CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202439Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XARELTO (rivaroxaban) tablets, for oral use
Initial U.S. Approval: 2011

WARNINGS: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning

A. **DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION**

Discontinuing XARELTO places patients at an increased risk of thrombotic events. If anticoagulation with XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant (2.1, 5.1, 14.1).

B. **SPINAL/EPIDURAL HEMATOMA**

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

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary (5.3).

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (5.3).

----------RECENT MAJOR CHANGES----------

Boxed Warning	11/2011
Indications and Usage (1.1)	11/2011
Dosage and Administration (2.1, 2.3)	11/2011
Contraindications (4)	11/2011
Warnings and Precautions (5.1, 5.2, 5.5)	11/2011

----------INDICATIONS AND USAGE----------

XARELTO is a factor Xa inhibitor indicated:

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (1.1)
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Nonvalvular Atrial Fibrillation:
  - For patients with CrCl >50 mL/min: 20 mg orally, once daily **with the evening meal** (2.1)
  - For patients with CrCl 15 50 mL/min: 15 mg orally, once daily **with the evening meal** (2.1)
  - Avoid use in patients with CrCl <15 mL/min (2.3)
- Prophylaxis of DVT: 10 mg orally, once daily with or without food (2.2)
- Hepatic impairment (for nonvalvular AF and prophylaxis of DVT indications):
  - Avoid use in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment or with any degree of hepatic disease associated with coagulopathy (2.3, 8.8).

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- Risk of bleeding: XARELTO can cause serious and fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (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. (5.4)

----------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)
- Prophylaxis of DVT:
  - Anticoagulants: Avoid concomitant use (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: discontinue drug or discontinue nursing (8.3)
- Renal impairment:
  - Prophylaxis of DVT: Avoid use in patients with severe impairment (CrCl <30 mL/min). Use with caution in moderate impairment (CrCl 30 to <50 mL/min) (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2011

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FULL PRESCRIBING INFORMATION

WARNINGS: (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 (2.1), 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 (rivaroxaban) 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 Prophylaxis of Deep Vein Thrombosis

XARELTO (rivaroxaban) is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

2 DOSAGE AND ADMINISTRATION

2.1 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)]*.

Switching from or to Warfarin - 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.

No clinical trial data are available to guide converting patients from XARELTO to warfarin. XARELTO affects INR, so INR measurements made during co-administration 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 or to Anticoagulants other than Warfarin - 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.

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)]*.

2.2 Prophylaxis of Deep Vein Thrombosis

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.

- 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.

2.3 General Dosing Instructions

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 *[see Use in Specific Populations (8.8)]*.

Renal Impairment

Nonvalvular Atrial Fibrillation

Avoid the use of XARELTO in patients with CrCl <15 mL/min. 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)]*.

Prophylaxis of Deep Vein Thrombosis

Avoid the use of XARELTO in patients with severe renal impairment (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 moderate renal impairment (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)]*.

Surgery and Intervention

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. 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. If oral medication cannot be taken after surgical intervention, consider administering a parenteral anticoagulant.

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.

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)]*.

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 *[see Warnings and Precautions (5.5)]*

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 (2.1) 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. Discontinue XARELTO in patients with active pathological hemorrhage.

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.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.3), (7.4), (7.5)]*.

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 Risk of Pregnancy Related Hemorrhage

XARELTO should be used with caution in pregnant women and 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).

5.5 Severe Hypersensitivity Reactions

There were postmarketing cases of anaphylaxis in patients treated with XARELTO to reduce the risk of DVT. Patients who have a history of a severe hypersensitivity reaction to XARELTO should not receive XARELTO *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

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, 11598 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) 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 1: Bleeding Events in ROCKET AF*

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

* 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, intraarticular, intramuscular with compartment syndrome, or retroperitoneal.

Prophylaxis of Deep Vein Thrombosis

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The mean duration of XARELTO treatment was 11.9 days in the total knee replacement study and 33.4 days in the total hip replacement studies. Overall, in the RECORD program, the mean age of the patients studied in the XARELTO group was 64 years, 59% were female and 82% were Caucasian. Twenty-seven percent (1206) of patients underwent knee replacement surgery and 73% (3281) underwent hip replacement surgery.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 2.

Table 2: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	**N = 4487** **n (%)**	**N = 4524** **n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N = 3281** **n (%)**	**N = 3298** **n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
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 (%)**	**N = 1226** **n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
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 drug reactions (ADRs) reported in ≥1% of XARELTO-treated patients are shown in Table 3.

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

System/Organ Class Adverse Reaction	XARELTO 10 mg (N = 4487) n (%)	Enoxaparin† (N = 4524) n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* ADR 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

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, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

- *Ketoconazole (combined P-gp and strong CYP3A4 inhibitor):* Steady-state rivaroxaban AUC and C_{max} 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 C_{max} 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 C_{max} 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 C_{max} increased by 30%.

- *Fluconazole (moderate CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 40% and 30%, respectively.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan), which cause significant increases in rivaroxaban exposure that may increase bleeding risk.

Prophylaxis of Deep Vein Thrombosis

When clinical 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.

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

In a drug interaction study, co-administration 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_{max}, respectively. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy.

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).

7.3 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. 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.

Prophylaxis of Deep Vein Thrombosis

Avoid concurrent use of XARELTO with other anticoagulants due to the increased bleeding risk. Promptly evaluate any signs or symptoms of blood loss *[see Warnings and Precautions (5.2)]*.

7.4 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. 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.

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)]*.

7.5 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 co-administered 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.

Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with clopidogrel *[see Warnings and Precautions (5.2)]*.

7.6 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 (e.g., amiodarone, diltiazem, verapamil, quinidine, ranolazine, dronedarone, felodipine, erythromycin, and azithromycin) may have significant 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)]. 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 Use in Specific Populations (8.7)]*.

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 (5.4)]*.

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 ≥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 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

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

Table 4: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Renal Insufficiency from a Dedicated Renal Impairment Study

Parameter		Renal Impairment Class [CrCl (mL/min)]		
		Mild [50 to 79] N=8	**Moderate [30 to 49] N=8**	**Severe [15 to 29] N=8**
Exposure	**AUC**	44	52	64
(% increase relative to normal)	**C_{max}**	28	12	26
FXa Inhibition	**AUC**	50	86	100
(% increase relative to normal)	**E_{max}**	9	10	12
PT Prolongation	**AUC**	33	116	144
(% increase relative to normal)	**E_{max}**	4	17	20

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

Patients with renal impairment taking P-gp and weak to moderate CYP3A4 inhibitors may have significant increases in exposure which may increase bleeding risk *[see Drug Interactions (7.6)]*.

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 (2.1)]*.

Prophylaxis of Deep Vein Thrombosis

The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with moderate renal impairment and reported a possible increase in total VTE in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with moderate renal impairment (CrCl 30 to <50 mL/min). Avoid the use

of XARELTO in patients with severe renal impairment (CrCl <30 mL/min) *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*.

8.8 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 5). 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 5: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Hepatic Insufficiency from a Dedicated Hepatic Impairment Study

Parameter		Hepatic Impairment Class (Child-Pugh Class)	
		Mild (Child-Pugh A) N=8	**Moderate (Child-Pugh B) N=8**
Exposure	**AUC**	15	127
(% increase relative to normal)	**C_{max}**	0	27
FXa Inhibition	**AUC**	8	159
(% increase relative to normal)	**E_{max}**	0	24
PT Prolongation	**AUC**	6	114
(% increase relative to normal)	**E_{max}**	2	41

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

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 *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*.

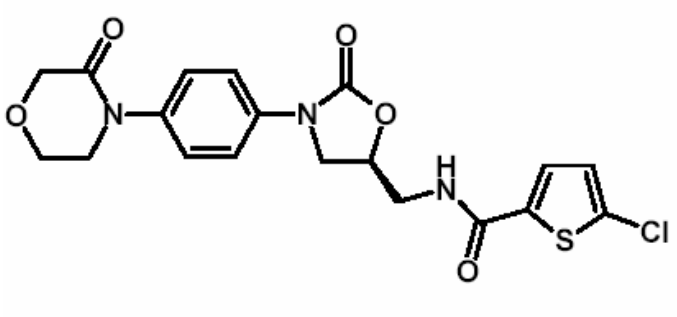
10 OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. 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 $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89. The structural formula is:



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

Each XARELTO tablet contains 10 mg, 15 mg, or 20 mg of rivaroxaban. The 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 *[see Dosage and Administration (2.2)]*.

The absolute bioavailability of rivaroxaban at a dose of 20 mg in the fasted state 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 the evening meal *[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 H_2-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}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}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.

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.

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, and 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 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 $CHADS_2$ 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 6 displays the overall results for the primary composite endpoint and its components.

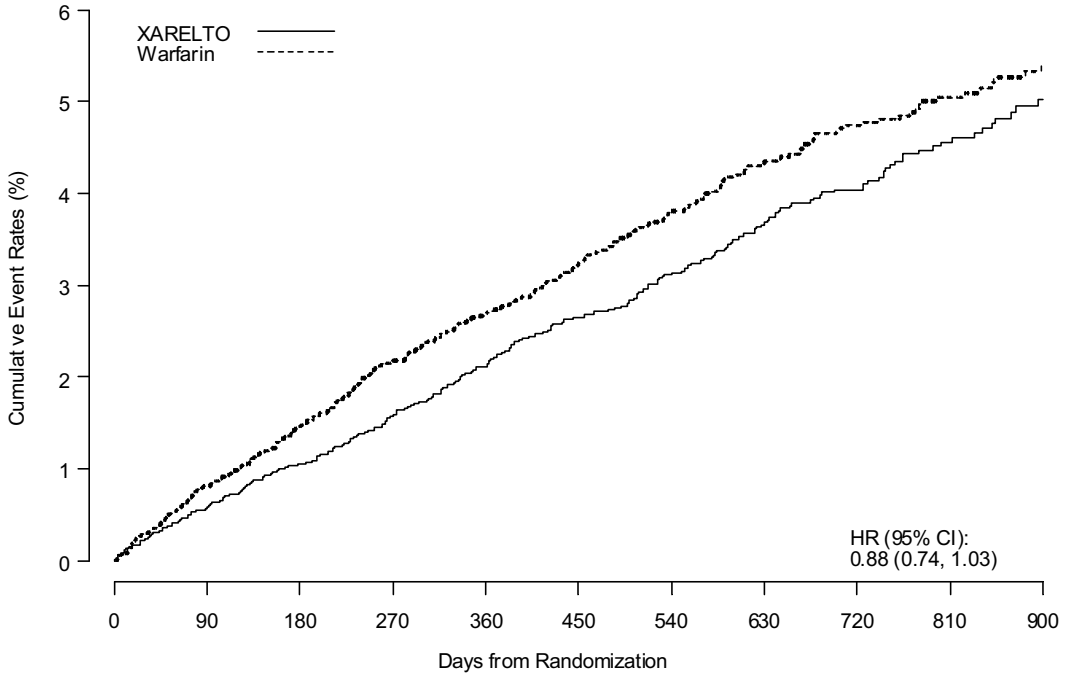
Table 6: Primary Composite Endpoint Results in ROCKET AF Study

	XARELTO		**Warfarin**		**XARELTO vs. Warfarin**
Event	**N = 7081 n (%)**	**Event Rate (per 100 Pt-yrs)**	**N = 7090 n (%)**	**Event Rate (per 100 Pt-yrs)**	**Hazard Ratio (95% CI)**
Primary Composite Endpoint*	269 (3.8)	2.1	306 (4.3)	2.4	0.88 (0.74, 1.03)
Stroke	253 (3.6)	2.0	281 (4.0)	2.2	
Hemorrhagic Stroke	33 (0.5)	0.3	57 (0.8)	0.4	
Ischemic Stroke	206 (2.9)	1.6	208 (2.9)	1.6	
Unknown Stroke Type	19 (0.3)	0.2	18 (0.3)	0.1	
Non-CNS Systemic Embolism	20 (0.3)	0.2	27 (0.4)	0.2	

* 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.

Figure 1: Time to First Occurrence of Stroke (any type) or Non-CNS Systemic Embolism by Treatment Group



Number of Subjects at Risk:

XARELTO	7081	6927	6774	6620	6470	5580	4779	3820	2951	2058	1321
Warfarin	7090	6910	6755	6590	6440	5561	4756	3807	2944	2069	1319

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 co-administration 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 Prophylaxis of Deep Vein Thrombosis

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 [± 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 7.

Table 7: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 1			RECORD 2		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**	**XARELTO 10 mg once daily**	**Enoxaparin† 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N = 1513**	**N = 1473**		**N = 834**	**N = 835**	
Total VTE	17 (1.1%)	57 (3.9%)	71% (95% CI: 50, 83), p<0.001	17 (2.0%)	70 (8.4%)	76% (95% CI: 59, 86), p<0.001
Components of Total VTE						
Proximal DVT	1 (0.1%)	31 (2.1%)		5 (0.6%)	40 (4.8%)	
Distal DVT	12 (0.8%)	26 (1.8%)		11 (1.3%)	43 (5.2%)	
Non fatal PE	3 (0.2%)	1 (0.1%)		1 (0.1%)	4 (0.5%)	
Death (any cause)	4 (0.3%)	4 (0.3%)		2 (0.2%)	4 (0.5%)	
Number of Patients	**N= 1600**	**N = 1587**		**N= 928**	**N = 929**	
Major VTE‡	3 (0.2%)	33 (2.1%)	91% (95% CI: 71, 97), p<0.001	6 (0.7%)	45 (4.8%)	87% (95% CI: 69, 94), p<0.001
Number of Patients	**N = 2103**	**N = 2119**		**N = 1178**	**N = 1179**	
Symptomatic VTE	5 (0.2%)	11 (0.5%)		3 (0.3%)	15 (1.3%)	

* 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 8.

Table 8: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Knee Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 3		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N = 813**	**N = 871**	
Total VTE	79 (9.7%)	164 (18.8%)	48% (95% CI: 34, 60), p<0.001
Components of events contributing to Total VTE			
Proximal DVT	9 (1.1%)	19 (2.2%)	
Distal DVT	74 (9.1%)	154 (17.7%)	
Non fatal PE	0	4 (0.5%)	
Death (any cause)	0	2 (0.2%)	
Number of Patients	**N = 895**	**N = 917**	
Major VTE†	9 (1.0%)	23 (2.5%)	60% (95% CI: 14, 81), p 0.024
Number of Patients	**N = 1206**	**N = 1226**	
Symptomatic VTE	8 (0.7%)	24 (2.0%)	

* 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.
- 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 health care 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 (5.4)]*.

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:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

© Janssen Pharmaceuticals, Inc. 2011

NDC 50458-578-10
Xarelto®
(rivaroxaban) Tablets
15 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
Rx only
(01)10350458578109
LOT
EXP.
10224301

(b) (4)

Reference ID: 3039818
10224301.pdf - Page 1 of 1 - October 27, 2011 - 12:23:41

NDC 50458-578-10

10 Blister Strips
10 Tablets Each

Xarelto®
(rivaroxaban)
Tablets 15 mg

Dispense the accompanying Medication Guide to each patient.

Each tablet contains: rivaroxaban 15 mg

Package Not Child Resistant

For Hospital Use Only.

Rx only

FOR SCAN INSPECTION OF DATA MATRIX CODE

N 50458-578-10 2

janssen

1022740D

janssen

Rx only

janssen

NDC 50458-578-10

Xarelto®
(rivaroxaban)
Tablets 15 mg

10 Blister Strips. 10 Tablets each.

Dosage: See package insert for full prescribing information.

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 reach of children.

For Hospital Use Only.

Active Ingredient Made in Germany

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

© Janssen 2011

Xarelto®
(rivaroxaban)
Tablets 15 mg

LOT:
EXP:

janssen

NDC 50458-578-10

10 Blister Strips
10 Tablets Each

Xarelto®
(rivaroxaban)
Tablets 15 mg

Dispense the accompanying Medication Guide to each patient.

Package Not Child Resistant

For Hospital Use Only.

Rx only

(b) (4)

Reference ID: 3039818

NDC 50458-578-30
30 Tablets
Xarelto®
(rivaroxaban)
Tablets 15 mg
Dispense the accompanying
Medication Guide to each patient.
10227600
janssen
Rx only
Each tablet contains:
rivaroxaban 15 mg
See package insert for
full prescribing information.
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 reach of children.
Active Ingredient Made in Germany
Finished Product Manufactured by:
Janssen Ortho, LLC, Gurabo, PR 00778
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
Licensed from: Bayer HealthCare AG
51368 Leverkusen, Germany
© Janssen 2011
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EXP:
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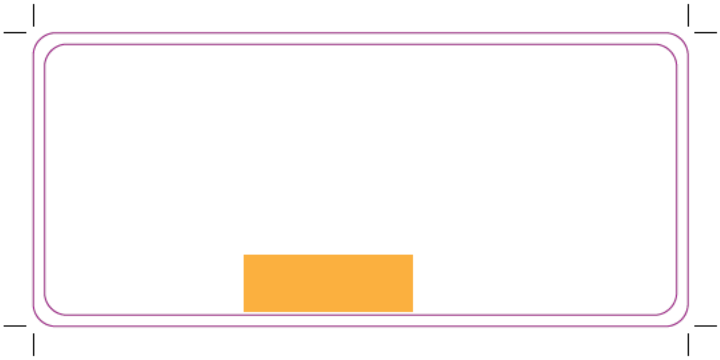

(b) (4)

NDC 50458-578-90
90 Tablets
Xarelto®
(rivaroxaban)
Tablets 15 mg
Dispense the accompanying Medication Guide to each patient.
10231000
janssen
Rx only
Each tablet contains:
rivaroxaban 15 mg
See package insert for full prescribing information.
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 reach of children.
Active Ingredient Made in Germany
Finished Product Manufactured by:
Janssen Ortho, LLC, Gurabo, PR 00778
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
Licensed from: Bayer HealthCare AG
51368 Leverkusen, Germany
© Janssen 2011
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EXP:
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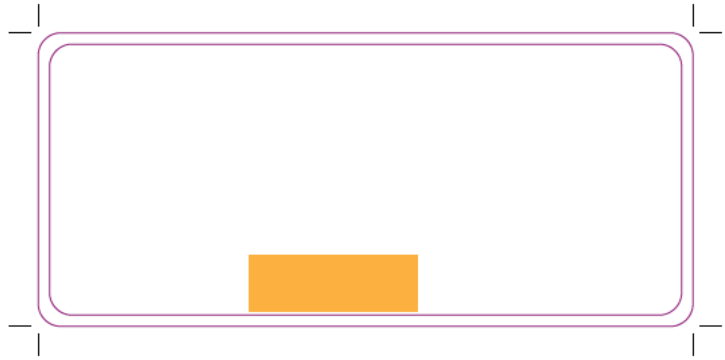

(b) (4)

Each tablet contains:
rivaroxaban 20 mg
See package insert for full prescribing information.
Store at 25°C (77°F) or room temperature; excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].
10227800

NDC 50458-579-99 5 tablets
SAMPLE - NOT FOR SALE

Xarelto®
(rivaroxaban)
Tablets 20 mg

Dispense the accompanying Medication Guide to each patient.

Keep out of reach of children.
Active Ingredient Made in Germany
Finished Product Manufactured by:
JOLLC, Gurabo, PR 00778
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
Licensed from: Bayer HealthCare AG,
51368 Leverkusen, Germany
© Janssen 2011
Rx Only LOT:
EXP:

(b) (4)

Reference ID: 3039818

Patient Education & Resource Kit

Includes:
- Patient Education
- Savings Information Card
- Resource Information

NDC 50458-579-99 Contains 5 tablets

Xarelto® (rivaroxaban) Tablets 20 mg

SAMPLE—NOT FOR SALE

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 reach of children.
Active Ingredient Made in Germany
Finished Product Manufactured by: JOLLC, Gurabo, PR 00778
Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560
Licensed from: Bayer HealthCare AG, 51368 Leverkusen, Germany

Rx only

janssen

LOT:
EXP:

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14227566

NDC 50458-579-99 Contains 5 tablets
Xarelto® (rivaroxaban) Tablets 20 mg
SAMPLE—NOT FOR SALE

Xarelto® (rivaroxaban) Tablets 20 mg

SAMPLE—NOT FOR SALE

NDC 50458-579-99
Contains 5 tablets
Xarelto® (rivaroxaban) Tablets 20 mg

Dispense the enclosed Medication Guide to each patient

SAMPLE—NOT FOR SALE

Each tablet contains: rivaroxaban 20 mg

Rx only

Patient Education & Resource Kit

Includes:
- Patient Education
- Savings Information Card
- Resource Information

Dosage: See package insert for full Prescribing Information.

Xarelto® (rivaroxaban) Tablets 20 mg

SAMPLE—NOT FOR SALE

(b) (4)

NDC 50458-579-10
Xarelto®
(rivaroxaban) Tablets
20 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
Rx only
(01)10350458579106
LOT
EXP.
10224601

(b) (4)

NDC 50458-579-10

10 Blister Strips
10 Tablets Each

Xarelto® (rivaroxaban) Tablets 20 mg

Dispense the accompanying Medication Guide to each patient.

Each tablet contains: rivaroxaban 20 mg

Package Not Child Resistant

For Hospital Use Only.

Rx only

FOR SCAN INSPECTION OF DATA MATRIX CODE

N 50458-579-10 9

janssen

10227500

janssen

Rx only

janssen

NDC 50458-579-10

Xarelto® (rivaroxaban) Tablets 20 mg

10 blister strips. 10 Tablets each.

Dosage: See package insert for full prescribing information.

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 reach of children.

For Hospital Use Only.

Active Ingredient Made in Germany

Finished Product Manufactured by:
Janssen Ortho, LLC
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Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

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Xarelto® (rivaroxaban) Tablets 20 mg

LOT:
EXP:

janssen

NDC 50458-579-10

10 Blister Strips
10 Tablets Each

Xarelto® (rivaroxaban) Tablets 20 mg

Dispense the accompanying Medication Guide to each patient.

Package Not Child Resistant

For Hospital Use Only.

Rx only

(b) (4)

Reference ID: 3039818

NDC 50458-579-30
30 Tablets
Xarelto®
(rivaroxaban)
Tablets 20 mg
Dispense the accompanying
Medication Guide to each patient.
Each tablet contains:
rivaroxaban 20 mg
See package insert for
full prescribing information.
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 reach of children.
Active Ingredient Made in Germany
Finished Product Manufactured by:
Janssen Ortho, LLC, Gurabo, PR 00778
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
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51368 Leverkusen, Germany
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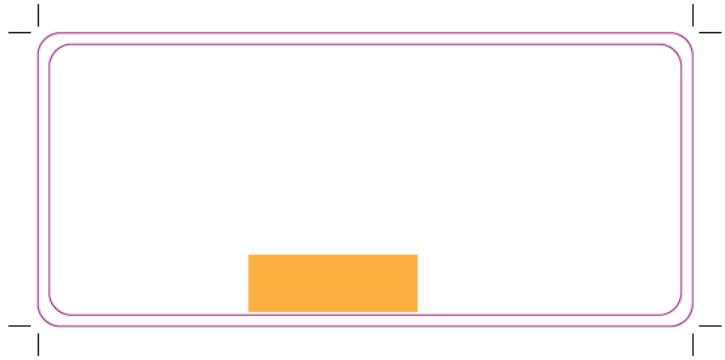
LOT:
EXP:
N 50458-579-30 7
10227700
janssen
Rx only



(b) (4)

NDC 50458-579-90
90 Tablets
Xarelto®
(rivaroxaban)
Tablets 20 mg
Dispense the accompanying
Medication Guide to each patient.
Each tablet contains:
rivaroxaban 20 mg
See package insert for
full prescribing information.
Store at 25°C (77°F) or room
temperature; excursions
permitted to 15°-30°C (59°-86°F)
[See USP Controlled Room
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Keep out of reach of children.
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Titusville, NJ 08560
Licensed from: Bayer HealthCare AG
51368 Leverkusen, Germany
©Janssen 2011
LOT:
EXP:
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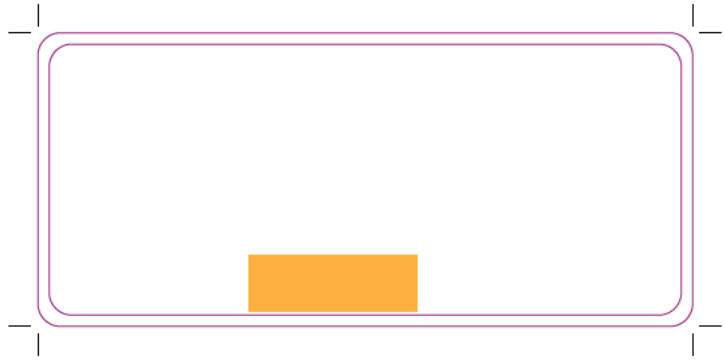
10231100
janssen
Rx only



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