Xarelto (rivaroxaban)
Policy Number: C6373-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
6/1/2015	1/29/2020	1/29/2021
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
NA	RxPA	Q2 2020 20200422C6373-A

PRODUCTS AFFECTED:
Xarelto (rivaroxaban)

DRUG CLASS:
Direct Factor Xa Inhibitors

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Retail Pharmacy

AVAILABLE DOSAGE FORMS:
Xarelto tablets 2.5MG, Xarelto tablets 10MG, Xarelto tablets 15MG, Xarelto tablets 20MG

FDA-APPROVED USES:
indicated: to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, for the treatment of deep vein thrombosis (DVT), for the treatment of pulmonary embolism (PE), for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months, for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery, in combination with aspirin, to reduce the risk of major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD)

COMPENDIAL APPROVED OFF-LABELED USES:
None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
non-valvular atrial fibrillation, treatment of deep vein thrombosis (DVT), treatment of pulmonary embolism (PE), prophylaxis of DVT in patients undergoing knee or hip replacement surgery, coronary artery disease (CAD) or peripheral artery disease (PAD)

REQUIRED MEDICAL INFORMATION:
A. NONVALVULAR ATRIAL FIBRILLATION:

1. Documentation of diagnosis with non-valvular atrial fibrillation
   AND
2. Must not have artificial heart valve

AND

3. Prescriber attests that patient has moderate to high risk for stroke based on the patient's CHA_2DS_2-VASc score used to assess patient's stroke risk.
   AND
4. The patient's renal function (creatinine clearance) will be assessed as clinically indicated and therapy will be adjusted accordingly.
   AND
5. Patient does NOT have moderate to severe mitral stenosis OR mechanical heart valve or mechanical prosthetic valves or bioprosthetic valvues If patient DOES have moderate to severe mitral stenosis OR a mechanical heart valve, warfarin MUST be used as the anticoagulant
   AND
6. IF THIS IS A NON-FORMULARY PRODUCT: Documentation of trial/failure of or intolerance to the preferred formulary alternatives for the iven diagnosis. If yes, please submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).

B. TREATMENT OF DVT AND/OR PE:

1. Documentation of diagnosis of a DVT or PE
   AND
2. The patient's renal function (creatinine clearance) will be assessed as clinically indicated and therapy will be adjusted accordingly.
3. IF THIS IS A NON-FORMULARY PRODUCT: Documentation of trial/failure of or intolerance to the preferred formulary alternatives for the iven diagnosis. If yes, please submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).

C. PROPHLAXIS OF DVT:

1. Patient has or is scheduled to have total knee replacement surgery
   OR
2. Patient has or is scheduled to have total hip replacement surgery
   OR
3. Documentation patient is at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months
   AND
4. IF THIS IS A NON-FORMULARY PRODUCT: Documentation of trial/failure of or intolerance to the preferred formulary alternatives for the iven diagnosis. If yes, please submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).

D. REDUCTION OF RISK IN MAJOR CARDIOVASCULAR EVENTS:

1. (a) Documentation of a diagnosis of chronic (>6 months) coronary artery disease
   AND
   (b)Patient is <65 years of age and documented atherosclerosis or revascularization involving at least 2 vascular beds or at least 2 additional risk factors: 1) Current smoker (within 1 year of randomization), 2) Diabetes mellitus, 3) Renal dysfunction with estimated glomerular filtration rate <60 ml/min, 4) Heart failure or 5) Non-lacunar ischemic stroke ≥1 month ago
   OR
2. Documentation of a diagnosis of chronic (>6 months) peripheral artery disease
   AND
3. Documentation member will concurrently be utilizing aspirin 100mg once daily
   AND

4. Member does NOT have any of the following: Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy or oral anticoagulant therapy, Stroke within 1 month or any history of hemorrhagic or lacunar stroke, Severe heart failure with known ejection fraction <30% or New York Heart Association (NYHA) class III or IV symptoms or Estimated glomerular filtration rate (eGFR)<15 mL/min
   AND
5. IF THIS IS A NON-FORMULARY PRODUCT: Documentation of trial/failure of or intolerance to the preferred formulary alternatives for the iven diagnosis. If yes, please submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).

E. CONTINUATION OF THERAPY UPON HOSPITAL DISCHARGE:
1. Documentation of recent hospital discharge(within 48 hours) in which Xarelto was started as an in-patient

DURATION OF APPROVAL:
Knee Replacement 12 days, Hip Replacement 35 days, AFib, DVT or PE: 12 months, Risk Reduction in CV events: 12 months

QUANTITY:
NONVALVULAR ATRIAL FIBRILLATION: 15mg (CrCl 15-50mL/min) or 20mg once daily,
TREATMENT OF DVT AND/OR PE: 15mg twice daily x 21 days, THEN 20mg once daily.
PROPHLAXIS OF DVT FOR RECURRENCE: 20mg once daily,
*****Duration of therapeutic anticoagulation (first episode, general recommendations): Optimal duration of therapy is unknown and is dependent on many factors, such as whether provoking events were present, patient risk factors for recurrence and bleeding, and individual preferences: Provoked venous thromboembolism: 3 months (provided the provoking risk factor is no longer present)* [7]
Unprovoked pulmonary embolism or deep vein thrombosis (proximal or isolated distal): ≥*3 months depending on risk of venous thromboembolism (VTE) recurrence and bleeding.* [7,8,9]

PROPHLAXIS OF DVT HIP REPLACEMENT: 10mg once daily x 35 days, PROPHYLAXIS OF DVT KNEE REPLACEMENT SURGERY: 10mg once daily x 12 days
REDUCTION OF RISK IN MAJOR CARDIOVASCULAR EVENTS: 2.5 mg twice daily

PRESCRIBER REQUIREMENTS:
NA

AGE RESTRICTIONS:
Must be at least 18 years of age.

CONTINUATION OF THERAPY:
A. NONVALVULAR ATRIAL FIBRILLATION, PROPHLAXIS OF DVT OR REDUCTION OF RISK IN MAJOR CARDIOVASCULAR EVENTS ONLY:
1. Continues to meet initial criteria
   AND
2. Current chart notes detailing response and adherence to therapy
   AND
3. Documentation that patient is not having intolerable or unacceptable toxicity

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Xarelto (rivaroxaban) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy.
Xarelto (Rivaroxaban) will not be covered as an alternative treatment for VTE in patients with cancer. This data is still investigational as this time and is not supported by NCCN or ASCO statements. (Reference 4, 5)
Black Box Warning: Discontinuing Xarelto can lead to higher risk of stroke. If discontinuation is warranted for reasons other than pathological bleeding, consider use of another anticoagulation agent. Administration of Xarelto while also receiving neuraxial anesthesia or undergoing spinal puncture can lead to epidural or spinal hematomas, which can result in long term or permanent paralysis. If discontinuation is warranted due to risk of bleeding with surgery or other procedures, temporarily stop Xarelto at least 24 hours before procedure. Restart after the procedure once adequate hemostasis has been established. Avoid if CrCl < 15mL/min. Avoid use with P-gp and strong CYP3A4 inhibitors/inducers.

OTHER SPECIAL CONSIDERATIONS:
None

BACKGROUND:
Xarelto is a factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of deep vein thrombosis (DVT), for the treatment of pulmonary embolism (PE), for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months, and for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery. Xarelto contains a black boxed warning for spinal/epidural hematoma and premature discontinuation of Xarelto increasing the risk of thrombotic events.
The first two randomized trials to directly compare direct oral anticoagulants vs low–molecular-weight heparin for management of venous thromboembolism (VTE) in patients with cancer suggest that direct oral anticoagulants may become the new standard of care. Direct oral anticoagulants appear to reduce the rate of recurrent VTE vs low–molecular-weight heparin in patients with cancer, albeit with an increased rate of bleeding. The findings of these studies were presented at the 2017 American Society of Hematology (ASH) Annual Meeting & Exposition.
The larger Hokusai VTE–Cancer trial1 showed the direct oral anticoagulant edoxaban was noninferior to the low–molecular-weight heparin (dalteparin [Fragmin]) for the composite endpoint of first recurrent VTE or major bleeding event at 12 months: 12.8% vs 13. 5%, respectively. These results were similar during the first 6 months of treatment, but major bleeding was more frequent with edoxaban.
First, the use of an open-label design is a potential weakness, but long-term administration of placebo injections was not considered to be appropriate. To mitigate potential bias, all events were adjudicated by a committee whose members were unaware of the treatment assignments. Second, the number of primary-outcome events was lower than expected; despite this limitation, noninferiority was established. Third, the median duration of the assigned treatment was shorter with dalteparin than with edoxaban, which may have influenced the relative efficacy of the two treatments. However, this difference was primarily due to the inconvenience of the use of subcutaneous dalteparin as compared with oral edoxaban, thus demonstrating the desirability of oral therapy in this context. In addition, the sensitivity analysis of events that occurred during treatment in the per-protocol population confirmed the results of the primary analysis. Finally, the trial included a

broad spectrum of patients with cancer who had received a wide array of cytotoxic and biologic therapies, but the sample size limits our ability to make definitive conclusions about outcomes associated with individual tumor types.

The “select-d” pilot trial2 showed that at 6 months, rivaroxaban had a lower cumulative VTE recurrence rate than dalteparin (4% vs 11%, respectively). The 6-month cumulative rate of major bleeding was 6% for rivaroxaban and 4% for dalteparin. Clinically relevant nonmajor bleeding was more frequently observed with rivaroxaban: 13% vs 4%, respectively.

First, we did not specifically study patients with a previous stroke. However, of those enrolled, 1032 also had a history of stroke, and the benefits of the combination of rivaroxaban and aspirin in preventing cardiovascular death, stroke, or myocardial infarction were consistent in these patients. Furthermore, the combination of rivaroxaban and aspirin resulted in a lower rate of ischemic stroke than aspirin alone. Second, although the majority of patients were receiving proven secondary prevention therapies, and the blood pressure and total cholesterol levels were serially recorded during the study, we did not specifically record statin use or low-density lipoprotein cholesterol levels at baseline, and the trial protocol did not specifically emphasize aggressive use of secondary prevention therapies to lower blood pressure and cholesterol levels. However, the results were consistent in patients with baseline blood pressure below or above the mean and in those with baseline cholesterol levels below or above the median, supporting the conclusion that the benefits of combination therapy are additive to those of other proven secondary preventive therapies. Third, trials that are stopped early for efficacy may overestimate the treatment effect. However, before the time of stopping, the data and safety monitoring board had observed a progressive increase in benefit of the combination of rivaroxaban and aspirin for more than 1 year. Furthermore, the data reported here include additional events that occurred before the cutoff but were not reported at the time of stopping the study and exclude some events that were refuted during adjudication. It is noteworthy that the results based on events reported by the sites and after adjudication are nearly identical.

APPENDIX:

CHA2DS2-VASc risk model

Clinical criteria

Sex

- ○ Female (1 point)
- ○ Male (0 points)

Age

- ○ ≤64 years old (0 points)
- ○ 65 to 74 years old (1 point)
- ○ ≥75 years old (2 points)

Comorbidities

- ☐ Heart failure (1 point)
- ☐ Hypertension (1 point)
- ☐ Diabetes mellitus (1 point)
- ☐ History of stroke, TIA, or thromboembolism (2 points)
- ☐ Vascular disease (history of MI, PAD, or aortic atherosclerosis) (1 point)

Unadjusted Stroke Rate

0 points:0.2% per year
1 point:0.6% per year
2 points:2.2% per year
3 points:3.2% per year
4 points:4.8% per year
5 points:7.2% per year
6 points:9.7% per year
7 points:11.2% per year
8 points:10.8% per year
9 points:12.2% per year

- Patients with a CHA_2DS_2-VASc score greater than 1 are at high risk and no further risk assessment needs to be performed.
- Patients with a CHA_2DS_2-VASc score of 0, who are uncommon, are at low risk.
- Patients with CHA_2DS_2-VASc score of 1 have a relatively broad range of risk. It is necessary to carefully consider the quantitative risk for individuals who have only one of the following: female sex, age between 65 and 74 years, or a diagnosis of hypertension, diabetes, vascular disease, or heart failure. In studies presented above, hypertension and vascular disease were at the lower end of the risk range while age between 65 and 74 was at the higher end.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Cancer-Associated Venous Thromboembolic Disease

NCCN Guidelines Index
Table of Contents
Discussion

THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM

- Anticoagulation options recommended for management of VTE in patients with cancer include regimens involving only one agent (monotherapy) as well as regimens that use more than one type of agent (combination therapy: VTE-E 2 of 5 and VTE-E 3 of 5). This section lists the recommended regimens, including dosing and duration, as well as a list of contraindications and warnings to help guide treatment selection.[1]
- Select regimen based on: Renal failure (CrCl <30 mL/min), inpatient/outpatient, FDA approval, cost, ease of administration, monitoring, bleeding risk assessment, and ability to reverse anticoagulation. (See Contraindications and Warnings on VTE-E 4 of 5).
- Baseline laboratory testing: CBC, renal and hepatic function panel, aPTT, and PT/INR.
- Follow institutional standard operating procedures (SOPs) for dosing schedules. If no SOPs then use the American College of Chest Physicians (ACCP) recommendations.[2]
- Following initiation of anticoagulant: Hemoglobin, hematocrit, and platelet count at least every 2–3 days for the first 14 days and every 2 weeks thereafter or as clinically indicated.

Monotherapy Options

Agent(s)	Dosing Details[a]
LMWH	
• Dalteparin (category 1)	200 units/kg SC daily for 30 days, then 150 units/kg once daily for 2–6 months[b,3,4]
• Enoxaparin	1 mg/kg SC every 12 hours[c,5-8]
Rivaroxaban	15 mg orally BID for 21 days, then 20 mg daily[9-12]
Fondaparinux	5 mg [<50 kg]; 7.5 mg [50–100 kg]; 10 mg [>100 kg] SC daily[13,14]
Unfractionated heparin (UFH) (category 2B)	
• UFH IV then SC	IV 80 units/kg load, then 18 units/kg/h, target aPTT of 2–2.5 x control or per hospital SOPs, then SC 250 units/kg every 12 hours[15]
• UFH SC	SC 333 unit/kg load, then SC 250 units/kg every 12 hours[15,16]
For patients who refuse or have compelling reasons to avoid LMWH,[d] the following DOACs may be acceptable alternatives for management of VTE:	
• Apixaban	10 mg orally BID for 7 days, then 5 mg BID[17,18]

[a] For recommended duration, see Duration of Anticoagulation as Recommended by Guideline on VTE-E, 3 of 5.
[b] Although each of the LMWH agents has been studied in randomized controlled trials in cancer patients, the efficacy of dalteparin in this population is supported by the highest quality evidence and is the only LMWH approved by the FDA for this indication.[3,19]
[c] Long-term management with enoxaparin dosing of 1 mg/kg SC every 12 hours has not been tested in cancer patients.
[d] Patients may refuse or be poor candidates for LMWH injections because they are painful, inconvenient, and expensive. These factors may contribute to poor compliance with long-term LMWH treatment.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References
VTE-E

Documentation Requirements:

Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

REFERENCES:

1. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, Patel S, Moores L - Chest - November 1, 2018; 154 (5); 1121-1201
2. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377:1319-30
3. Xarelto [package insert]. Janssen Pharmaceuticals, Inc. Titusville, NJ; October 2017.
4. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)

Annie M. Young, Andrea Marshall, Jenny Thirlwall, Oliver Chapman, Anand Lokare, Catherine Hill, Danielle Hale, Janet A. Dunn, Gary H. Lyman, Charles Hutchinson, Peter MacCallum, Ajay Kakkar, F.D. Richard Hobbs, Stavros Petrou, Jeremy Dale, Christopher J. Poole, Anthony Maraveyas, and Mark Levine Journal of Clinical Oncology 2018 36:20, 2017-2023

5. Raskob, G., van Es, N., Verhamme, P., Carrier, M., Di Nisio, M., & Garcia, D. et al. (2018). Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. New England Journal Of Medicine, 378(7), 615-624. doi: 10.1056/nejmoa1711948
6. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017.
7. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315-352. doi: 10.1016/j.chest.2015.11.026.
8. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines [published correction appears in Chest. 2012;142(6):1698-1704]. Chest. 2012;141(2)(suppl):e419S-e496S. doi: 10.1378/chest.11-2301.
9. Baglin T, Bauer K, Douketis J, Buller H, Srivastava A, Johnson G; SSC of the ISTH. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. J Thromb Haemost. 2012;10(4):698-702