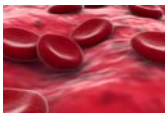

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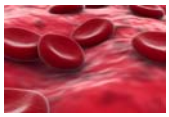


Idarucizumab (Praxbind™) – For Front Line Clinicians

What is it and how does it work?[1,2]

- Idarucizumab is a monoclonal antibody fragment specifically designed to only bind dabigatran in the bloodstream. It forms a complex with dabigatran and prevents it from having any effects on blood coagulation.
- Idarucizumab competes with thrombin for dabigatran, however, it has a much stronger affinity to bind dabigatran than thrombin and therefore rapidly and completely removes dabigatran from the circulation
- Most patients have complete normalization of clotting tests following the administration of idarucizumab

Who should get it?[1]

- Adult patients treated with dabigatran when rapid reversal of the anticoagulant effects of dabigatran is required for:
  - Emergency surgery / urgent procedures
  - Life-threatening or uncontrolled bleeding

Who should NOT get it?[1]

- Idarucizumab is not intended for dabigatran reversal for elective procedures (cost is similar to Prothrombin Complex Concentrate), or for patients who require reversal of other oral anticoagulants
- The risk in patients with known hypersensitivity (e.g. anaphylactoid reaction) to idarucizumab or to any of the excipients needs to be weighed cautiously against the potential benefit of such an emergency treatment

If a patient receives it, what do I need to know?[1]

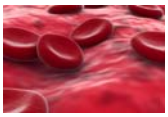
- Thromboembolic Risk – Idarucizumab itself is not thrombogenic, but by reversing dabigatran it exposes patients to the thrombotic risk of their underlying disease. Clinical judgment should dictate when anticoagulation should resume; dabigatran may be restarted as early as 24 hours after idarucizumab.
- Recurrence or Continuation of Bleeding – Idarucizumab only removes dabigatran from the circulation. It does not repair other causes of bleeding (e.g. damaged vessels) which may require urgent repair. Monitor for signs/symptoms of bleeding and seek assistance accordingly.
- Adverse Effects (>5%): Frequency similar to placebo in trials with healthy volunteer and included: hypokalemia (7%), delirium (7%), constipation (7%), pyrexia (6%), and pneumonia (6%)
- Symptoms of potential hypersensitivity (including rash, pyrexia, pruritus, bronchospasm and hyperventilation) have been reported

Where and how should it be stored?[1]

- Idarucizumab is stored in a refrigerator in its original box (2-8°C). It is both light and temperature sensitive.
- Prior to use, unopened vials may be kept at room temperature (25°C) for up to 48 hours if stored in the original package to protect from light, or up to 6 hours if exposed to light
- An opened vial can be kept unrefrigerated (15 - 25°C) for up to 1 hour away from direct heat and light, as long as the temperature is not greater than 25°C

Where and how should it given?[1]

- Administration should be in facilities such as an emergency department or operating room equipped to clinically assess the patient and subsequently administer IV therapies,
- Administration of the contents of 2 vials represents a complete 5 g dose. Administered as 2 consecutive infusions over 5-10 minutes each or as consecutive bolus injections.
- Small amounts of dabigatran are continuously released from tissues back into the circulation. By 12 hours after idarucizumab, there can be mild elevations in some clotting parameters.



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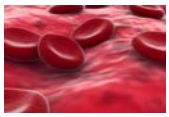

Idarucizumab Specifics[1]

Product Supplied	Two single-use vials each containing idarucizumab 2.5 g/50mL
Dose & Administration	Dose is 5 g. Administer 2 of the 2.5 g doses by IV infusion (5-10 mins for each vial) or as consecutive IV boluses. Begin administration within 1 hour of removing from vial. Visually inspect vials. Do not use if solution shows haziness, particulate matter, discoloration or leakage. If using a pre-existing intravenous line, flush with normal saline before and after administration. Do not administer any other infusion in parallel via the same IV line.
Half Life	47 minutes (distribution phase); 10.4 hours (terminal)
Metabolism	Biodegradation into small peptides and amino acids which are then reabsorbed and incorporated in general protein synthesis.
Excretion	Urine recovery 32% within 6 hours, then less than 1% in following 18 hours. No dosage adjustment in renal impairment or geriatrics (greater than 65 years of age). No data in patients with hepatic impairment, pregnancy, nursing women, pediatrics.
Volume of distribution	9.1 L
Drug Interactions	No interactions with volume expanders, coagulation factor concentrates, rFVIIa and anticoagulants other than dabigatran.
Contraindications	Hypersensitivity to idarucizumab or any ingredient in the formulation or component of the container.
Monitoring	Signs / symptoms of bleeding. If an anaphylactic reaction or other serious allergic reaction occurs, administration should be discontinued immediately and appropriate therapy initiated. If confirmation of reversal is required, the following coagulation parameters may be considered: aPTT, dilute thrombin time, ECT, ACT.
Duration of Reversal	Sustained reversal of dabigatran plasma concentration occurred up to 12 hours in more than 90% of patients (interim analysis of REVERSE AD trial).[3] In some cases, the entry of unbound dabigatran from tissues may re-establish some degree of anticoagulant effect of dabigatran in the plasma, typically 12 or more hours following idarucizumab administration. [3]
Safety with Repeat Idarucizumab Doses	Limited data supports the safety with administration of an additional 5g idarucizumab dose[4] – highest dose for healthy subjects was 7.5 g (n=6). [5]
Sorbitol Excipient – Hereditary Fructose Intolerance (HFI)	Product contains 4g of sorbitol. Those with HFI administered sorbitol may have increase in uric acid, hypoglycemia, hypophosphatemia, metabolic acidosis, acute liver failure and death. Minimum dose of sorbitol/fructose to yield severe reaction is unknown.
Clinical Trial Program Experience to Date[3-6]	There are no randomized, placebo controlled trials in bleeding patients. 3 clinical trials in healthy volunteers (n=224) Conditionally approved for use in Canada pending results of an open label trial in approximately 500 patients for major bleeding or emergent procedure use.

References

1) Praxbind™. Product Monograph. Boehringer Ingelheim Pharma GmbH & Co. KG. Burlington, Ontario. April 29,2016.
2) Schiele F et al. Blood 2013;131:121(18):3554-3562.
3) Pollack CV et al. N Engl J Med 2015;373:511-520.
4) Glund S et al. Blood 2014; 124:344. (ASH Annual Meeting 2014; Session 332: Abstract 344)
5) Glund S et al. Lancet 2015;386:680-690.
6) Pollack CV et al. Thromb Haemost 2015; 114: 198-205