Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

New Drug Evaluation: Betrixaban Capsules

Date of Review: November 2017
Generic Name: Betrixaban
PDL Class: Anticoagulants

End Date of Literature Search: 07/12/17
Brand Name (Manufacturer): Bevyxxa
Dossier Received: No

Research Questions:

1. Is there comparative evidence that betrixaban improves outcomes (i.e., venous thromboembolism [VTE], mortality) more than other anticoagulants in patients that are acutely ill at risk of thrombosis?
2. Is there evidence that betrixaban is safer than other anticoagulants used in patients who are acutely ill?
3. Are there subpopulations of patients, such as those with Medicaid coverage or specific age groups, at risk for thrombosis for which betrixaban may be more effective or associated with less harm than other anticoagulants?

Conclusions:

- One fair quality study was used for approval of betrixaban.[1] Oral betrixaban 80 mg for 35-42 days was compared to enoxaparin 40 mg subcutaneously for 10±4 days in patients (n=7513) hospitalized for an acute medical illness and at high risk of thrombosis (patients 75 years or older, patients 60-74 years with an elevated D-dimer level ≥2 times the upper limit of normal, or patients 40 to 59 years with a D-dimer of ≥2 upper limit of normal and a history of either venous thromboembolism [VTE] or cancer [excluding non-melanoma carcinoma of the skin]). The mean patient age was 76 years old, 45% of patients were male and 93% were white. The primary efficacy outcome was the composite of asymptomatic proximal deep-vein thrombosis (DVT) and symptomatic VTE (DVT, non-fatal pulmonary embolism [PE] or death from VTE).
- The protocol was amended to analyze patients based on highest risk of VTE and each subsequent analysis was based on the superiority of the previous findings in this order: cohort1 (patients with elevated D-dimer levels), cohort 2 (patients with elevated D-dimer and age of at least 75 years) and overall patient cohort (all enrolled patients).[1]
- There is low quality evidence that betrixaban was not superior to enoxaparin for extended duration anticoagulation based on the occurrence of the primary endpoint, from cohort 1 patients, in 6.9% of patients treated with betrixaban compared to 8.5% of patients in the enoxaparin group (relative risk [RR] 0.81; 95% CI 0.65 to 1.00; P = 0.054).[1]
    - Incidence of asymptomatic proximal DVT accounted for the majority of the composite endpoint events; 105/132 (80%) of betrixaban treated patients and 129/166 (78%) of enoxaparin treated patients from cohort 1. The clinical significance of asymptomatic DVT is unknown. A more clinically relevant outcome is symptomatic DVT which represented 11% of the composite endpoint events in each group.

Author: Kathy Sentena, PharmD

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- Analysis of subsequent groups were considered exploratory since the results of the first analysis did not demonstrate superiority. However, the FDA used these analyses to support the approval of betrixaban. In cohort 2, betrixaban was associated with 5.6% occurrence of the primary outcome compared to 7.1% in the enoxaparin group (ARR 1.5%/NNT 67; RR 0.80; 95% CI, 0.66 to 0.98; P=0.03).[1] In the overall population, the primary outcome occurred in 5.3% of betrixaban patients and 7.0% of enoxaparin patients (ARR 1.7%/NNT59; RR 0.76; 95% CI, 0.63 to 0.92; P=0.006).[1] There was insufficient evidence to determine a mortality difference between betrixaban and enoxaparin.

- There is low quality evidence that the risk of major bleeding is similar between betrixaban given for 35-42 days and enoxaparin given for 10 days, 0.6% vs. 0.7%, respectively. Clinically relevant non-major bleeding was higher in the betrixaban group compared to enoxaparin (ARR 1.2%/number needed to harm [NNH] 83).[1] Given the risk of bleeding and efficacy findings, it is unclear if the benefit of betrixaban treatment outweighs the risk.
- The external validity to Medicaid patients is low. Patients enrolled in the study were 76 years, which is older than the average Medicaid patient in Oregon, as 78% are under the age of 45 years.[2] Efficacy comparisons are limited by differences in treatment durations between the two groups, lack of analysis of efficacy assessment during treatment compared to extended treatment time points and the efficacy results being driven by asymptomatic DVT findings which is unknown clinical significance.

Recommendations:

- Add betrixaban to the anticoagulant PDL class as a non-preferred drug and subject to the non-preferred drug prior authorization (PA) criteria.

Background:

Non-vitamin K oral antagonists (NOAC) are an increasingly utilized oral option for patients requiring anticoagulation. Approved NOACs are dabigatran, rivaroxaban, apixaban, edoxaban and the newest agent, betrixaban.[3–7] Betrixaban is a factor Xa inhibitor, similar to rivaroxaban, apixaban and edoxaban. It is the first NOAC to be approved for prevention of VTE in medically ill patients who are hospitalized and at risk of VTE.[7] There is no published literature of efficacy of betrixaban for other indications; however, betrixaban is being studied in phase 2 trials for stroke prevention in patients with atrial fibrillation and for VTE prevention.[8]

Two other NOACs have been studied in patients who are medically ill and at risk of VTE. A study of extended anticoagulation prophylaxis with rivaroxaban was found to be non-inferior to enoxaparin and associated with increased risk of bleeding.[9] Apixaban was also studied for extended prophylaxis in medically ill patients and was not superior to enoxaparin and had more major bleeds than enoxaparin (ARR 0.28%/NNH 357).[10] Oral anticoagulants and approved indications are outlined in **Table 1**.

Table 1. Oral anticoagulants and FDA approved indications. [3–7,11]

Drug	Orthopedic VTE Prophylaxis	VTE Treatment	Stroke Prevention in NVAF	VTE Prevention in Acute Medical Illness
Warfarin (Coumadin)	Yes	Yes	Yes	-----
Dabigatran (Pradaxa®)	Yes	Yes	Yes	------
Rivaroxaban (Xarelto®)	Yes	Yes	Yes	------
Apixaban (Eliquis®)	Yes	Yes	Yes	------
Edoxaban (Savaysa™)	-----	Yes	Yes	------
Betrixaban (Bevyxxa™)	-----	-----	-----	Yes

Abbreviations: NVAF – non-valvular atrial fibrillation; VTE – venous thromboembolism

The most important outcomes in assessing therapy for treatment and prevention of VTE include the occurrence or reoccurrence of VTE, major bleeding and all-cause mortality. Additional relevant outcomes include: minor bleeding, cardiovascular events and withdrawals due to adverse events. Early research relied primarily on symptomatic VTE and fatal PE as measures of antithrombotic prophylaxis efficacy. Recent studies have incorporated the use of the surrogate outcome, asymptomatic DVT detected by mandatory venography, as a common component of the primary outcome.[12] The American College of Chest Physicians (ACCP) guidelines find this outcome "fundamentally unsatisfactory" due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding.[13] The guidelines provide suggestions to estimate reductions in symptomatic thrombosis, dependent upon available evidence. Many studies that evaluate the effectiveness of anticoagulants in VTE prevention, rely on asymptomatic DVT events to determine treatment differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates.[12]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The approval of betrixaban was based off of one fair quality, double-dummy RCT comparing extended treatment with oral betrixaban 80 mg daily for 35-42 days and SQ placebo for 10±4 days to SQ enoxaparin 40 mg once daily for 10±4 days and oral placebo for 35 to 42 days in patients hospitalized for acute medical illness and at high risk of thrombosis.[1] Patients randomized to betrixaban were given a loading dose of 160 mg. Doses of enoxaparin and betrixaban were reduced in patients with severe renal insufficiency to enoxaparin 20 mg daily and betrixaban 40 mg daily (loading dose of 80 mg). Patients enrolled in the study were 40 years or older and hospitalized for acute medical illness (heart failure, respiratory failure, rheumatic disorders, infectious disease, or ischemic stroke). The most common reason for hospitalization was for acute decompensated heart failure which occurred in 45% of patients. The protocol was amended to increase the number of patients at high risk of VTE after trial initiation.[1] High risk was defined as the following: patients at least 75 years of age, patients 60-74 years of age with an elevated D-dimer level at least 2 times the upper limit of normal, or patients 40 to 59 years of age with a D-dimer of at least 2 times the upper limit of normal and a history of either VTE or cancer (excluding non-melanoma carcinoma of the skin). Patients expected to require prolonged anticoagulation were excluded as well as those with end stage renal disease (CrCl ≤ 15 mL/min) or liver dysfunction. Patients were stratified by D-dimer levels (greater than 2 times the upper limit of normal [ULN] or less than 2 times the ULN). The primary efficacy endpoint was a composite of asymptomatic proximal DVT between day 32 and 47, symptomatic proximal or distal DVT, symptomatic nonfatal pulmonary embolism, or death from VTE between day 1 and day 42.[1]

Results were analyzed based on a sequential analysis in three pre-specified cohorts: 1) patients with elevated D-dimer level (cohort 1), 2) patients with an elevated D-dimer (cohort 1 patients) and an age of at least 75 years old (cohort 2), 3) and all enrolled patients (overall population cohort). Based on a pre-specified sequential statistical analysis plan, between-group differences in the first cohort had to reach statistical significance in order to calculate between-group differences in subsequent cohorts.[1] If significance was not met, then the subsequent analyses would be considered exploratory.

In cohort 1, less patients in the betrixaban group experienced the composite primary outcome compared to enoxaparin, 6.9% versus 8.5%, respectively (RR 0.81; 95% CI, 0.65 to 1.0; P=0.054).[1] Median treatment days were 36 for betrixaban and 9 for enoxaparin. Results for the primary composite outcome was driven by the number of asymptomatic DVTs which represented 80% of the total events for betrixaban and 78% for enoxaparin (from cohort 1 patients). The results for secondary outcomes were considered exploratory since superiority of betrixaban compared to enoxaparin was not achieved for the primary outcome. In the

second cohort, the primary efficacy outcome occurred in 5.6% of betrixaban treated patients and 7.1% of enoxaparin treated patients (ARR 1.5%/NNT 67; RR 0.80; 95% CI, 0.66 to 0.98; P=0.03).[1] In the overall population, betrixaban had an occurrence of the primary outcome of 5.3% compared to 7.0% with enoxaparin (ARR 1.7%/NNT 59; RR 0.76; 95% CI, 0.63 to 0.92; P=0.006).[1] For both the cohort 2 population and for the overall population, the incidence of asymptomatic DVT accounted for a majority of the events, 80% in both groups. There was no treatment effect in patients randomized to the betrixaban 40 mg group compared to enoxaparin (RR 1.03; 95% CI, 0.68 to 1.57).[14] The FDA found that the efficacy of betrixaban was supported by analyses that used the mITT population (all randomized patients that received study drug).[14] The results of cohort 2 and subgroup analyses also supported the effectiveness of betrixaban.[14]

In general, this was a fair quality trial with adequate randomization. Attrition was high in both groups, 33% for betrixaban and 30% for enoxaparin. Limitations to this study include a higher inclusion rate of patients that have an elevated D-dimer, which are not always a reliable indicator of risk of thrombosis. The different dosing durations between groups may bias results in favor of betrixaban; however, the intent of the study was to determine the benefits of extended anticoagulation treatment in this population compared to the current standard of 6-14 days of treatment. Efficacy assessment of asymptomatic proximal DVT by ultrasound on or before day 47 doesn't support the efficacy claim of extended treatment benefit because assessment of the treatment effect and extended treatment effect were not delineated. Additionally, the clinical significance of asymptomatic DVT is unclear. The external validity of these results to Medicaid patients is low due to the average patient age being 76 years

Clinical Safety:
The safety population was comprised of 3,716 betrixaban treated patients and 3,716 enoxaparin treated patients.[1] Adverse reactions occurring in greater than 2% of patients are listed in **Table 2**. For the outcome of major bleeding, betrixaban was associated with 25 (0.67%) events and enoxaparin was associated with 21 (0.57%) events (RR 1.19; 95% CI, 0.67 to 2.12).[7] The most common cause of major bleeding was gastrointestinal 19/25 (51% of major bleeds) for betrixaban treated patients and 9/21 (24%) for enoxaparin treated patients.[14] Intracranial bleeds occurred in 2 patients in the betrixaban group and 7 cases in patients receiving enoxaparin.[14] Betrixaban was found to cause 91 (2.5%) major or clinically relevant nonmajor bleeding events compared to 38 (1.02%) events with enoxaparin (ARR 1.4%/NNH 71).[1] Withdrawal rates were most commonly due to bleeding, 2.4% in the betrixaban group and 1.2% in the enoxaparin group (p-value not provided).

Table 2. Adverse Reactions of Betrixaban (in ≥ 2% of patients) During the Phase 3 Trial.[7]

Adverse Reaction	Betrixaban N= 3,716	Enoxaparin N = 3,716
Epistaxis	58 (2%)	24 (1%)
Hematuria	62 (2%)	28 (1%)
Urinary Tract Infection	123 (3%)	87 (2%)
Constipation	110 (3%)	102 (3%)
Hypokalemia	93 (3%)	84 (2%)

Table 3. Pharmacology and Pharmacokinetic Properties.[7]

Parameter	
Mechanism of Action	Inhibition of factor Xa decreasing thrombin generation
Oral Bioavailability	34%

Distribution and Protein Binding	Volume of distribution is 32 L/kg and protein binding is 60%
Elimination	85% feces and 11% urine
Half-Life	19-27 hours
Metabolism	CYP-independent hydrolysis in the plasma

Abbreviations: CYP = cytochrome P450

Similar to other anticoagulants, betrixaban has a black box warning for the risk of epidural or spinal hematomas in patients who are receiving neuraxial anesthesia or undergoing spinal puncture.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality
2) Symptomatic venous thromboembolism
3) Major bleeds
4) Stroke
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Composite of asymptomatic proximal DVT and symptomatic VTE (DVT, non-fatal PE or death from VTE)

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes (safety population)	ARR/NNH	Risk of Bias/ Applicability
1. Cohen, et al[1] DD, RCT, MC, AC	1. Betrixaban 80 mg once daily (B)† 2. Enoxaparin 40 mg SQ once daily (E)* † First dose was a loading dose of 160 mg. Treatment duration was 35-42 days * Treatment duration was 10 ± 4 days	Demographics: Mean age: 76 yr Age ≥75 yr: 62% Male: 45% Hospital days: 10 White: 93% Previous thrombo-prophylaxis ≤96 hours: 51% HF: 45% Infection: 29% D-dimer ≥2 ULN: 100% Key Inclusion Criteria: - Adults 40 to ≤60 years and one additional risk	mITT*: B: 3721 E: 3720 PP: B: 2503 E: 2628 Attrition: B: 33% E: 30% * All patients randomized and received study drug	Primary Endpoint: Composite of asymptomatic proximal DVT and symptomatic VTE (DVT, non-fatal PE or death from VTE) (**Cohort 1**): B: 132 (6.9%) E: 166 (8.5%) RR 0.81 (95% CI, 0.65 to 1.0) P=0.054 Components of Primary Endpoint **(Cohort 1)** Asymptomatic proximal DVT: B: 105 (5.5%) E: 129 (6.6%) P-value not provided	NS NA	Major bleeding: B: 15 (0.6%) E: 17 (0.7%) RR 0.88 (95% CI, 0.44 to 1.76) P=0.72 Clinically relevant non-major bleeding: B: 72 (3.1%) E: 44 (1.9%) RR 1.64 (95% CI, 1.13 to 2.37) P< 0.009 Stroke (entire study population): B: 24 (0.6%) E: 41 (1.1%)	NS 1.2/83	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Patients were randomized 1:1 via an interactive voice-response system. Randomization was stratified by dose and D-dimer levels. Performance Bias: (unclear) medications were masked by using a double-dummy design. Blinding of patients and providers was not described other than using a double-blind design. Detection Bias: (low) Outcomes were adjudicated by an independent central end-point committee who were blinded to treatment assignment. Attrition Bias: (unclear) Attrition was not reported separately for cohort 1 patients. Overall attrition was high in both groups but similar to other studies that require asymptomatic assessment of VTE.

		factor for VTE or >60 years - Elevated D-dimer level (2x ULN) - Hospitalized for <96 hours for acute medical illness - Reduced mobility - Risk factors for VTE <u>Key Exclusion Criteria</u>: - Age <75 years and D-dimer <2x ULN - Anticipated anticoagulation for a prolonged period during the trial - Life expectancy <8 weeks - Risk of increased bleeding - Severe renal insufficiency and requires concomitant P-gp inhibitor -Contraindications to anticoagulation therapy - Abnormal liver function tests		Symptomatic proximal or distal DVT: B: 14 (0.7%) E: 19 (1.0%) p-value not provided Symptomatic Non-fatal PE: B: 5 (0.3%) E: 17 (0.9%) P-value not provided <u>Exploratory Endpoints:</u> Composite of asymptomatic proximal DVT and symptomatic VTE (**Cohort 2**): B: 160 (5.6%) E: 204 (7.1%) RR 0.80 (95% CI, 0.66 to 0.98) P=0.03 Composite of asymptomatic proximal DVT and symptomatic VTE (**Overall population**): B: 165 (5.3%) E: 223 (7.0%) RR 0.76 (95% CI, 0.63 to 0.92) P=0.006	NA NA 1.5%/ 67 1.7%/ 59	RR 0.59 (95% CI, 0.35 to 0.97) P=0.03 <u>All-cause Mortality:</u> B: 210 (5.7%) E: 215 (5.8%) P-value not provided	0.5/200 NA	<u>Reporting Bias</u>: (low) Prespecified outcomes were reported. Study was funded by industry. **Applicability**: <u>Patient</u>: Patients with severe renal insufficiency received reduced doses of enoxaparin (20 mg daily) or betrixaban (loading dose of 80 mg and daily dose of 40 mg). Patients taking p-glycoprotein inhibitors received betrixaban 40 mg daily. <u>Intervention</u>: Appropriate betrixaban doses were used. <u>Comparator</u>: Enoxaparin given as 40mg SQ once daily is an appropriate comparator but treatments were given for a longer duration in the intervention group which would bias efficacy in favor of betrixaban. <u>Outcomes</u>: DVT and VTE occurrence is an appropriate outcome; however, the clinical significance of asymptomatic events is unknown. <u>Setting</u>: Patients from 460 sites in 35 countries. <u>Conclusion</u>: Extended treatment with betrixaban was non-inferior to enoxaparin when given for a longer duration with similar rates of major bleeding in patients who were at high risk of thrombosis.

<u>Abbreviations</u> [alphabetical order]: AC = active controlled; ARR = absolute risk reduction; CI = confidence interval; DD = double-dummy; DVT = deep vein thrombosis; HF = heart failure; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; P-gp= p-glycoprotein; PP = per protocol; RCT = randomized controlled trial; RR = relative risk; ULN = upper limit of normal; VTE = venous thromboembolism; yr = years.

References:

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14. The Food and Drug Administration. Clinical/Statistical Review(s) - Betrixaban. Application Number: 208383Orig1S000. *Center for Drug Evaluation and Research (CDER)*. 2016.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BEVYXXA safely and effectively. See full prescribing information for BEVYXXA.

BEVYXXA ™ (betrixaban) capsules, for oral use
Initial U.S. Approval: 2017

WARNING: SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning.

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. (5.2)

INDICATIONS AND USAGE

BEVYXXA is a 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. (1)

Limitations of Use:
Safety and efficacy of BEVYXXA have not been established in patients with prosthetic heart valves because this population has not been studied. (1)

DOSAGE AND ADMINISTRATION

The recommended dose of BEVYXXA is an initial single dose of 160 mg, followed by 80 mg once daily, taken at the same time each day with food. The recommended duration of treatment is 35 to 42 days. (2.1)

- Reduce dose for patients with severe renal impairment. (2.2)
- Reduce dose for patients on P-glycoprotein (P-gp) inhibitors. (2.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 40 mg and 80 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding. (4)
- Severe hypersensitivity reaction to betrixaban BEVYXXA. (4)

WARNINGS AND PRECAUTIONS

- Risk of Bleeding: Can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.1)
- Severe Renal Impairment: Increased risk of bleeding events; reduce BEVYXXA dose (2.2, 5.3)
- Concomitant P-gp Inhibitors: Increased risk of bleeding events; reduce BEVYXXA dose (2.3, 5.4)

ADVERSE REACTIONS

Most common adverse reaction (incidence >5%) is bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Portola Pharmaceuticals at 1-855-767-7167 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- P-gp inhibitors increase the blood levels of betrixaban. Reduce BEVYXXA dose. (7.1)
- Anticoagulants: Avoid concomitant use. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if potential benefit outweighs the potential risk to the mother or fetus (8.1)
- Renal Impairment: Reduce dose. (8.6)
- Hepatic impairment: Avoid use (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2017