XARELTO® (rivaroxaban) tablets

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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 (7.4)].

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 unfractonated heparin being administered by continuous infusion, stop the infusion and start XARELTO at the same time.

2.3 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 the 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.

2.4 Missed Dose

- For patients receiving 2.5 mg twice daily: if a dose is missed, the patient should take a single 2.5 mg XARELTO dose as recommended at the next scheduled time.
- For patients receiving 15 mg twice daily: The patient should take XARELTO immediately to ensure intake of 30 mg XARELTO per day. Two 15 mg tablets may be taken at once.
- For patients receiving 20 mg, 15 mg or 10 mg once daily: The patient should take the missed XARELTO dose immediately. The dose should not be doubled within the same day to make up for a missed dose.

2.5 Administration Options

For patients who are unable to swallow whole tablets, 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 Clinical Pharmacology (12.3)]. Administration via nasogastric (NG) tube or gastric feeding tube: After confirming gastric placement of the tube, 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 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 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

- 2.5 mg tablets: Round, light yellow, and film-coated with a triangle pointing down
- 10 mg tablets: Round, light red, biconvex and film-coated with a triangle pointing down above a “20” 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 (2.2, 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.

Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, P2Y12 platelet inhibitors, dual antiplatelet therapy, 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 CYP3A inhibitors increases rivaroxaban exposure and may increase bleeding risk [see Drug Interactions (7.2)].
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 (8.7)].

5.6 Use with P-gp and Strong CYP3A Inhibitors or Inducers

Avoid concomitant use of XARELTO with known combined P-gp and strong CYP3A inhibitors [see Drug Interactions (7.2)].

Avoid concomitant use of XARELTO with drugs that are known combined P-gp and strong CYP3A 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 receive thrombolysis or pulmonary embolectomy.

5.10 Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

Direct-acting oral anticoagulants (DOACs), including XARELTO, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

6 ADVERSE REACTIONS

The following clinically significant 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, 31,691 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; 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3); 3993 patients who received 10 mg orally once daily for prophylaxis of VTE and VTE-related death in acutely ill medical patients (MAGELLAN) and 9194 patients who received XARELTO 2.5 mg orally twice daily, in combination with aspirin 100 mg once daily, for the reduction in risk of major cardiovascular events in patients with chronic CAD or PAD (COMPASS).

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 2: 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 (ICH)²</td>
<td>55 (0.5)</td>
<td>84 (0.7)</td>
<td>0.67 (0.47, 0.93)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke³</td>
<td>36 (0.3)</td>
<td>58 (0.5)</td>
<td>0.63 (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)³</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>Non-intracranial</td>
<td>24 (0.2)</td>
<td>42 (0.4)</td>
<td>0.58 (0.35, 0.96)</td>
</tr>
<tr>
<td></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-Maj.

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

† 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.

¶ 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 live.

Table 3: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® N=4130 n (%)</th>
<th>Enoxaparin/VKA N=4116 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 (0.1)</td>
<td>8 (0.2)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>2 (0.1)</td>
<td>4 (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 (0.1)</td>
<td>10 (0.2)</td>
</tr>
<tr>
<td>Retropertoneal</td>
<td>1 (0.1)</td>
<td>8 (0.2)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>2 (0.1)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Intra-articular</td>
<td>0</td>
<td>4 (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>
</tbody>
</table>

Clinical relevant non-major bleeding 357 (8.6) 357 (8.7)

Any bleeding 1169 (28.3) 1153 (28.0)

Note: The 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.

**Risk of Major Bleeding Events by Baseline Characteristics in ROCKET AF Trial**

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

Table 4: Bleeding Events* in EINSTEIN CHOICE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® N=4120 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>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>
</tbody>
</table>

Any bleeding 151 (13.4) 138 (12.2)

* 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.

**EINSTEIN CHOICE**

EINSTEIN CHOICE studied 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 4 shows the number of patients experiencing bleeding events in the EINSTEIN CHOICE study.

**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 4 shows the number of patients experiencing bleeding events in the EINSTEIN CHOICE study.**

**Reduction in the Risk of Recurrence of DVT and/or 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 incidence rates of 1.7% versus 1.5%, respectively. The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients.
Table 5: 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>Total treated patients</td>
<td>N=4487 n (%)</td>
<td>N=4524 n (%)</td>
</tr>
<tr>
<td>Major bleeding event</td>
<td>12 (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></th>
<th>XARELTO 10 mg N=3281 n (%)</th>
<th>Enoxaparin† 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></th>
<th>XARELTO 10 mg N=1206 n (%)</th>
<th>Enoxaparin† N=1226 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>1 (0.1)</td>
<td>0</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 (≥5%) occurred during the first week after surgery.

### Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

In the MAGELLAN study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events. Cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed. Patients with bronchiectasis/pulmonary cavitation, active cancer (e.g., undergoing acute, in-hospital cancer treatment), dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months all had an excess of bleeding with XARELTO compared with enoxaparin/placebo and are excluded from all MAGELLAN data presented in Table 6. The incidence of bleeding leading to drug discontinuation was 2.5% for XARELTO vs. 1.4% for enoxaparin/placebo.

Table 6 shows the number of patients experiencing various types of bleeding events in the MAGELLAN study.

Table 6: Bleeding Events in MAGELLAN* Study—Safety Analysis Set - On Treatment Plus 2 days

<table>
<thead>
<tr>
<th>MAGELLAN Study†</th>
<th>XARELTO 10 mg N=3218 n (%)</th>
<th>Enoxaparin 40 mg/placebo N=3229 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding‡</td>
<td>22 (0.7)</td>
<td>15 (0.5)</td>
</tr>
<tr>
<td>Critical site bleeding†</td>
<td>7 (0.2)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Fatal bleeding†</td>
<td>3 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding events (CRNM)</td>
<td>93 (2.9)</td>
<td>34 (1.1)</td>
</tr>
</tbody>
</table>

* Patients at high risk of bleeding (i.e. bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months) were excluded.
† Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.
‡ Defined as clinically overt bleeding associated with a drop in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.
§ Fatal bleeding is adjudicated death with the primary cause of death from bleeding.
**Patients received either XARELTO or placebo once daily for 35 ±4 days starting in hospital and continuing post hospital discharge or received enoxaparin or placebo once daily for 10 ±4 days in the hospital.

Reduction of Risk of Major Cardiovascular Events in Patients with Chronic CAD or PAD

In the COMPASS trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 2.7% for XARELTO 2.5 mg twice daily in combination with aspirin 100 mg once daily vs. 1.2% for aspirin 100 mg once daily.

Table 7 shows the number of patients experiencing various types of major bleeding events in the COMPASS trial.

Table 7: Major Bleeding Events* in COMPASS - On Treatment Plus 2 days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO plus aspirin† N=9134 n (%/year)</th>
<th>Aspirin alone† N=9107 n (%/year)</th>
<th>XARELTO plus aspirin vs. Aspirin alone HR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified ISTH Major Bleeding§</td>
<td>263 (1.6)</td>
<td>144 (0.9)</td>
<td>1.84 (1.50, 2.26)</td>
</tr>
<tr>
<td>- Fatal bleeding event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage (ICH)</td>
<td>12 (&lt;0.1)</td>
<td>8 (&lt;0.1)</td>
<td>1.51 (0.62, 3.69)</td>
</tr>
<tr>
<td>Non-intracranial</td>
<td>6 (&lt;0.1)</td>
<td>3 (&lt;0.1)</td>
<td>2.01 (0.50, 8.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (&lt;0.1)</td>
<td>1.21 (0.37, 3.96)</td>
</tr>
<tr>
<td>- Symptomatic bleeding in critical organ (non-fatal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>58 (0.3)</td>
<td>43 (0.3)</td>
<td>1.36 (0.91, 2.01)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>23 (0.1)</td>
<td>21 (0.1)</td>
<td>1.09 (0.61, 1.96)</td>
</tr>
<tr>
<td>Other ICH</td>
<td>18 (0.1)</td>
<td>13 (&lt;0.1)</td>
<td>1.38 (0.68, 2.82)</td>
</tr>
<tr>
<td></td>
<td>6 (&lt;0.1)</td>
<td>9 (&lt;0.1)</td>
<td>0.67 (0.24, 1.88)</td>
</tr>
<tr>
<td>- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)</td>
<td>7 (&lt;0.1)</td>
<td>6 (&lt;0.1)</td>
<td>1.17 (0.39, 3.46)</td>
</tr>
<tr>
<td>- Bleeding leading to hospitalization (non-fatal, not in critical organ, not requiring reoperation)</td>
<td>188 (1.1)</td>
<td>91 (0.5)</td>
<td>2.08 (1.62, 2.67)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>117 (0.7)</td>
<td>49 (0.3)</td>
<td>2.40 (1.72, 3.35)</td>
</tr>
</tbody>
</table>

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.
† Treatment schedule: XARELTO 2.5 mg twice daily plus aspirin 100 mg once daily, or aspirin 100 mg once daily
‡ Defined as i) fatal bleeding, or ii) symptomatic bleeding in a critical area or organ, such as intraspinal, intracranial, retroperitoneal, adrenal gland or kidney; or iii) bleeding into the surgical site requiring reoperation, or iv) bleeding leading to hospitalization.
§ CI: confidence interval; HR: hazard ratio; ISTH: International Society on Thrombosis and Hemostasis
Figure 2 shows the risk of modified ISTH major bleeding events across major subgroups.

Figure 2: Risk of Modified ISTH Major Bleeding Events by Baseline Characteristics in COMPASS – On Treatment Plus 2 Days

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 8.

Table 8: 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>XARELTO 20 mg</th>
<th>Enoxaparin/VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1718</td>
<td>N=1711</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>46 (2.7)</td>
<td>25 (1.5)</td>
</tr>
<tr>
<td>General disorders and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (1.4)</td>
<td>15 (0.9)</td>
</tr>
<tr>
<td>Musculoskeletal and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>50 (2.9)</td>
<td>31 (1.8)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>23 (1.3)</td>
<td>13 (0.8)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>36 (2.2)</td>
<td>22 (1.3)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>24 (1.4)</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Depression</td>
<td>20 (1.2)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>28 (1.6)</td>
<td>18 (1.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN PE Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>XARELTO 20 mg</td>
<td>Enoxaparin/VKA</td>
</tr>
<tr>
<td></td>
<td>N=2412</td>
<td>N=2405</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<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
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. Optimal evaluation for 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 are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO for the mother and possible risks to the fetus when prescribing 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
Disorders Associated with Maternal and/or Embryofetal Risk
Pregnancy is a risk factor for venous thromboembolism and that risk is increased in women with inherited or acquired thrombophilias. Pregnant women with thrombophilic disease have an increased risk of maternal complications including pre-eclampsia. Maternal thromboembolic disease increases the risk for intrapartum 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 and/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.

Data

Human Data
There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage. In an in vitro placenta perfusion model, unbound rivaroxaban was rapidly transferred across the human placenta.

Animal Data
Rivaroxaban crosses the placenta in animals. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weights) in pregnant rabbits when given oral doses of ≥3 mg/kg/day. 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 during the period of organogenesis. This dose corresponds to about 14 times the human exposure of unbound drug. In rats, peripartal 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).

8.2 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. 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 within 32 hours after administration was 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 37% were 65 years and over and about 16% were >75 years. In EINSTEIN CHOICE, approximately 39% were 65 years and over and about 12% were >75 years. In the MAGELLAN study, approximately 67% were 65 years and over and about 37% were >75 years. In the COMPASS study, approximately 76% were 65 years and over and about 17% 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 [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 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed [see Clinical Pharmacology (12.3)].

Nonvalvular Atrial Fibrillation
 Patients with Chronic Kidney Disease not on Dialysis
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 <30 mL/min were not studied, but administration of XARELTO 15 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment [see 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 will result in rivaroxaban concentrations 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.

Treatment of DVT and/or PE and Reduction in the Risk of Recurrence of DVT and/or 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 thromboembolism 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.

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding
In the MAGELLAN study, patients with a baseline CrCl <30 mL/min were excluded. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Reduction of Risk of Major Cardiovascular Events in Patients with Chronic CAD or PAD
Patients with Chronic Kidney Disease not on Dialysis
Patients with a CrCl <15 mL/min at screening were excluded from COMPASS, and limited data are available for patients with a CrCl of 15-30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg XARELTO twice daily is expected to give an exposure similar to that in patients with moderate renal impairment [see Clinical Pharmacology (12.3)], whose efficacy and safety outcomes were similar to those with preserved renal function.

Patients with End-Stage Renal Disease on Dialysis
No clinical outcome data is available for the use of XARELTO with aspirin in patients with ESRD on dialysis since these patients were not enrolled in COMPASS. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 2.5 mg twice daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in moderate renal impaired patients in the COMPASS study [see Clinical Pharmacology (12.2, 12.3)]. It is not known whether these concentrations will lead to similar CV risk reduction and bleeding risk in patients with ESRD on dialysis as was seen in COMPASS.
XARELTO® (rivaroxaban) tablets

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 overdose 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-morpholinyl)phenyl]-1,3-oxazolidin-5-yl)methyl)-2-thiophenecarboxamide. The molecular formula of rivaroxaban is C19H18ClN3O5S 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 2.5 mg, 10 mg, 15 mg, or 20 mg of rivaroxaban. The inactive ingredients of XARELTO Tablets are: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and hydroxypropyl methylcellulose. The molecular formula of XARELTO 2.5 mg is C19H18ClN3O5S and the molecular weight is 435.89. The structural formula is:

Rivaroxaban is a factor Xa (FXa) inhibitor, 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 C19H18ClN3O5S and the molecular weight is 435.89. The structural formula is:

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)].

Table 10: Percentage Increase in Rivaroxaban PK and PD Measures in Subjects with Renal Impairment Relative to Healthy Subjects from Clinical Pharmacology Studies

<table>
<thead>
<tr>
<th>Measure</th>
<th>Parameter</th>
<th>Creatinine Clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50-79</td>
</tr>
<tr>
<td>Exposure</td>
<td>AUC</td>
<td>44</td>
</tr>
<tr>
<td>FXa Inhibition</td>
<td>AUEC</td>
<td>50</td>
</tr>
<tr>
<td>PT Prolongation</td>
<td>AUEC</td>
<td>33</td>
</tr>
</tbody>
</table>

*Separate stand-alone study.
PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the plasma concentration-time curve; AUEC = Area under the effect-time curve

Hepatic Impairment
Anti-Factor Xa activity was similar in subjects with normal hepatic function and in mild hepatic impairment (Child-Pugh A class). There is no clear understanding of the impact of hepatic impairment beyond this degree on the coagulation cascade and its relationship to efficacy and safety.

12.3 Pharmacokinetics
Absorption
The absolute bioavailability of rivaroxaban is dose-dependent. For the 2.5 mg and 10 mg dose, it is estimated to be 80% to 100% and is not affected by food. XARELTO 2.5 mg and 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 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 (2.1)].

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. 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 (30 mg single dose) with the PPI omeprazole (40 mg once daily) did not show an effect on the bioavailability and exposure of rivaroxaban (see Figure 4).

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% 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 stomach which can result in reduced absorption and related drug exposure.
In a study with 44 healthy subjects, both mean AUC and Cmax values for 20 mg rivaroxaban administered orally as a crushed tablet mixed in applesauce were comparable to that after the whole tablet. However, for the crushed tablet suspended in water and administered via an NG tube followed by a liquid meal, only mean AUC was comparable to that after the whole tablet, and Cmax was 18% lower.

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 [14C]-rivaroxaban dose was recovered as inactive metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4 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 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 0.5 – 4.5 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 3.

Figure 3: Effect of Specific Populations on the Pharmacokinetics of Rivaroxaban

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 3). 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 10). 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 (3 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 3). 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) and minimal to moderate hepatic impairment (Child-Pugh A) (see Figure 3).

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 4).

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 4).

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 20% 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 Interactions
In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2C9, nor induces CYP1A2, 2B6, 2C19, or 3A. In vitro data also indicates a low rivaroxaban inhibitory potential for P-gp and ABCG2 transporters.

The effects of concomitantly administered drugs on the pharmacokinetics of rivaroxaban exposure are summarized in Figure 4 [see Drug Interactions (7)].
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 CYP3A 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 AUC\textsubscript{inf} and a 56% and 64% increase in C\textsubscript{max}, respectively. Similar trends in pharmacodynamic effects were also observed.

### 12.6 GT/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 \textit{in vitro} or in the mouse micronucleus test \textit{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 exposures 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 \textit{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) [NCT00403767]}, 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 CHADS\textsubscript{2} 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 11 displays the overall results for the primary composite endpoint and its components.
Table 12: 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>Primary Composite Endpoint</td>
<td>N=1731</td>
<td>N=1718</td>
<td></td>
</tr>
<tr>
<td>Death (PE)</td>
<td>36 (2.1)</td>
<td>51 (3.0)</td>
<td>0.68 (0.44, 1.04)</td>
</tr>
<tr>
<td>Death (PE cannot be excluded)</td>
<td>1 (&lt;0.1)</td>
<td>0</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>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 7 and 8 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 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 DVT Study

Note: The figure above presents effects in various subgroups all of which are heterogeneity among groups should not be over-interpreted.
XARELTO® (rivaroxaban) tablets

Figure 8: 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

Figure 9: 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

14.4 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 Regulation of 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, NCT00332020, NCT00361894] 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 (± standard deviation [SD]) was 63 ± 12.2 (range 18 to 93) years with 49% of patients ≥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 (± 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 14.

Table 14: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery - Modified Intent-to-Treat Population

XARELTO® (rivaroxaban) tablets

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

EINSTEIN CHOICE Study

XARELTO® was included in a reduction in the risk of recurrence of DVT and of PE was evaluated in the EINSTEIN CHOICE study [NCT0064439], a multi-national, double-blind, superiority study comparing XARELTO (10 mg 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 13 displays the overall results for the primary composite endpoint and its components.

Table 13: Primary Composite Endpoint and its Components Results* in EINSTEIN CHOICE Study – Full Analysis Set

Number of Patients at Risk
Enoxaparin/VKA (N=2419) 2316 2260 2155 2146 2113 835 797 773 746 722 675 2280 2155 2133 837 794 745 715 725 672
XARELTO® (N=2419) 2350 2251 2160 2167 2333 837 794 755 737 725 672 2311 2180 2167 837 794 755 737 725 672

* 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.

Figure 9 is a plot of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups.

In RECORD 1 and 2, a total of 6727 patients were randomized and 6579 received study drug. The mean age (± standard deviation [SD]) was 63 ± 12.2 (range 18 to 93) years with 49% of patients ≥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 (± 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 14.

Table 14: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery - Modified Intent-to-Treat Population

...
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 as defined an estimated creatinine clearance <30 ml/min or patients with significant liver disease (hepatitis or cirrhosis). The mean exposure duration (± SD) to active study medication (1.3%).

The study recruited patients with one or more of the following VTE risk factors, i.e. prolonged immobilization, age ≥75 years, history of cancer, history of VTE, history of heart failure, and had additional risk factors for VTE. The population at risk of VTE was estimated to be around 25% of the patients mainly due to no ultrasonographic exclusion criteria being met.

## Table 15: 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 2</th>
<th>RECORD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>N=813</td>
<td>N=871</td>
</tr>
<tr>
<td>Total VTE</td>
<td>79 (9.7%)</td>
<td>164 (18.8%)</td>
</tr>
<tr>
<td>Components of events contributing to Total VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>9 (1.1%)</td>
<td>19 (2.2%)</td>
</tr>
<tr>
<td>Distal DVT</td>
<td>74 (9.1%)</td>
<td>154 (17.7%)</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>0</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Death (any cause)</td>
<td>0</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>N=895</td>
<td>N=917</td>
</tr>
<tr>
<td>Major VTE</td>
<td>9 (1.0%)</td>
<td>23 (2.5%)</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>8 (0.7%)</td>
<td>24 (2.0%)</td>
</tr>
</tbody>
</table>

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

## 14.5 Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

The efficacy and safety of XARELTO for prophylaxis of venous thromboembolism in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding was evaluated in the MAGELLAN study (Multicenter, randomized, parallel Group Efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patients comparing rivaroxaban with enoxaparin NCT00571649). MAGELLAN was a multicenter, randomized, double-blind, parallel-group efficacy and safety study comparing XARELTO to enoxaparin, in the prevention of VTE in hospitalized acutely ill medical patients during the in-hospital and post-hospital discharge period. Eligible patients included adults who were at least 40 years of age, hospitalized for an acute medical illness, at risk of VTE due to moderate or severe immobility, and had additional risk factors for VTE. The population at risk of VTE was required to have one or more of the following: VTE risk factors, i.e. prolonged immobilization, age ≥75 years, history of cancer, history of VTE, history of heart failure, thrombophila, acute infectious disease contributing to the hospitalization and BMI ≥35 kg/m². The causes for hospitalization included heart failure, active cancer, acute ischemic stroke, acute infectious and inflammatory disease and acute respiratory insufficiency. Patients were randomized to receive either XARELTO 10 mg once daily for 35.4 days starting in hospital and continuing post hospital discharge (n=4060) or enoxaparin 40 mg once daily for 10 ± 4 days starting in hospital followed by placebo post-discharge (n=4051).

The major efficacy outcome in the MAGELLAN trial was a composite endpoint that included asymptomatic proximal deep venous thrombosis (DVT) in lower extremity, symptomatic proximal or distal DVT in the lower extremity, symptomatic non-fatal pulmonary embolism (PE), and death related to venous thromboembolism (VTE).

A total of 6024 patients were evaluable for the major efficacy outcome analysis (2967 on XARELTO 10 mg once daily and 3057 on enoxaparin/placebo). The mean age was 68.9 years, with 37.1% of the subject population ≥75 years. VTE risk factors included severe immobilization at study entry (99.9%), D-dimer > 2X ULN (43.7%), history of heart failure (35.6%), BMI ≥ 35 kg/m² (15.2%), chronic venous insufficiency (14.9%), acute infectious disease (13.9%), severe varicosis (12.5%), history of cancer (16.2%), history of VTE (4.5%), hormone replacement therapy (1.1%), and thrombophilia (0.3%). 

### Table 16: Efficacy Results at Day 35 (modified Intent-To-Treat) and at Day 10 (per protocol) in the MAGELLAN Study

<table>
<thead>
<tr>
<th>Events from Day 1 to Day 35, mITT analysis set</th>
<th>XARELTO 10 mg N=2967 n (%)</th>
<th>Enoxaparin 40 mg/placebo N=3057 n (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Endpoint at Day 35</td>
<td>131 (4.4%)</td>
<td>175 (5.7%)</td>
<td>0.77 (0.62, 0.96)</td>
</tr>
<tr>
<td>Symptomatic non-fatal PE</td>
<td>10 (0.3%)</td>
<td>14 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic DVT in lower extremity</td>
<td>13 (0.4)</td>
<td>15 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic proximal DVT in lower extremity</td>
<td>103 (3.5)</td>
<td>133 (4.4)</td>
<td></td>
</tr>
<tr>
<td>VTE related death</td>
<td>19 (0.6)</td>
<td>30 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 17: Efficacy Results at Day 35 (modified Intent-to-Treat) and at Day 10 (per protocol) in the MAGELLAN Study

<table>
<thead>
<tr>
<th>Events from Day 1 to Day 10, PP analysis set</th>
<th>XARELTO 10 mg N=2938 n (%)</th>
<th>Enoxaparin 40 mg N=2953 n (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Endpoint at Day 10</td>
<td>78 (2.7)</td>
<td>82 (2.7)</td>
<td>0.97 (0.71, 1.31)</td>
</tr>
<tr>
<td>Symptomatic non-fatal PE</td>
<td>6 (0.2)</td>
<td>2 (&lt;0.1)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic DVT in lower extremity</td>
<td>7 (0.2)</td>
<td>6 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic proximal DVT in lower extremity</td>
<td>71 (2.4)</td>
<td>71 (2.4)</td>
<td></td>
</tr>
<tr>
<td>VTE related death</td>
<td>3 (0.1)</td>
<td>6 (0.2)</td>
<td></td>
</tr>
</tbody>
</table>

### mITT Analysis Set plus all-cause mortality

| Other Composite Endpoint at Day 35            | 266 (8.6)                   | 293 (9.2)                       | 0.93 (0.80, 1.03) |
| Symptomatic non-fatal PE                      | 10 (0.3)                    | 14 (0.4)                        |             |
| Symptomatic DVT in lower extremity            | 13 (0.4)                    | 15 (0.5)                        |             |
| Asymptomatic proximal DVT in lower extremity  | 103 (3.3)                   | 133 (4.2)                       |             |

### All-cause mortality

| VTE related death                             | 159 (5.1)                   | 153 (4.8)                       |             |

mITT: modified intent-to-treat; PP: per protocol; DVT: Deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; CI: Confidence Interval; RR: Relative Risk

Patients with bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months (19.4%) all had an excess of bleeding with XARELTO compared with enoxaparin/placebo. Therefore, patients meeting these criteria were excluded from the following analyses presented below.

Table 17 provides the efficacy results for the subgroup of patients not at a high risk of bleeding.
The evidence for the efficacy and safety of XARELTO for the reduction in the risk of stroke, myocardial infarction, or cardiovascular death in patients with coronary artery disease (CAD) or peripheral artery disease (PAD) was derived from the double-blind Cardiovascular Outcomes for People using Anticoagulation Study (COMPASS) [NCT01776424]. A total of 27,395 patients were evenly randomized to rivaroxaban 2.5 mg orally twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg orally twice daily alone, or aspirin 100 mg once daily alone. Because the 5 mg dose alone was not superior to aspirin alone, only the results from the 2.5 mg dose plus aspirin are discussed below.

Patients with established CAD or PAD were eligible. Patients with CAD who were younger than 65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional cardiovascular risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [eGFR] <60 mL per minute, heart failure, or non-lacunar ischemic stroke ≥1 month earlier). Patients with PAD were either symptomatic with ankle brachial index <0.90 or had asymptomatic carotid artery disease death, MI, and/or CV procedure.

The mean duration of follow-up was 23 months. Relative to aspirin alone, XARELTO plus aspirin reduced the rate of the primary composite outcome of stroke, myocardial infarction or cardiovascular death. The benefit was observed early with a constant treatment effect over the entire treatment period (see Table 18 and Figure 10).
XARELTO® (rivaroxaban) tablets

Figure 11: Time to first occurrence of primary efficacy outcome (stroke, myocardial infarction, cardiovascular death) in COMPASS

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16 HOW SUPPLIED/STORAGE AND HANDLING

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

- 2.5 mg tablets are round, light yellow, and film-coated with a triangle pointing down above a “2.5” marked on one side and “Xa” on the other side. The tablets are supplied in the packages listed:
  - NDC 50458-577-60 Bottle containing 60 tablets
  - NDC 50458-577-18 Bottle containing 180 tablets
  - NDC 50458-577-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

- 10 mg tablets are round, light red, biconvex film-coated tablets marked with a triangle pointing down above a “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 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 50458-579-30 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)

- 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 50458-579-88 Bulk bottle containing 1000 tablets
  - NDC 50458-579-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

- Starter Pack for treatment of deep vein thrombosis and treatment of pulmonary embolism:
  - NDC 50458-584-51 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.

17 PATIENT COUNSELING INFORMATION

Advising the patient to read the FDA-approved patient labeling (Medication Guide).

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.

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Janssen

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What is the most important information I should know about XARELTO?

XARELTO may cause serious side effects, including:

• Increased risk of blood clots if you stop taking XARELTO. People with atrial fibrillation (a type of irregular heartbeat) that is not caused by a heart valve problem (non-valvular) 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.

• Increased risk of bleeding. XARELTO can cause bleeding which can be serious and may lead to death. This is because XARELTO is a blood thinner medicine (anticoagulant) that lowers blood clotting. During treatment with 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 have certain other medical problems.

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
- long-term (chronic) use of 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 use in people with artificial heart valves.

XARELTO is not for use in people with antiphospholipid syndrome (APS), especially with positive triple antibody testing, who have a history of blood clots.
**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 that is not caused by a heart valve problem. 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.
- help prevent a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.
- help prevent blood clots in certain people hospitalized for an acute illness and after discharge who are at risk of getting blood clots because of the loss of or decreased ability to move around (mobility) and other risks for getting blood clots and who do not have a high risk of bleeding.

XARELTO is used with low dose aspirin to:
- reduce the risk of serious heart problems, heart attack and stroke in people with coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) or peripheral artery disease (a condition where the blood flow to the legs is reduced).

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 Medication Guide for a complete list of ingredients in XARELTO.

**Before taking XARELTO, tell your doctor about all of your medical conditions, including if you:**
- have or ever had bleeding problems
- have liver or kidney problems
- have antiphospholipid syndrome (APS)
- 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 can pass into your breast milk. Talk to your doctor about the best way to feed your baby during treatment with XARELTO.

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, causing side effects. Certain medicines may increase your risk of bleeding. See “What is the most important information I should know about XARELTO?”

**Especially tell your doctor if you take:**
- ketoconazole
- erythromycin
- phenytoin
- St. John’s wort
- ritonavir
- carbamazepine
- rifampin
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.
• Your doctor will decide how long you should take XARELTO.
• XARELTO may need to be stopped for one or more days before any surgery or medical or dental procedure. Your doctor will tell you when to stop taking XARELTO and when to start taking XARELTO again after your surgery or procedure.
• If you need to stop taking XARELTO for any reason, talk to the doctor who prescribed XARELTO to you to find out when you should stop taking it. Do not stop taking XARELTO without first talking to the doctor who prescribes it to you.
• If you have difficulty swallowing XARELTO tablets whole, talk to your doctor about other ways to take XARELTO.
• 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.

If you take XARELTO for:
○ Atrial fibrillation that is not caused by a heart valve problem:
  ▪ 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.

○ 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 10 mg dose, take XARELTO with or without food.
  ▪ For the 15 mg and 20 mg doses, take XARELTO with food at the same time 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.

○ 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.

○ Blood clots in people hospitalized for an acute illness:
  ▪ Take XARELTO 1 time a day, with or without food, while you are in the hospital and after you are discharged as prescribed by your doctor.
  ▪ 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.

○ Reducing the risk of serious heart problems, heart attack and stroke in coronary artery disease or peripheral artery disease:
  ▪ Take XARELTO 2 times a day with or without food.
  ▪ If you miss a dose of XARELTO, take your next dose at your regularly scheduled time.

What are the possible side effects of XARELTO?
XARELTO may cause serious side effects:
• See “What is the most important information I should know about XARELTO?”

The most common side effect of XARELTO was bleeding.
Call your doctor for medical advice about side effects. 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 2.5 mg tablets is Opadry® Light Yellow and contains: ferric oxide yellow, hypromellose, polyethylene glycol 3350, and titanium dioxide.
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
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For more information go to www.XARELTO-US.com or call 1-800-526-7736.

This Medication Guide has been approved by the U.S. Food and Drug Administration
Revised: 10/2019

cp-62541v5