Idarucizumab (PRAXBIND)
National Drug Monograph
December 2015
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 when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action
Idarucizumab is a specific reversal agent for dabigatran, a direct oral anticoagulant (DOAC, formerly called TSOAC). Idarucizumab is a humanized monoclonal antibody fragment (Fab) that binds free and thrombin-bound dabigatran and its acyl glucuronide metabolites with higher affinity than dabigatran has to thrombin and neutralizes the anticoagulant effect.

Idarucizumab is specific to dabigatran only and will not reverse the effects of anticoagulants including Factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban) or other direct thrombin inhibitors (e.g., argatroban, bivalirudin).

Indication(s) Under Review in this document
Idarucizumab is indicated for patients treated with dabigatran when reversal of the anticoagulant effects of dabigatran is needed:
- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding

Dosage Form(s) Under Review
Intravenous (IV) solution packaged as two vials of 2.5 grams per 50 ml

REMS
☐ REMS  ☒ No REMS  ☐ Postmarketing Requirements

See Other Considerations for additional REMS information

Pregnancy
Animal reproductive and development studies have not been conducted with idarucizumab.

See Special Populations for additional information

Executive Summary

Efficacy
- The accelerated FDA approval of idarucizumab was based on three, randomized, controlled, phase 1 volunteer trials and supportive data from an interim analysis of an ongoing phase 3 study of idarucizumab in patients on dabigatran with life-threatening or uncontrolled bleeding or a need for urgent invasive procedure. The studies focused on the intermediate endpoint of laboratory assessed anticoagulant reversal rather than on clinical outcomes.
- In the phase 1 trials, idarucizumab was found to reduce unbound dabigatran levels to undetectable levels immediately following administration. Effects were sustained for at least 24 hours. Additionally, the following coagulation parameters returned to baseline after idarucizumab administration: dilute thrombin time (dTT), ecarin clotting time (ECT), thrombin time (TT), activated partial thromboplastin time (aPTT), and activated clotting time (ACT). Effects were immediate, complete, and sustained.
- An interim analysis of the first 90 patients of the ongoing, phase 3, prospective, multicenter, single arm cohort RE-VERSE AD study has been published. The efficacy and safety of idarucizumab for the reversal of the anticoagulant effects of dabigatran was evaluated in patients with overt, uncontrollable, or life-threatening bleeding (group A), or patients in need of surgery or other invasive procedure requiring normal hemostasis and which could not be delayed for at least 8 hours (group B). Patients had a mean age of 77 years, and most were receiving dabigatran for the non-valvular atrial fibrillation (NVAF) indication. The primary endpoint of the maximum reversal of the anticoagulant effect of dabigatran (using
dTT or ECT assessed by a central laboratory) was 100% (95% Confidence Interval [CI] 100 to 100) and was apparent immediately following the first of two bolus infusions. The majority of patients in group B underwent urgent procedures, and 92% were reported by the investigator to have normal hemostasis intraoperatively. In the two-thirds of patients in group A that were evaluable, the median time to investigator-assessed bleeding cessation was 11.4 hours.

### Safety
- In volunteer studies, idarucizumab was well tolerated, with headache reported most commonly. No significant or unexpected safety signals were identified in treated patients from the interim analysis of the phase 3 RE-VERSE AD study, though safety information is overall limited to the experience in 123 patients so far.
- **Warnings:**
  - Thromboembolic risk due to patient’s underlying disease
  - Re-elevation of coagulation parameters observed in limited number of patients
  - Hypersensitivity reactions reported
  - Risk of serious adverse reactions in patients with hereditary fructose intolerance due to sorbitol excipient
- Immunogenicity is a potential with all proteins including idarucizumab.

### Projected Place in Therapy
- Idarucizumab is the first agent approved for the specific reversal of a DOAC and has been shown to immediately and completely reverse the anticoagulant effects of dabigatran as measured by laboratory coagulation parameters and unbound dabigatran concentrations. Impact on clinical outcomes is unclear.
- Dabigatran has been available in the U.S. since 2010 without a specific reversal agent. The half-life of dabigatran is 12-17 hours in patients with normal renal function, which is significantly shorter than warfarin. Before the availability of idarucizumab, management of bleeding in patients on dabigatran has largely been supportive. In severe life-threatening situations where all other options have been exhausted, 4-factor prothrombin complex concentrate or activated prothrombin complex concentrate have been used (though supporting evidence is lacking).
- In total, evidence supporting the use of idarucizumab is considered to be of low quality since data are limited to phase 1 volunteer studies and an interim analysis of a phase 3, open label, single arm cohort study which were designed to assess laboratory endpoints of anticoagulation reversal rather than health outcomes.
- **Summary:**
  - Use of idarucizumab should be reserved for patients on dabigatran with 1) life-threatening or uncontrolled bleeding or 2) for truly emergent procedures that cannot be delayed at least 8 hours and where normal hemostasis is required. **Note: idarucizumab is a specific reversal agent for *dabigatran only*; idarucizumab will not reverse the effects of other anticoagulants (including factor Xa inhibitors and other direct thrombin inhibitors).**
  - Providers should balance the need for complete anticoagulant reversal and the resulting increased risk of thromboembolism from the patient’s underlying disease. Anticoagulant therapy should be restarted as soon as medically appropriate.
  - Re-elevation of coagulation parameters between 12 and 24 hours after idarucizumab administration has been reported in a limited number of patients in clinical study. If clinically relevant re-bleeding occurs along with elevated coagulation parameters, an additional 5 gram dose of idarucizumab may be considered. Similarly, if a patient requires an additional surgery or procedure in the presence of elevated coagulation parameters, an additional dose of idarucizumab may be considered.
However, the safety and efficacy of repeat treatment with idarucizumab has not been established.

- Idarucizumab has been primarily studied in the NVAF population receiving dabigatran and has not been well studied in patients receiving dabigatran for venous thromboembolism.
- Use caution in patients with hereditary fructose intolerance. Serious adverse reactions may occur upon parenteral administration of sorbitol in these patients. Consider that the usual dose of idarucizumab contains 4 grams of sorbitol as an excipient.

**Background**

**Purpose for review**

Issues to be determined:

- Evidence of need
- Does idarucizumab offer advantages to currently available alternatives?
- Does idarucizumab have advantages over current VANF agents?
- What safety issues need to be considered?
- Does idarucizumab have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use

**Other therapeutic options**

None

**Efficacy (FDA Approved Indications)**

A literature search was performed on PubMed/Medline (1966 to November 2015) using the search terms <idarucizumab> . The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All relevant randomized controlled trials published in peer-reviewed journals were included.

**Review of Efficacy**

Idarucizumab was granted accelerated approval by the FDA. Under the FDA’s accelerated approval process, drugs used in serious conditions where there is an unmet clinical need may be approved based on a surrogate or an intermediate clinical endpoint. Approval of idarucizumab was based on three phase 1, randomized, controlled trials enrolling a total of 283 volunteers that evaluated plasma levels of unbound dabigatran and coagulation parameters following idarucizumab administration. Supportive data were also provided by an interim analysis of an ongoing phase 3, open-label, single arm study of idarucizumab in patients on dabigatran with life-threatening or uncontrolled bleeding or a need for urgent invasive procedure. In this study, coagulation parameters were measured to evaluate the effectiveness of idarucizumab. In total, idarucizumab has been shown to effectively reverse the anticoagulant effect of dabigatran as measured by coagulation parameters and unbound dabigatran concentrations. Effects are immediate, complete, and sustained in the majority of subjects for at least 24 hours.

**Phase 1 Trials**

- There were three, randomized, placebo-controlled phase 1 studies conducted in volunteers to assess the safety, dose-response, and effect of idarucizumab. Limited information is published. A total of 283 volunteers were enrolled, and 224 subjects received idarucizumab. Most subjects were healthy young males, but females, subjects with mild or moderate renal impairment, and elderly were also included. In summary, idarucizumab was found to reduce plasma concentrations of unbound dabigatran to undetectable levels immediately following administration. Effects were sustained for at least 24 hours. Additionally, the following coagulation parameters returned to baseline after idarucizumab administration: dTT, ECT, TT, aPTT, and ACT.

**Phase 3 Trial: RE-VERSE AD**

- RE-VERSE AD is an ongoing, phase 3, prospective, multicenter, single arm cohort study evaluating the efficacy and safety of idarucizumab for the reversal of the anticoagulant effects of dabigatran in patients with
overt, uncontrollable, or life-threatening bleeding (group A), or patients in need of surgery or other invasive procedure requiring normal hemostasis and which could not be delayed for at least 8 hours (group B). The need for a reversal agent was determined by the judgment of the treating clinician, designed to be similar to a real world population who would likely receive idarucizumab.

- The primary endpoint was the maximum reversal of the anticoagulant effect of dabigatran (using dTT or ECT). Clinical outcomes were assessed as secondary endpoints. Interim results for the first 90 patients have been published, and the prescribing information includes data from a total of 123 patients. All patients received 5 grams of idarucizumab as two bolus infusions given no more than 15 minutes apart. The ECT and dTT were measured at a centralized laboratory and were used to assess anticoagulation status and reversal and were not accessible to providers at the time of the decision to administer idarucizumab. Patients were followed until death or at least one month.

- A total of 90 patients (51 in group A and 39 in group B) were assessed in the published interim analysis. The population was 56% male and had a mean age of 77 years and creatinine clearance (CrCl) of 62 ml/min. Most patients were receiving dabigatran for the NVAF indication. About two-thirds of the population was receiving dabigatran 110 mg twice daily dose (not available in the U.S.) and one-third was receiving the 150 mg twice daily dose (not available in the U.S.). The majority of patients (but not all) had elevated dTT or ECT at baseline.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated dTT</td>
<td>78%</td>
<td>72%</td>
<td>76%</td>
</tr>
<tr>
<td>Elevated ECT</td>
<td>92%</td>
<td>87%</td>
<td>90%</td>
</tr>
<tr>
<td>Bleeding type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>39%</td>
<td>-</td>
<td>22%</td>
</tr>
<tr>
<td>Intracranial</td>
<td>35%</td>
<td>-</td>
<td>20%</td>
</tr>
<tr>
<td>Trauma</td>
<td>18%</td>
<td>-</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>22%</td>
<td>-</td>
<td>12%</td>
</tr>
<tr>
<td>Surgical indication*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone fracture</td>
<td>-</td>
<td>21%</td>
<td>9%</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>-</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Acute renal insufficiency, catheter placement</td>
<td>-</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Acute appendicitis</td>
<td>-</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Joint/wound infection</td>
<td>-</td>
<td>8%</td>
<td>3%</td>
</tr>
</tbody>
</table>

dTT=dilute thrombin time; ECT=ecarin clotting time; group A=bleeders; group B=urgent surgery/procedure; *Indications occurring in more than 2 patients shown

The primary endpoint was conducted in the patients with elevated baseline dTT or ECT (see Table 1). The median maximum percentage reversal in the evaluable patients was 100% (95% CI 100 to 100) and was apparent after the end of the first infusion. Unbound dabigatran levels dropped below the threshold (20 ng/mL) needed to produce an anticoagulant effect in all but one patient after administration of the first vial of idarucizumab. In the majority of patients, unbound dabigatran levels remained low at 4, 12, and 24 hours after idarucizumab administration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized dTT</td>
<td>98%</td>
<td>93%</td>
</tr>
<tr>
<td>Normalized ECT</td>
<td>89%</td>
<td>88%</td>
</tr>
<tr>
<td>Sustained dTT below ULN at 12 and 24 hrs</td>
<td>90%</td>
<td>81%</td>
</tr>
<tr>
<td>Sustained ECT below ULN at 12 and 24 hrs</td>
<td>72%</td>
<td>54%</td>
</tr>
</tbody>
</table>

dTT=dilute thrombin time; ECT=ecarin clotting time; ULN=upper limit of normal

- The median time to bleeding cessation in the 35 evaluable patients out of 51 patients in group A was 11.4 hours as assessed by the investigator. Unevaluable patients were either missing a baseline bleeding assessment (n=3) or information on when bleeding stopped (n=13). In group B, 36 of 39 patients underwent urgent procedures,
and normal intraoperative hemostasis was reported by the investigator in 92% of cases. One additional patient in group B treated with idarucizumab avoided the need for emergent hemodialysis following a massive overdose of dabigatran.

Potential Off-Label Use

- None

Safety

(for more detailed information refer to the product package insert)

<table>
<thead>
<tr>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boxed Warning¹</td>
</tr>
<tr>
<td>Contraindications¹</td>
</tr>
</tbody>
</table>
| Warnings/Precautions¹ | • Thromboembolic risk: Reversal of anticoagulation in patients on dabigatran exposes patients to the thrombotic risk of their underlying disease. Consider restarting anticoagulant therapy as soon as medically appropriate.  
• Re-elevation of coagulation parameters: In a limited number of patients, re-elevation of coagulation parameters (e.g., aPTT or ECT) has been observed within 12 to 24 hours of idarucizumab administration. If reappearance of clinically relevant bleeding occurs or the need for an additional emergent surgery/procedure arises in patients with re-elevated coagulation parameters, an additional 5 gram dose of idarucizumab may be considered. However, the safety and effectiveness of repeated treatment with idarucizumab have not been established. In 6 healthy subjects, re-dosing of idarucizumab 2 months after the first infusion was not associated with additional safety concerns or allergic reactions.  
• Hypersensitivity reactions: Adverse reactions suggestive of hypersensitivity have occurred in clinical studies. In patients with known hypersensitivity to idarucizumab (or its components), the risks must be weighed against the benefits of emergency treatment of idarucizumab. If an anaphylactic type of reaction occurs with idarucizumab, immediately discontinue and initiate appropriate treatment.  
• Risk of serious adverse reactions in patients with hereditary fructose intolerance due to sorbitol excipient: Idarucizumab contains 4 grams of sorbitol as an excipient. Serious adverse reactions (including fatal) have been reported following parenteral administration of sorbitol in patients with hereditary fructose intolerance. The minimum amount of sorbitol associated with serious adverse reactions is not known. |

Safety Considerations¹,⁴

Data on the safety of idarucizumab was mainly derived from the three phase 1 volunteer studies that included 224 subjects that received the drug (from a total of 283 subjects). The majority of volunteers were healthy young males but some females and subjects with mild or moderate renal impairment as well as elderly subjects were also included. Supportive data were provided from 123 patients in the ongoing, phase 3 RE-VERSE AD study.

Immunogenicity: There is a potential for immunogenicity with all proteins including idarucizumab. From the phase 1 volunteer studies (n=283), pre-existing anti-idarucizumab antibodies were detected in 13% of subjects. In 4% of the subjects that received idarucizumab, low titers of anti-idarucizumab antibodies were newly detected, with persistence in some subjects. The majority of anti-idarucizumab antibodies detected lacked specificity to the dabigatran-binding portion of idarucizumab. No impact on the pharmacokinetics or the reversal effect of idarucizumab was observed.

Adverse Reactions¹,⁴,⁵

<table>
<thead>
<tr>
<th>Common adverse reactions</th>
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</table>
| • Volunteer trials (incidence ≥5%): headache  
• RE-VERSE AD (incidence ≥5% in the interim analysis [n=123]): hypokalemia, delirium, constipation, pyrexia, pneumonia |
Death/Serious adverse reactions

- Volunteer trials: no deaths or serious adverse reactions
- RE-VERSE AD:
  - Deaths: 26/123 (29%)
  - Thromboembolic events: 5/123 (4%)
    - Early (within 72 hours after idarucizumab): 1/5
    - Late (>72 hours after idarucizumab): 4/5
    - None of the patients were receiving anticoagulation at the time of the event; all events considered attributable to underlying disease
  - Other serious adverse events: 21/90 (23%) included death, thromboembolic event, gastrointestinal bleed, postoperative wound infection, delirium, right ventricular failure, pulmonary edema

Discontinuations due to adverse reactions

None were reported in volunteer trials. None were noted in phase 3 RE-VERSE AD study; idarucizumab was administered as a single, intravenous bolus.

Note: Due to some differences in the safety endpoints reported from the ongoing RE-VERSE AD trial, data from both the prescribing information (n=123) and the published interim analysis (n=90) were used in the above safety section with the denominator as noted.

Drug Interactions

Drug-Drug Interactions

- None listed in prescribing information.
- Coagulation factor concentrates: In-vitro data suggest that idarucizumab’s actions were not affected.
- Crystalloids, colloids, and washed red cell transfusions: Animal studies suggest that neutralization of dabigatran by idarucizumab is not affected by 50% hemodilution with commonly used volume replacement therapies.

Risk Evaluation

As of November 18, 2015:

Comments

- Sentinel event advisories
  - None
  - Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

- Idarucizumab and Idarubicin – ISMP alert, November 2015
  - Close call reported. ISMP suggestions to prevent errors include barcode scanning of drug vials prior to compounding, using computer alerts and tall man letters (e.g., idarucIZUMAB and IDArubicin), confirming patient’s need, adding auxiliary labels, and storing antineoplastics in separate refrigerators (as per USP chapter <800>).

<table>
<thead>
<tr>
<th>NME Drug Name</th>
<th>Lexi-Comp</th>
<th>First DataBank</th>
<th>ISMP</th>
<th>Clinical Judgment</th>
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</thead>
<tbody>
<tr>
<td>Idarucizumab</td>
<td></td>
<td></td>
<td></td>
<td>Bevacizumab</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Idelasinib</td>
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<tr>
<td>Praxbind</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Pradaxa Plavix</td>
</tr>
</tbody>
</table>

(Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- Storage requirements: Idarucizumab must be refrigerated (2°C - 8°C); do not freeze or shake. See package insert for more information on deviations from recommended storage.
FDA approval: Continued approval is contingent upon additional results from the RE-VERSE AD trial.\(^2\)

Pharmacokinetics: Idarucizumab exhibits limited extravascular distribution and is rapidly eliminated, with an initial half-life of 47 minutes and terminal half-life of 10.3 hours. About one-third of the dose was recovered in the urine within the first 6 hours, and the remainder is thought to be eliminated via protein catabolism in the kidney.

Pharmacodynamics: Plasma concentrations of unbound dabigatran were immediately reduced to levels below quantification following administration. Low unbound dabigatran levels were sustained throughout the observation period up to at least 24 hours. Coagulation parameters (dTT, ECT, aPTT, TT, and ACT) returned to baseline. In a limited number of patients, re-distribution of dabigatran from the periphery to the plasma resulted in re-elevation of coagulation parameters.

Dosing and Administration\(^1\)

- The recommended dose of idarucizumab is 5 grams (100 ml) given intravenously.
- Idarucizumab is supplied as two 2.5 gram per 50 ml vials per package.
- Idarucizumab may be administered as either two consecutive infusions (using an infusion set to spike and hang the vials themselves) or as two consecutive bolus injections using a syringe to withdraw the vials’ contents for injection.
- Refer to the package insert for full administration information.
- Restoring antithrombotic therapy: Reversing anticoagulation exposes patients to the thrombotic risk of the underlying disease for which they are receiving an anticoagulant. Consider restarting anticoagulant therapy as soon as medically appropriate. Dabigatran can be started 24 hours after idarucizumab administration.

Special Populations (Adults)\(^1\)

<table>
<thead>
<tr>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
</tr>
<tr>
<td>Pregnancy</td>
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<tr>
<td>Lactation</td>
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<tr>
<td>Females and Males of Reproductive Potential</td>
</tr>
<tr>
<td>Renal Impairment</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
</tr>
<tr>
<td>Pharmacogenetics/genomics</td>
</tr>
</tbody>
</table>

Projected Place in Therapy

- Idarucizumab is the first agent approved for the specific reversal of a DOAC and has been shown to immediately and completely reverse the anticoagulant effects of dabigatran. Impact on clinical outcomes is unclear.
- Dabigatran has been available in the U.S. since 2010 without a specific reversal agent. The half-life of dabigatran is 12-17 hours in patients with normal renal function, which is significantly shorter than warfarin. Before the availability of idarucizumab, management of bleeding in patients on dabigatran has largely been
supportive (discontinuation of dabigatran, mechanical compression, volume replacement, blood product transfusions). Activated charcoal may be used for recent ingestion. Dabigatran is removed by hemodialysis. In severe life-threatening situations where all other options have been exhausted, 4-factor prothrombin complex concentrate or activated prothrombin complex concentrate have been used (though supporting evidence is lacking). 7

- In the RE-LY trial, major bleeding events in patients taking dabigatran 150 mg twice daily occurred at a rate of 3.3% per year. Life-threatening and intracranial bleeding occurred at rates of 1.5% and 0.3% per year, respectively. 8 In a pooled analysis of all phase 3 data evaluating major bleeding outcomes with dabigatran vs. warfarin, 30-day mortality rates tended to be lower in the dabigatran group vs. warfarin (9.1% vs. 13%; pooled odds ratio 0.68; 95% CI 0.46-1.01; p=0.057). Patients with major bleeds on dabigatran were older, had renal insufficiency, and used aspirin or non-steroidal anti-inflammatory drugs more frequently. 9 Risks of bleeding outside of a clinical trial setting may differ.

- Dabigatran is on VANF with CFU. For the treatment of NVAF, dabigatran is the preferred DOAC. Dabigatran is also an acceptable first-line option for the treatment of venous thromboembolism (VTE). A VA PBM clinical algorithm takes into consideration patient-specific factors to guide appropriate and safe selection of dabigatran, another DOAC, or warfarin. The study population in the interim analysis of RE-VERSE AD was an older, mainly NVAF population, which is applicable to VA.

- In total, evidence supporting the use of idarucizumab is considered to be of low quality since data are limited to phase 1 volunteer studies and an interim analysis of a phase 3, open label, single arm cohort study which were designed to assess laboratory endpoints of anticoagulation reversal rather than health outcomes.

- Place in Therapy:
  - Use of idarucizumab should be reserved for patients on dabigatran with 1) life-threatening or uncontrolled bleeding or 2) for truly emergent procedures that cannot be delayed at least 8 hours and where normal hemostasis is required. Note: idarucizumab is a specific reversal agent for *dabigatran only*; idarucizumab will not reverse the effects of other anticoagulants (including factor Xa inhibitors and other direct thrombin inhibitors).
  - Providers should balance the need for complete anticoagulant reversal and the resulting increased risk of thromboembolism from the patient’s underlying disease. Anticoagulant therapy should be restarted as soon as medically appropriate.
  - Re-elevation of coagulation parameters between 12 and 24 hours after idarucizumab administration has been reported in a limited number of patients in clinical study. If clinically relevant re-bleeding occurs along with elevated coagulation parameters, an additional 5 gram dose of idarucizumab may be considered. Similarly, if a patient requires additional surgery or procedure in the presence of elevated coagulation parameters, an additional dose of idarucizumab may be considered. However, the safety and efficacy of repeat treatment with idarucizumab has not been established.
  - Idarucizumab has been primarily studied in the NVAF population receiving dabigatran and has not been well studied in patients receiving dabigatran for venous thromboembolism.
  - Use caution in patients with hereditary fructose intolerance. Serious adverse reactions may occur upon parenteral administration of sorbitol in these patients. Consider that the usual dose of idarucizumab contains 4 grams of sorbitol as an excipient.

References

### Appendix A: GRADEing the Evidence

<table>
<thead>
<tr>
<th>Designations of Quality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with &gt; 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.</td>
</tr>
</tbody>
</table>