

Cardiac Diseases and Therapies

ANTICOAGULANT ANTIDOTES

IDARUCIZUMAB CLINICIAN SUMMARY

BACKGROUND

Idarucizumab is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran and its metabolites:

- affinity for dabigatran is approximately 350 times greater than the affinity of dabigatran for thrombin¹; once the dabigatran-idarucizumab complex is formed, there is a very slow off-rate (i.e. binding is practically irreversible)
- does not bind thrombin substrates; does not have any procoagulant activity when used alone¹
- dabigatran-specific; does not impact the effects of other anticoagulant medications such as factor Xa inhibitors apixaban and rivaroxaban¹

INDICATION

Idarucizumab is indicated in Canada for adult patients treated with dabigatran (Pradaxa®) when rapid specific reversal of the anticoagulant effects of dabigatran is required for:

- emergency surgery/urgent procedures
- life-threatening or uncontrolled bleeding

Note: It has been approved by Health Canada **with conditions** based on *promising evidence of clinical effectiveness* and pending the full clinical trial results to verify its effectiveness. Patients should be advised of the conditional nature of the authorization.

Place in Therapy at UHN

Idarucizumab is approved at UHN for:

1. For **life-threatening bleeding** in patients who are **anticoagulated with dabigatran** and require immediate reversal of anticoagulation (examples include intracranial hemorrhage, uncontrolled gastrointestinal bleeding, pericardial bleeding, or bleeding with shock or persistent hemodynamic instability).
2. Patients who present on dabigatran in need of **emergency surgery** (e.g. aortic dissection, ruptured viscus, ischemic bowel, multi-system trauma) considered to be procedures that are unable to be postponed 8hrs

Approval by the Hematology service is required, unless delay in communication would result in a risk of imminent serious harm to the patient, in which case notification of the Hematology service may occur after administration.^[1]

Accessing Idarucizumab at UHN

Requires hematology consult and approval* (Page via locating).

Only exception is if the bleeding condition is critical (eg. intracranial hemorrhage) and a delay in hematology consultation will result in serious imminent harm to the patient

Drug is available in TGH Emergency Department, TWH Emergency Department, Central Pharmacy – refrigerated

Documentation requirements: Form kept with drug; MRP to complete. One copy kept with chart, one sent to Pharmacy

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DOSE AND ADMINISTRATION

Recommended dose:

- 5g IV, administered as 2 consecutive 2.5g infusions each over 5-10 minutes
- NO DOSE ADJUSTMENT required in renal dysfunction

Administration:

- IV infusion or bolus injection via IV pump
- 2.5g in 50mL solution comes premixed in single-use vials; no further dilution required
- REQUIRES SEPARATE IV LINE; should not be mixed with any other solution; if using preexisting line, flush with sterile 0.9% sodium chloride.

Pharmacologic Profile

Onset	Immediate
Half-life	Distribution phase: 47 minutes Terminal phase: 10 hours
Metabolism/ Elimination	All pathways involve biodegradation to smaller molecules (i.e. small peptides or amino acids)

Laboratory Monitoring

- Dilute thrombin time (DTT) and Ecarin clotting time (ECT) were used to quantify the presence of dabigatran in the clinical trial but are either not available or impractical to use in our clinical setting
- In practice, activated partial thromboplastin time (aPTT) is the most readily available test to qualitatively detect the presence of dabigatran; Thrombin time (TT) may also be used but can be elevated even in the presence of clinically insignificant levels of dabigatran.
- In addition to laboratory tests ordered to clinically manage the patient, both aPTT and TT should be ordered and drawn, but administration of idarucizumab should NOT be delayed; the results will be used for tracking and follow up of patients.

CONTRAINDICATIONS

- History of hypersensitivity to idarucizumab
- History of hypersensitivity to acetic acid, polysorbate 20, sodium acetate trihydrate, and/or sorbitol
 - NOTE: risk of serious adverse reactions in patients with Hereditary Fructose Intolerance due to the sorbitol excipient. These reactions include hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure with breakdown of excretory and synthetic function.
 - A 5 g dose of idarucizumab contains 4 g of sorbitol as an excipient.

SPECIAL POPULATIONS

The safety and efficacy of idarucizumab has NOT been established in pregnant or nursing patients, patients with hepatic dysfunction or in the pediatric population (>18y)

DRUG INTERACTIONS

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Data is limited. Preclinical investigations have shown no interactions with volume expanders, coagulation factor concentrates, recombinant FVIIa and anticoagulants other than dabigatran.

ADVERSE REACTIONS

Re-elevation of Coagulation Parameters

Elevated coagulation parameters have been observed 12-24 hours after administration of 5 g of idarucizumab. In the REVERSE-AD trial, increases in the unbound dabigatran concentrations (greater than 20 ng per milliliter — a level above which produces some anticoagulant effect) were found after 12 hours in 6 patients and 24 hours in 16 patients [REVERSE-AD reference]. If reappearance of clinically relevant bleeding and elevated coagulation parameters are observed after administration of idarucizumab, an additional dose of 5 g can be considered [monograph reference]. However, the efficacy and safety of repeat treatment is uncertain and has not been tested. The highest dose of PRAXBIND studied in healthy subjects was 8 g (n=6). No safety signals have been identified in this group.

Hypersensitivity Reactions

Mild symptoms of hypersensitivity such as pyrexia, bronchospasm, hyperventilation, rash, and pruritis have been reported [REVERSE-AD reference, monograph reference].

Immunogenicity

As idarucizumab is a humanized monoclonal antibody fragment, there exists the potential for immunogenicity. Pre-existing antibodies with cross-reactivity to idarucizumab have been reported but no impact on the pharmacokinetics or the reversal effect of idarucizumab or hypersensitivity reactions were observed [monograph reference].

Data on re-exposure to idarucizumab after developing anti-idarucizumab antibodies is limited. In a subgroup of 6 subjects, idarucizumab was administered a second time, two months after the first administration. No anti-idarucizumab antibodies were detected in these subjects prior to the second administration. In one subject, treatment-emergent anti-idarucizumab antibodies were detected after the second administration [EMA reference].

Proteinuria

Proteinuria has been observed. The transient proteinuria usually peaked about 4 h after administration of idarucizumab and normalised within 12 - 24 hours. In single cases the transient proteinuria persisted for more than 24 hours.

RESTARTING ANTITHROMBOTIC THERAPY:

Reversing dabigatran returns patients to their baseline risk of thrombosis from their underlying disease. Dabigatran can be initiated at or after 24 hours of the administration of idarucizumab if clinically warranted. Idarucizumab has no impact on the effect of other anticoagulant or antithrombotic medications. **As soon as medically appropriate, all patients should be reassessed for resumption of antithrombotic therapy.** [monograph reference].

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STORAGE & STABILITY:

Idarucizumab vials should be stored in the original package to protect from light, and refrigerated (2-8°C) until use or until the expiry date. Prior to use, it 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. For single-use only; it does not contain preservatives.

REFERENCES

1. Schiele F, van Ryn J, Canada K et al. A specific antidote for dabigatran: functional and structural characterization. *Blood*. 2013;121(18):3554-62.
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3. Pollack C, Reilly P, Eikelboom J et al. Idarucizumab for Dabigatran Reversal. *New England Journal of Medicine*. 2015;373(6):511-520. doi:10.1056/nejmoa1502000.
4. Eikelboom JW, Quinlan DJ, vanRyn J et al. Idarucizumab: the antidote for reversal of dabigatran. *Circulation* 2015;132:2412-2422.

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Notice to Healthcare Providers:

The Pharmacotherapy Handbook is intended to be used as a tool to aid in the appropriate prescribing and administration of cardiovascular formulary agents.

This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

Due to the rapidly changing nature of cardiovascular treatments and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Your comments on the usefulness of the resources contained in the Handbook are welcomed and may be forwarded to Amita Woods, Department of Pharmacy Services (amita.woods@uhn.ca).

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