Formulary Review: PRAXBIND®
Generic Name: Idarucizumab
Manufacturer: Boehringer Ingelheim Pharmaceuticals, Inc.
FDA Approval: October 2015
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Executive Summary

FDA-approved indication: Idarucizumab is the first and only FDA approved monoclonal antibody for the reversal of dabigatran (Pradaxa®).

Unlabeled indications: N/A

Pharmacology/Pharmacokinetics:

Mechanism of Action	Idarucizumab, is a humanized monoclonal antibody fragment with specific binding affinity for dabigatran and its metabolites that is ~350 times greater than that of thrombin, which results in reversing the anticoagulant effect within minutes.
Absorption	$T_{1/2}$ = 47 minutes (initial); 10.3 hours (terminal)
	Onset: effects observed within minutes. Hemostasis restored at a median of 11.4 hours
	Duration: at least 24 hours
Distribution	V_d: 8.9 L
Metabolism	Biodegredation to small peptides and amino acids
Excretion	32% excreted in the urine within the first 6 hours and <1% in the following 18 hours

Clinical Efficacy: Reversal of dabigatran: PRAXBIND has been investigated for safety and efficacy in pharmacokinetic/pharmacodynamics trials of healthy volunteers and in a single cohort case series study with dabigatran-treated patients who have life-threatening dabigatran-related bleeding or require emergency surgery which is ongoing. Three randomized, placebo-controlled trials in healthy volunteers have been conducted to investigate the safety, dose-response, and effect of idarucizumab on reducing unbound dabigatran and coagulation parameters. Of the 283 subjects enrolled, 224 received at least 1 dose of idarucizumab. An interim analysis of the ongoing single cohort case series trial included data for 123 patients: 66 patients with serious bleeding (Group A) and 57 requiring an urgent procedure (Group B). The median age was 77 years and the median creatinine clearance was 55 mL/min. Approximately 67% of patients in Group A and 63% of patients in Group B had been treated with dabigatran 110 mg BID. Lab results were available for 90 patients (51 in Group A and 39 in Group B). Among the 90 patients with available data, the median maximum reversal of the anticoagulant effect of dabigatran as measured by ECT or dTT in the first 4 hours after administration of 5 g idarucizumab was 100%, with more than 89% achieving complete reversal. Reversal of the pharmacodynamics effects was evident immediately after administration.

Adverse Drug Reactions: Most common adverse drug events were delirium (7%), headache (5%), hypokalemia (7 %), fever (6%), pneumonia (6%), and hypersensitivity reactions. Life threatening adverse reactions that occurred in <1% of patients included, VTE, right sided heart failure, circulatory shock, and cardiac arrest.

Drug Interactions: There are no known significant interactions.

Contraindications: None per the manufacturer.

Warnings/Precautions:

Thromboembolic risk: Patients taking dabigatran have an underlying disease state that puts them at risk for thromboembolic events. Reversing the anticoagulant effect of dabigatran can re-expose patients to the thromboembolic risk of their underlying disease state. Restarting anticoagulation as soon as is medically appropriate should be considered.

Re-evaluation of coagulation parameters: Elevation of coagulation parameters [activated partial thromboplastin time (aPTT) or ecarin clotting time (ECT)] 12 to 24 hours after the administration of idarucizumab was observed in some patients during the RE-VERSE AD study. If clinically significant bleeding recurs along with elevation of coagulation parameters, a second 5 g dose of idarucizumab may be considered. The safety and efficacy of repeat doses has not been established.

Hypersensitivity reactions: There is insufficient experience with idarucizumab in patients to evaluate the hypersensitivity risk. If an anaphylactic or serious reaction to idarucizumab exists, discontinue administration.

Risk of serious adverse reactions in patients with hereditary fructose intolerance due to sorbitol excipient: In patients with a hereditary fructose intolerance who have received parenteral administration of sorbitol, serious adverse reactions, including death, have been reported. The recommended dose of idarucizumab contains 4 g of sorbitol. In patients receiving idarucizumab, the metabolic load of fructose/sorbitol should be considered from all sources.

Pregnancy/Lactation:

Animal reproductive studies have not been conducted, and it is not known if idarucizumab is excreted in breast milk.

Dosage and Administration:

Dose	5 gm, administered as two separate 2.5 gm doses no more than 15 minutes apart) via IV infusion
Administration (See administration image below)	Must be administered as an undiluted solution via bolus injection (figure 3) or intravenous infusion directly from the vial (figure 2). Each vial is administered over 5 minutes if done via infusion. Flush the line prior to administration with 0.9% sodium chloride. Begin administration within 1 hour of removing the solution from the vial. Do not mix with other medicinal products.

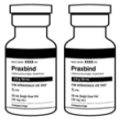

Figure 1 Recommended dose of PRAXBIND provided as two vials.

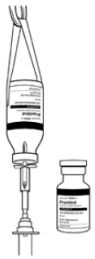

Figure 2 Two consecutive infusions by hanging vials.

Figure 3 Inject both vials consecutively via syringe.

Dose Modifications: None

Nursing implications: Monitor patient for signs or symptoms of hypersensitivity reactions, stroke, or myocardial infarction.

Reconstitution/Stability: Store vials in a refrigerated setting at 2°C- 8°C (36-46 °F). Do not freeze or shake vials. Vials need to be stored in their original container and protected from light. Unopened vials are stable at room temperature (25 C) for up to 48 hours. If given via bolus injection, withdraw the drug from each vial consecutively into a syringe for administration, DO NOT DILUTE. It is recommended per the manufacturer that the drug be used within 1 hour after being placed in the syringe.

Potential for medication errors:

Idarucizumab	Idarubicin
PRAXBIND	Pradaxa Digibind

Summary: Idarucizumab is the first FDA approved reversal agent for life-threatening dabigatran-related bleeding or for patients requiring emergent surgery while on dabigatran. It was approved under accelerated approval based reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers in the RE-VERSE AD study.

Recommendation: Recommend adding idarucizumab to hospital formulary for the reversal of life-threatening dabigatran-related bleeding.

Cost:

Cost per 2.5 gm/50 mL vial	$3500
Total cost per dose	$7000

Hazardous waste: Use appropriate precautions during handling and disposal.

References:

Boehringer Ingelheim Press Release. FDA Approves PRAXBIND® (idarucizumab), Specific Reversal Agent for Pradaxa® (dabigatran etexilate mesylate). http://us.boehringer-ingelheim.com/news_events/press_releases/press_release_archive/2015/10-16-2015-fda-approves-praxbind-idarucizumab-specific-reversal-agent-pradaxa-dabigatran-etexilate-mesylate.html Accessed January 5, 2016

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