Drug Monograph

Drug/Drug Class: **Xarelto® (Rivaroxaban) 15 mg and 20 mg tablet / Anticoagulant Agent**

Prepared for: MO HealthNet
Prepared by: ACS, A Xerox Company

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, or require prior authorization for use.
Dosage Forms & Manufacturer:	Each tablet of Xarelto® 15 mg contains Rivaroxaban 15 mg and each tablet of Xarelto® 20 mg contains Rivaroxaban 20 mg. Janssen Pharmaceuticals, Inc. Titusville, NJ 08560.
Summary of Findings:	Rivaroxaban is a direct, selective, reversible factor Xa inhibitor that has demonstrated efficacy for the prophylaxis of DVT in adult patients undergoing knee or hip replacement surgery. Rivaroxaban is orally active, can be administered once daily as a fixed dose, and does not require drug monitoring. However, no antidote for reversal of its anticoagulation effects is available and the clinical significance of transient increases in liver enzymes has yet to be determined.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☒ Appropriate Indications ☒ PA Not Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug or not (open access). While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[1]

According to the American Academy of Orthopedic Surgeons, more than 800,000 Americans undergo knee or hip replacement surgery each year and the procedures are associated with an increased risk for DVT.

Dosage Form(s)[1]

Each tablet of Xarelto® 15 mg contains Rivaroxaban 15 mg and each tablet of Xarelto® 20 mg contains Rivaroxaban 20 mg.

Manufacturer

Janssen Pharmaceuticals, Inc. Titusville, NJ 08560.

Indication(s)[1]

Xarelto® is indicated for the prophylaxis of DVT which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery and to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Clinical Efficacy[1-10] (mechanism of action/pharmacology, comparative efficacy)

The approval of rivaroxaban was primarily based upon 3 randomized, double-blind, comparative clinical trials involving over 9000 patients undergoing elective THR or TKR surgery (The Regulation of Coagulation in Major Orthopedic Surgery Reducing the Risk of DVT and PE or RECORD trials 1, 2, and 3). Results indicated treatment with rivaroxaban resulted in significantly greater efficacy, both in head-to-head comparison with enoxaparin and when comparing extended-duration (5 weeks) rivaroxaban with short-duration (2 weeks) enoxaparin followed by placebo.

DEEP VEIN THROMBOSIS PROPHYLAXIS - HIP REPLACEMENT SURGERY CONCLUSION (1,3,4)

Rivaroxaban is effective for the prophylaxis of DVT in patients undergoing elective THR surgery.

STUDY DESIGN	Two multinational, randomized, double-blind, comparative clinical trials (RECORD 1 and 2; n=6727).
INCLUSION CRITERIA	Patients aged >= 18 years undergoing elective THR surgery.
EXCLUSION	Patients undergoing staged bilateral total hip replacement, patients

CRITERIA	with severe renal impairment (estimated creatinine clearance < 30 mL/min), or patients with significant liver disease (hepatitis, cirrhosis).
TREATMENT REGIMEN	Patients were randomized to receive oral rivaroxaban 10 mg once daily (initiated 6 to 8 hours after wound closure and continued for 35 days) or subQ enoxaparin 40 mg once daily (initiated 12 hours before surgery, reinitiated 6 to 8 hours after wound closure, and continued for 35 days). In RECORD 1, the mean exposure duration (+/- SD) to rivaroxaban and enoxaparin was 33.3 +/- 7 days and 33.6 +/- 8.3 days, respectively. In RECORD 2, the mean exposure duration to rivaroxaban and enoxaparin was 33.5 +/- 6.9 days 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.
RESULTS	In RECORD 1, total venous thromboembolism (VTE) rates were 1.1% for patients receiving rivaroxaban compared with 3.9% for enoxaparin (relative risk reduction (RRR), 71%; 95% confidence interval (CI), 50% to 83%; p < 0.001). In RECORD 2, total VTE rates were 2% and 8.4%, respectively, in the same groups (RRR, 76%; 95% CI, 59% to 86%; p < 0.001).
SAFETY	In RECORD 1, major bleeding occurred in 0.3% of rivaroxaban patients and 0.1% of enoxaparin patients. In RECORD 2, one major bleeding event occurred in each treatment group.

DEEP VEIN THROMBOSIS PROPHYLAXIS - KNEE REPLACEMENT SURGERY
CONCLUSION (1,5)
Rivaroxaban is effective for the prophylaxis of DVT in patients undergoing elective TKR surgery.

STUDY DESIGN	Multinational, randomized, double-blind, comparative clinical trial (RECORD 3; n=1,684).
INCLUSION CRITERIA	Patients aged >= 18 years undergoing elective TKR surgery.
EXCLUSION CRITERIA	Patients with severe renal impairment (estimated creatinine clearance < 30 mL/min) or significant liver disease (hepatitis, cirrhosis).
TREATMENT REGIMEN	Same as RECORD 1 and 2, except the duration of therapy was 10 to 14 days. The mean exposure duration (+/- SD) to rivaroxaban and enoxaparin was 11.9 +/- 2.3 days and 12.5 +/- 3 days, respectively.
RESULTS	Total VTE rates were 9.7% for patients receiving rivaroxaban compared with 18.8% for patients receiving enoxaparin (RRR, 48%; 95% CI, 34% to 60%; p < 0.001).
SAFETY	Major bleeding occurred in 0.6% of rivaroxaban patients and 0.5% of enoxaparin patients.

PHARMACOKINETICS (1,2)

	Rivaroxaban
Absolute bioavailability	80% to 100%
Protein binding	92% to 95%
Volume of distribution	50 L
Metabolism	Oxidative degradation in liver via CYP3A4/5 and CYP2J2; hydrolysis.
Excretion	Urine (66%) Feces (28%)
Half-life	5 to 9 hours

Warnings[1]

CONTRAINDICATIONS (1)

- Hypersensitivity to rivaroxaban
- Active major bleeding

WARNINGS AND PRECAUTIONS (1)

- Risk of bleeding: Serious and fatal bleeding may occur.
- Pregnancy-related hemorrhage: Use with caution in pregnant women due to potential for obstetric hemorrhage and/or emergent delivery; promptly evaluate signs/symptoms of blood loss.
- Spinal/epidural anesthesia or puncture: Increased risk for epidural or spinal hematoma; monitor during anesthesia for neurologic impairment and treat immediately.
- Renal impairment: Avoid use in patients with severe renal impairment (CrCl < 30 mL/min) due to increased exposure and pharmacodynamic effects; observe closely and promptly evaluate signs/symptoms of blood loss with moderate renal impairment (CrCl 30 to < 50 mL/min); discontinue in patients who develop acute renal failure during therapy.
- Hepatic impairment: Moderate hepatic impairment significantly increases exposure and pharmacodynamic effects; avoid use with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or any hepatic disease associated with coagulopathy.

Adverse Effects[1]

Bleeding events	**Rivaroxaban**	**Enoxaparin**
• Any bleeding event	5.8%	5.6%
• Major bleeding event	0.3%	0.2%

Other events, >= 1%

• Wound secretion	2.8%	2.0%
• Pruritus	2.1%	1.8%
• Pain in extremity	1.7%	1.2%
• Blister	1.4%	0.9%
• Muscle spasm	1.2%	0.7%
• Syncope	1.2%	0.7%

Drug Interactions[1]

- Clopidogrel
- Combined P-gp and strong CYP3A4 inducers: carbamazepine, phenytoin, rifampicin, rifampin, St. John's wort
- Combined P-gp and strong CYP3A4 inhibitors: clarithromycin, conivaptan, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir
- Combined P-gp and weak or moderate CYP3A4 inhibitors: amiodarone, azithromycin, diltiazem, dronedarone, erythromycin, felodipine, ranolazine, verapamil

Dosage and Administration[1]

The recommended dose is 10 mg 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, 35 days of treatment is recommended. For patients undergoing knee replacement surgery, 12 days of treatment is recommended.

Cost Comparison[2] (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/MONTH
Rivaroxaban	Xarelto®	Janssen	10 mg tablets	1 tablet QD	$ 243.00

*AWP (Average Wholesale Price)

*The Average Wholesale Price (AWP) as published by Thomson Reuters is in most cases the manufacturer's suggested AWP and does not necessarily reflect the actual AWP charged by a wholesaler. Thomson Reuters bases the AWP data it published on AWP reported by manufacturers or AWP is calculated based on a markup specified by the manufacturer. This markup is typically based on the Wholesale Acquisition Cost (WAC) or Direct Price (DIRP), as provided by the manufacturer, but may be based on other pricing provided by the manufacturer. Please refer to the AWP Policy available at http://www.micromedex.com/products/redbook/awp/ for more information on the published AWP information.

Conclusion

Rivaroxaban is a direct, selective, reversible factor Xa inhibitor that has demonstrated efficacy for the prophylaxis of DVT in adult patients undergoing knee or hip replacement surgery. According to the American Academy of Orthopedic Surgeons, more than 800,000

Americans undergo knee or hip replacement surgery each year and the procedures are associated with an increased risk for DVT. Rivaroxaban is orally active, can be administered once daily, and does not require drug monitoring. No antidote for reversal of its anticoagulation effects is currently available and the clinical significance of transient increases in liver enzymes has yet to be determined. Rivaroxaban is also being studied for its potential use in managing acute pulmonary embolism, preventing stroke in patients with atrial fibrillation, and in managing acute coronary syndromes.

Recommendation

Rivaroxaban should be considered for inclusion in the state specific Preferred Drug List (PDL) as a treatment option for prophylaxis of deep vein thrombosis (DVT) in patients undergoing total knee (TKR) or hip replacement (THR) surgery.

References

1. Product Information: Xarelto®, rivaroxaban tablets. Janssen Pharmaceuticals, Inc., Titusville, NJ, 07/2011.
2. Tanzi MG: Anticoagulant therapies: Review of available and upcoming agents. Pharmacy Today 2011; 17(1):58-64.
3. Eriksson BI, Borris LC, Friedman RJ et al: Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008; 358:2765–2775.
4. Kakkar AK, Brenner B, Dahl OE et al: Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: A double-blind, randomised controlled trial. Lancet 2008; 372:31–39.
5. Lassen MR, Ageno W, Borris LC et al: Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008; 358:2776–2786.
6. Turpie AG, Lassen MR, Davidson BL et al: Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD 4): A randomised trial. Lancet 2009; 373:1673–1680.
7. EINSTEIN Investigators, Bauersachs R, Berkowitz SD et al: Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363(26):2499-2510.
8. Stevenson M, Scope A, Holmes M et al: Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal. Health Technol Assess 2009; 13(Suppl 3):43-48.
9. Paramanathan V: Rivaroxaban: Future in anticoagulation practice? Hematology 2008; 13(5):257-260.
10. Buller HR, Lensing AW, Prins MH et al: EINSTEIN-DVT Dose-Ranging Study investigators: A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the EINSTEIN-DVT Dose-Ranging Study. Blood 2008; 112(6):2242-2247.
11. Agnelli G, Gallus A, Goldhaber SZ et al: ODIXa-DVT Study Investigators: Treatment of proximal deep vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep Vein Thrombosis) study. Circulation 2007; 116(2):180-187.
12. Eriksson BI, Borris LC, Dahl OE et al: Dose-escalation study of rivaroxaban (BAY 59-7939) - an oral, direct Factor Xa inhibitor for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Res 2007; 120(5):685-693.

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Date: February 13, 2012