are reduced when values are corrected for body weight.

Elderly
The terminal elimination half-life is 11 to 13 hours in the elderly subjects aged 60 to 76 years [see Use in Specific Populations (8.5)].

Renal Impairment
The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects [CrCl ≥80 mL/min (n=8)] and in subjects with varying degrees of renal impairment (see Figure 2). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed [see Use in Specific Populations (8.6)].

Hemodialysis in ESRD subjects: Systemic exposure to rivaroxaban administered as a single 15 mg dose in ESRD subjects dosed 3 hours after the completion of a 4-hour hemodialysis session (post-dialysis) is 56% higher when compared to subjects with normal renal function (see Table 7). The systemic exposure to rivaroxaban administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 600 mL/min and a blood flow rate in the range of 320 to 400 mL/min is 47% higher compared to those with normal renal function. The extent of the increase is similar to the increase in patients with CrCl 15 to 50 mL/min taking XARELTO 15 mg. Hemodialysis had no significant impact on rivaroxaban exposure. Protein binding was similar (86% to 89%) in healthy controls and ESRD subjects in this study.

Hepatic Impairment
The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects (n=16) and subjects with varying degrees of hepatic impairment (see Figure 2). No patients with severe hepatic impairment (Child-Pugh C) were studied. Compared to healthy subjects with normal liver function, significant increases in rivaroxaban exposure were observed in subjects with moderate hepatic impairment (Child-Pugh B) (see Figure 2). Increases in pharmacodynamic effects were also observed [see Use in Specific Populations (8.7)].
Drug Interactions

In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A4 nor induces CYP1A2, 2B6, 2C19, or 3A4. In vitro data also indicates a low rivaroxaban inhibitory potential for P-gp and ABCG2 transporters. The effects of coadministered drugs on the pharmacokinetics of rivaroxaban exposure are summarized in Figure 3 (see Drug Interactions (7) for dosing recommendations).

Figure 3: Effect of Coadministered Drugs on the Pharmacokinetics of Rivaroxaban

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>PK</th>
<th>Fold Change and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined P-gp and Strong CYP3A4 Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halofantrine</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Combined P-gp and Moderate CYP3A4 Inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Moderate CYP3A4 Inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Combined P-gp and Strong CYP3A4 Inducer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Other Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Allopurin</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Diclofen</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Masitinib</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Omegapril</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Crmax</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>[7]</td>
</tr>
</tbody>
</table>

Change Relative to Rivaroxaban Alone

Anticoagulants

In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and XARELTO (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. In another study, single doses of warfarin (15 mg) and XARELTO (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Neither enoxaparin nor warfarin affected the pharmacokinetics of rivaroxaban (see Figure 3).

NSAIDs/Aspirin

In ROCKET AF, concomitant aspirin use (almost exclusively at a dose of 100 mg or less) during the double-blind phase was identified as an independent risk factor for major bleeding. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with XARELTO. Neither naproxen nor aspirin affected the pharmacokinetics of rivaroxaban (see Figure 3).

Clopidogrel

In two drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and XARELTO (15 mg single dose) were coadministered in healthy subjects, an increase in bleeding time to 45 minutes was observed in approximately 45% and 30% of subjects in these studies, respectively. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. There was no change in the pharmacokinetics of either drug.

Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4

Enzymes and Drug Transport Systems

In a pharmacokinetic trial, XARELTO was administered as a single dose in subjects with mild (CrCl = 50 to 79 mL/min) or moderate renal impairment (CrCl = 30 to 49 mL/min) receiving multiple doses of erythromycin (a combined P-gp and moderate CYP3A4 inhibitor). Compared to XARELTO administered alone in subjects with normal renal function (CrCl >80 mL/min), subjects with mild and moderate renal impairment concomitantly receiving erythromycin reported a 76% and 99% increase in AUCinf and a 56% and 64% increase in Cmax, respectively. Similar trends in pharmacodynamic effects were also observed.

12.6 QT/QTc Prolongation

In a thorough QT study in healthy men and women aged 50 years and older, no QTc prolonging effects were observed for XARELTO (15 mg and 45 mg, single-dose).

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rivaroxaban was not carcinogenic when administered by oral gavage to mice or rats for up to 2 years. The systemic exposures (AUCs) of unbound rivaroxaban in male and female mice at the highest dose tested (60 mg/kg/day) were 1- and 2-times, respectively, the human exposure of unbound drug at the human dose of 20 mg/day. Systemic exposures of unbound drug in male and female rats at the highest dose tested (60 mg/kg/day) were 2- and 4-times, respectively, the human exposure.

Rivaroxaban was not mutagenic in bacteria (Ames-Test) or clastogenic in V79 Chinese hamster lung cells in vitro or in the mouse micronucleus test in vivo.

No impairment of fertility was observed in male or female rats when given up to 200 mg/kg/day of rivaroxaban orally. This dose resulted in exposure levels, based on the unbound AUC, at least 13 times the exposure in humans given 20 mg rivaroxaban daily.

14 CLINICAL STUDIES

14.1 Stroke Prevention in Nonvalvular Atrial Fibrillation

The evidence for the efficacy and safety of XARELTO was derived from Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) [NCT00303767], a multi-national, double-blind, study comparing XARELTO (at a dose of 20 mg once daily with the evening meal in patients with CrCl >50 mL/min and 15 mg once daily with the evening meal in patients with CrCl 30 to 50 mL/min) to warfarin (titrated to INR 2.0 to 3.0) to reduce the risk of stroke and non-central nervous system (CNS) systemic embolism in patients with nonvalvular atrial fibrillation (AF). Patients had to have one or more of the following additional risk factors for stroke:

- a prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or
- 2 or more of the following risk factors:
  - age >75 years,
  - hypertension,
  - heart failure or left ventricular ejection fraction <35%, or
  - diabetes mellitus

ROCKET AF was a non-inferiority study designed to demonstrate that XARELTO preserved more than 50% of warfarin’s effect on stroke and non-CNS systemic embolism as established by previous placebo-controlled studies of warfarin in atrial fibrillation.

A total of 14264 patients were randomized and followed on study treatment for a median of 590 days. The mean age was 71 years and the mean CHADS2 score was 3.5. The population was 60% male, 83% Caucasian, 15% Asian and 1.3% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 55% of patients, and 38% of patients had not taken a vitamin K antagonist (VKA) within 6 weeks at time of screening. Concomitant diseases of patients in this study included hypertension 91%, diabetes 40%, congestive heart failure 63%, and prior myocardial infarction 17%. At baseline, 37% of patients were on aspirin (almost exclusively at a dose of 100 mg or less) and few patients were on clopidogrel. Patients were enrolled in Eastern Europe (39%); North America (19%); Asia, Australia, and New Zealand (15%); Western Europe (15%); and Latin America (13%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0, lower during the first few months of the study.

In ROCKET AF, XARELTO was demonstrated non-inferior to warfarin for the primary composite endpoint of time to first occurrence of stroke (any type) or non-CNS systemic embolism [HR (95% CI): 0.88 (0.74, 1.03)], but superiority to warfarin was not demonstrated. There is insufficient experience to determine how XARELTO and warfarin compare when warfarin therapy is well-controlled.

Table 8 displays the overall results for the primary composite endpoint and its components.
Table 8: Primary Composite Endpoint Results in ROCKET AF Study (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Event</th>
<th>XARELTO (N=7081)</th>
<th>Warfarin (N=7090)</th>
<th>Hazard Ratio and 95% CI</th>
<th>HR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Endpoint*</td>
<td>269 (3.8)</td>
<td>306 (4.3)</td>
<td>0.88 (0.74, 1.03)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>253 (3.6)</td>
<td>281 (4.0)</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic Stroke†</td>
<td>33 (0.5)</td>
<td>57 (0.8)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>206 (2.9)</td>
<td>208 (2.9)</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Unknown Stroke Type</td>
<td>19 (0.3)</td>
<td>18 (0.3)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Non-CNS Systemic Embolism</td>
<td>20 (0.3)</td>
<td>27 (0.4)</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

* The primary endpoint was the time to first occurrence of stroke (any type) or non-CNS systemic embolism. Data are shown for all randomized patients followed to site notification that the study would end.

† Defined as primary hemorrhagic strokes confirmed by adjudication in all randomized patients followed up to site notification.

Figure 4 is a plot of the time from randomization to the occurrence of the first primary endpoint event in the two treatment arms.

Figure 5: Risk of Stroke or Non-CNS Systemic Embolism by Treatment Group (Intent-to-Treat Population)

Figure 5 shows the risk of stroke or non-CNS systemic embolism across major subgroups.

Table 9 displays the overall results for the primary composite endpoint and of the 95% confidence interval for the hazard ratio being less than 2.0. In each study the conclusion of non-inferiority was based on the upper limit of DVT HR (95% CI): 0.68 (0.44, 1.04); EINSTEIN PE HR (95% CI): 1.12 (0.75, 1.68).

In the EINSTEIN DVT and EINSTEIN PE studies, XARELTO was demonstrated to be non-inferior to enoxaparin/VKA for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE [EINSTEIN DVT HR (95% CI): 0.62 (0.44, 0.84); EINSTEIN PE HR (95% CI): 0.91 (0.75, 1.11)]. In each study the conclusion of non-inferiority was based on the upper limit of the 95% confidence interval for the hazard ratio being less than 2.0. In the EINSTEIN DVT and EINSTEIN PE studies, 49% of patients had an idiopathic DVT/PE at baseline. Other risk factors included previous episode of DVT/PE (19%), recent surgery or trauma (18%), immobilization (16%), use of estrogen-containing drug (8%), known thrombophilic conditions (6%), or active cancer (5%).

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Table 9: Primary Composite Endpoint Results* in EINSTEIN DVT and EINSTEIN PE Studies – Intent-to-Treat Population

<table>
<thead>
<tr>
<th>Event</th>
<th>XARELTO 20 mg†</th>
<th>Enoxaparin/VKA†</th>
<th>XARELTO vs. Enoxaparin/VKA Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN DVT Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Composite Endpoint</td>
<td>36 (2.1)</td>
<td>51 (3.0)</td>
<td>0.68 (0.44, 1.04)</td>
</tr>
<tr>
<td>Death (PE)</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Death (PE cannot be excluded)</td>
<td>3 (0.2)</td>
<td>6 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic PE and DVT</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Symptomatic recurrent PE only</td>
<td>20 (1.2)</td>
<td>18 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic recurrent DVT only</td>
<td>14 (0.8)</td>
<td>28 (1.6)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN PE Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Composite Endpoint</td>
<td>50 (2.1)</td>
<td>44 (1.8)</td>
<td>1.12 (0.75, 1.68)</td>
</tr>
<tr>
<td>Death (PE)</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td></td>
</tr>
<tr>
<td>Death (PE cannot be excluded)</td>
<td>8 (0.3)</td>
<td>6 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic PE and DVT</td>
<td>0</td>
<td>2 (&lt;0.1)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic recurrent PE only</td>
<td>23 (1.0)</td>
<td>20 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic recurrent DVT only</td>
<td>18 (0.7)</td>
<td>17 (0.7)</td>
<td></td>
</tr>
</tbody>
</table>

* For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (3, 6 or 12 months) irrespective of the actual treatment duration. If the same patient had several events, the patient may have been counted for several components.
† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA (enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)).

Figures 6 and 7 are plots of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups in EINSTEIN DVT and EINSTEIN PE studies, respectively.

Figure 6: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN DVT Study

Figure 7: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN PE Study

14.3 Reduction in the Risk of Recurrence of DVT and/or PE – EINSTEIN CHOICE Study

XARELTO for reduction in the risk of recurrence of DVT and/or PE was evaluated in the EINSTEIN CHOICE study [NCT02064439], a multi-national, double-blind, superiority study comparing XARELTO (10 or 20 mg once daily with food) to 100 mg acetylsalicylic acid (aspirin) once daily in patients who had completed 6 to 12 months of anticoagulant treatment for DVT and/or PE following the acute event. The intended treatment duration in the study was up to 12 months. Patients with an indication for continued therapeutic-dose anticoagulation were excluded.

Because the benefit-risk assessment favored the 10 mg dose versus aspirin compared to the 20 mg dose versus aspirin, only the data concerning the 10 mg dose is discussed below.

A total of 2275 patients were randomized and followed on study treatment for a mean of 290 days for the XARELTO and aspirin treatment groups. The mean age was approximately 59 years. The population was 56% male, 70% Caucasian, 14% Asian and 3% Black. In the EINSTEIN CHOICE study, 51% of patients had DVT only, 33% had PE only, and 16% had PE and DVT combined. Other risk factors included idiopathic VTE (43%), previous episode of DVT/PE (17%), recent surgery or trauma (12%), prolonged immobilization (10%), use of estrogen containing drugs (5%), known thrombophilic conditions (6%), Factor V Leiden gene mutation (4%), or active cancer (3%).

In the EINSTEIN CHOICE study, XARELTO 10 mg was demonstrated to be superior to aspirin 100 mg for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE.

Table 10 displays the overall results for the primary composite endpoint and its components.

Table 10: Primary Composite Endpoint and its Components Results* in EINSTEIN CHOICE Study – Full Analysis Set

<table>
<thead>
<tr>
<th>Event</th>
<th>XARELTO 10 mg N=1,127 n (%)</th>
<th>Acetylsalicylic Acid (Aspirin) 100 mg N=1,131 n (%)</th>
<th>XARELTO 10 mg vs. Aspirin 100 mg Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Endpoint</td>
<td>12 (1.2)</td>
<td>50 (4.4)</td>
<td>0.26 (0.14, 0.47) p&lt;0.0001</td>
</tr>
<tr>
<td>Symptomatic recurrent DVT</td>
<td>8 (0.7)</td>
<td>29 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic recurrent PE</td>
<td>5 (0.4)</td>
<td>19 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Death (PE)</td>
<td>0 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
<td></td>
</tr>
<tr>
<td>Death (PE cannot be excluded)</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td></td>
</tr>
</tbody>
</table>

* For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (12 months) irrespective of the actual treatment duration. The individual component of the primary endpoint represents the first occurrence of the event.
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Figure 8 is a plot of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups.

**Figure 8: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Full Analysis Set) – EINSTEIN CHOICE Study**

XARELTO was studied in 9011 patients (4487 XARELTO-treated, 4524 enoxaparin-treated patients) in the RÉgulation de Coagulation in Orthopedic Surgery to Prevent DVT and PE, Controlled, Double-blind, Randomized Study of BAY 59-7939 in the Extended Prevention of VTE in Patients Undergoing Elective Total Hip or Knee Replacement (RECORD 1, 2, and 3) [NCT00329628, NCT00330209, NCT00381894] studies.

The two randomized, double-blind, clinical studies (RECORD 1 and 2) in patients undergoing elective total hip replacement surgery compared XARELTO 10 mg once daily starting at least 6 to 10 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin. In RECORD 3, the enoxaparin regimen was 40 mg once daily started 12 hours preoperatively. The mean age (± SD) of patients in the study was 68.0 ± 9.0 (range 28 to 91) years with 66% of patients ≥65 years. Sixty-eight percent (68%) of patients were female. Eighty-one percent (81%) of patients were White, less than 7% were Asian, and less than 2% were Black. The study excluded patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min or patients with significant liver disease (hepatitis or cirrhosis). In RECORD 1, the mean exposure duration (± SD) to active XARELTO and enoxaparin was 33.3 ± 7.0 and 33.6 ± 8.3 days, respectively. In RECORD 2, the mean exposure duration to active XARELTO and enoxaparin was 33.5 ± 6.9 and 12.4 ± 2.9 days, respectively. After Day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration. The efficacy data for RECORD 1 and 2 are provided in Table 11.

### Table 11: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery - Modified Intent-to-Treat Population

<table>
<thead>
<tr>
<th>Treatment Dosage and Duration</th>
<th>RECORD 1</th>
<th>RECORD 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>XARELTO 10 mg once daily</td>
<td>Enoxaparin 40 mg once daily</td>
<td>RRR*, p-value</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>N=1513</td>
<td>N=1473</td>
</tr>
<tr>
<td>Total VTE</td>
<td>17 (1.1%)</td>
<td>57 (3.9%)</td>
</tr>
<tr>
<td>Components of Total VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>1 (0.1%)</td>
<td>31 (2.1%)</td>
</tr>
<tr>
<td>Distal DVT</td>
<td>12 (0.8%)</td>
<td>26 (1.8%)</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>3 (0.2%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Death (any cause)</td>
<td>4 (0.3%)</td>
<td>4 (0.3%)</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>N=1600</td>
<td>N=1587</td>
</tr>
<tr>
<td>Major VTE</td>
<td>3 (0.2%)</td>
<td>33 (2.1%)</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>N=2103</td>
<td>N=2119</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>5 (0.2%)</td>
<td>11 (0.5%)</td>
</tr>
</tbody>
</table>

* Relative Risk Reduction; CI = confidence interval
† Includes the placebo-controlled period of RECORD 2
‡ Proximal DVT, nonfatal PE or VTE-related death

One randomized, double-blind, clinical study (RECORD 3) in patients undergoing elective total knee replacement surgery compared XARELTO 10 mg once daily started at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin. In RECORD 3, the enoxaparin regimen was 40 mg once daily started 12 hours preoperatively. The mean age (± SD) of patients was 68.0 ± 9.0 (range 28 to 91) years with 66% of patients ≥65 years. Sixty-eight percent (68%) of patients were female. Eighty-one percent (81%) of patients were White, less than 7% were Asian, and less than 2% were Black. The study excluded patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min or patients with significant liver disease (hepatitis or cirrhosis). The mean exposure duration (± SD) to active XARELTO and enoxaparin was 11.9 ± 2.3 and 12.5 ± 3.0 days, respectively. The efficacy data are provided in Table 12.

### Table 12: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Knee Replacement Surgery - Modified Intent-to-Treat Population

<table>
<thead>
<tr>
<th>Treatment Dosage and Duration</th>
<th>RECORD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>XARELTO 10 mg once daily</td>
<td>Enoxaparin 40 mg once daily</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>N=813</td>
</tr>
<tr>
<td>Total VTE</td>
<td>79 (9.7%)</td>
</tr>
<tr>
<td>Components of events contributing to Total VTE</td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>9 (1.1%)</td>
</tr>
<tr>
<td>Distal DVT</td>
<td>74 (9.1%)</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>0</td>
</tr>
<tr>
<td>Death (any cause)</td>
<td>0</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>N=895</td>
</tr>
<tr>
<td>Major VTE†</td>
<td>9 (1.0%)</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>8 (0.7%)</td>
</tr>
</tbody>
</table>

* Relative Risk Reduction; CI = confidence interval
† Proximal DVT, nonfatal PE or VTE-related death

16 HOW SUPPLIED/STORAGE AND HANDLING

XARELTO (rivaroxaban) Tablets are available in the strengths and packages listed below:

- 10 mg tablets are round, light red, biconvex film-coated tablets marked “10” on one side, and “Xa” on the other side. The tablets are supplied in the packages listed:
  - NDC 50458-580-30 Bottle containing 30 tablets
  - NDC 50458-580-90 Bottle containing 90 tablets
  - NDC 50458-580-10 Blister package containing 10 tablets (10 blister cards containing 10 tablets each)

- 15 mg tablets are round, red, biconvex film-coated tablets with a triangle pointing down above a “20” on one side and “Xa” on the other side. The tablets are supplied in the packages listed:
  - NDC 50458-578-30 Bottle containing 30 tablets
  - NDC 50458-578-90 Bottle containing 90 tablets
  - NDC 50458-578-10 Blister package containing 10 tablets (10 blister cards containing 10 tablets each)

- 20 mg tablets are triangle-shaped, dark red film-coated tablets with a triangle pointing down above a “20” marked on one side and “Xa” on the other side. The tablets are supplied in the packages listed:
  - NDC 50458-576-30 Bottle containing 30 tablets
  - NDC 50458-576-90 Bottle containing 90 tablets
  - NDC 50458-576-10 Blister package containing 10 tablets (10 blister cards containing 10 tablets each)

- 30-day starter blister pack containing 51 tablets: 42 tablets of 15 mg and 9 tablets of 20 mg

Store at 25°C (77°F) or room temperature; excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep out of the reach of children.
Patients should be counseled about the benefits and risks of XARELTO (rivaroxaban). They should be advised to inform their healthcare professional if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions.

**Patient Counseling Information**

See FDA-approved patient labeling (Medication Guide).

**Instructions for Patient Use**

- Advise patients to take XARELTO only as directed.
- Remind patients not to discontinue XARELTO without first talking to their healthcare professional.
- Advise patients with atrial fibrillation to take XARELTO once daily with the evening meal.
- Advise patients for initial treatment of DVT and/or PE to take XARELTO 15 mg or 20 mg tablets with food at approximately the same time every day [see Dosage and Administration (2.5)].
- Advise patients who are at a continued risk of recurrent DVT and/or PE after at least 6 months of initial treatment, to take XARELTO 10 mg once daily with or without food [see Dosage and Administration (2.6)].
- Advise patients who cannot swallow the tablet whole to crush XARELTO and combine with a small amount of applesauce followed by food [see Dosage and Administration (2.10)].
- For patients requiring an NG tube or gastric feeding tube, instruct the patient or caregiver to crush the XARELTO tablet and mix it with a small amount of water before administering via the tube [see Dosage and Administration (2.10)].
- If a dose is missed, advise the patient to take XARELTO as soon as possible on the same day and continue on the following day with their recommended daily dose regimen.

**Bleeding Risks**

- Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it may take them longer than usual to stop bleeding, and that they may bruise and/or bleed more easily when they are treated with XARELTO [see Warnings and Precautions (5.2)].
- If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately [see Boxed Warning].

**Invasive or Surgical Procedures**

Instruct patients to inform their healthcare professional that they are taking XARELTO before any invasive procedure (including dental procedures) is scheduled.

**Concomitant Medication and Herbals**

Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions [see Drug Interactions (7)].
What is the most important information I should know about XARELTO?

- **For people taking XARELTO for atrial fibrillation:**
  People with atrial fibrillation (an irregular heart beat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. XARELTO lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking XARELTO, you may have increased risk of forming a clot in your blood.

  **Do not stop taking XARELTO without talking to the doctor who prescribes it for you. Stopping XARELTO increases your risk of having a stroke.**

  If you have to stop taking XARELTO, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.

- **XARELTO can cause bleeding** which can be serious, and rarely may lead to death. This is because XARELTO is a blood thinner medicine (anticoagulant) that reduces blood clotting. While you take XARELTO you are likely to bruise more easily and it may take longer for bleeding to stop.

  You may have a higher risk of bleeding if you take XARELTO and take other medicines that increase your risk of bleeding, including:
  - aspirin or aspirin containing products
  - non-steroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (Coumadin®, Jantoven®)
  - any medicine that contains heparin
  - clopidogrel (Plavix®)
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - other medicines to prevent or treat blood clots

  Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

  **Call your doctor or get medical help right away if you develop any of these signs or symptoms of bleeding:**
  - unexpected bleeding or bleeding that lasts a long time, such as:
    - nose bleeds that happen often
    - unusual bleeding from the gums
    - menstrual bleeding that is heavier than normal or vaginal bleeding
  - bleeding that is severe or you cannot control
  - red, pink or brown urine
  - bright red or black stools (looks like tar)
  - cough up blood or blood clots
  - vomit blood or your vomit looks like “coffee grounds”
  - headaches, feeling dizzy or weak
  - pain, swelling, or new drainage at wound sites

- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like XARELTO, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine

  If you take XARELTO and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots. Tell your doctor right away if you have back pain, tingling, numbness, muscle weakness (especially in your legs and feet), loss of control of the bowels or bladder (incontinence).

- **XARELTO is not for people with artificial heart valves.**
What is XARELTO?

XARELTO is a prescription medicine used to:

• reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to the formation of blood clots, which can travel to the brain, causing a stroke, or to other parts of the body.
• treat blood clots in the veins of your legs (deep vein thrombosis or DVT) or lungs (pulmonary embolism or PE)
• reduce the risk of blood clots happening again in people who continue to be at risk for DVT or PE after receiving treatment for blood clots for at least 6 months.
• reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery

It is not known if XARELTO is safe and effective in children.

Do not take XARELTO if you:

• currently have certain types of abnormal bleeding. Talk to your doctor before taking XARELTO if you currently have unusual bleeding.
• are allergic to rivaroxaban or any of the ingredients in XARELTO. See the end of this leaflet for a complete list of ingredients in XARELTO.

Before taking XARELTO, tell your doctor about all of your medical conditions, including if you:

• have ever had bleeding problems
• have liver or kidney problems
• are pregnant or plan to become pregnant. It is not known if XARELTO will harm your unborn baby.
  - Tell your doctor right away if you become pregnant during treatment with XARELTO. Taking XARELTO while you are pregnant may increase the risk of bleeding in you or in your unborn baby.
  - If you take XARELTO during pregnancy tell your doctor right away if you have any signs or symptoms of bleeding or blood loss. See “What is the most important information I should know about XARELTO?” for signs and symptoms of bleeding.
• are breastfeeding or plan to breastfeed. XARELTO may pass into your breast milk. You and your doctor should decide if you will take XARELTO or breastfeed.

Tell all of your doctors and dentists that you are taking XARELTO. They should talk to the doctor who prescribed XARELTO for you before you have any surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way XARELTO works. Certain medicines may increase your risk of bleeding. See “What is the most important information I should know about XARELTO?”
How should I take XARELTO?

• Take XARELTO exactly as prescribed by your doctor.
• Do not change your dose or stop taking XARELTO unless your doctor tells you to.
• Your doctor may change your dose if needed.
• If you take XARELTO for:
  o atrial fibrillation:
    ▪ Take XARELTO 1 time a day with your evening meal.
    ▪ If you miss a dose of XARELTO, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
  o blood clots in the veins of your legs or lungs:
    ▪ Take XARELTO 1 or 2 times a day as prescribed by your doctor.
    ▪ For the 15 mg and 20 mg doses, XARELTO should be taken with food.
    ▪ For the 10 mg dose, XARELTO may be taken with or without food.
    ▪ Take your XARELTO doses at the same times each day.
    ▪ If you miss a dose:
      ➢ If you take the 15 mg dose of XARELTO 2 times a day (a total of 30 mg of XARELTO in 1 day): Take XARELTO as soon as you remember on the same day. You may take 2 doses at the same time to make up for the missed dose. Take your next dose at your regularly scheduled time.
      ➢ If you take XARELTO 1 time a day: Take XARELTO as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
  o hip or knee replacement surgery:
    ▪ Take XARELTO 1 time a day with or without food.
    ▪ If you miss a dose of XARELTO, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
• If you have difficulty swallowing the XARELTO tablet whole, talk to your doctor about other ways to take XARELTO.
• Your doctor will decide how long you should take XARELTO.
• Your doctor may stop XARELTO for a short time before any surgery, medical or dental procedure. Your doctor will tell you when to start taking XARELTO again after your surgery or procedure.
• Do not run out of XARELTO. Refill your prescription of XARELTO before you run out. When leaving the hospital following a hip or knee replacement, be sure that you will have XARELTO available to avoid missing any doses.
• If you take too much XARELTO, go to the nearest hospital emergency room or call your doctor right away.

What are the possible side effects of XARELTO?

• See “What is the most important information I should know about XARELTO?”

Call your doctor for medical advice about side effects that you have. You may report side effects to FDA at 1 800-FDA-1088.

How should I store XARELTO?

• Store XARELTO at room temperature between 68°F to 77°F (20°C to 25°C).

Keep XARELTO and all medicines out of the reach of children.
General information about the safe and effective use of XARELTO.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XARELTO for a condition for which it was not prescribed. Do not give XARELTO to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or doctor for information about XARELTO that is written for health professionals.

What are the ingredients in XARELTO?
Active ingredient: rivaroxaban
Inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.
The proprietary film coating mixture for XARELTO 10 mg tablets is Opadry® Pink and contains: ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide.
The proprietary film coating mixture for XARELTO 15 mg tablets is Opadry® Red and contains: ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide.
The proprietary film coating mixture for XARELTO 20 mg tablets is Opadry® II Dark Red and contains: ferric oxide red, polyethylene glycol 3350, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.
Finished Product Manufactured by: Janssen Ortho LLC  Gurabo, PR 00778 or Bayer AG 51368 Leverkusen, Germany
Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560  Licensed from: Bayer HealthCare AG 51368 Leverkusen, Germany
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For more information call 1-800-526-7736 or go to www.XARELTO-US.com.

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