Bevyxxa (betrixaban)
Policy Number: C16349-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
7/1/2019	12/18/2019	12/18/2020
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
NA	RxPA	Q1 2020 20200122C16349-A

PRODUCTS AFFECTED:
Bevyxxa (betrixaban)

DRUG CLASS:
Direct oral anticoagulant; Factor Xa inhibitor

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Retail Pharmacy

AVAILABLE DOSAGE FORMS:
Capsules: 40 mg and 80 mg

FDA-APPROVED USES:
indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
Limitations of use: Safety and effectiveness have not been established in patients with prosthetic heart valves (has not been studied).

COMPENDIAL APPROVED OFF-LABELED USES:
None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: Extended VTE prophylaxis in hospitalized patients

REQUIRED MEDICAL INFORMATION:
A. PROPHYLAXIS OF VENOUS THROMBOEMBOLISM:
1. Documentation that Member has received Bevyxxa during hospitalization and will be continue therapy following discharge from hospital- start date of therapy required. AND
2. Member is at increased risk for VTE (examples of risk factors include but is not limited to severe restricted mobility, age ≥75 years, history of cancer, history of VTE, or concurrent infectious disease) AND
3. Member has not received more than 42 days of Bevyxxa therapy

DURATION OF APPROVAL:

Up to a total treatment of 42 days

QUANTITY:
1 capsule per day, max 80mg per day

PRESCRIBER REQUIREMENTS:
none

AGE RESTRICTIONS:
18 years of age or older

CONTINUATION OF THERAPY:

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Bevyxxa (betrixaban) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications include active pathological bleeding and hypersensitivity to any component of the medication.

OTHER SPECIAL CONSIDERATIONS:
Safety and efficacy of Bevyxxa have not been established in patients with prosthetic heart valves because this population has not been studied. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery; use only if potential benefits outweighs the risks to the mother and fetus. Dose should be reduced in patients with severe renal impairment (CrCl 15-30 ml/min) or in patients on a P- glycoprotein (P-gp) inhibitor. When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic 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. Do not remove an epidural catheter earlier than 72 hours after the last administration of Bevyxxa. Do not administer the next Bevyxxa dose earlier than 5 hours after the removal of the catheter.

BACKGROUND:
Bevyxxa is a factor Xa (FXa) inhibitor indicated for the prophylaxis VTE in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.

Efficacy
The APEX trial was a randomized, double-blind, double-dummy, active-controlled, multinational clinical trial designed to compare the efficacy of extended-duration betrixaban (for 35 to 42 days) with a standard enoxaparin regimen (10±4 days) for thromboprophylaxis in patients who were hospitalized with an acute medical illness. The primary efficacy outcome was a composite of asymptomatic proximal deep-vein thrombosis between Day 32 and Day 47, symptomatic proximal or distal deep-vein thrombosis, symptomatic nonfatal pulmonary embolism, or death from venous thromboembolism between Day 1 and Day 42. Two cohorts were established within the overall study population. Cohort 1 included patients who had an elevated baseline d- dimer level (i.e., at least two times the upper limit of the normal range), and Cohort 2 included the patients in Cohort 1 plus those who were 75 years of age or older. In Cohort 1, the primary efficacy outcome occurred in 6.9% of the betrixaban group and 8.5% of the enoxaparin group (relative risk in the betrixaban group, 0.81; 95% confidence interval [CI], 0.65 to 1.00; P =

0.054). In Cohort 2, the primary efficacy outcome occurred in 5.6% of the betrixaban group and 7.1% of the enoxaparin group (relative risk, 0.80; 95% CI, 0.66 to 0.98; P = 0.03). In the overall population, the primary efficacy outcome occurred in 5.3% of the betrixaban group and 7.0% of the enoxaparin group (relative risk, 0.76; 95% CI, 0.63 to 0.92; P = 0.006). Statistical analysis was done in a fixed hierarchical sequence to adjust for the type I error rate. Because there was no significant difference in the primary outcome in Cohort 1, subsequent analyses were considered exploratory.

Safety
Bevyxxa may increase the risk of bleeding. The primary and secondary safety outcomes of the APEX trial were bleeding-related events. In the overall safety population, the incidence of major bleeding was 0.7% (25/3716) in the Bevyxxa group and 0.6% (21/3716) in the enoxaparin group. There were 19 cases of gastrointestinal bleeding in the Bevyxxa group and nine in the enoxaparin group. There were two cases of intracranial bleeding in the betrixaban group and seven in the enoxaparin group. There was one case of fatal bleeding in each group. The incidence of clinically relevant non-major bleeding was 2.5% (91/3716) in the Bevyxxa group and 1.0% (38/3716) in the enoxaparin group.

Bevyxxa carries a black box warning that epidural or spinal hematomas may occur in patients treated with Bevyxxa who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased with the use of in-dwelling epidural catheters or the concomitant use of medical products affecting homeostasis. These hematomas may result in long-term or permanent paralysis. Because of the risk of epidural or spinal hematomas, special consideration must be made when scheduling patients for spinal procedures who are currently using Bevyxxa.

APPENDIX:
None

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. Bevyxxa (betrixaban) [prescribing information]. South San Francisco, CA: Portola Pharmaceuticals Inc; July 2019.
2. Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM; APEX Investigators. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med. 2016 Aug 11;375(6):534-44. doi: 10.1056/NEJMoa1601747
3. Gibson CM, Halaby R, Korjian S, et al. The safety and efficacy of full- versus reduced-dose betrixaban in the Acute Medically Ill VTE (Venous Thromboembolism) Prevention With

Extended-Duration Betrixaban (APEX) trial. Am Heart J. 2017;185:93-100. doi: 10.1016/j.ahj.2016.12.004.
4. Turpie AG, Bauer KA, Davidson BL, et al. A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). Thromb Haemost. 2009;101(1):68-76.