Drug Monograph

Brand Name: Bevyxxa

Generic Name: Betrixaban

Manufacturer[1-3]: Portola Pharmaceuticals, Inc
- Available as 40 and 80mg capsules ($1,800 for #100)

Drug Class[1-3]: Direct Oral Anticoagulant (Factor Xa Inhibitor)

Uses[1-3]: VTE Prophylaxis (labeled)
- VTE prophylaxis in hospitalized adults at risk of thromboembolic complications due to restricted mobility/other risk factors (not studied with prosthetic valves)

Mechanism of Action[1-3]: Direct and selective inhibition of Factor Xa to inhibit fibrin clot formation. Factor Xa converts prothrombin to thrombin, activating platelets and catalyzing the conversion of fibrinogen to fibrin. No direct effect on platelet aggregation.

Pharmacokinetics[1-3]:

Pharmacokinetics	T_{max}	3-4 hrs	Major Route:	
	V_d	32 L/kg	Metabolism	CYP-independent hydrolysis
			Elimination	Feces (85%), Urine (11%)
	$t_{1/2}$	19-27 hrs	CYP	(<1%) 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 3A4
	CL	0.96 L kg^{-1} hr^{-1}		
	Protein Binding	60%	Metabolites	Inactive
	Bioavailability	34%	Urine	11% (17.8% unchanged)

Efficacy:

Citation	Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, et. al. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. NEJM. 2016;375(6):534-544.
Study Design	Randomized, Placebo-Controlled, Double-Blind, Double-Dummy, Multinational
Description	**Treatment Groups:** (n=3759) enoxaparin SQ 40mg QD x10+4 days *plus* betrixaban PO 80mg QD x35-42 days <u>or</u> (n=3754) enoxaparin placebo x10+4 days *plus* betrixaban PO 80mg QD x35-42 days Cohort 1 had elevated D-dimer levels, Cohort 2 was ≥75yo or had an elevated D-dimer level, and an overall population cohort was used **Inclusion:** 40yo, hospitalized <96hrs (for HF, respiratory failure, ID, rheumatic disease, ischemic stroke), reduced mobility and specific risk factors for VTE US or other vascular-imaging (DVT) or CT or pulmonary angiography (PE) were used to confirm clinically suspected cases, and all patients regardless received mandatory US after last dose of study medication or matching placebo

	Outcomes: (primary) composite of asymptomatic proximal DVT between day 32-47, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE between day 1-42; (secondary) composite of symptomatic VTE through day 42; (secondary) composite of asymptomatic proximal DVT between day 32-47, symptomatic DVT, nonfatal PE, or death from any cause through day 42; (safety) major bleeding at any point until 7 days after discontinuation of all study medications **Results:** not statistically significant (so all efficacy outcomes are considered exploratory) – 6.9% vs. 8.5% and 5.6% vs. 7.1% occurrence of primary outcome in betrixaban and enoxaparin groups for Cohort 1 and Cohort 2 respectively; symptomatic VTE in 0.9% vs. 1.5%, major bleeding in 0.7% vs. 0.6%, and nonmajor bleeding 3.1% vs. 1.6% in betrixaban and enoxaparin groups respectively
Limitations	Lacked statistical significance (likely due to diminished power) Investigators failed to US in 15% of patients Enrollment criteria was amended after 35% enrollment
Conclusion	Although an oral option would be beneficial for patients who require short-term anticoagulation following discharge and are poor candidates for a subcutaneous option in this setting, the lack of statistical significance and the higher incidence of bleeding with betrixaban raises concerns. Because it did show comparable incidence to apixaban and rivaroxaban compared to enoxaparin as well as some efficacy in regards to VTE events, it could be considered as an alternative to enoxaparin and other DOACs for VTE prophylaxis depending on availability and patient preference.
Citation	Turpie AGG, Bauer KA, Davidson BL, Fisher WD, Gent M 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;101:68-76.
Study Design	Randomized, Parallel-Group, Multicenter
Description	**Treatment Groups:** (n=88) betrixaban PO 15mg BID, (n=84) betrixaban PO 40mg BID, or (n=43) enoxaparin SQ 30mg x1014days with self-administration used after discharge **Inclusion:** 18-75yo, 50-120kg, scheduled for elective primary unilateral TKR within 1-30 days, without reproductive potential (female) **Exclusion:** bleeding disorders, recent internal bleeding episode, high risk for bleeding, PLT <100,000/mm^3, Hgb <10g/dL, Hct <30%, thrombolytic and anticoagulant agents within 7 days prior to surgery **Outcomes:** (primary) VTE, defined as composite of proximal and/or distal DVT or symptomatic proximal CVT or PE, up to day 10-14 with the addition of any VTE up to 6 weeks post-TKR reported; (safety) overt bleeding events both major and clinically significant nonmajor

	Results: VTE occurrence 20% vs. 15.4% vs. 10% for betrixaban 15mg, betrixaban 40mg, and enoxaparin respectively; bleeding events occurred in 0% vs. 2.4% vs. 7% of betrixaban 15mg, betrixaban 40mg, and enoxaparin respectively
Limitations	Blinding was only to betrixaban dose level, not to enoxaparin vs. betrixaban, and randomization occurred within 6 hours of surgery completion at a 2:2:1 ratio favoring betrixaban Exclusion criteria provided the study with only arguably "good" candidates and removed any patient on anticoagulants Dosed BID in anticipation of a "future CR formulation" Self-administration following discharge favors betrixaban due to the ease of administration compared to SQ enoxaparin Betrixaban was potentially underdosed Many conflicts of interest existed (and it showed in the wording)
Conclusion	When providing VTE prophylaxis for a patient following TKR, enoxaparin would be preferred given the efficacy. Should patient adherence become a significant factor and only an oral agent will do, betrixaban could be considered.
Citation	Connolly SJ, Eikelboom J, Dorian P, Hohnloser SH, Gretler DD et. al. Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). European Heart Journal. 2013;34:1498-1505.
Study Design	Randomized, Multinational
Description	**Treatment Groups:** 1:1:1:1 (n=127) betrixaban PO 40mg QD, (n=127) betrixaban PO 60mg QD, (n=127) betrixaban PO 80mg QD, or (n=127) warfarin to target INR 2-3 **Inclusion:** new/existing non-valvular AF, ≥18yo, in AF or atrial flutter at time of enrollment or documented within the previous year, ≥1 risk factor for stroke resulting in an indication for anticoagulation with a vitamin K antagonist; if currently on warfarin, INR ≤2.2 **Exclusion:** <40kg, need for HD/PD, AF due to reversible causes, active bleeding, history of congenital/acquired bleeding disorder, history of intracranial/intraocular bleeding within 6 months, significant liver disease, conditions other than AF that required chronic anticoagulation, persistent uncontrolled HTN, verapamil use **Outcomes:** (primary) time to occurrence of major/clinically relevant nonmajor bleeding; (secondary) any bleeding; (secondary) time to occurrence of death, ischemic/non-ischemic stroke, MI, systemic embolism **Results:** compliance in betrixaban groups was around 96% for all – major or nonmajor bleeding occurred in 1, 5, 5, and 7 patients in the betrixaban 40, 60, 80mg and warfarin groups respectively; any bleeding event occurred in 22, 32, 24, and 40 patients in the betrixaban 40, 60, 80mg and warfarin groups respectively

Limitations	Only deals with use in non-valvular AF and had a small sample size Assignment to betrixaban or warfarin was not blinded Other anticoagulants were allowed during the study (but almost equal across all groups) Operated under an assumption of 5.7% bleeding in warfarin group at 3 months Warfarin group was open-label (betrixaban groups were double-blind) Comparison of safety was dependent on ability to maintain patient INR within the therapeutic range (TTR 63.4%)
Conclusion	Betrixaban can be considered as an alternative to warfarin for the prevention of VTE in patients with atrial fibrillation.

Contraindications: Severe Hypersensitivity to Betrixaban; Active Pathological Bleed

Precautions:

- May increase the risk of bleeding; serious, potentially fatal bleeding may occur
- Premature discontinuation without alternative anticoagulation increases risk of thrombotic events (although anticoagulant effect may persist for ≥72 hours)
- Not recommended for use in hepatic impairment
- Increased bleeding risk with worsening renal impairment (15-29 mL/min)
- Box Warning – spinal or epidural hematoma when receiving neuraxial anesthesia or spinal puncture (risk increased with in-dwelling epidural catheters)
    - Avoid removal of epidural catheter for ≥72 hours after last dose
    - Avoid use for ≥5 hours after epidural catheter removal
    - Delay administration for ≥72 hours if traumatic puncture occurs

Adverse Effects:

- Bleeding (5%)
- Hypokalemia (3%)
- Urinary Tract Infection (3%)
- Constipation (3%)
- Diarrhea (2%)
- Hypertension (2%)
- Hematuria (2%)
- Hemorrhage (2%)
- Epistaxis (2%)
- Headache (2%)
- Nausea (2%)

Drug Interactions:

Decreased excretion of active drug may occur with P-gycoprotein inhibitors		
Amiodarone	Azithromycin	Clarithromycin
Ketoconazole	Verapamil	
Enhanced anticoagulation effect may be seen with concomitant		
Apixaban	Dabigatran	Dasatinib
Desirudin	Edoxaban	Hemin
Ibrutinib	Limaprost	Mifepristone
NSAIDs	Omega-3 Fatty Acids	P_2Y_{12} Inhibitors
Pentosan Polysulfate Na	Prostacyclin Analogues	Rivaroxaban
Salicylates	SSRIs	Sugammadex
Tibolone	Tipranavir	Urokinase
Vitamin E	Vorapaxar	

Diminished anticoagulation effect may be seen with concomitant		
Estrogens	Progestine	*Telavancin*
Enhancement of concomitant drug effects (and possible toxicity) may occur with		
Collagenase	Defetasirox	Deoxycholic Acid
Ibritumomab	Lumacaftor	Nintedanib
Obinutuzumab	Omacetaxine	Tositumomab

Dosing/Administration:

- 160 mg PO single dose on day 1, then 80 mg PO daily for 35-42 days
  - Reduce dose 50% if receiving concomitant P-gp inhibitors
  - Reduce dose 50% if CrCl is <30 mL/min
    - Avoid if CrCl is <15 mL/min
    - Avoid if renal impairment and concomitant P-gp inhibitors
  - Avoid in hepatic impairment (intrinsic coagulation abnormalities)
  - Avoid if BMI >40 kg/m^2 or ABW >120 kg
    - If used, measure peak and trough via antifactor Xa
- Administration
  - Take at the same time each day with food
  - Take a missed dose as soon as possible on the same day
  - Do not double up for a missed dose

Special Circumstances:

- Avoid in pregnancy unless benefit outweighs potential risk
  - Adverse fetal events not observed in animal studies
  - May increase risk of bleeding during labor and delivery
  - Insufficient data for safety of DOACs in pregnancy
- Unknown presence in breast milk
- No specific reversal agent and unknown if hemodialysis will remove it
  - Protamine, Vitamin K, and Tranexamic Acid not expected to be effective

Conclusion:

Betrixaban has the benefit of an oral route of administration over and relatively equivalent bleeding risk to enoxaparin. It safety appears to be dose-dependent as does its efficacy, and balancing the two is important. Although it does appear to have some efficacy in the prevention of VTE, other agents seem to be preferred due to greater safety or increased efficacy (such as rivaroxaban or apixaban). Given the limitations of current literature and the availability of less expensive oral options, this medication should be considered an alternative utilized when other therapies are unavailable or not tolerated.

References:

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