Brand Name: Xarelto®

Generic Name: Rivaroxaban

Manufacturer[1]: Janssen Pharmaceuticals, Inc.

Drug Class[1]: Anticoagulant- Factor Xa Inhibitor

Uses[1,2]:

Labeled Uses: Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip or knee replacement surgery.

Unlabeled Uses: Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Mechanism of Action[1,2]:

Inhibits platelet activation and fibrin clot formation via direct, selective, and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways.

Pharmacokinetics[1,2,4]:

Absorption:

T_{max}	2-4 hours
V_d	50 L
$t_{½}$	5-9 hours; 11-13 hours (elderly)
Clearance	10 L/hr
Protein binding	92-95% (albumin)
Bioavailability	80-100%

Metabolism: Rivaroxaban undergoes hydrolysis and oxidative degradation catalyzed by CYP3A4/5 and CYP 2J2. Rivaroxaban has no active or major circulating metabolites. It is a substrate of ABCG2 and the efflux transporter proteins P-glycoprotein.

Elimination: Rivaroxaban is primarily excreted through the kidneys into the urine (66%); 36% appears as unchanged drug and 30% as inactive metabolites. Unchanged drug is excreted into the urine through active tubular secretion and glomerular filtration (5:1 ratio). Rivaroxaban is also 28% recovered in the kidneys; 7% as unchanged drug and 21% as inactive metabolites.

Efficacy:

Lassen, M.R., Ageno, W., Borris, L.C., Lieberman, J.R., Rosencher, N., Bandel, T.J. , et al. "Rivaroxaban Versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty. N Engl J Med. 200; 358: 2776-86.

Study Design: Multicenter, randomized, double-blind, double-dummy, parallel-group study

Description of Study: *Methods*: Patients scheduled for a total knee replacement were randomized to receive 10 mg once daily oral rivaroxaban or 40 mg subcutaneous (SQ) enoxaparin daily. Rivaroxaban patients were to begin treatment 6 to 8 hours after surgery and 12 hours before surgery for enoxaparin. The primary efficacy outcome was the composite of any deep vein thrombosis, nonfatal pulmonary embolism, or death from any cause within 13 to 17 days following surgery. Secondary efficacy outcomes were major venous thromboembolism and symptomatic venous thromboembolism. Major bleeding was the primary safety outcome. *Results*: One of the primary efficacy outcomes occurred in 9.6% (79/824) patients who received rivaroxaban and 18.9% (166/878) patients who received enoxaparin. Of the secondary outcomes, major venous thromboembolism occurred in 1.0% (9/908) patients and 2.6% (24/952) patients of the rivaroxaban and enoxaparin groups, respectively. Symptomatic venous thromboembolism occurred less frequently in the rivaroxaban group compared with the enoxaparin group. Major bleeding occurred in 0.6% and 0.5% of patients in the rivaroxaban and enoxaparin groups, respectively. Adverse events occurred in 12.0% of rivaroxaban patients and 13.0% enoxaparin patients and were mainly GI related.

Limitations[8]: The trial was supported by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research and Development, the manufacturers of Xarelto®. All authors have received honoraria and consulting fees from Bayer Healthcare and two authors were employed Bayer HealthCare. In this trial, enoxaparin was dosed at 40 mg SQ every 24 hours. According to ACCP guidelines, after total knee replacement, 30 mg SQ every 12 hours or 40 mg SQ every 24 hours is recommended. However, the 40 mg dosing is not approved by the FDA and may be less efficacious in this patient population. To strengthen this study, the comparative group should be dosed at the 40 mg dosing that is commonly used in the U.S.

Conclusion: In this study, it was found that rivaroxaban was superior in preventing deep vein thrombosis, nonfatal pulmonary embolism, and death to enoxaparin 40 mg daily. The once daily, fixed dose of rivaroxaban does not require routine laboratory monitoring. Similar rates of bleeding were seen between enoxaparin and rivaroxaban. Further study is warranted in rivaroxaban's ability to prevent venous thrombosis as compared to enoxaparin 30 mg twice daily. This information will provide more useful information when comparing rivaroxaban to the commonly used dosage regimen of enoxaparin.

Patel, M.R., Mahaffey, K.W., Garg, J., Pan, G., Singer, D.E., Hacke, W., et al. "Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. " N Engl J Med. 2011: 365 (10): 883-91.

Study Design: Multicenter, randomized, double-blind, double-dummy, event-driven, parallel-group study

Description of Study: *Methods:* Patients included in the study were at moderate-to-high risk for stroke and met the study's inclusion criteria. Patients were randomly assigned to receive either rivaroxaban 20 mg daily (or 15 mg daily for patients with creatinine clearance between 30 ml/min and 49 ml/min) or adjusted-dose warfarin (target INR of 2.0 to 3.0). In order to maintain blinding, patients received an additional placebo tablet and sham INR results were generated for those receiving rivaroxaban. The primary efficacy end point was the composite of stroke and systemic embolism. Secondary efficacy outcomes were a composite of stroke, systemic embolism, or death from cardiovascular causes; a composite of stroke, systemic embolism, death from cardiovascular cause, or myocardial

infarction; and individual components of the composite end points. The primary safety end point was a composite of major and nonmajor and clinically relevant bleeding events. The primary analysis was performed in the per-protocol population, which included all patients who received at least one dose of a study drug. *Results:* 14,264 patients underwent randomization. 23.7% of rivaroxaban patients and 22.2% warfarin patients ended their assigned therapy before the end date. For the primary outcome results, 188 patients in the rivaroxaban group and 241 patients in the warfarin group experienced stroke or systemic embolism (95% CI, 0.66 to 0.96). In the intent-to-treat analysis, the primary endpoint occurred in 269 patients in the rivaroxaban group and in 306 patients in the warfarin group (95% CI, 0.74 to 1.03; p = 0.12). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group and 1449 in the warfarin group (95% CI, 0.96 to 1.11; p= 0.44). There were significant reductions in the rate of fatal bleeding (p= 0.003) and intracranial hemorrhage (p= 0.02).

Limitations: The study was supported by Johnson & Johnson Pharmaceutical Research and Development and Bayer Healthcare, the manufacturers of Xarelto®. In addition, several authors were employed by Bayer Healthcare. A limitation of this study was the mean proportion of time in which the INR was in therapeutic range in the warfarin group (55%). This percentage was lower than in previous trials of other new anticoagulants in treating atrial fibrillation (range, 64 to 68%). If the percentage had been higher this would have made for a stronger comparison between warfarin and rivaroxaban. Also, atrial fibrillation is not an FDA approved indication for rivaroxaban and appropriate dosing is unknown. The ROCKET-AF trial is the only study investigating the use of rivaroxaban in atrial fibrillation. 20 mg a day is twice the dose that has been approved for total hip and knee replacement. Limited data exists on the appropriate dose of rivaroxaban in this patient population.

Conclusion: In patients with nonvalvular atrial fibrillation, once-daily rivaroxaban was noninferior to adjusted-dose warfarin for the prevention of systemic embolism or stroke. Between the two study groups, no significant difference was found in rates of major or clinically relevant nonmajor bleeding. However, intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

Eriksson, B.I., Borris, L.C., Friedman, R.J., Hass, S., Hiusman, M.V., Kakkar, A.K., et al. "Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty." N Engl J Med. 2008; 358 (26): 2765-75.

Study Design: Randomized, multinational, double-blind, parallel-group study

Description of Study: *Methods:* Patients scheduled for total hip replacement were randomized to receive either oral rivaroxaban, 10 mg once daily or subcutaneous enoxaparin, 40 mg once daily. Rivaroxaban was started six to eight hours after wound closure. Enoxaparin was started 12 hours before surgery and restarted six to eight hours after wound closure. Both drugs were administered for a total duration of 35 days. Patients were concurrently given placebo tablets or injections. The primary efficacy outcome was the composite of deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause for the 36 days following surgery. The secondary efficacy outcome was major venous thromboembolism and major bleeding was the primacy safety outcome. *Results:* In total, 3153 patients were included in the superiority analysis and 4433 patients in the safety analysis. The primary efficacy outcome occurred in 1.1% (19/1595) of rivaroxaban patients

and 3.7% (58/1558) of enoxaparin patients (95% CI, 1.5 to 3.7; p < 0.001). The secondary outcome occurred in 0.2% (4/1686) of rivaroxaban patients and 2.0% (33/1678) of enoxaparin patients (95% CI, 1.0 to 2.5; p < 0.001). Major bleeding occurred in 0.3% (6/2209) and 0.1% (2/2224) of rivaroxaban and enoxaparin patients, respectively(p= 0.18).

Limitations: This study was supported by Bayer HealthCare and Johnson & Johnson. Dr. Eriksson had received consulting and lecture fees from Bayer HealthCare. In addition, several authors had received consulting fees from Bayer Healthcare and others were employed Bayer Healthcare. A possible limitation of this study is the dose of enoxaparin used. Enoxaparin may be dosed at 40 mg SQ daily for 30 mg SQ twice daily. Unlike with total knee replacement, in total hip replacement 40 mg SQ once daily is commonly prescribed. In this study, the lower of the two dosing regimens was used. Rivaroxaban may not be as efficacious as the higher dose of enoxaparin.

Conclusion: This study found that rivaroxaban 10 mg daily was significantly more effective than 40 mg enoxaparin for prophylaxis of venous thromboembolism. The safety profiles of the two drugs were found to be similar. Rivaroxaban use was not associated with any significant increases in major bleeding or other bleeding events as compared to enoxaparin. Rivaroxaban shows promise in the use of thromboprophylaxis in total hip arthroplasty.

Contraindications[1]:

Bleeding: Rivaroxaban increases the risk for bleeding and can lead to serious and fatal bleeding. Rivaroxaban use is contraindicated in patients who have active major bleeding. Those considered to have an active major bleed include those with GI bleeding or hemorrhagic stroke in the acute phase. Bleeding may occur at any site during rivaroxaban use. Caution should be used in patients with any disease state that involves an increased risk of bleeding such as abnormal vaginal bleeding, acute infective diverticulitis, endocarditis, decreased platelets, dissecting aneurysm, hyperactive or diabetic retinopathy, inflammatory bowel disease, menstruation, non-hemorrhagic stroke, peptic ulcer disease, recent GI bleeding, severe hepatic or renal disease, threatened abortion, uncontrolled hypertension, and in patients with bleeding diathesis.

Hypersensitivity: Rivaroxaban is contraindicated in patients who have hypersensitivity to the drug.

Precautions[1,2]:

Adolescents, children, infants, and neonates: Efficacy and safety have not been established in adolescents, children, infants, and neonates.

Anticoagulant therapy: Patients receiving anticoagulant therapy, platelet inhibitors, fibrolytics, or NSAIDs should use caution due to an increased risk of bleeding. Closely monitor patients who receive concurrent therapy.

Breast-feeding: Rivaroxaban excretion into human milk is unknown. Rivaroxaban should be discontinued during breast-feeding due to possible serious adverse reaction in nursing infants.

Dental work, dental disease: Patients who are anti-coagulated with rivaroxaban are at increased risk of bleeding during dental procedures. Patients should inform healthcare providers of their anticoagulant therapy before having dental work done. Patients, especially those with dental disease, should be educated on proper oral hygiene.

Epidural anesthesia, spinal anesthesia: Weigh the risks versus the benefits before undergoing neuraxial intervention patients who have been anti-coagulated. Epidural or spinal hematomas may result. Monitor patients frequently who have had epidural anesthesia, lumbar puncture, or spinal anesthesia for signs and symptoms of neurological impairment.

Geriatric: Consideration of renal function before initiation of rivaroxaban therapy in patients older than 65 years is recommended by the manufacturer. Geriatric patients demonstrate higher plasma concentrations. Rivaroxaban had similar efficacy in geriatric patients as it did in younger patients in clinical trials.

Hepatic disease: Rivaroxaban use should be avoided in patients with moderate or severe hepatic disease or any coagulopathy associated with hepatic disease. Clinical data demonstrates increases in rivaroxaban exposure and pharmacodynamic effects in patients with moderate hepatic impairment. No clinical data is available for patients with severe hepatic impairment.

Lactose intolerance: Drug formulation contains lactose. Use in patients with lactose or galactose intolerance is not recommended.

Pregnancy: Rivaroxaban is a pregnancy category C drug. No well-controlled trials exist in pregnant women and dosing has not been established. Animal studies did not show increased risk of structural malformations, but did show increased post-implantation pregnancy loss in rabbits. Women who are pregnant or intend to become pregnant should notify their healthcare provider.

Renal failure: Rivaroxaban use should be avoided in cases of renal failure and severe renal impairment (creatinine clearance < 30 ml/min) due to increased exposure and pharmacodynamic effects. Rivaroxaban should be discontinued in patients who develop acute renal failure. Closely observe patients with moderate renal impairment (creatinine clearance > 30 to <50 ml/min) and assess for signs of blood loss.

Adverse Reactions[2]:

Occurring in 1% to 10% of patients:

Central nervous system: syncope (1%)

Dermatologic: pruritus (2%), blister (1%)

Gastrointestinal: nausea (1%)

Hematologic: bleeding (6%; major < 1%), thrombocytopenia (< 100,000/mm^3 or <50% baseline: 3%), anemia (1%)

Hepatic: GGT increased (>3 times ULN: 7%), ALT increased (>3 times ULN: 3%), AST increased (>3 times ULN: 3%), bilirubin increase (> 1.5 times ULN: 3%)

Local: wound secretion (3%)

Neuromuscular & Skeletal: extremity pain (2%), muscle spasm (1%)

Occurring in less than 1% of patients in post marketing and/or case reports:

Abdominal pain, agranulocytosis, alkaline phosphatase increased, allergic dermatitis, amylase increased, anaphylaxis, BUN increased, cholestasis, cytolytic hepatitis, constipation, creatinine increased, diarrhea, dizziness, dyspepsia, dysuria, eccymosis, fatigue, fever, headache, hematoma (epidural, subdural), hematuria, hemiparesis, hemorrhage (cerebral, retroperitoneal), hypersensitivity, hypotension, jaundice, LDH increased, lipase increased, pain, peripheral edema, rash, Steven-Johnson syndrome, tachycardia, thrombocythemia, urticaria, vomiting, weakness, xerostomia

Drug Interactions[2]:

Anticoagulants: Rivaroxaban's anticoagulant effects may be enhanced when coadministered with anticoagulants.

Antiplatelet agents: Rivaroxaban's anticoagulant effects may be enhanced when coadministered with anticoagulants.

Azithromycin, Clarithromycin: Rivaroxaban's serum concentration may be increased.

Collagenase (systemic): Rivaroxaban may increase the risk of injection site bruising and/or bleeding with Collagenase.

CYP3A4 inducers (strong): Rivaroxaban's serum concentration may be decreased.

CYP3A4 inhibitors (strong): Rivaroxaban's serum concentration may be increased.

Dasatinib: Rivaroxaban's anticoagulant effects may be enhanced.

Deferasirox: May decrease the serum concentration of CYP3A4 substrates.

Deferasirox: Rivaroxaban may increase the risk for GI ulceration/irritation or GI bleeding with Deferasirox.

Diltiazem: Rivaroxaban's serum concentration may be increased.

Erythromycin: Rivaroxaban's serum concentration may be increased.

Grapefruit juice: Rivaroxaban's serum concentrations and effects may be increased.

Herbs (anticoagulant/antiplatelet properties): Rivaroxaban's adverse/toxic effects may be increased. Bleeding may occur.

Ibritumomab: Rivaroxaban may increase the adverse/toxic effect of Ibritumomab. Both agents may lead to an increased risk of bleeding.

Nonsteriodal anti-inflammatory agents: Anticoagulant effects may be increased.

Pentosan polysulfate sodium: Anticoagulant effects may be increased.

P-glycoprotein/ABCB1 inducers: May decrease the serum concentration of P-glycoprotein/ABCB1 substrates.

P-glycoprotein/ABCB1 inhibitors: P-glycoprotein substrates may increase the serum concentration of P-glycoprotein/ABCB1 inhibitors. Rivaroxaban's serum concentrations may be increased.

Prostacyclin analogues: Anticoagulation effects may be increased; specifically, the risk of bleeding.

Salicylates: Anticoagulation effects may be increased.

St. Johns Wort: Rivaroxaban's serum concentrations may be decreased.

Thrombolytic agents: Anticoagulation effects may be increased.

Tocilizumab: Serum concentration of CYP3A4 substrates may be decreased.

Tositumomab and iodine 131 tositumomab: Rivaroxaban may increase the risk of bleeding-related adverse effects.

Verapamil: Rivaroxaban's serum concentration may be increased.

Dosing/Administration[1,2,4,9]:

NOTE: Administer initial dose at least 6-10 hours after surgery once hemostasis has been established.

Adult Dosing:

Approved Indications

- *Knee replacement*: 10 mg PO daily for 12 to 14 days after surgery.
- *Hip replacement*: 10 mg PO daily for 35 days after surgery.
- *Coadministration with P-glycoprotein and strong CYP3A4 inducer*: Consider increasing the dose to 20 mg PO daily with food. Avoid use if possible.

Unapproved Indications

- *Atrial fibrillation:* 20 mg PO daily or 15 mg PO daily in patients with creatinine clearance of 30 to 49 ml/min (dose based on ROCKET-AF trial)

***Neonates, Infants, Children, and Adolescents*:**

- Efficacy and safety have not been established.

Maximum Dosage Limits (Adults and Geriatrics):

- 10 mg PO daily
- 20 mg PO daily if given with a P-glycoprotein and strong CYP3A4 inhibitors

Hepatic Impairment:

- *Mild impairment (Child-Pugh Class A):* No dose adjustment required, but avoidance is recommended
- *Moderate impairment (Child-Pugh Class B)*: Avoid use
- *Severe impairment (Child-Pugh Class C)*: Avoid use

Renal Impairment:

- *CrCl 30 to < 50 ml/min:* Closely observe patients and promptly assess any signs or symptoms of blood loss.
- *CrCl < 30ml/min:* Use of rivaroxaban should be avoided due to an increased exposure and pharmacodynamic effects. Use should be discontinued in patients who develop acute renal failure.

Use in special circumstances:

Overdosage[3]: There are currently no antidotes for rivaroxaban. Anticoagulant therapy should be stopped at least one to two days before surgery in patients with healthy renal function. For patients who need rapid reversal, there are measures you can follow, but no specific guidelines exist. Activated charcoal may be used within 2 hours to absorb any residual drug. Adequate diuresis should be maintained since it is primarily renally excreted. It is not dialyzable. Measures such as fresh frozen plasma or recombinant factor VIIa are likely to be ineffective because rivaroxaban inhibits the clotting factors.

Conclusion:

Rivaroxaban is a promising new medication with a novel mechanism of action. It is the only direct factor Xa inhibitor on the market and has been shown to be superior in its approved indications in preventing venous thrombosis after total knee and total hip replacement surgeries. Further study is warranted for its use in atrial fibrillation, but it does prove beneficial over warfarin in that it does not require routine laboratory monitoring. It is a more cost effective therapy compared to other available anticoagulants, such as enoxaparin and fondaparinux. Rivaroxaban's cost is comparable to that of the indirect factor Xa inhibitor, dabigatran, but dabigatran requires twice daily dosing. Practitioners should use caution in prescribing this medication in patients receiving CYP enzyme inhibitors and inducers, and those with renal or hepatic impairment. Additionally the lack of a reversal agent is a consideration in patients requiring immediate surgery or in cases of overdose. Rivaroxaban appears to be a clinically useful drug and a valued addition to the anticoagulant family.

Recommended References:

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Prepared by: Carla M. Shoaf, Doctor of Pharmacy Candidate