PDL DRUG REVIEW

Proprietary Name: Bevyxxa®
Common Name: betrixaban
PDL Category: Anticoagulants

Comparable Products	Preferred Drug List Status
Enoxaparin	Preferred
Xarelto	Preferred

Summary

Pharmacology/Usage: Betrixaban, the active ingredient of Bevyxxa®, is an oral factor Xa (FXa) inhibitor that selectively blocks the active site of FXa and does not require a co-factor (such as anti-thrombin III) for activity. Betrixaban inhibits free FXa and prothrombinase activity. By directly inhibiting FXa, betrixaban decreases thrombin generation (TG). Betrixaban has no direct effect on platelet aggregation.

Indication: 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. The safety and effectiveness of Bevyxxa® have not been established in patients with prosthetic heart valves because this population has not been studied.

There is no pregnancy category for this medication; however, the risk summary indicates there are no available data with use in pregnant women, but treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. Use during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Hard gelatin capsule: 40mg, 80mg

Recommended Dosage: Take an initial single dose of 160mg, followed by 80mg once daily. Give doses at the same time of day with food, and the recommended treatment duration is 35 to 42 days. If a dose is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; however, the dose should not be doubled to make up for a missed dose.

Dose adjustments are not required for mild or moderate renal impairment or with mild hepatic impairment. However, avoid use in patients with moderate and severe hepatic impairment or with any hepatic disease associated with coagulopathy. For patients with severe renal impairment, the recommended dose is an initial single dose of 80mg, followed by 40mg once daily. Monitor closely and assess any signs or symptoms of blood loss in these patients.

Drug Interactions: Betrixaban is a substrate of P-gp and concomitant P-gp inhibitors (e.g. amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin) results in an increased exposure of betrixaban. Reduce the dose of Bevyxxa® for patients receiving or starting concomitant P-gp inhibitors.

Co-administration of Bevyxxa® with P-gp inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's wort) may result in a decrease in systemic exposure of betrixaban and its effects. Thus, avoid the concomitant use of Bevyxxa® in patients receiving P-gp inducers.

Co-administration of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding. Immediately assess any signs or symptoms of blood loss if patients are treated concomitantly with anticoagulants, aspirin, other platelet aggregation inhibitors, and/or NSAIDs.

Box Warning: Bevyxxa® has a box warning of spinal/epidural hematoma. Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Bevyxxa®) minus reported % incidence for enoxaparin. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included epistaxis (1%), hematuria (1%), urinary tract infection (1%), constipation (0%), hypokalemia (1%), hypertension (0%), headache (0%), nausea (0%), and diarrhea (0%).

Bevyxxa® increases the risk of bleeding and can cause serious and potentially fatal bleeding. Promptly assess any signs or symptoms of blood loss. Concomitant use of drugs affecting hemostasis increases the risk of bleeding. Advise patients of signs and symptoms of blood loss and to report them immediately. There is no established way to reverse the anticoagulant effect of Bevyxxa®, which can be expected to persist for at least 72 hours after the last dose. It is not known if hemodialysis removes Bevyxxa®. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of Bevyxxa®.

The following includes the incidence of bleeding events with Bevyxxa® as compared with enoxaparin in the overall safety population through 7 days after discontinuation of all study drugs: Major bleeding (0.67% vs 0.57%; p=0.554), GI bleed (0.51% vs 0.24%), intracranial hemorrhage (0.05% vs 0.19%), intraocular (0% vs 0.03%), fatal bleeding (0.03% vs 0.03%), and clinically relevant non-major bleeding (CRNM; 2.45% vs 1.02%, p<0.001). Reports of bleeding with Bevyxxa® 80mg as compared with enoxaparin 40mg through 7 days after discontinuation included major bleeding (0.50% vs 0.53%), CRNM bleed (2.21% vs 1.10%), and major or CRNM bleed (2.71% vs 1.64%). Reports of bleeding with Bevyxxa® 40mg as compared with enoxaparin 20mg in patients with severe renal impairment through 7 days after discontinuation included major bleeding (2% vs 0.8%), CRNM bleed (4% vs 1.6%), and major or CRNM bleed (6% vs 2.4%).

Contraindications: In patients with active pathological bleeding and severe hypersensitivity reaction to betrixaban

Manufacturer: Portola Pharmaceuticals

Analysis: The safety and efficacy of Bevyxxa® were assessed in a randomized, double-blind, double-dummy, multinational study (N=7,513; APEX clinical trial) that compared extended duration Bevyxxa® (35 to 42 days) to short duration of enoxaparin (6 to 14 days) in the prevention of VTE in hospitalized, acutely medically ill patients with risk factors for VTE. Eligible patients included adults at least 40 years of age, hospitalized for an acute medical illness, at risk for VTE due to moderate or severe immobility, and had additional risk factors for VTE (one of the following, including ≥75 years of age; 60 through 74 years of age with D-dimer ≥2 upper limit of normal; or 40 through 59 years of age with D-dimer ≥2 upper limit of normal and a history of either VTE or cancer). Expected duration of hospitalization was at least 3 days and patients were expected to be moderately or severely

immobilized for at least 24 hours. Causes of hospitalization included heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke.

The mean age of included patients was 76.4 years, while 55% of the population were female and 93% were white. The most prevalent acute medical illness at hospitalization was acutely decompensated heart failure (45%), followed by acute infection without septic shock (29%), acute respiratory failure (12%), acute ischemic stroke (11%), and acute rheumatic disorders (3%). While the APEX study was ongoing (after 35% enrollment), it was amended to ensure enrollment of patients ≥75 years of age or with D-dimer values ≥2 times the upper limit of normal (ULN). The trial excluded patients whose condition required prolonged anticoagulation, were at increased risk of bleeding, had liver dysfunction, were on dual antiplatelet therapy, or who had both severe renal insufficiency and required the concomitant use of a P-gp inhibitor.

The efficacy of Bevyxxa® was based upon the composite outcome of the occurrence of any of the following events up to day 35 visit: asymptomatic proximal deep vein thrombosis (DVT; detected by ultrasound); symptomatic proximal or distal DVT; non-fatal pulmonary embolism (PE); or VTE-related death. Efficacy analyses were based on the modified Intent-to-Treat (mITT) population, which consisted of all patients who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary outcomes. Results can be seen in the table below, which was adapted from the prescribing information. Note that symptomatic events include symptomatic DVT, non-fatal PE, or VTE-related death.

	Bevyxxa® (N=3721)	Enoxaparin (N=3720)	Relative Risk (RR)
Composite Outcome	165 (4.4%)	223 (6%)	0.75
Asymptomatic Event	133 (3.6%)	176 (4.7%)	
Symptomatic DVT	14 (0.4%)	22 (0.6%)	
Non-fatal PE	9 (0.2%)	18 (0.5%)	
VTE-related death	13 (0.3%)	17 (0.5%)	
Symptomatic Events	35 (0.9%)	54 (1.5%)	0.64

For patients with D-dimer ≥2 ULN at baseline, the event rate is 5.7% with Bevyxxa® vs 7.2% with enoxaparin (RR 0.79). For patients with D-dimer ≥2 ULN at baseline or age ≥75 years, the event rate is 4.7% with Bevyxxa® vs 6% with enoxaparin (RR 0.78).

Results for the primary efficacy analysis that were stratified at randomization to the 80mg Bevyxxa® dose group can be seen in the table below, which was adapted from the prescribing information.

	Bevyxxa® (N=2878)	Enoxaparin (N=2926)	Relative Risk
Composite Outcome	120 (4.2%)	180 (6.2%)	0.68
Asymptomatic Event	100 (3.5%)	146 (5.0%)	
Symptomatic DVT	11 (0.4%)	17 (0.6%)	
Non-fatal PE	4 (0.1%)	14 (0.5%)	
VTE-related death	8 (0.3%)	12 (0.4%)	
Symptomatic Events	22 (0.8%)	41 (1.4%)	0.55

Patients who were randomized to 40mg Bevyxxa® (those with severe renal impairment or receiving P-gp inhibitors) had VTE rates similar to the enoxaparin arm, which can also be seen in the table below.

	Severe Renal Impairment			Concomitant use of P-gp Inhibitor		
	Bevyxxa® (N=174)	Enoxaparin (N=149)	Relative Risk	Bevyxxa® (N=669)	Enoxaparin (N=645)	Relative Risk
Composite Outcome	12 (6.9%)	10 (6.7%)	1.0	33 (4.9%)	33 (5.1%)	1.0
Asymptomatic Event	9 (5.2%)	7 (4.7%)		24 (3.6%)	23 (3.6%)	
Symptomatic DVT	0	1 (0.7%)		3 (0.4%)	4 (0.6%)	
Non-fatal PE	2 (1.1%)	2 (1.3%)		3 (0.4%)	2 (0.3%)	
VTE-related death	2 (1.1%)	0		3 (0.4%)	5 (0.8%)	
Symptomatic Events	4 (2.3%)	3 (2.0%)		9 (1.3%)	10 (1.6%)	

Place in Therapy: Bevyxxa® is an oral factor Xa (FXa) inhibitor 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. The safety and efficacy of Bevyxxa® have not been established in patients with prosthetic heart valves because this population has not been studied.

Per the full text APEX study by Cohen et al[2], the cohort with the elevated d-dimer level was cohort 1 and results were found to not be significantly superior to the active comparator (primary efficacy outcome occurred in 6.9% betrixaban vs 8.5% enoxaparin; RR 0.81, p=0.054). Thus, results from the cohort with the elevated d-dimer level or an age of at least 75 years (cohort 2: 5.6% betrixaban vs 7.1% enoxaparin for primary outcome; RR 0.8, p=0.03), as well as the overall population which included all the patients in the trial (cohort: 5.3% betrixaban vs 7.0% enoxaparin; RR 0.76, p=0.006) were considered to be exploratory due to the lack of separation noted in cohort 1. This was due to the study design that required superiority to be demonstrated in cohort 1 as a pre-specified outcome prior to allowing continued evaluation of the other cohorts as primary outcomes. The authors concluded that there was no significant difference between betrixaban and enoxaparin in the primary outcome with acutely ill patients with an elevated D-dimer level.

There is no evidence that Bevyxxa® is safer or more effective than the currently available, more cost-effective medications. It is therefore recommended that Bevyxxa® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Bevyxxa [package insert]. South San Francisco, CA: Portola Pharmaceuticals, Inc; 2019.
[2] Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. NEJM. 2016; 375(6): 534-44.