Coagulation Factor Xa (Recombinant), Inactivated-zhzo (Andexanet Alfa)

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Abstract

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Keywords

anticoagulants, drug information, formulary management/P&T, adverse drug reactions

Generic Name: Coagulation factor Xa (recombinant), inactivated-zhzo (andexanet alfa)

Proprietary Name: *Andexxa* (Portola Pharmaceuticals)

Approval Rating: 1 BLA

Therapeutic Class: Factor Xa inhibitor reversal agents

Similar Drugs: None

Sound-/Look-Alike Names: Amantadine, *Aminosyn*, *Anemagen*

Indications

Coagulation factor Xa (recombinant), inactivated-zhzo (formally known as “andexanet alfa”) is approved by the Food and Drug Administration (FDA) for use in patients treated with the factor Xa inhibitors apixaban and rivaroxaban, when acute reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.¹

Coagulation factor Xa (recombinant), inactivated-zhzo has been studied for reversal of the effects of the factor Xa inhibitor edoxaban and the low-molecular-weight heparin enoxaparin.^{2,3} However, the prescribing information for coagulation factor Xa (recombinant), inactivated-zhzo stresses that it has not been shown to be effective for, nor is it indicated for, the treatment of bleeding related to any factor Xa inhibitors other than apixaban and rivaroxaban.¹

Clinical Pharmacology

Coagulation factor Xa (recombinant), inactivated-zhzo is a modified recombinant protein derived from human coagulation

factor Xa. Coagulation factor Xa (recombinant), inactivated-zhzo protein lacks a membrane-binding gamma-carboxyglutamic acid domain and is catalytically inactive due to a mutation of the serine residue to alanine.^{2,4,5}

In contrast to human coagulation factor Xa, coagulation factor Xa (recombinant), inactivated-zhzo does not assemble into a prothrombinase complex to cleave prothrombin to thrombin and prothrombin fragments F1 and F2. There is no detectable procoagulant or anticoagulant activity associated with coagulation factor Xa (recombinant), inactivated-zhzo. In addition to having high affinity for direct factor Xa inhibitors, coagulation factor Xa (recombinant), inactivated-zhzo acts as a decoy for these drugs, binding to them in a dose-dependent manner and preventing the antidote–direct factor Xa inhibitor complex from acting on the coagulation cascade. Coagulation factor Xa (recombinant), inactivated-zhzo does not interfere with factor Xa hemostasis function.^{4,5} Coagulation factor Xa (recombinant), inactivated-zhzo is able to bind rivaroxaban and apixaban.¹

Coagulation factor Xa (recombinant), inactivated-zhzo is produced in a genetically engineered Chinese hamster ovary cell expression system.^{1,4}

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Pharmacokinetics

Coagulation factor Xa (recombinant), inactivated-zhzo's pharmacokinetics are best described by a 2-compartment model with a saturable binding component.⁶ Its volume of distribution is equivalent to the blood volume of 5 L.¹

Plasma clearance is 4.3 L/hour, and the elimination half-life ranges from 5 to 7 hours.^{1,7}

The pharmacodynamic half-life appears to be approximately 1 hour. The administration of andexanet bolus has resulted in reversal of anti-factor Xa activity for 2 to 4 hours.^{7,8} Coagulation factor Xa (recombinant), inactivated-zhzo has been administered as an intravenous (IV) bolus push followed by a 1- to 2-hour infusion to extend the action of the drug.⁸

Comparative Efficacy

Indication: Reversal of Anticoagulant Effects of Factor Xa Inhibitors

Coagulation factor Xa (recombinant), inactivated-zhzo was approved under the FDA's accelerated approval process based on the change from baseline in anti-factor Xa activity in healthy volunteers. Its continued approval is contingent upon results of required studies designed to demonstrate an improvement in hemostasis in patients.^{1,9}

Guidelines

Guideline: Guideline for managing patients on a factor Xa inhibitor—apixaban or rivaroxaban

Reference: Queensland Health, 2014¹⁰

Comments: Factor Xa inhibitor therapy should be discontinued if bleeding occurs, and the site of bleeding should be investigated. Coagulation screening (activated partial thromboplastin time, prothrombin time, anti-factor Xa, and fibrinogen assays) should be performed. For patients experiencing a mild bleed, the next factor Xa inhibitor dose should be withheld or treatment discontinued if necessary, and local measures to stop bleeding and treat any aggravating factors should be initiated. In the case of moderate bleeding, the factor Xa inhibitor should be discontinued, Hematology Services should be contacted, and mechanical compression should be applied or surgical intervention or wound packing considered. Because factor Xa inhibitors are renally excreted, patients should receive IV fluid replacement to maintain good urine output. Platelets should be considered if levels are less than 70 to $80 \times 10^9/L$ or if patient is receiving an antiplatelet agent, and oral activated charcoal should be administered if the last dose of the factor Xa inhibitor was ingested within the previous 8 hours. For severe to life-threatening bleeds, implement all measures for moderate bleeding. In addition, prothrombin complex concentrate should be administered and an antifibrinolytic

(eg, tranexamic acid) considered until the bleed is under control. Recombinant factor VIIa may be used if critical; if bleeding continues, consult with Hematology Services.

Studies

Drug: Coagulation Factor Xa (Recombinant), Inactivated-Zhzo vs Placebo for reversal of apixaban or rivaroxaban anticoagulation effects

Reference: Siegal DM, et al, 2015 (ANNEXA-A and ANNEXA-R trials)^{1,8}

Study Design: Randomized, 2-part, double-blind, placebo-controlled, phase 3 studies

Study Funding: Portola Pharmaceuticals, with support from Bayer, Bristol-Myers Squibb, Johnson & Johnson, and Pfizer

Patients: 145 healthy older volunteers (50-75 years of age). Mean age of participants was 57.9 years, and the majority (61%) were men. Exclusion criteria were history of abnormal bleeding, active bleeding, or risk factors for bleeding; history of thrombosis or risk factors for thrombosis; and history of adult asthma or use of inhaled medications. Of the 145 subjects randomized, 101 received active coagulation factor Xa (recombinant), inactivated-zhzo and 44 received placebo. In the ANNEXA-A study (N = 65 apixaban-treated subjects), 48 subjects received coagulation factor Xa (recombinant), inactivated-zhzo, and 17 received placebo. In the ANNEXA-R study (N = 80 rivaroxaban-treated subjects), 53 subjects received coagulation factor Xa (recombinant), inactivated-zhzo, and 27 received placebo.

Intervention: In the ANNEXA-A study, subjects received oral apixaban 5 mg twice daily for 3.5 days, and in the ANNEXA-R study, subjects received oral rivaroxaban 20 mg/day for 4 days. Subjects were randomized 3:1 (ANNEXA-A) or 2:1 (ANNEXA-R) to receive coagulation factor Xa (recombinant), inactivated-zhzo or matching placebo. Each study was performed in 2 consecutive parts: Part 1 examined a coagulation factor Xa (recombinant), inactivated-zhzo IV bolus alone, and part 2 examined a coagulation factor Xa (recombinant), inactivated-zhzo IV bolus followed by a continuous 120-minute infusion. In ANNEXA-A, participants received coagulation factor Xa (recombinant), inactivated-zhzo as a 400 mg IV bolus (part 1) or as a 400 mg IV bolus followed by a continuous infusion of 4 mg/min for 120 minutes (part 2). In ANNEXA-R, subjects received coagulation factor Xa (recombinant), inactivated-zhzo as an 800 mg IV bolus (part 1) or as an 800 mg IV bolus followed by a continuous infusion of 8 mg/min for 120 minutes (part 2).

Results:

Primary End Point(s)

- Percent change in anti-factor Xa activity in the modified intention-to-treat (mITT) population (subjects who underwent randomization, received any amount

of coagulation factor Xa [recombinant], inactivated-zhzo or placebo, and had a baseline measurement of anti-factor Xa activity and at least 1 measurement of anti-factor Xa activity after administration of coagulation factor Xa [recombinant], inactivated-zhzo or placebo): Anti-factor Xa activity was rapidly reduced (within 2 to 5 minutes) to a greater extent after administration of a bolus dose of coagulation factor Xa (recombinant), inactivated-zhzo compared with placebo. After completion of the bolus dose, reversal of anti-factor Xa activity continued for 2 hours. Anti-factor Xa activity slowly returned to levels observed in the placebo-treated subjects.

- ANNEXA-A: Mean reduction after bolus administration alone was 94% with coagulation factor Xa (recombinant), inactivated-zhzo compared with 21% with placebo ($P < .001$); after bolus administration plus infusion, mean reduction was 92% with coagulation factor Xa (recombinant), inactivated-zhzo compared with 33% with placebo ($P < .001$).
- ANNEXA-R: Mean reduction after bolus administration alone was 92% with coagulation factor Xa (recombinant), inactivated-zhzo compared with 18% with placebo ($P < .001$); after bolus administration plus infusion, mean reduction was 97% in the coagulation factor Xa (recombinant), inactivated-zhzo group compared with 45% in the placebo group ($P < .001$).

Secondary End Point(s)

- Proportion of subjects with at least an 80% reduction in anti-factor Xa activity from baseline to nadir in the mITT population:
 - ANNEXA-A: All subjects treated with coagulation factor Xa (recombinant), inactivated-zhzo had at least an 80% reduction in anti-factor Xa activity, compared with no subjects treated with placebo ($P < .001$). The number needed to treat (NNT) was 1.
 - ANNEXA-R: All except 1 patient treated with coagulation factor Xa (recombinant), inactivated-zhzo had at least an 80% reduction in anti-factor Xa activity, compared with no subjects randomized to placebo ($P < .001$). The NNT was 1.
- Change in unbound factor Xa inhibitor plasma concentration from baseline to nadir:
 - ANNEXA-A: Mean concentration of unbound apixaban was reduced within 2 to 5 minutes to a greater extent with coagulation factor Xa (recombinant), inactivated-zhzo bolus alone (by 9.3 ng/mL vs 1.9 ng/mL with placebo; $P < .001$). Mean concentration of unbound apixaban was also reduced to a greater extent with coagulation factor Xa (recombinant), inactivated-zhzo bolus plus infusion (by 6.5 ng/mL vs 3 ng/mL with placebo;

$P < .001$). Mean concentration of apixaban after administration of coagulation factor Xa (recombinant), inactivated-zhzo was 3.5 ng/mL.

- ANNEXA-R: Mean concentration of unbound rivaroxaban was reduced within 2 to 5 minutes to a greater extent with coagulation factor Xa (recombinant), inactivated-zhzo bolus alone (by 23.4 ng/mL vs 4.2 ng/mL with placebo; $P < .001$). Mean plasma concentration of rivaroxaban was also reduced to a greater extent with coagulation factor Xa (recombinant), inactivated-zhzo bolus plus infusion (by 30.3 ng/mL vs 12.1 ng/mL with placebo; $P < .001$). Mean concentration of rivaroxaban after administration of coagulation factor Xa (recombinant), inactivated-zhzo was 4 ng/mL.
- Change in thrombin generation (measured as the change in endogenous thrombin potential) from baseline to peak after administration of coagulation factor Xa (recombinant), inactivated-zhzo or placebo: In 2 to 5 minutes after administration of coagulation factor Xa (recombinant), inactivated-zhzo, thrombin generation had been restored.
 - ANNEXA-A: After the bolus alone dose, mean change in thrombin generation was significantly greater in the coagulation factor Xa (recombinant), inactivated-zhzo group (1323 nM•min vs 88.2 nM•min in the placebo group; $P < .001$).
 - ANNEXA-R: After the bolus alone dose, mean change in thrombin generation was significantly greater in the coagulation factor Xa (recombinant), inactivated-zhzo group (1314.2 nM•min vs 173.9 in the placebo group; $P < .001$).
- Occurrence of endogenous thrombin potential above the lower limit of baseline-derived range at its peak after study medication administration: Mean thrombin generation at its peak after administration of coagulation factor Xa (recombinant), inactivated-zhzo increased above the baseline mean in each coagulation factor Xa (recombinant), inactivated-zhzo-treated group. The mean thrombin generation was approximately 22% above the value that represented 1 standard deviation more than the mean and 7% above the value that represented 2 standard deviations more. Thrombin generation returned to within 2 standard deviations within 30 minutes after coagulation factor Xa (recombinant), inactivated-zhzo administration.

Comments: Subjects were randomized via an interactive web-based response system to conceal allocation. Efficacy analyses used an mITT population. The amount of coagulation factor Xa (recombinant), inactivated-zhzo required to reverse the effects of rivaroxaban was higher than that required for apixaban because of rivaroxaban's higher initial maximum plasma concentration and larger

volume of distribution. An exact Wilcoxon rank sum test was used to compare end points. The authors reported that 145 subjects were needed to meet 99% power, and alpha level was set at 5%. A hierarchical approach was used for testing end points, and all were tested in sequence. The effects of coagulation factor Xa (recombinant), inactivated-zhzo lasted for about 1 to 2 hours after completion of the infusion before returning to levels observed in placebo subjects. One case of an allergic reaction occurred during a coagulation factor Xa (recombinant), inactivated-zhzo infusion and was treated with a single dose of diphenhydramine. Nonneutralizing antibodies were detected in some patients, but there were no cases of neutralizing antibodies. Adverse events included constipation, dysgeusia, flushing and feeling hot, and urticaria. The studies were conducted at 2 clinical sites in the United States.

Limitations: The inclusion of only healthy older volunteers between 50 and 75 years of age limits the application of the study findings. Subjects were only administered apixaban for 3.5 days or rivaroxaban for 4 days, making it difficult to generalize the results to patients who have been taking these medications for months or years. These studies were not conducted in subjects with a current bleed and therefore could not evaluate whether coagulation factor Xa (recombinant), inactivated-zhzo is effective in stopping an active bleed. The end points were all surrogate markers, and the majority of the outcomes were pharmacodynamic rather than clinical outcomes.

Reference: Connolly SJ, et al, 2016 (ANNEXA-4 trial)^{1,11}

Comments: This is an ongoing multinational, prospective, open-label study using coagulation factor Xa (recombinant), inactivated-zhzo in patients presenting with acute major bleeding who have recently received a factor Xa inhibitor (apixaban, edoxaban, enoxaparin, rivaroxaban). Safety data were initially available for only 67 patients in 2016; the data presented in the product labeling includes 185 patients. Twenty-five patients (14%) died prior to the day 30 follow-up visit, and 8 patients died within 10 days after the coagulation factor Xa (recombinant), inactivated-zhzo infusion. Thromboembolic events occurred in 33 patients (17.8%), and the median time to the first event was 6 days.

Contraindications, Warnings, and Precautions

Contraindications

The prescribing information states there are no contraindications to use of coagulation factor Xa (recombinant), inactivated-zhzo. Though not stated in the product labeling, hypersensitivity reactions to coagulation factor Xa (recombinant), inactivated-zhzo or to any of its inactive ingredients should be considered.¹

Warnings and Precautions

Coagulation factor Xa (recombinant), inactivated-zhzo has a boxed warning regarding potential thromboembolic risks (eg, arterial and venous thromboembolic events), ischemic events (eg, myocardial infarction, ischemic stroke), cardiac arrest, and sudden death related to therapy. Patients should be monitored for thromboembolic events and for symptoms and signs that precede cardiac arrest.¹

The safety of coagulation factor Xa (recombinant), inactivated-zhzo has not been evaluated in patients who experienced thromboembolic events or disseminated intravascular coagulation within 2 weeks prior to the life-threatening bleeding event requiring treatment with coagulation factor Xa (recombinant), inactivated-zhzo. The safety of coagulation factor Xa (recombinant), inactivated-zhzo also has not been evaluated in patients who received prothrombin complex concentrates, recombinant factor VIIa, or whole blood products within 7 days prior to the bleeding event.¹

In the ANNEXA-4 study, there was a rapid and substantial decrease in anti-factor Xa activity with administration of the coagulation factor Xa (recombinant), inactivated-zhzo IV bolus; this decrease was sustained through the continuous infusion. Following the infusion, anti-factor Xa activity increased and achieved a peak effect within 4 hours after the infusion. Anti-factor Xa activity subsequently declined at a rate similar to the clearance of the factor Xa inhibitor.¹

Because coagulation factor Xa (recombinant), inactivated-zhzo is a protein, immunogenicity is possible. Antibodies have been detected in some patients, but none of the antibodies were neutralizing, and none cross-reacted with factor X or factor Xa.¹

The safety and effectiveness of coagulation factor Xa (recombinant), inactivated-zhzo during pregnancy, labor, and delivery have not been evaluated.¹

There is no information regarding the presence of coagulation factor Xa (recombinant), inactivated-zhzo in human milk, or its effects on breastfeeding infants or milk production.¹

Safety and efficacy of coagulation factor Xa (recombinant), inactivated-zhzo have not been established in pediatric patients.¹

Adverse Reactions

The most common adverse reactions (incidence of 5% or greater) in patients receiving coagulation factor Xa (recombinant), inactivated-zhzo were urinary tract infections and pneumonia; in healthy volunteers, the most common adverse reactions (incidence of 3% or greater) were infusion-related reactions (eg, flushing, feeling hot, cough, dysgeusia, dyspnea).¹

In a phase 3 clinical trial enrolling healthy older volunteers, there were no serious or severe adverse events. The most common adverse events were gastrointestinal (GI) effects (eg, constipation, dysgeusia), flushing and feeling hot, and urticaria.

Table 1. Coagulation Factor Xa (Recombinant), Inactivated-Zhzo Dose Based on Rivaroxaban or Apixaban Dose.¹

Factor Xa inhibitor	Factor Xa inhibitor last dose	Timing of Factor Xa Inhibitor Last Dose Before Coagulation Factor Xa (Recombinant), Inactivated-Zhzo Initiation	
		<8 hours or unknown	≥8 hours
Rivaroxaban	≤10 mg	Low dose	Low dose
	>10 mg/unknown	High dose	Low dose
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg/unknown	High dose	Low dose

There was 1 case of erythematous hives, which was successfully treated with a single dose of diphenhydramine. There were no cases of neutralizing antibody formation, but 17% of patients treated with coagulation factor Xa (recombinant), inactivated-zhzo developed nonneutralizing antibodies, which usually appeared 15 to 30 days after treatment.⁸

Drug Interactions

Coagulation factor Xa (recombinant), inactivated-zhzo directly inhibits the anticoagulant activity of factor Xa inhibitors.⁸ No formal drug-drug interaction studies have been published.¹

Recommended Monitoring

Patients should be monitored for arterial and venous thromboembolic events, ischemic events, and symptoms and signs that precede cardiac arrest.¹

Dosing

Coagulation factor Xa (recombinant), inactivated-zhzo has 2 approved dosing regimens. The initial low-dose IV bolus regimen is 400 mg at a target rate of 30 mg/min followed by 4 mg/min for up to 120 minutes. The initial high-dose IV bolus regimen is 800 mg at a target rate of 30 mg/min followed by 8 mg/min for up to 120 minutes. Selection of the low- versus high-dose regimen is based on the specific factor Xa inhibitor, dose of factor Xa inhibitor, and time since the patient's last dose of the factor Xa inhibitor (see Table 1).¹

The lyophilized powder needs to be reconstituted prior to IV administration. Each 100 mg vial is reconstituted by slowly injecting 10 mL of sterile water for injection using a 10 mL syringe and a 20-gauge (or higher) needle, directing the solution onto the inside wall of the vial to minimize foaming. Gently swirl the vial to ensure dissolution of the cake or powder, but do not shake; shaking the vial may cause the contents to foam. The reconstituted solution should then be withdrawn using a 60 mL or larger syringe with a 20-gauge or higher needle. The solution for injection should then be transferred from the syringe into an empty polyolefin or polyvinyl chloride IV bag with a volume of 250 mL or less. The IV line for administration must contain a 0.2 or 0.22

micron in-line polyethersulfone or equivalent low protein-binding filter. The bolus infusion is then infused at a target rate of approximately 30 mg/min. Within 2 minutes after the end of the bolus infusion, the continuous IV infusion should be administered at the recommended rate for the prescribed dose for up to 120 minutes.¹

All vials and syringes and any remaining solution should be discarded.

When medically appropriate, antithrombotic therapy should be restarted to avoid exposing patients to the thrombotic risk of their underlying disease.¹

Product Availability and Storage

Coagulation factor Xa (recombinant), inactivated-zhzo was approved in May 2018.^{1,9} It is available in single-use, preservative-free vials containing 100 mg of coagulation factor Xa formulated with the inactive ingredients tromethamine (Tris), L-arginine hydrochloride, sucrose (2% w/v), mannitol (5% w/v), and polysorbate 80 (0.01% w/v) at pH 7.8.¹

Vials containing reconstituted coagulation factor Xa (recombinant), inactivated-zhzo are stable at room temperature for up to 8 hours, or may be stored for up to 24 hours at 2°C to 8°C (36°F-46°F).¹

IV bags containing reconstituted coagulation factor Xa (recombinant), inactivated-zhzo are stable at room temperature for up to 8 hours, or may be stored for up to 16 hours at 2°C to 8°C (36°F-46°F).¹

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

No REMS is required for coagulation factor Xa (recombinant), inactivated-zhzo.^{1,9}

Conclusion

Coagulation factor Xa (recombinant), inactivated-zhzo is approved for use in patients treated with the factor Xa inhibitors apixaban and rivaroxaban, when acute reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. At this time, data regarding efficacy during clinical bleed are limited, but studies are underway to evaluate this

use. Coagulation factor Xa (recombinant), inactivated-zhzo is the first antidote to active bleeding during apixaban and rivaroxaban therapy. It is not approved to reverse the effects of other factor Xa inhibitors. When medically appropriate, antithrombotic therapy should be restarted to avoid exposing patients to the thrombotic risk of their underlying disease.

Declaration of Conflicting Interests

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