Betrixaban (BEVYXXA)
National Drug Monograph
December 2019

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[i]

Description/Mechanism of Action

- Betrixaban is a direct, selective inhibitor of factor Xa (FXa) that decreases thrombin generation. Betrixaban blocks the active site of FXa and does not require a co-factor for activity. Betrixaban has no effect on platelet aggregation.

Indication(s) Under Review in This Document

- Betrixaban is 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.
- *Limitation of Use:* Betrixaban has not been studied in patients with prosthetic heart valves. Safety and efficacy of betrixaban have not been established in this population.
- Betrixaban (BEVYXXA) Prescribing Information 7-2019

Dosage Form(s) Under Review

- Oral capsules: 40 mg and 80 mg
- Dosing overview: 160 mg initially, followed by 80 mg once daily with food for 35 to 42 days. Dose reductions are recommended for patients with renal impairment or who are taking P-glycoprotein (P-gp) inhibitors.

Clinical Evidence Summary

Efficacy Considerations

- FDA approval of betrixaban was based on one randomized controlled trial (APEX) that compared extended duration betrixaban (35 to 42 days) to shorter duration enoxaparin (10 to 14 days) in patients hospitalized with a prespecified acute medical illness and who carried additional risk factors for VTE.[ii,iii]
- The primary efficacy endpoint was a composite of asymptomatic proximal or distal deep vein thrombosis (DVT) day 32-47, symptomatic proximal or distal DVT, nonfatal pulmonary embolism (PE), or VTE-related death day 1-42.
- The study protocol was modified during enrollment to enrich the study population to include patients at higher risk of VTE and expected to be the most likely to benefit from treatment.
- APEX was a multinational trial that studied hospitalized medical patients at high risk of VTE. About two-thirds of the population were 75 years of age or older, and a similar portion had an elevated D-dimer. Seven percent of patients were from North America, and the most common reasons for hospitalization were heart failure and infection.

Table 1: Efficacy results from clinical trials[ii,iii]

<table>
<tr><th>Study</th><th>Design</th><th>Results</th></tr>
<tr>
<td>APEX (2016)</td>
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Randomized, double-blind, active control trial of prolonged duration betrixaban (35-42 days) vs. shorter duration enoxaparin (10-14 days)
Population: Patients ≥40 yrs old hospitalized for a specified acute medical illness, immobile, and at risk for VTE
Key inclusions†: 40-60 yr old required to have D-dimer ≥2xULN AND history of VTE or cancer; 60-74 yr old required to have D-dimer ≥2x ULN.
Key exclusions: need for prolonged anticoagulation, increased bleeding risk, ESRD (CrCl < 15 ml/min or on dialysis), DAPT
Interventions: enoxaparin 40 mg SC once daily for 10-14 days vs. betrixaban 160 mg x1, then 80 mg oral once daily for 35-42 days; 50% dose reductions of both drugs for prespecified conditions
Primary endpoint analyzed based on prespecified hierarchical hypothesis testing of patients who received study drug and had all endpoints evaluable in the following cohorts:

Cohort 1: Patients with elevated D-dimer (≥2x ULN)
Cohort 2: Patients with elevated D-dimer (≥2x ULN) or ≥75 yrs old
Overall population: All evaluable patients
mITT (used by FDA and not part of hierarchical analysis): All patients who took study drug and had follow-up assessment data on at least one primary or secondary endpoint

Primary Endpoint: composite of asymptomatic proximal or distal DVT day 32-47, symptomatic proximal or distal DVT, nonfatal PE, or VTE-related death day 1-42.

†Protocol amended after ~35% enrollment to enrich population with higher risk pts (either ≥75 yrs or D-dimer ≥2x ULN)
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Baseline/Disposition

15.4% of patients excluded from the primary efficacy analysis because of no evaluable ultrasound

<table>
<tr><th>Characteristic</th><th>N=7,513</th></tr>
<tr><td>Age (mean)</td><td>76 yr</td></tr>
<tr><td>D-dimer ≥2x ULN</td><td>62%</td></tr>
<tr><td>Age ≥75 yrs</td><td>68%</td></tr>
<tr><td>Cancer history</td><td>12%</td></tr>
<tr><td>VTE history</td><td>8%</td></tr>
</table>

Primary Efficacy Endpoint Results

<table>
<tr><th></th><th>BETRIX (%)</th><th>ENOX (%)</th><th>RR (95% CI)</th></tr>
<tr><td>Cohort 1 (n=3,870)</td><td>6.9</td><td>8.5</td><td>0.81 (0.65-1.00)</td></tr>
<tr><td>Cohort 2 (n=5,735)</td><td>5.6*</td><td>7.1</td><td>0.80 (0.66-0.98)</td></tr>
<tr><td>Overall (n=6,286)</td><td>5.3*</td><td>7.0</td><td>0.76 (0.63-0.92)</td></tr>
<tr><td>mITT (n=7,441)</td><td>4.4*</td><td>6.0</td><td>0.75 (0.61-0.91)</td></tr>
</table>

Secondary Endpoint: Symptomatic VTE (day 1-42)

<table>
<tr><th></th><th>BETRIX (%)</th><th>ENOX (%)</th><th>RR (95% CI)</th></tr>
<tr><td>Cohort 1 (n=4,627)</td><td>1.3</td><td>1.9</td><td>0.67 (0.42-1.07)</td></tr>
<tr><td>Cohort 2 (n=6,814)</td><td>1.0</td><td>1.4</td><td>0.71 (0.46-1.09)</td></tr>
<tr><td>mITT (n=7,441)</td><td>0.9*</td><td>1.5</td><td>0.64 (0.42-0.98)</td></tr>
</table>
Evaluated in a mITT population that included pts who received study drug with at least one evaluable endpoint

Conclusions: No benefit of extended betrixaban vs. short term enoxaparin in the prespecified Cohort 1. Exploratory analyses in additional cohorts suggested a possible benefit of betrixaban.

*p = <0.05
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CI=confidence interval; CrCL=creatinine clearance; DAPT=dual antiplatelet therapy; ESRD=end stage renal disease; mITT=modified intent to treat; ULN=upper limit of normal

- For the primary efficacy endpoint in the prespecified Cohort 1 patient population (patients with elevated D-dimer and with all endpoints evaluable), extended duration betrixaban failed to show a statistically significant improvement compared to short term enoxaparin. Given the predefined hierarchical testing methods, all other analyses were considered exploratory.
- Exploratory analyses conducted in other populations (Cohort 2, overall, and modified intent to treat, mITT) suggested a favorable effect of betrixaban vs. enoxaparin.

- The FDA evaluated the primary efficacy endpoint of betrixaban using the mITT population that included a broader population of all patients who took study drug and had at least one evaluable primary or secondary endpoint. The FDA concluded that a beneficial effect of betrixaban is supported by these data.
- There was no net clinical benefit (considering efficacy and safety) with betrixaban vs. enoxaparin in the primary efficacy analysis, though results looked more favorable in the exploratory analyses.
- Selected subgroup analyses:
    - **80 mg vs. 40 mg betrixaban dose:** Approximately 20% of the population received a reduced dose of betrixaban (based on severe renal impairment or concomitant use of a P-gp inhibitor). When results were separated by dose, the 80 mg betrixaban dose was associated with a statistically significant reduction in primary endpoint events compared to enoxaparin. There was no difference in primary events identified in patients who received the 40 mg betrixaban dose vs. enoxaparin. Higher drug concentrations were present in patients receiving 80 mg compared to 40 mg of betrixaban.[iv]
    - **Symptomatic VTE events:** Symptomatic VTE was a composite of VTE-related death, nonfatal PE, or symptomatic DVT day 1-42 and was evaluated in the mITT population that included patients regardless of whether an evaluable ultrasound was available. No statistically significant advantage of betrixaban was found in patients with additional risk factors (e.g., elevated D-dimer or age 75 or older), though betrixaban appeared more favorable than enoxaparin as evaluated in all patients. See Table 1.

Safety Considerations

- **Boxed warnings:** Risk of epidural or spinal hematomas in patients receiving neuraxial anesthesia or undergoing spinal puncture (general risk of anticoagulants)
- **Contraindications:** Active pathological bleeding, severe hypersensitivity
- **Other warnings / precautions**:
    - Risk of bleeding
    - Spinal/epidural anesthesia or puncture
    - Use in severe renal impairment (increased bleeding)
    - Concomitant use of P-gp inhibitors (increased bleeding)
- **Adverse reactions**
    - **Common:** Bleeding
    - **Serious Adverse events / Deaths / Discontinuation:**
        - Deaths: The mortality rate was similar between betrixaban and enoxaparin groups.
        - Discontinuations due to adverse events were similar between groups (8.6% with betrixaban vs. 8.3% with enoxaparin).

Safety Results from Clinical Trials

- The main source of safety data for betrixaban is the APEX trial. The primary safety endpoint was major bleeding (according to International Society of Thrombosis and Hemostasis [ISTH]) through 7 days after study drug discontinuation.[ii,iii]
- Betrixaban was associated with a similar rate of major bleeding compared to enoxaparin. Clinically relevant nonmajor bleeding was more than 2-fold higher with betrixaban. Fatal bleeding was rare in both groups. There was an excess of GI bleeding events but fewer intracranial hemorrhages with betrixaban compared to enoxaparin.
- When separated by dose, there were more major and clinically relevant nonmajor (CRNM) bleeding events with reduced dose betrixaban vs. reduced dose enoxaparin.

- Per subgroup analyses, a significant interaction was noted with gender where betrixaban was associated with a higher incidence of major bleeding in females. There was a trend of increased major or CRNM bleeding with betrixaban as creatinine clearance decreased and with concomitant use of a strong P-gp inhibitor.[v]

Table 2: Key Safety results from the APEX trial[i,ii]

Outcome	BETRIX (n=3,716)	ENOX (n=3,716)	RR (95% CI)
Major bleeding	25 (0.7)	21 (0.57)	1.19 (0.66-2.11)
GI bleeding	19 (0.51)	9 (0.24)	n/a
Intracranial bleeding	2 (0.05)	7 (0.19)	
Clinically relevant nonmajor bleeding	91 (2.45)*	38 (1.02)	2.39 (1.64-3.49)

Outcomes shown in overall safety population; CI= confidence interval; RR=relative risk; *p <0.05

Other Considerations

- **Drug interactions:** Betrixaban is a P-gp substrate. Concomitant use of betrixaban with strong P-gp inhibitors results in several fold increases in betrixaban exposure.
- **Peri-procedural considerations:** Betrixaban reaches peak concentrations at 3 to 4 hours. The half-life of betrixaban ranges from 19 to 27 hours, which is longer than other direct oral anticoagulants (DOACs).
- **Severe renal impairment** – Patients with severe renal impairment appeared to be at increased risk of bleeding with betrixaban based on results from the APEX trial.
- **Reversal agent**: There is no specific reversal agent FDA approved for betrixaban.
- **Reduced betrixaban 40 mg dose**: In the APEX trial, patients with severe renal impairment or who were taking a P-gp inhibitor were assigned a reduced dose of 40 mg of betrixaban. Per subgroup analysis based on betrixaban dose, no efficacy benefit was identified in patients who received the 40 mg dose. Further, there appeared to be an increased incidence of bleeding. The FDA review concluded that since the 40 mg betrixaban dose was assigned based on patient specific factors rather than by random assignment, there is not enough evidence to determine whether the 80 mg betrixaban dose should be recommended in the general population.[iii,v]

Other Therapeutic Options

Alternative treatments for VTE prophylaxis in hospitalized, acutely ill medical patients are listed in table 3 below.

Table 3 Potential Treatment Alternatives for VTE Prophylaxis in Acutely Ill Medical Patients

Drug	Formulary status	Clinical Guidance	Other Considerations
Betrixaban	NF	• **FDA Indication (2019):** VTE prophylaxis in patients hospitalized with an acute medical illness who have additional risk factors for VTE	• 80 mg (or 40 mg) orally once daily for 35-42 days • Increased bleeding risk in severe renal impairment or with concomitant use of P-gp inhibitors
Apixaban	F	• Off-label • ADOPT trial (2011): no benefit of extended duration apixaban and more major bleeding vs. enoxaparin	n/a
Dabigatran	F	• Off-label	• Not studied
Rivaroxaban	F	• **FDA Indication (2019):** Prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high bleed risk in hospital and after discharge • not yet reviewed by PBM • MAGELLAN trial (2013): extended duration rivaroxaban - superior to standard duration enoxaparin in reducing VTE at day 35; increased bleeding; net clinical harm • MARINER trial (2018): extended duration rivaroxaban started on day of discharge for 45 days (low dose) – no reduction in VTE/VTE-death; low risk of bleeding	• 10 mg orally once daily in hospital and after discharge for total of 31 to 39 days • Avoid in CrCl <15 ml/min (very limited data in CrCl <30 ml/min)
Enoxaparin	F	• **FDA Indication:** medical patients with acute illness and at high risk for VTE (during hospitalization) • Extended duration off-label • EXCLAIM trial (2010): extended duration enoxaparin reduced VTE but increased major bleeding	• 40 mg SQ once daily • Risk of thrombocytopenia • Reduced dose in CrCl <30 ml/min
Dalteparin	F	• **FDA Indication:** medical patients with acute illness and at high risk for VTE (during hospitalization) • Extended duration off-label	• 5000 units SQ once daily • Risk of thrombocytopenia
Fondaparinux	F	• Off-label • ARTEMIS (2006): Fondaparinux reduced VTE vs. placebo in acutely ill medical patients (6 to 14 days' duration); low risk of bleeding	• 2.5 mg SQ once daily • Avoid in CrCl < 30 ml/min
Heparin	F	• **FDA Indication:** medical patients with acute illness at moderate to high risk of VTE (during hospitalization) • Extended duration off-label	• 5000 units SQ every 8 to 12 hr • Risk of thrombocytopenia • No adjustment in renal failure

F=formulary; NF=nonformulary

Projected Place in Therapy

- Patients hospitalized with acute medical illnesses including stroke, heart failure, respiratory failure, infectious disease, and rheumatic disease are at increased risk of VTE during and following the hospital

admission. Additional factors that further elevate VTE risk include advanced age, immobility, elevated D-dimer, cancer, and history of VTE.

- Even though the risk of VTE persists after hospital discharge, the use of extended durations of pharmacologic VTE prophylaxis in medically ill patients beyond discharge has not been shown to provide a consistent net benefit in considering both the reduction in VTE and increase in bleeding.
- The injectable anticoagulants LMWH, heparin, and fondaparinux are superior to placebo and mechanical methods for the prevention of VTE in hospitalized medical patients.
- Of the available DOACs, betrixaban, rivaroxaban, and apixaban have been studied in acutely ill, hospitalized medical patients and compared to enoxaparin. All of the DOACs are administered orally and were studied for extended durations beyond hospital discharge (30 to 35 days total) and compared to short term enoxaparin.
    - Rivaroxaban received FDA approval in this setting (October 2019) in patients not at a high risk of bleeding based on findings from the MAGELLAN and MARINER trials.
    - Apixaban failed to show a benefit and was associated with an increased risk of bleeding compared to enoxaparin in the ADOPT trial. Apixaban remains off-label for this indication.
    - Betrixaban was studied in a predominantly elderly population at high risk of VTE and failed to show a significant reduction in VTE vs. enoxaparin in the prespecified, primary analysis of the APEX trial. Exploratory analyses in broader population suggested a possible benefit of betrixaban. Though there was no increase in major bleeding, there was a greater than 2-fold increase in clinically relevant nonmajor bleeding and an excess of gastrointestinal bleeding with betrixaban vs. enoxaparin.
- In a meta-analysis that included 5 trials evaluating extended duration prophylaxis in acutely ill medical patients, extended duration prophylaxis was associated with a reduction in symptomatic VTE or VTE related death compared to the standard of care at the expense of an increase in major and fatal bleeding.[vi] An earlier meta-analysis that included 3 trials available at the time found no benefit of extended duration of prophylaxis compared to standard of care and a 2 to 3 fold increased risk in bleeding.
- The American Society of Hematology (ASH) 2018 guidelines for the management of VTE address prophylaxis in acutely ill medical patients. Based on their systematic review of the DOAC trials (which included the APEX trial), ASH provides a strong recommendation for the use of LMWH over DOACs, given the little-to-no benefit in reducing VTE or mortality compared to enoxaparin and an increased risk of major bleeding. In addition, ASH provides a strong recommendation for inpatient use of VTE prophylaxis over inpatient plus extended duration prophylaxis with either LMWH or DOACs based on little absolute benefit and increased major bleeding.[vii]
- CHEST Guidelines (2012) suggest against the use of extended duration VTE prophylaxis in acutely ill medical patients beyond the acute hospital stay based on the EXCLAIM study evaluating enoxaparin. The guidelines were published prior to the DOAC trials. [viii]
- In summary, a clear efficacy benefit of extended duration betrixaban over short term enoxaparin has not been definitively determined. Though there was no increase in major bleeding, clinically relevant nonmajor bleeding was more than doubled with betrixaban. The current cost of betrixaban is significantly higher than most alternatives. In total, data do not support the general, widespread use of extended duration VTE prophylaxis in acutely ill medical patients after hospital discharge, though there may be individual patients where the anticipated benefits outweigh the potential increased risk of bleeding.

References

[i] Betrixaban (BEVYXXA) Prescribing Information. Portola Pharmaceuticals, Inc. South San Francisco, CA. July 2019.
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[v] U.S. Food and Drug Administration Betrixaban (BEVYXXA) Clinical Review. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208383Orig1s000MedR.pdf . Accessed on December 30, 2019.
[vi] Bajaj NS, Vaduganathan M, Qamar A, et al. Extended prophylaxis for venous thromboembolism after hospitalization for medical illness: a trial sequential and cumulative meta-analysis.
[vii] Schunemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Advances. 2018;2(22):3198-3225. PLoS Med. 2019;16(4):e1002797. Epub 2019 Apr 29.
[viii] Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients. CHEST. 2012;141(2)(Suppl):e195S-e226s.

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