

**Reversal Agents for Direct Oral Anticoagulants (DOACs)
Recommendations for Use
Coagulation factor Xa [recombinant], inactivated-zhzo (Andexanet alfa) (ANDEXXA)
Idarucizumab (PRAXBIND)
4-Factor Prothrombin Complex Concentrate (4F-PCC) (KCENTRA)
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monographs on these agents at the [PBM INTRAnet](#) site for further information.

NOTE: Facilities that could potentially treat patients requiring anticoagulant reversal are expected to have reversal agents readily and emergently available when clinically necessary. In the setting of emergent, life-threatening situations where reversal agents will be used, the product should be made available immediately, when appropriate. Facilities should proactively develop local policies and processes to avoid any delays in care regarding emergent reversal requests (for details on dealing with such situations, please see VHA Formulary Management Process Handbook 1108.08). It is further recommended that reversal agents be restricted to, or overseen by, locally designated specialty service(s) (e.g., Hematology, Critical care, Emergency Medicine, Neurology, Neurosurgery, etc.).

The following criteria/ recommendations may be used to educate providers, pharmacy, and other staff on safe and appropriate use of reversal agents in advance of need, to retrospectively conduct a review of reversal agent use, or to facilitate an immediate review in emergency situations.

GENERAL PRINCIPLES

- **Reversing anticoagulation exposes patients to the thrombotic risk of their underlying disease. Certain reversal agents may pose additional thrombotic risk. Use of reversal agents should be considered ONLY in severe, life threatening bleeding and where the potential risk of thromboembolism is deemed less than the consequences of continued bleeding.**
- DOACs have relatively short half-lives. Bleeding that occurs in patients taking DOACs is often able to be managed by temporarily discontinuing the anticoagulant and providing supportive care. Intracranial hemorrhage (ICH) and fatal bleeding rates were low in pivotal registry trials evaluating DOACs despite no reversal agents being available at that time.
- Supportive care may include discontinuing the anticoagulant, maintaining adequate diuresis, compression, surgical repair, fluid and/or blood replacement, and hemodynamic support.
- Use of reversal agents for DOACs should be reserved for patients with a known recent exposure to a DOAC.

- Due to the elevated risk of thromboembolism, consider restarting anticoagulant therapy as soon as medically appropriate.
- High quality data of the impact of reversal agents on clinical outcomes in DOAC associated bleeding are lacking. There is no randomized trial evidence demonstrating that the administration of reversal agents improves clinical outcomes. FDA approval of andexanet and idarucizumab was based primarily on laboratory evidence of anticoagulant reversal.
- Consider administration of activated charcoal for known recent DOAC ingestion within the past 2-4 hours.
- Consider the presence of other antithrombotic drugs (e.g., antiplatelet agents) and discontinue as appropriate.

Overview of PBM guidance on the choice of a reversal agent on DOACs

DOAC	Reversal agent – BLEEDING	Reversal agent – PROCEDURE
Apixaban	1 st Andexanet if available	4F-PCC
Rivaroxaban	2 nd 4F-PCC	
Betrixaban	4F-PCC	4F-PCC
Edoxaban	4F-PCC	4F-PCC
Dabigatran	1 st Idarucizumab if available 2 nd 4F-PCC or aPCC	1 st Idarucizumab if available 2 nd 4F-PCC or aPCC

4F-PCC=4 factor prothrombin complex concentrate (KCentra); aPCC=activated PCC (FEIBA)

Note: aPCC (FEIBA) may be used if 4F-PCC is unavailable; some may prefer aPCC over PCC for dabigatran reversal if idarucizumab is unavailable.

ANDEXANET ALFA (ANDEXXA)

Reversal of apixaban or rivaroxaban in the setting of bleeding

EXCLUSION CRITERIA *(Patients with any of the following should NOT receive andexanet)*

- Patient took last dose of rivaroxaban or apixaban more than 18 hours ago.
- Patient had a recent major thromboembolic event (e.g., past 2 weeks).

INCLUSION CRITERIA *(ALL of the following should be fulfilled in order to receive andexanet)*

- Patient has been taking rivaroxaban or apixaban, and provider is reasonably certain that therapeutic anticoagulant levels are present (e.g., patient history and timing of last dose, laboratory testing if available).
- Patient has life-threatening bleeding or critical site bleeding (e.g., ICH).
- Standard measures for bleeding management (e.g., discontinuing anticoagulant, compression, surgical repair, fluid and/or blood replacement, hemodynamic support) are insufficient.
- Patient's risk of thromboembolism is deemed less than the consequences of continued bleeding (see Safety in Issues for Consideration).

ISSUES FOR CONSIDERATION:

- **Safety:**
 - **BOXED WARNING:** Andexanet has been associated with arterial and venous thromboembolic events, ischemic events, cardiac arrest, and sudden deaths. Restart anticoagulant therapy as soon as medically appropriate to reduce the risk of thromboembolic events.
 - **Infusion related reactions:** Infusion reactions occurred with andexanet in 18% of volunteers during clinical trials. Symptoms were mild to moderate in severity and included flushing, feeling hot, cough, dysgeusia, and dyspnea.
 - **Thrombotic events:** In ANNEXA-4, 10% of patients experienced a thrombotic event within the 30-day follow-up period. Anticoagulation reversal exposes patients to the thrombotic risk of their underlying disease. It is unknown whether andexanet is associated with additional procoagulant effect. Andexanet should only be considered in situations where the risk of thromboembolism is deemed less than consequences of bleeding.
- **Limitations:**
 - In the absence of comparative data, it is unknown whether andexanet is associated with benefit or harm compared to discontinuing anticoagulant alone or the use of nonspecific reversal agents (e.g., 4F-PCC).
 - Andexanet has not been evaluated and is not approved for use as a reversal agent for emergently required procedures and/or surgery.
 - Andexanet is not approved for use as a reversal agent for FXa inhibitors other than apixaban or rivaroxaban.
 - Andexanet has not been evaluated in patients who received prior interventions (e.g., PCC, recombinant factor VIIa, or whole blood products within the past week).
 - Anti-factor Xa levels return to placebo levels about 2 hours after stopping the infusion. Safety and efficacy of an additional dose have not been established and is not recommended.

IDARUCIZUMAB (PRAXBIND)

Reversal of dabigatran in the setting of bleeding or emergent surgery/urgent procedures

INCLUSION CRITERIA *(ALL of the following should be fulfilled in order to receive idarucizumab)*

- Patient has been taking dabigatran, and provider is reasonably certain that therapeutic anticoagulant levels are present (e.g., patient history and timing of last dose, laboratory testing if available).
- Patient has life-threatening or critical site bleeding (e.g., ICH) OR is in need of a truly emergent procedure that cannot be delayed for at least 8 hours and where normal hemostasis is required.
- If reversal is desired in the setting of bleeding, standard measures for bleeding management (e.g., discontinuing anticoagulant, compression, surgical repair, fluid and/or blood replacement, hemodynamic support) are insufficient.
- Patient's risk of thromboembolism is deemed less than the consequences of continued bleeding or delay of the procedure or surgery (see Safety in Issues for Consideration).

ISSUES FOR CONSIDERATION

- **Safety:**
 - **Thromboembolic risk:** Reversing anticoagulation exposes patients to the thrombotic risk of the underlying disease for which they are receiving an anticoagulant. In REVERSE-AD, 4.8% of patients experienced a thromboembolic event within the 30-day follow-up period. Consider restarting anticoagulant therapy as soon as medically appropriate. Dabigatran can be started 24 hours after idarucizumab administration.
 - **Hypersensitivity reactions:** Adverse events indicative of hypersensitivity reactions have been reported with idarucizumab.
 - **Patients with hereditary fructose intolerance due to sorbitol excipient:** Serious adverse reactions have been reported in patients with hereditary fructose intolerance who have received parenteral administration of sorbitol, including death. The recommended dose of idarucizumab contains 4 g of sorbitol as an excipient. Consider the combined metabolic load of sorbitol/fructose from all sources, including idarucizumab.
- **Re-elevation of coagulation parameters:** Laboratory evidence of anticoagulant reversal after idarucizumab administration is observed immediately in nearly all patients is sustained for at least 24 hours in most patients. In a limited number of patients, re-elevation of coagulation parameters has been observed. Safety and effectiveness of repeat doses of idarucizumab have not been established.
- **Procoagulant effect:** Idarucizumab is not known to exhibit procoagulant effects.
- **Specificity for dabigatran:** Idarucizumab is **specific** for dabigatran only and will not reverse the effects of other anticoagulants including Factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, betrixaban) or other direct thrombin inhibitors (e.g., argatroban, bivalirudin).

4-FACTOR PROTHROMBIN COMPLEX CONCENTRATE (4F-PCC) (KCENTRA)

Reversal of DOACs in the setting of bleeding or emergent surgery/urgent procedures

OFF-LABEL

EXCLUSION CRITERIA (*Patients with any of the following should NOT receive 4F-PCC*)

- Patient with known anaphylactic or severe systemic reaction to 4F-PCC or any components (heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin).
- Patient with disseminated intravascular coagulation.
- Patient with history of heparin induced thrombocytopenia (4F-PCC contains heparin).

INCLUSION CRITERIA (*ALL of the following should be fulfilled in order to receive 4F-PCC*)

- Patient has been taking a DOAC, and provider is reasonably certain that therapeutic anticoagulant levels are present (e.g., patient history and timing of last dose, laboratory testing if available).
- Specific reversal agent (andexanet or idarucizumab) that is FDA approved for the patient's condition is not readily available (e.g., andexanet for life-threatening bleeding in a patient with recent apixaban or rivaroxaban exposure).
- Patient has life-threatening or critical site bleeding (e.g., ICH) OR is in need of a truly emergent procedure that cannot be delayed and where normal hemostasis is required.
- If reversal is desired in the setting of bleeding, standard measures for bleeding management (e.g., compression, surgical repair, volume replacement, hemodynamic support) are insufficient.
- Patient's risk of thromboembolism is deemed less than the consequences of continued bleeding or delay of the procedure or surgery (see Safety in Issues for Consideration)

ISSUES FOR CONSIDERATION

- **OFF-LABEL:** 4F-PCC is a blood coagulation factor replacement product (Factors II, VII, IX, and X, and Proteins C and S) FDA approved for the urgent reversal of vitamin K antagonists (VKA) in patients with acute major bleeding or need for an urgent surgery or invasive procedure. In the absence of a specific reversal agent for DOACs, 4F-PCC has been used as a nonspecific reversal agent. Evidence on the use of 4F-PCC for DOAC reversal is of low quality and limited to observational studies in bleeding patients, studies in healthy volunteers, and animal data. Use of 4F-PCC in this setting remains off-label. If available, a specific reversal agent (andexanet or idarucizumab) is preferred over 4F-PCC for situations where the specific reversal agent is FDA approved.
- **Safety:**
 - **BOXED WARNING – Arterial and Venous Thromboembolic complications:** 4F-PCC has been associated with fatal and nonfatal arterial and venous thromboembolic events in patients being treated with VKAs in clinical trials and in post marketing surveillance. Reversing anticoagulation exposes patients to the thrombotic risk of the underlying disease for which they are receiving an anticoagulant. To reduce risk, consider restarting anticoagulant therapy as soon as medically appropriate.
 - In clinical trials evaluating 4F-PCC in VKA reversal, more thromboembolic events occurred in patients receiving 4F-PCC compared to those who received plasma, especially in patients with a history of a thromboembolic event.
 - Patients with a recent thromboembolic event (past 3 months) were excluded from clinical trials.
 - **4F-PCC may not be suitable in patients with thromboembolic events in the prior 3 months.**

- **Hypersensitivity reactions:** Hypersensitivity reactions have been observed with 4F-PCC.
- **Transmission:** Because 4F-PCC is made from human blood, it may carry a risk of transmitting infection. 4F-PCC is manufactured using two virus reduction steps to minimize the risk of transmitting potentially infectious agents; however, blood-derived products may still carry risk.
- **Note: If 4F-PCC is unavailable, FEIBA may be considered.** FEIBA (Factor VIII inhibitor bypassing agent, also called aPCC) contains mainly nonactivated Factors II, IX, and X and mainly activated Factor VII. aPCC (FEIBA) is FDA approved for treatment and prophylaxis of bleeding in hemophilia A and B patients with inhibitors. In the absence of a specific reversal agent for DOACs, aPCC (FEIBA) has been used as a nonspecific reversal agent. Evidence on the use of aPCC (FEIBA) for DOAC reversal is of low quality and limited to small case series, healthy volunteer studies, and animal data. Use in this setting remains off-label. aPCC (FEIBA) for DOAC related bleeding is generally less well studied than 4F-PCC. A single dose of 50 units per kg has been used. FEIBA may be preferable to 4F-PCC by some for reversal of dabigatran if idarucizumab is unavailable.

DOSE AND ADMINISTRATION

(See prescribing information for more details)

ANDEXANET ALFA (ANDEXXA)

- Dose is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since last dose of FXa inhibitor
- Andexanet is administered as a single dose of an intravenous (IV) bolus followed by a continuous infusion for up to 120 minutes. Note: the rates for the bolus and infusion are different.
- Andexanet is supplied in packages of 4 single use vials, 100 mg or 200 mg strength that require refrigeration and reconstitution. Multiple vials are needed for a dose. Andexanet must be administered through a 0.2 or 0.22 micron in-line polyethersulfone or equivalent low-protein binding filter.

Andexanet alfa dose based on apixaban or rivaroxaban dose

Drug	Dose	Time since last dose	
		<8 hr or unknown	≥8 hr
Rivaroxaban	≤10 mg	Low dose	Low dose
	>10 mg or unknown	High dose	
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg or unknown	High dose	

- Low dose = 400 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 4 mg/min for up to 120 min (480 mg)
- High dose = 800 mg IV bolus at a target rate of 30 mg/min followed by continuous infusion at 8 mg/min for up to 120 min (960 mg)

IDARUCIZUMAB (PRAXBIND)

- Idarucizumab is given as a single dose of 5 gm (2 vials, each containing 2.5 gm).
- Idarucizumab may be administered IV as 2 consecutive infusions by hanging the vials or by bolus injection of both vials via syringe. Facilities may choose to prefer the administration method of hanging vials to expedite delivery (e.g., from pharmacy to patient care area) and potentially reduce waste (e.g., if drug is drawn up by mistake or the patient ultimately doesn't receive the drug).
- Idarucizumab is supplied in packages of 2 single-use, 2.5 gm vials that require refrigeration.

4F-PCC (KCENTRA) (OFF-LABEL)

- Doses reported in the literature vary. A dose of 50 units per kg has been most consistently associated with reversal of laboratory parameters and bleeding in the setting of DOACs, though lower doses (e.g., 25 units per kg) have also been used. Also, a fixed dose of 2000 units has also been studied in bleeding patients and has been recommended by the Anticoagulation Forum 2019 DOAC Reversal Guidance.
- Dosing is calculated based on the quantity (international units) of factor IX in the product.*Exact contents are labeled on the vial and will vary from vial to vial* (e.g., 500 unit vial may contain a range of 400 to 620 units per vial, and 1000 unit vial may contain a range of 800-1240 units per vial).
- 4F-PCC is administered by IV infusion at a rate of 0.12 ml/kg/min (~3 units/kg/min) up to a maximum rate of 8.4 ml/min (~210 units/min).
- 4F-PCC is supplied in single vials of 500 units (range 400-620) and 1000 units (range 800-1240) that require reconstitution and can be stored at 2-25°C.

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