XARELTO® (rivaroxaban) tablets, for oral use

Initial U.S. Approval: 2011

WARNING: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, and (B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning

DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Discontinuing XARELTO places patients at an increased risk of thrombotic events. To reduce this risk, consider administering another anticoagulant if XARELTO must be discontinued for a reason other than pathological bleeding (2.3, 5.1, 14.1).

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).

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA

1 INDICATIONS AND USAGE

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

1.2 Treatment of Deep Vein Thrombosis and Pulmonary Embolism (PE) in Patients with Nonvalvular Atrial Fibrillation

1.3 Treatment of Pulmonary Embolism

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Food Effect Information

2.2 Switching to and from XARELTO

2.3 Nonvalvular Atrial Fibrillation

2.4 Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Risk of Recurrence of DVT and PE

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Active pathological bleeding (4)

Severe hypersensitivity reaction to XARELTO (4)

5 WARNINGS AND PRECAUTIONS

Risk of bleeding: XARELTO can cause serious and fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (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)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, 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 (7.1, 7.2)

Anticoagulants: Avoid concomitant use (7.3)

USE IN SPECIFIC POPULATIONS

Nursing mothers: discontinue drug or discontinue nursing (8.3)

Renal impairment: Avoid or adjust dose based on CrCl (8.7)

Hepatic impairment: Avoid use in patients with Child-Pugh B and C hepatic impairment or with any degree of hepatic disease associated with coagulopathy (8.8)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2012
7.4 Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Females of Reproductive Potential
8.7 Renal Impairment
8.8 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.6 QT/QTc Prolongation

13 NON-CLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
17.1 Instructions for Patient Use
17.2 Bleeding Risks
17.3 Invasive or Surgical Procedures
17.4 Concomitant Medication and Herbals
17.5 Pregnancy and Pregnancy-Related Hemorrhage
17.6 Nursing
17.7 Females of Reproductive Potential

*Sections or subsections omitted from the full prescribing information are not listed.
WARNING: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA

A. DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION
Discontinuing XARELTO places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following XARELTO discontinuation in clinical trials in atrial fibrillation patients. If anticoagulation with XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant [see Dosage and Administration (2.3), 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 [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 of Pulmonary Embolism
XARELTO is indicated for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial 6 months treatment for DVT and/or PE.

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in Risk of Stroke in Nonvalvular Atrial Fibrillation (2.3)</td>
<td></td>
</tr>
<tr>
<td>CrCl &gt;50 mL/min:</td>
<td>20 mg once daily with the evening meal</td>
</tr>
<tr>
<td>CrCl 15 to 50 mL/min:</td>
<td>15 mg once daily with the evening meal</td>
</tr>
<tr>
<td>Treatment of DVT (2.4)</td>
<td>15 mg twice daily with food, for first 21 days</td>
</tr>
<tr>
<td>Treatment of PE (2.4)</td>
<td>▼after 21 days, transition to ▼</td>
</tr>
<tr>
<td></td>
<td>20 mg once daily with food, for remaining treatment</td>
</tr>
<tr>
<td>Reduction in the Risk of Recurrence of DVT and of PE (2.4)</td>
<td>20 mg once daily with food</td>
</tr>
<tr>
<td>Prophylaxis of DVT Following Hip or Knee Replacement Surgery (2.5)</td>
<td>Hip replacement: 10 mg once daily for 35 days</td>
</tr>
<tr>
<td></td>
<td>Knee replacement: 10 mg once daily for 12 days</td>
</tr>
</tbody>
</table>

2.1 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.

2.2 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 (7.3)].

Switching from Anticoagulants other than Warfarin to XARELTO - For patients currently receiving an anticoagulant other than warfarin, start XARELTO 0 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.

2.3 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 (8.7)].

2.4 Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of 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. The recommended dose of XARELTO for reduction in the risk of recurrence of DVT or PE is 20 mg taken orally once daily with food at approximately the same time each day [see Clinical Studies (14.2)].
2.5 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 at least 6 to 10 hours after surgery once hemostasis has been established [see Dosage and Administration (2.6)].

- 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.

2.6 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.

2.7 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, 15 or 10 mg once daily: The patient should take the missed XARELTO dose immediately.

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 Stroke after Discontinuation in Nonvalvular Atrial Fibrillation
Discontinuing 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 must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant [see Dosage and Administration (2.3) 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.

A specific antidote for rivaroxaban is not 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. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving rivaroxaban. Use of procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rFVIIa) may be considered but has not been evaluated in clinical trials.

Reference ID: 3212129
Concomitant use of other drugs affecting hemostasis increases the risk of bleeding. These include aspirin, P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs) [see Drug Interactions (7.3)].

Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) increases rivaroxaban exposure and may increase bleeding risk [see Drug Interactions (7.1)].

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].

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.

5.4 Use in Patients with Renal Impairment

Nonvalvular Atrial Fibrillation
Avoid the use of XARELTO in patients with CrCl <15 mL/min since drug exposure is increased. Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly. Discontinue XARELTO in patients who develop acute renal failure while on XARELTO [see Use in Specific Populations (8.7)].

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE
Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population [see Use in Specific Populations (8.7)].

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO should discontinue the treatment [see Use in Specific Populations (8.7)].
5.5 Use in Patients with Hepatic Impairment

No clinical data are available for patients with severe hepatic impairment.

Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased [see Use in Specific Populations (8.8)].

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

Avoid concomitant use of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) [see Drug Interactions (7.1)].

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 Drug Interactions (7.2)].

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 nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

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, 16326 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); 4728 patients
who received either XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily (EINSTEIN DVT, EINSTEIN PE) or 20 mg orally once daily (EINSTEIN Extension) to treat DVT, PE, and to reduce the risk of recurrence of DVT and of 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.

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO N = 7111 n (%)</th>
<th>Event Rate (per 100 Pt-yrs)</th>
<th>Warfarin N = 7125 n (%)</th>
<th>Event Rate (per 100 Pt-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding†</td>
<td>395 (5.6)</td>
<td>3.6</td>
<td>386 (5.4)</td>
<td>3.5</td>
</tr>
<tr>
<td>Bleeding into a critical organ‡</td>
<td>91 (1.3)</td>
<td>0.8</td>
<td>133 (1.9)</td>
<td>1.2</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>27 (0.4)</td>
<td>0.2</td>
<td>55 (0.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Bleeding resulting in transfusion of ≥2 units of whole blood or packed red blood cells</td>
<td>183 (2.6)</td>
<td>1.7</td>
<td>149 (2.1)</td>
<td>1.3</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>221 (3.1)</td>
<td>2.0</td>
<td>140 (2.0)</td>
<td>1.2</td>
</tr>
</tbody>
</table>

* For all sub-types of major bleeding, single events may be represented in more than one row, and individual patients may have more than one event.
† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. Hemorrhagic strokes are counted as both bleeding and efficacy events. Major bleeding rates excluding strokes are 3.3 per 100 Pt-yrs for XARELTO vs. 2.9 per 100 Pt-yrs for warfarin.
‡ The majority of the events were intracranial, and also included intraspinal, intraocular, pericardial, intrarticular, intramuscular with compartment syndrome, or retroperitoneal.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and to Reduce the Risk of Recurrence of DVT and of 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. 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†</th>
<th>Enoxaparin/ VKA†</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>Retropertitoneal†</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>Intra-articular†</td>
<td>0</td>
<td>4 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal non-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 (28.3)</td>
<td>1153 (28.0)</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)]
‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group
§ 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

EINSTEIN Extension Study

In the EINSTEIN Extension clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1.8% for XARELTO vs. 0.2% for placebo treatment groups. The mean duration of treatment was 190 days for both XARELTO and placebo treatment groups.

Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN Extension study.
Table 3: Bleeding Events* in EINSTEIN Extension Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO† 20 mg N = 598 n (%)</th>
<th>Placebo N = 590 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event†</td>
<td>4 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Decrease in Hb ≥2 g/dL</td>
<td>4 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Transfusion of ≥2 units of whole blood or packed red blood cells</td>
<td>2 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>32 (5.4)</td>
<td>7 (1.2)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>104 (17.4)</td>
<td>63 (10.7)</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 20 mg once daily; matched placebo once daily
‡ There were no fatal or critical organ bleeding events.

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></th>
<th>XARELTO 10 mg</th>
<th>Enoxaparin†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total treated patients</strong></td>
<td>N = 4487</td>
<td>N = 4524</td>
</tr>
<tr>
<td>n (%)</td>
<td>14 (0.3)</td>
<td>9 (0.2)</td>
</tr>
<tr>
<td>Major bleeding event</td>
<td></td>
<td></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 &gt;2 units of whole blood or packed cells</td>
<td>4 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td><strong>Any bleeding event‡</strong></td>
<td>261 (5.8)</td>
<td>251 (5.6)</td>
</tr>
</tbody>
</table>

| **Hip Surgery Studies**       | N = 3281      | N = 3298    |
| n (%)                         | 7 (0.2)       | 3 (0.1)     |
| Major bleeding event          |               |             |
| Fatal bleeding                | 1 (<0.1)      | 0           |
| Bleeding into a critical organ| 1 (<0.1)      | 1 (<0.1)    |
| Bleeding that required re-operation | 2 (0.1) | 1 (<0.1)    |
| Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells | 3 (0.1) | 1 (<0.1) |
| **Any bleeding event‡**       | 201 (6.1)     | 191 (5.8)   |

| **Knee Surgery Study**        | N = 1206      | N = 1226    |
| n (%)                         | 7 (0.6)       | 6 (0.5)     |
| Major bleeding event          |               |             |
| Fatal bleeding                | 0             | 0           |
| Bleeding into a critical organ| 1 (0.1)       | 2 (0.2)     |
| Bleeding that required re-operation | 5 (0.4) | 4 (0.3)     |
| Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells | 1 (0.1) | 0           |
| **Any bleeding event‡**       | 60 (5.0)      | 60 (4.9)    |

* 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 Extension study are shown in Table 5.
Table 5: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN Extension Study

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>XARELTO N = 598 n (%)</th>
<th>Placebo N = 590 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Abdominal pain upper</td>
<td>10 (1.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>8 (1.3)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Toothache</td>
<td>6 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Fatigue</td>
<td>6 (1.0)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>Sinusitis</td>
<td>7 (1.2)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>7 (1.2)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Back pain</td>
<td>22 (3.7)</td>
<td>7 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Osteoarthritis</td>
<td>10 (1.7)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Oropharyngeal pain</td>
<td>6 (1.0)</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

* Adverse reaction (with Relative Risk >1.5 for XARELTO versus placebo) occurred after the first dose and up to 2 days after the last dose of study drug. Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical adverse reactions, the patient is counted only once in a category. The same patient may appear in different categories.

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 6.

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

<table>
<thead>
<tr>
<th>System/Organ Class</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 125 (2.8)</td>
<td>89 (2.0)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity 74 (1.7)</td>
<td>55 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Muscle spasm 52 (1.2)</td>
<td>32 (0.7)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Syncope 55 (1.2)</td>
<td>32 (0.7)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus 96 (2.1)</td>
<td>79 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Blisters 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 rivaroxaban. 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

Gastrointestinal disorders: retroperitoneal hemorrhage

Hepatobiliary disorders: jaundice, cholestasis, cytolytic hepatitis

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

7 DRUG INTERACTIONS

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters (e.g., P-gp) may result in changes in rivaroxaban exposure.

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

In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin, erythromycin and fluconazole), increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. The increases in exposure ranged from 30% to 160%. Significant increases in rivaroxaban exposure may increase bleeding risk [see Clinical Pharmacology (12.3)].

When data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.
Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors [see Warnings and Precautions (5.6)].

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

Results from drug interaction studies and population PK analyses from clinical studies indicate coadministration of XARELTO with a combined P-gp and strong CYP3A4 inducer (e.g., rifampicin, phenytoin) decreased rivaroxaban exposure by up to 50%. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy [see Clinical Pharmacology (12.3)].

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)].

7.3 Anticoagulants and NSAIDs/Aspirin

Single doses of enoxaparin and XARELTO given concomitantly resulted in an additive effect on anti-factor Xa activity. Single doses of warfarin and XARELTO resulted in an additive effect on factor Xa inhibition and PT. Concomitant aspirin use has been identified as an independent risk factor for major bleeding in efficacy trials. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with XARELTO. Coadministration of the platelet aggregation inhibitor clopidogrel and XARELTO resulted in an increase in bleeding time for some subjects [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)].

7.4 Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

Patients with renal impairment receiving full dose XARELTO in combination with drugs classified as combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, quinidine, ranolazine, dronedarone, felodipine, erythromycin, and azithromycin) may have increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected.
XARELTO should be used in patients with CrCl 15 to 50 mL/min who are receiving concomitant combined P-gp and weak or moderate CYP3A4 inhibitors only if the potential benefit justifies the potential risk [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Category C

There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus [see Warnings and Precautions (5.7)].

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of $\geq 10$ mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 14 times the human exposure of unbound drug.

8.2 Labor and Delivery

Safety and effectiveness of XARELTO during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

8.3 Nursing Mothers

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue XARELTO, taking into account the importance of the drug to the mother.
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 37% were 65 years and over and about 16% 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 Females of Reproductive Potential
Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

8.7 Renal Impairment
In a pharmacokinetic study, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% 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 and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function [see Dosage and Administration (2.3)].

Treatment of DVT and/or PE, and Reduction in the Risk of Recurrence of DVT and of PE
In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery
The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. Observe closely and promptly evaluate any signs or
symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

8.8 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. A specific antidote for rivaroxaban is not available. 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 expected to be dialyzable [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].

11 DESCRIPTION

Rivaroxaban, a factor Xa inhibitor, is the active ingredient in XARELTO Tablets with the chemical name 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. The molecular formula of rivaroxaban is C_{19}H_{18}ClN_{3}O_{5}S and the molecular weight is 435.89. The structural formula is:

![Structural formula of rivaroxaban](attachment:image.png)

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 inactive ingredients of XARELTO are: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Additionally, the proprietary film coating mixture used for XARELTO 10 mg tablets is Opadry® Pink and XARELTO 15 mg tablets is Opadry® Red, containing ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide, and for XARELTO 20 mg tablets is Opadry® II Dark Red, containing ferric oxide red, polyethylene glycol 3350, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XARELTO is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of rivaroxaban is dose-dependent. For the 10 mg dose, it is estimated to be 80% to 100% and is 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%. Coadministration of XARELTO with food increases the bioavailability of the 20 mg dose (mean AUC and C max increasing by 39% and 76% respectively with food). XARELTO 15 mg and 20 mg tablets should be taken with food [see Dosage and Administration (2.1)].

The maximum concentrations (C max) of rivaroxaban appear 2 to 4 hours after tablet intake. The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH. Coadministration of XARELTO (30 mg single dose) with the H2-receptor antagonist ranitidine (150 mg twice daily), the antacid aluminum hydroxide/magnesium hydroxide (10 mL) or XARELTO (20 mg single dose) with the PPI omeprazole (40 mg once daily) did not show an effect on the bioavailability and exposure of rivaroxaban.

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and C max 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 via a method that could deposit drug directly into the proximal small intestine (e.g., feeding tube) which can result in reduced absorption and related drug exposure.

Distribution
Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism
Approximately 51% of an orally administered $[^{14}\text{C}]$-rivaroxaban dose was recovered as 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
Following oral administration of a $[^{14}\text{C}]$-rivaroxaban dose, 66% of the radioactive dose was recovered in urine (36% as unchanged drug) and 28% was recovered in feces (7% as unchanged drug). Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 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

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
In clinical studies, elderly subjects exhibited higher rivaroxaban plasma concentrations than younger subjects with mean AUC values being approximately 50% higher, mainly due to
reduced (apparent) total body and renal clearance. Age related changes in renal function may play a role in this age effect. The terminal elimination half-life is 11 to 13 hours in the elderly [see Use in Specific Populations (8.5)].

Body Weight
Extremes in body weight (<50 kg or >120 kg) did not influence (less than 25%) rivaroxaban exposure.

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 Table 7). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CrCl (mL/min)</th>
<th>50 to 79</th>
<th>30 to 49</th>
<th>15 to 29</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N = 8</td>
<td>N = 8</td>
<td>N = 8</td>
</tr>
<tr>
<td>Exposure</td>
<td>AUC</td>
<td>44</td>
<td>52</td>
<td>64</td>
</tr>
<tr>
<td>(% increase relative to normal)</td>
<td>C_{max}</td>
<td>28</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>FXa Inhibition</td>
<td>AUC</td>
<td>50</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>(% increase relative to normal)</td>
<td>E_{max}</td>
<td>9</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>PT Prolongation</td>
<td>AUC</td>
<td>33</td>
<td>116</td>
<td>144</td>
</tr>
<tr>
<td>(% increase relative to normal)</td>
<td>E_{max}</td>
<td>4</td>
<td>17</td>
<td>20</td>
</tr>
</tbody>
</table>

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect; and CrCl = creatinine clearance

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 Table 8). 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). Increases in pharmacodynamic effects were also observed.
Table 8: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Hepatic Insufficiency from a Dedicated Hepatic Impairment Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hepatic Impairment Class (Child-Pugh Class)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild (Child-Pugh A)</td>
</tr>
<tr>
<td></td>
<td>N = 8</td>
</tr>
<tr>
<td>Exposure AUC (%) increase relative to normal</td>
<td>15</td>
</tr>
<tr>
<td>Cmax (%) increase relative to normal</td>
<td>0</td>
</tr>
<tr>
<td>FXa Inhibition AUC (%) increase relative to normal</td>
<td>8</td>
</tr>
<tr>
<td>Emax (%) increase relative to normal</td>
<td>0</td>
</tr>
<tr>
<td>PT Prolongation AUC (%) increase relative to normal</td>
<td>6</td>
</tr>
<tr>
<td>Emax (%) increase relative to normal</td>
<td>2</td>
</tr>
</tbody>
</table>

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; Cmax = maximum concentration; Emax = maximum effect

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.

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

In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors the following increases in rivaroxaban exposure were observed. Similar increases in pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were also observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

- **Ketoconazole (combined P-gp and strong CYP3A4 inhibitor):** Steady-state rivaroxaban AUC and Cmax increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.

- **Ritonavir (combined P-gp and strong CYP3A4 inhibitor):** Single-dose rivaroxaban AUC and Cmax increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.

- **Clarithromycin (combined P-gp and strong CYP3A4 inhibitor):** Single-dose rivaroxaban AUC and Cmax increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.

- **Erythromycin (combined P-gp and moderate CYP3A4 inhibitor):** Both the single-dose rivaroxaban AUC and Cmax increased by 30%.
• **Fluconazole (moderate CYP3A4 inhibitor):** Single-dose rivaroxaban AUC and C\text{max} increased by 40% and 30%, respectively.

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

In a drug interaction study, coadministration of XARELTO (20 mg single dose with food) with a drug that is a combined P-gp and strong CYP3A4 inducer (rifampicin titrated up to 600 mg once daily) led to an approximate decrease of 50% and 22% in AUC and C\text{max}, respectively. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy.

**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. Enoxaparin did not affect the pharmacokinetics of rivaroxaban. In another study, single doses of warfarin (15 mg) and XARELTO (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Warfarin did not affect the pharmacokinetics of rivaroxaban.

**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. In a single-dose drug interaction study there were no pharmacokinetic or pharmacodynamic interactions observed after concomitant administration of naproxen or aspirin (acetylsalicylic acid) with XARELTO.

**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**

Based on simulated pharmacokinetic data, patients with renal impairment receiving full dose XARELTO in combination with drugs classified as combined P-gp and weak or moderate CYP3A4 inhibitors may have increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected.
While increases in rivaroxaban exposure can be expected under such conditions, results from an analysis in the ROCKET AF trial, which allowed concomitant use with combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, chloramphenicol, cimetidine, and erythromycin), did not show an increase in bleeding in patients with CrCl 30 to <50 mL/min [Hazard Ratio (95% CI): 1.05 (0.77, 1.42)] [see Use in Specific Populations (8.7)].

**Drugs that are Substrates of CYP3A4 and/or Drug Transport Systems**

In addition, there were no significant pharmacokinetic interactions observed in studies comparing concomitant rivaroxaban 20 mg and 7.5 mg single dose of midazolam (substrate of CYP3A4), 0.375 mg once-daily dose of digoxin (substrate of P-gp), or 20 mg once daily dose of atorvastatin (substrate of CYP3A4 and P-gp) in healthy volunteers.

**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 ROCKET AF, a multinational, 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, 13% 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 of 55%, 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 9 displays the overall results for the primary composite endpoint and its components.
Table 9: Primary Composite Endpoint Results in ROCKET AF Study

<table>
<thead>
<tr>
<th>Event</th>
<th>XARELTO N = 7081</th>
<th>Event Rate (per 100 Pt-yrs)</th>
<th>Warfarin N = 7090</th>
<th>Event Rate (per 100 Pt-yrs)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Endpoint*</td>
<td>269 (3.8)</td>
<td>2.1</td>
<td>306 (4.3)</td>
<td>2.4</td>
<td>0.88 (0.74, 1.03)</td>
</tr>
<tr>
<td>Stroke</td>
<td>253 (3.6)</td>
<td>2.0</td>
<td>281 (4.0)</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>33 (0.5)</td>
<td>0.3</td>
<td>57 (0.8)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>206 (2.9)</td>
<td>1.6</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>0.2</td>
<td>18 (0.3)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Non-CNS Systemic Embolism</td>
<td>20 (0.3)</td>
<td>0.2</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.

Figure 1 is a plot of the time from randomization to the occurrence of the first primary endpoint event in the two treatment arms.
The efficacy of XARELTO was generally consistent across major subgroups.

The protocol for ROCKET AF did not stipulate anticoagulation after study drug discontinuation, but warfarin patients who completed the study were generally maintained on warfarin. XARELTO patients were generally switched to warfarin without a period of coadministration of warfarin and XARELTO, so that they were not adequately anticoagulated after stopping XARELTO until attaining a therapeutic INR. During the 28 days following the end of the study, there were 22 strokes in the 4637 patients taking XARELTO vs. 6 in the 4691 patients taking warfarin.

Few patients in ROCKET AF underwent electrical cardioversion for atrial fibrillation. The utility of XARELTO for preventing post-cardioversion stroke and systemic embolism is unknown.
14.2 Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE

EINSTEIN Deep Vein Thrombosis and EINSTEIN Pulmonary Embolism Studies

XARELTO for the treatment of DVT and/or PE and for the reduction in the risk of recurrence of DVT and of PE was studied in EINSTEIN DVT and EINSTEIN PE, multi-national, open-label, non-inferiority studies comparing XARELTO (at an initial dose of 15 mg twice daily with food for the first three weeks, followed by XARELTO 20 mg once daily with food) to enoxaparin 1 mg/kg twice daily for at least five days with VKA and then continued with VKA only after the target INR (2.0-3.0) was reached. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent and patients with creatinine clearance <30 mL/min, significant liver disease, or active bleeding were excluded from the studies. The intended treatment duration was 3, 6, or 12 months based on investigator's assessment prior to randomization.

A total of 8281 (3449 in EINSTEIN DVT and 4832 in EINSTEIN PE) patients were randomized and followed on study treatment for a mean of 208 days in the XARELTO group and 204 days in the enoxaparin/VKA group. The mean age was approximately 57 years. The population was 55% male, 70% Caucasian, 9% Asian and about 3% Black. About 73% and 92% of XARELTO-treated patients in the EINSTEIN DVT and EINSTEIN PE studies, respectively, received initial parenteral anticoagulant treatment for a median duration of 2 days. Enoxaparin/VKA-treated patients in the EINSTEIN DVT and EINSTEIN PE studies received initial parenteral anticoagulant treatment for a median duration of 8 days. Aspirin was taken as on treatment concomitant antithrombotic medication by approximately 12% of patients in both treatment groups. Patients randomized to VKA had an unadjusted mean percentage of time in the INR target range of 2.0 to 3.0 of 58% in EINSTEIN DVT study and 60% in EINSTEIN PE study, with the lower values occurring during the first month of the study.

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%).

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): 0.68 (0.44, 1.04); EINSTEIN PE HR (95% CI): 1.12 (0.75, 1.68)]. 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.
Table 10 displays the overall results for the primary composite endpoint and its components for EINSTEIN DVT and EINSTEIN PE studies.

Table 10: 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><strong>EINSTEIN DVT Study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 1731 n (%)</td>
<td>N = 1718 n (%)</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 only</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><strong>EINSTEIN PE Study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 2419 n (%)</td>
<td>N = 2413 n (%)</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 only</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 2 and 3 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.

Reference ID: 3212129
Figure 2: 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

![Graph showing cumulative event rate (%)]

- Cumulative Event Rate (%)
- HR (95% CI): 0.68 (0.44, 1.04)

Number of Patients at Risk
- Enoxaparin/VKA (N=1718): 1616, 1581, 1565, 1368, 1358, 1301, 380, 362, 342, 325, 297, 264
- XARELTO (N=1731): 1668, 1648, 1638, 1424, 1412, 1369, 400, 369, 364, 345, 309, 266

Reference ID: 3212129
EINSTEIN Extension Study

XARELTO for reduction in the risk of recurrence of DVT and of PE was studied in the EINSTEIN Extension study, a multi-national, double-blind, superiority study comparing XARELTO (20 mg once daily with food) to placebo in patients who had completed 6 to 14 months of treatment for DVT and/or PE following the acute event. The intended treatment duration was 6 or 12 months based on investigator's assessment prior to randomization.

A total of 1196 patients were randomized and followed on study treatment for a mean of 190 days for both XARELTO and placebo treatment groups. The mean age was approximately 58 years. The population was 58% male, 78% Caucasian, 8% Asian and about 2% Black. Aspirin was taken as on-treatment concomitant antithrombotic medication by approximately 12% of patients in both treatment groups. In the EINSTEIN Extension study about 60% of patients had a history of proximal index DVT without PE event and 29% of patients had a PE without
symptomatic DVT event. About 59% of patients had an idiopathic DVT/PE. Other risk factors included previous episode of DVT/PE (16%), immobilization (14%), known thrombophilic conditions (8%), or active cancer (5%).

In the EINSTEIN Extension study XARELTO was demonstrated to be superior to placebo for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE [HR (95% CI): 0.18 (0.09, 0.39)].

Table 11 displays the overall results for the primary composite endpoint and its components.

<table>
<thead>
<tr>
<th>Event</th>
<th>XARELTO 20 mg</th>
<th>Placebo</th>
<th>XARELTO vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 602 n (%)</td>
<td>N = 594 n (%)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Primary Composite Endpoint</td>
<td>8 (1.3)</td>
<td>42 (7.1)</td>
<td>0.18 (0.09, 0.39)</td>
</tr>
<tr>
<td>Death (PE)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>p-value=&lt;0.0001</td>
</tr>
<tr>
<td>Death (PE cannot be excluded)</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Symptomatic recurrent PE</td>
<td>2 (0.3)</td>
<td>13 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic recurrent DVT</td>
<td>5 (0.8)</td>
<td>31 (5.2)</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 (6 or 12 months) irrespective of the actual treatment duration.

Figure 4 is a plot of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups.
14.3 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

XARELTO was studied in 9011 patients (4487 XARELTO-treated, 4524 enoxaparin-treated patients) in the RECORD 1, 2, and 3 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 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin 40 mg once daily started 12 hours preoperatively. In RECORD 1 and 2, a total of 6727 patients were randomized and 6579 received study drug. The mean age \(\pm\) standard deviation (SD) was 63 \(\pm\) 12.2 (range 18 to 93) years with 49% of patients \(\geq\)65 years and 55% of patients were female. More than 82% of patients were White, 7% were Asian, and less than 2% were Black. The studies excluded patients undergoing staged bilateral total hip replacement, 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 (\(\pm\) SD) to active XARELTO and enoxaparin was 33.3 \(\pm\) 7.0 and 33.6 \(\pm\) 8.3 days, respectively. In RECORD 2, the mean exposure duration to active XARELTO and enoxaparin was 33.5 \(\pm\) 6.9 and 12.4 \(\pm\) 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 12.

Table 12: 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>
<th>RECORD 1</th>
<th>RECORD 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XARELTO</td>
<td>Enoxaparin</td>
<td>RRR*, p-value</td>
<td>XARELTO</td>
</tr>
<tr>
<td>XARELTO 10 mg once daily</td>
<td>N = 1513</td>
<td>N = 1473</td>
<td>71% (95% CI: 50, 83), p&lt;0.001</td>
<td>17 (2.0%)</td>
</tr>
<tr>
<td>Enoxaparin 40 mg once daily</td>
<td>57 (3.9%)</td>
<td>17 (0.6%)</td>
<td>40 (4.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Components of Total VTE

<table>
<thead>
<tr>
<th></th>
<th>N = 1600</th>
<th>N = 1587</th>
<th>N = 928</th>
<th>N = 929</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT</td>
<td>3 (0.2%)</td>
<td>33 (2.1%)</td>
<td>6 (0.7%)</td>
<td>45 (4.8%)</td>
</tr>
<tr>
<td>Distal DVT</td>
<td>12 (0.8%)</td>
<td>26 (1.8%)</td>
<td>11 (1.3%)</td>
<td>43 (5.2%)</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>4 (0.3%)</td>
<td>4 (0.3%)</td>
<td>2 (0.2%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Death (any cause)</td>
<td>4 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Components of Total VTE</td>
<td>N = 1600</td>
<td>N = 1587</td>
<td>N = 928</td>
<td>N = 929</td>
</tr>
<tr>
<td>Major VTE†</td>
<td>3 (0.2%)</td>
<td>33 (2.1%)</td>
<td>6 (0.7%)</td>
<td>45 (4.8%)</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>5 (0.2%)</td>
<td>11 (0.5%)</td>
<td>3 (0.3%)</td>
<td>15 (1.3%)</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 in the study was 68 ± 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 13.
Table 13: 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 N = 813</td>
<td>N = 871</td>
</tr>
<tr>
<td>Total VTE</td>
<td></td>
</tr>
<tr>
<td>79 (9.7%)</td>
<td>164 (18.8%)</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 N = 895</td>
<td>N = 917</td>
</tr>
<tr>
<td>Major VTE†</td>
<td>9 (1.0%)</td>
</tr>
<tr>
<td>Number of Patients N = 1206</td>
<td>N = 1226</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 with a triangle pointing down above a “10” on one side, and an “Xa” on the other side. The tablets are supplied in the packages listed:**
  - NDC 50458-580-30 Bottle containing 30 tablets
  - NDC 50458-580-10 Blister package containing 100 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 “15” marked 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 100 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 50458-579-30  Bottle containing 30 tablets
  NDC 50458-579-90  Bottle containing 90 tablets
  NDC 50458-579-10  Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

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.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Instructions for Patient Use

• Advise patients to take XARELTO only as directed.
• Remind patients to not 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 with 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 (2.4)].
• 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.

17.2 Bleeding Risks

• Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it might 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 tingling, numbness (especially in the lower limbs) and muscular weakness. If any of these symptoms occur, advise the patient to contact his or her physician immediately [see Boxed Warning].
17.3 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.

17.4 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)].

17.5 Pregnancy and Pregnancy-Related Hemorrhage
- Advise patients to inform their physician immediately if they become pregnant or intend to become pregnant during treatment with XARELTO [see Use in Specific Populations (8.1)].
- Advise pregnant women receiving XARELTO to immediately report to their physician any bleeding or symptoms of blood loss [see Warnings and Precautions (5.7)].

17.6 Nursing
Advise patients to discuss with their physician if they are nursing or intend to nurse during anticoagulant treatment [see Use in Specific Populations (8.3)].

17.7 Females of Reproductive Potential
Advise patients who can become pregnant to discuss pregnancy planning with their physician [see Use in Specific Populations (8.6)].

Active Ingredient Made in Germany

Finished Product Manufactured by:
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Gurabo, PR 00778

Manufactured for:
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