AVAILABLE NATIONWIDE

Andexxa®

Coagulation Factor Xa (Recombinant), Inactivated-zhzo

Dosing Guide

SELECT IMPORTANT SAFETY INFORMATION

WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS

See full prescribing information for complete boxed warning

Treatment with ANDEXXA has been associated with serious and life-threatening adverse events, including:

- **Arterial and venous thromboembolic events**
- **Ischemic events, including myocardial infarction and ischemic stroke**
- **Cardiac arrest**
- **Sudden deaths**

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.

INDICATION

ANDEXXA (coagulation factor Xa (recombinant), inactivated-zhzo) is a recombinant modified human factor Xa (FXa) protein indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies that demonstrate an improvement in hemostasis in patients.

Limitations of Use

ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban or rivaroxaban.

Please see Important Safety Information throughout, and accompanying full Prescribing Information including Boxed Warning on thromboembolic risks, ischemic risks, cardiac arrest, and sudden death.

ANDEXXA has 2 dosing regimens[1]

IV bolus followed by continuous infusion

ANDEXXA LOW DOSE*

Initial IV Bolus	Continuous IV Infusion
400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes (480 mg)

Total Number of 200-mg Vials

5 (2 vials bolus + 3 vials infusion)

ANDEXXA HIGH DOSE*

Initial IV Bolus	Continuous IV Infusion
800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes (960 mg)

Total Number of 200-mg Vials

9 (4 vials bolus + 5 vials infusion)

*The safety and effectiveness of more than one dose have not been evaluated.

For Portola Medical Information, please call 1-866-777-5947.

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ANDEXXA® dosing regimens[1]

Drug FXa Inhibitor	Dose Strength of Last Dose	Time Since Last Dose Taken	
		<8 Hours or Unknown	≥8 Hours
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg or unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	Low dose
	>10 mg or unknown	High dose	

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thromboembolic and Ischemic Risks

The thromboembolic and ischemic risks were assessed in 352 bleeding subjects who received ANDEXXA. Of the 63 subjects who experienced a thrombotic event, the median time to first event was 7 days, and 21 subjects experienced the event within the first three days. A total of 63 (18%) experienced 88 thromboembolic or ischemic events. Of the 352 subjects who received ANDEXXA, 223 received at least one anticoagulation dose within 30 days after treatment. Of these 223, 18 subjects (8%) had a thrombotic event and/or ischemic event after resumption.

Monitor patients treated with ANDEXXA for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac arrest. To reduce thromboembolic risk, resume anticoagulant therapy as soon as medically appropriate following treatment with ANDEXXA.

The safety of ANDEXXA has not been evaluated in patients who experienced thromboembolic events or disseminated intravascular coagulation within two weeks prior to the life-threatening bleeding event requiring treatment with ANDEXXA. Safety of ANDEXXA also has not been evaluated in patients who received prothrombin complex concentrates, recombinant factor VIIa, or whole blood products within seven days prior to the bleeding event.

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Reconstitution and Preparation Guide[1]

NOTE: For efficient and timely infusion, it is recommended that the IV bolus dose of ANDEXXA be prepared first and administered to the patient.

RECONSTITUTION

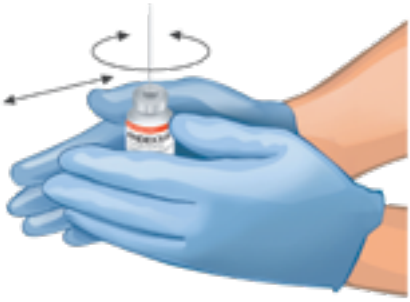
- Reconstituted ANDEXXA in vials is stable at room temperature for up to 8 hours
- Reconstituted vials may be stored for up to 24 hours at 2˚C-8˚C
- Reconstituted ANDEXXA in IV bags is stable at room temperature for up to 8 hours

IV bolus preparation

- Determine total number of vials required (see "ANDEXXA has 2 dosing regimens" table on opposite side of this brochure)

- Reconstitute the 200-mg vial of ANDEXXA with 20 mL of Sterile Water for Injection (SWFI)
- Using a 20-mL (or larger) syringe and 20-gauge (or higher) needle, slowly inject the SWFI, directing the solution onto the inside wall of the vial to minimize foaming
- To reduce the total reconstitution time needed during preparation, reconstitute all required vials in succession

- To ensure dissolution of the cake or powder, gently swirl each vial until complete dissolution of powder occurs



DO NOT SHAKE
the vials as it can lead to foaming.

- Dissolution time for each vial is approximately 3 to 5 minutes
- If dissolution is incomplete, discard the vial, and do not use the product

- Inspect reconstituted vials for particulate matter and discoloration prior to administration:
  - — Solution should be clear, colorless to light yellow

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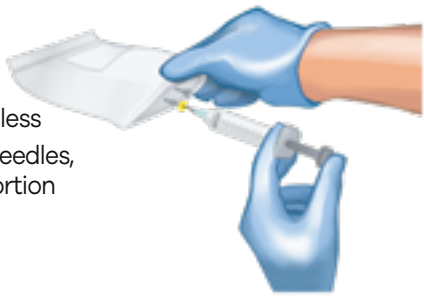
Reconstitution and Preparation Guide[1]

- Use 60-mL (or larger) syringe with a 20-gauge (or higher) needle to withdraw the reconstituted ANDEXXA solution from each of the vials until the required dosing volume is achieved. Note the total volume withdrawn into the syringe
- Transfer the ANDEXXA solution from the syringe into an empty polyolefin or polyvinyl chloride IV bag with a volume of 250 mL or less
- Finally, discard all used syringes, needles, and vials, including any unused portion of reconstituted solution



Helpful tip

The continuous IV infusion dose can then be prepared while the bolus dose is being administered to the patient so that it is ready for administration immediately (within 2 minutes) following the bolus dose.

Continuous IV infusion preparation

- Follow the same procedure outlined for IV bolus preparation. Reconstitute the total number of vials needed based on the dose requirements. More than one 40 to 60-mL syringe, or an equivalent 100-mL syringe, may be used for transfer of reconstituted solution to the IV bag
- Infusion will require a 0.2 or 0.22 micron in-line polyethersulfone or equivalent low protein-binding filter

ADMINISTRATION

- Upon reconstitution, the parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration
- Administer ANDEXXA intravenously, using a 0.2 or 0.22 micron in-line polyethersulfone or equivalent low protein-binding filter
- Start the bolus at a target rate of approximately 30 mg/min
- Within 2 minutes following the bolus dose, administer the continuous IV infusion for up to 120 minutes

RESTARTING ANTICOAGULANT THERAPY

Patients treated with FXa inhibitor therapy have underlying disease states that predispose them to thromboembolic events. Reversing FXa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. To reduce the risk of thrombosis, resume anticoagulant therapy as soon as medically appropriate following treatment with ANDEXXA.

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WARNINGS AND PRECAUTIONS (continued)

Re-elevation or Incomplete Reversal of Anti-FXa Activity

The time course of anti-FXa activity following ANDEXXA administration was consistent among the healthy volunteer studies and the ANNEXA-4 study in bleeding patients. Compared to baseline, there was a rapid and substantial decrease in anti-FXa activity corresponding to the ANDEXXA bolus. This decrease was sustained through the end of the ANDEXXA continuous infusion. The anti-FXa activity returned to the placebo levels approximately two hours after completion of a bolus or continuous infusion. Subsequently, the anti-FXa activity decreased at a rate similar to the clearance of the FXa inhibitors.

Seventy-one subjects were anticoagulated with apixaban and had baseline levels of anti-FXa activity > 150 ng/mL. Nineteen subjects who were anticoagulated with rivaroxaban had elevated baseline anti-FXa activity levels >300 ng/mL. Forty-eight of the 71 apixaban-treated subjects (68%) experienced a > 90% decrease from baseline anti-FXa activity after administration of ANDEXXA. Ten of the 19 rivaroxaban subjects (53%) experienced a > 90% decrease from baseline anti-FXa activity after administration of ANDEXXA.

ADVERSE REACTIONS

The most common adverse reactions (≥ 5%) in bleeding patients receiving ANDEXXA were urinary tract infections and pneumonia.

The most common adverse reactions (≥ 3%) in healthy subjects treated with ANDEXXA were infusion-related reactions.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Using an electrochemiluminescence (ECL)-based assay, 145 ANDEXXA-treated healthy subjects were tested for antibodies to ANDEXXA as well as antibodies cross-reacting with Factor X (FX) and FXa. Low titers of anti-ANDEXXA antibodies were observed in 26/145 healthy subjects (17%); 6% (9/145) were first observed at Day 30 with 20 subjects (14%) still having titers at the last time point (Days 44 to 48). To date, the pattern of antibody response in patients in the ongoing ANNEXA-4 study has been similar to that observed in healthy volunteers. Of the 236 subjects with available samples, 6.8% (16/236) had antibodies against ANDEXXA. None of these anti-ANDEXXA antibodies were neutralizing. No neutralizing antibodies cross-reacting with FX or FXa were detected in healthy subjects (0/145) or in bleeding patients (0/209) to date.

To report SUSPECTED ADVERSE REACTIONS, contact Portola Pharmaceuticals, Inc. at 1-866-777-5947 or the FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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REFERENCE: 1. Andexxa [prescribing information]. South San Francisco, CA: Portola Pharmaceuticals Inc.; 2020.

For further information, please visit **ANDEXXA.com**

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