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) film-coated oral tablets

Initial U.S. Approval: 2011

WARNING: SURGICAL SETTINGS--SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients who are anticoagulated and 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.**

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

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions (5.1) and Drug Interactions (7)]*.

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

XARELTO is a factor Xa inhibitor indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. (1)

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

- 10 mg orally, once daily with or without food (2)

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

Tablet: 10 mg (3)

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

- Hypersensitivity to XARELTO (4)
- Active major bleeding (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. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reaction (>5%) was bleeding. (6)

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: Avoid concomitant use unless the lack of a significant interaction is proven (7.1)
- Combined P-gp and weak or moderate CYP3A4 inhibitors: Avoid concomitant use unless the benefit outweighs the bleeding risk in patients with renal impairment (7.2)
- Combined P-gp and strong CYP3A4 inducers: Avoid concomitant use or consider an increased dose (2.1, 7.3)
- Anticoagulants: Avoid concomitant use (7.4)
- Clopidogrel: Avoid concomitant use unless the benefit outweighs the bleeding risk (7.6)

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

- Nursing mothers: discontinue drug or discontinue nursing (8.3)
- Renal impairment: 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)
- Hepatic impairment: Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or in patients with any degree of hepatic disease associated with coagulopathy (8.8)

See 17 for PATIENT COUNSELING INFORMATION.

Issued: July 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SURGICAL SETTINGS--SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients who are anticoagulated and 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.**

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

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions (5.1) and Drug Interactions (7)]*.

1 INDICATIONS AND USAGE

XARELTO (rivaroxaban) Tablets are 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

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.

If a dose of XARELTO is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and continued on the following day with the once daily intake as recommended.

Administration via GI feeding tube:

Rivaroxaban absorption is dependent on the site of drug release in the gastrointestinal (GI) tract (gastric versus small intestine). When administering XARELTO as a crushed tablet via a feeding tube, confirm gastric placement of the tube *[see Clinical Pharmacology (12.3)]*.

2.1 Use with P-gp and Strong CYP3A4 Inducers

Concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) should be avoided. A XARELTO dose increase to 20 mg (i.e., two 10 mg tablets) should be considered if these drugs must be coadministered. The 20 mg dose should be taken with food *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

XARELTO 10 mg tablets are 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.

4 CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- hypersensitivity to XARELTO
- active major bleeding *[see Warnings and Precautions (5.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 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.

5.2 Risk of Bleeding

XARELTO increases the risk of bleeding and can cause serious and fatal bleeding. Major hemorrhages including intracranial, epidural hematoma, gastrointestinal, retinal, and adrenal bleeding have been reported. Use XARELTO with caution in conditions with increased risk of hemorrhage.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include platelet aggregation inhibitors, other antithrombotic agents, fibrinolytic therapy, thienopyridines and chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.4), (7.5), (7.6)]*.

Bleeding can occur at any site during therapy with XARELTO. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site. Promptly evaluate any signs or symptoms of blood loss.

5.3 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).

5.4 Renal Impairment

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

5.5 Hepatic Impairment

Clinical data in patients with moderate hepatic impairment indicate a significant increase in rivaroxaban exposure and pharmacodynamic effects. No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy *[see Use in Specific Populations (8.8)]*.

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Trials

In three randomized, controlled clinical trials (RECORD 1-3) in elective joint replacement surgery, 4487 patients received XARELTO 10 mg orally once daily. 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, 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.

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.

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

6.2 Hemorrhage

The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions (5.2)]*. The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 1.

Table 1: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD1-3)

	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.

6.3 Other Adverse Reactions

Table 2 shows other adverse drug reactions (ADRs) reported in ≥1% of XARELTO-treated patients in the RECORD clinical studies.

Table 2: 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)

The following ADR occurred in <1% of XARELTO-treated patients in the clinical studies:

Renal and urinary disorders: dysuria

The laboratory abnormalities in Table 3 were observed in clinical studies:

Table 3: Laboratory Abnormalities in RECORD 1-3 Clinical Studies

Laboratory Abnormality	XARELTO 10 mg	Enoxaparin*
Alanine aminotransferase >3 x ULN	114/4441 (2.6%)	167/4456 (3.8%)
Aspartate aminotransferase >3 x ULN	122/4441 (2.8%)	152/4456 (3.4%)
Total bilirubin >1.5 x ULN	140/4442 (3.2%)	128/4456 (2.9%)
Gamma-glutamyltransferase >3 x ULN	292/4442 (6.6%)	391/4457 (8.8%)
Platelet counts <100,000/mm^3 or <50% of baseline value	116/4425 (2.6%)	131/4447 (3.0%)

* Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

6.4 Postmarketing Experience

The following additional adverse reactions have been reported in countries where XARELTO has been marketed. 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 disorder: 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 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%.

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.

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 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 XARELTO with drugs that are combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine), 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. Since these increases may increase bleeding risk, use XARELTO in this situation only if the potential benefit justifies the potential risk *[see Use in Specific Populations (8.7)]*.

7.3 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). Consider increasing the XARELTO dose if these drugs must be coadministered *[see Dosage and Administration (2.1)]*.

7.4 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. The safety of long-term concomitant use of these drugs has not been studied.

Avoid concurrent use of XARELTO with other anticoagulants due to the increased bleeding risk other than during therapeutic transition periods where patients should be observed closely. Promptly evaluate any signs or symptoms of blood loss *[see Warnings and Precautions (5.2)]*.

7.5 NSAIDs/Aspirin

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. The safety of long-term concomitant use of these drugs has not been studied.

NSAIDs/aspirin are known to increase bleeding, and bleeding risk may be increased when these drugs are used concomitantly with XARELTO.

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

7.6 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.

Avoid concurrent administration of clopidogrel with XARELTO unless the benefit outweighs the risk of increased bleeding *[see Warnings and Precautions (5.2)]*.

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.

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 11 times the human exposure of unbound drug, based on AUC comparisons at the maximum recommended human dose of 10 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 40 times the human exposure of unbound drug.

8.2 Labor and Delivery

Safety and effectiveness of rivaroxaban 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 17 times maximum human exposure of the unbound drug at the human dose of 10 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 the drug, 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 53% were 65 years and over, while about 15% 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.

Elderly subjects exhibited an increase in exposure that may be caused by age related changes in renal function. For patients 65 years of age and older, consideration should be given to assessment of renal function prior to starting therapy with XARELTO. Promptly evaluate any signs or symptoms of blood loss *[see Clinical Pharmacology (12.3)]*.

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 (% increase relative to normal)	AUC	44	52	64
	C_{max}	28	12	26
FXa Inhibition (% increase relative to normal)	AUC	50	86	100
	E_{max}	9	10	12
PT Prolongation (% increase relative to normal)	AUC	33	116	144
	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 any degree of renal impairment with concurrent use of P-gp and weak to moderate CYP3A4 inhibitors may have significant increases in exposure which may increase bleeding risk *[see Drug Interactions (7.2)]*.

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 Warnings and Precautions (5.2, 5.4)]*.

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 (% increase relative to normal)	AUC	15	127
	C_{max}	0	27
FXa Inhibition (% increase relative to normal)	AUC	8	159
	E_{max}	0	24
PT Prolongation (% increase relative to normal)	AUC	6	114
	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

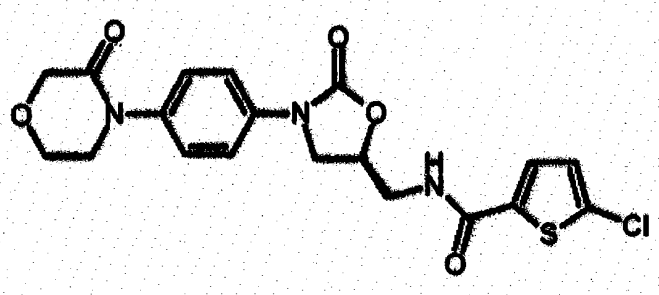
Avoid the use of XARELTO in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy *[see Warnings and Precautions (5.2, 5.5)]*.

10 OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. A specific antidote of rivaroxaban is not available. 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 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 of rivaroxaban. The inactive ingredients of XARELTO are: Microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and Opadry® Pink, a proprietary filmcoating mixture containing polyethylene glycol 3350, hypromellose, titanium dioxide, and ferric oxide red.

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. There are no data on the use of the International Normalized Ratio (INR). The predictive value of these coagulation parameters for bleeding risk or efficacy has not been established.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of rivaroxaban is high (estimated to be 80% to 100%) for the 10 mg dose. Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake.

Rivaroxaban pharmacokinetics are linear with no relevant accumulation beyond steady-state after multiple doses. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose.

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) or the antacid aluminum hydroxide/magnesium hydroxide (10 mL) 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 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 *[see Dosage and Administration (2)]*.

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.

Special Populations

Gender

Gender did not influence the pharmacokinetics or pharmacodynamics of XARELTO.

Race

Healthy Japanese subjects were found to have 50% higher exposures compared to other ethnicities including Chinese.

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 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.

12.4 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 3- and 5-times, respectively, the human exposure of unbound drug at the human dose of 10 mg/day. Systemic exposures of unbound drug in male and female rats at the highest dose tested (60 mg/kg/day) were 4- and 10-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 33 times the exposure in humans given 10 mg rivaroxaban daily.

14 CLINICAL STUDIES

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 6.

Table 6: 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=2109		N=1078	N=1072	
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 7.

Table 7: 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 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)

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

17.1 Instructions for Patient Use

- Advise patients to take XARELTO only as directed.
- Remind patients not to discontinue XARELTO prematurely without first talking to their healthcare professional.
- If a dose is missed, advise the patient to take XARELTO as soon as possible and continue on the following day with their once daily dose regimen.

17.2 Bleeding Risks

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.

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)]*.

17.3 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)]*.

17.4 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 (5.3)]*.

17.5 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)]*.

17.6 Females of Reproductive Potential

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

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