Brand Name[1,2]: Andexxa®
Generic Name[1]: Coagulation facor Xa (recombinant), inactivated-zhzo
Manufacturer[1,2]**:** Baxter Pharmaceutical Solutions, LLC.
Drug Class[1,2]**:** Reversal Agent
Uses[1,2]:

Labeled Uses: Indicated for patients with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Unlabeled Uses: Has been used for other DOACs and Lovenox.

Mechanism of Action:[1,2,3]: Factor Xa inhibitors promote anticoagulation by binding to both free Factor Xa in plasma and Factor Xa attached to the prothrombinase complex. This ultimately leads to the blockade of thrombin generation or clot formation. Andexanet alfa is a factor Xa decoy that binds to factor Xa inhibitors such as apixaban and rivaroxaban with high affinity and prevents them from binding to endogenous factor Xa. It was also shown to sequester factor Xa inhibitors, leading to reversing their anticoagulant effects and restoring the activity of endogenous factor Xa. Andexanet alfa may also achieve procoagulation via binding and inhibiting the activity of Tissue Factor Pathway Inhibitor (TFPI), which is an endogenous inhibitor of Factor Xa. Inhibition of TFPI by andexanet alfa resulted in a transient increase in the level of prothrombin fragments 1 and 2, thrombin-antithrombin complex and D-dimer. Subsequently, this may result in increased tissue factor-initiated thrombin generation. Since it is a genetically modified variant of human factor Xa, andexanet alfa is not able to cleave and activate prothrombin nor assemble into the prothrombinase complex.[1]

Pharmacokinetics: Absorption[1,2,3,4]**:**

C_{max}	79.8 ug/mL
Vd	5L
$T_{1/2}$ (Elimination)	5 to 7 hours
Clearance	4.3 L/hour
Protein Binding	No Information Available
Bioavailability	Not Applicable (IV only)

Metabolism[1,2,3,4]**:** There is limited information on metabolism of andexanet alfa

Elimination[1,2,3,4]**:** There is limited information on elimination of andexanet alfa

Efficacy
Citation: Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med. 2015 Dec 17;373(25):2413-24.

Description of Study: *Study Design*: Two-part randomized, double-blind, placebo-controlled study *Methods*: For each factor Xa inhibitor, a two-part randomized placebo-controlled study was conducted to evaluate andexanet administered as a bolus or as a bolus plus a 2-hour infusion. Healthy adults, ages

50 to 75 years old, were given apixaban, rivaroxaban, or placebo then administered andexanet alfa as a bolus dose (part 1) or a bolus dose plus a continuous infusion (part 2). A total of 101 participants (48 in the apixaban study and 53 in the rivaroxaban study) were randomly assigned to receive andexanet, and 44 participants (17 in the apixaban study and 27 in the rivaroxaban study) were randomly assigned to receive placebo. In the ANNEXA-A study, participants received 5 mg of apixaban orally twice daily for 3.5 days to achieve steady-state plasma levels at the highest approved dose. Three hours after the last dose of apixaban on day 4 (at or near the time of the highest plasma concentration), andexanet was administered as a 400-mg intravenous bolus (30 mg per minute) (part 1) or as a 400-mg intravenous bolus followed by a continuous infusion of 4 mg per minute for 120 minutes (480 mg in total) (part 2). In the ANNEXA-R study, participants received 20 mg of rivaroxaban orally once daily (the highest approved dose) for 4 days. On day 4, at 4 hours after the last dose of rivaroxaban (at or near the maximum plasma concentration), andexanet was administered as an 800-mg intravenous bolus (30 mg per minute) (part 1) or as an 800-mg intravenous bolus followed by a continuous infusion of 8 mg per minute for 120 minutes (960 mg in total) (part 2). Part 1 examined the intravaneous bolus dose and part 2 examned the continuous 120-minute infusion. The primary outcome for both studies was the mean percent change in anti–factor Xa activity. The secondary efficacy end points were the proportion of participants with an 80% or greater reduction in anti–factor Xa activity from baseline to the nadir after administration of andexanet or placebo; the change in unbound inhibitor plasma concentration from baseline to the nadir after administration of andexanet or placebo; the change in thrombin generation, measured as the change in endogenous thrombin potential, from baseline to peak after administration of andexanet or placebo; and the occurrence of an endogenous thrombin potential above the lower limit of the baseline-derived range at its peak after administration of andexanet or placebo (between 2 and 10 minutes after the end of the bolus) or after the infusion. For part 2, an additional secondary end point was the percent change in anti–factor Xa activity from baseline to the post-bolus nadir. Adverse effects were also evaluated throughout the trial. *Results:* ANNEXA-A Outcome Results: The primary outcome is change in Anti-Xa activity for apixaban vs. placebo. The results for part 1 (bolus only) was 94% vs. 21% ($P<0.001$) and part 2 (bolus and continuous infusion) was 92% vs. 33% ($P<0.001$). ANNEXA-R Outcome Results: The primary outcome is change in Anti-Xa activity (rivaroxaban vs. placebo, respectively). The results for part 1 (bolus only) was 92% vs. 18% ($P<0.001$) and part 2 (bolus and continuous infusion) was 2: 97% vs. 45% ($P<0.001$). All the participants who were treated with andexanet had at least 80% reversal of anti–factor Xa activity, a secondary outcome measure, with the exception of one participant who did not receive the full dose of andexanet because of a malfunction with the intravenous administration; none of participants who received placebo had an 80% or greater reversal of anti–factor Xa activity ($P<0.001$). Adverse events were also observed in the trial. There were no severe adverse events, no thrombotic events, antibodies to factor X or factor Xa were not detected in any participants, and non-neutralizing antibodies against andexanet

were detected in 2% of patients who received placebo and in 17% who received andexanet. Neutralizing antibodies were not detected. Adverse effects observed were mild but included, GI upset, administration site reactions, or urticaria.
Limitations: The study was conducted in healthy volunteers and patients who require urgent reversal of factor Xa inhibition activity due to bleeding or for emergency surgery were excluded. Thus it is not clear if andexanet would improve outcomes in patients with major bleeding. The trial only studied Andexanet alfa effects on rivaroxaban and apixaban. Anti-factor Xa's clinical relevance is unclear and is the basis of the reversal agents success.
Conclusion: Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects.

Citation: Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, et. al. ANNEXA-4 Investigators. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016 Sep 22;375(12):1131-41.

Description of Study: *Study Design* Multicenter, prospective, open-label, single-group study. *Methods*: The Andexxa-4 study was designed to assess efficacy and safety of andexanet in patients with acute major bleeding occurring while taking a factor Xa inhibitor, not limited to rivaroxaban and apixaban. Andexxa-4 evaluated 352 patients who had acute major bleeding within 18 hours after administration of apixaban, rivaroxaban, or edoxaban at any dose or enoxaparin at a dose of at least 1 mg per kilogram of body weight per day. There were 128 patients (36%) receiving rivaroxaban (median daily dose, 20 mg), 194 (55%) receiving apixaban (median daily dose, 10 mg), 10 (3%) receiving edoxaban (daily dose, 30 mg [5 patients] or 60 mg [5 patients]), and 20 (6%) receiving enoxaparin. The patients received a bolus of andexanet, followed by a 2-hour infusion. The following doses were used in the protocol: for all patients who had received apixaban and those who had received rivaroxaban more than 7 hours before bolus administration, the bolus dose was 400 mg over a period of 15 minutes and the infusion dose was 480 mg. For patients who had received enoxaparin, edoxaban, or a dose of rivaroxaban 7 hours or less before bolus administration or at an unknown time, the bolus dose was 800 mg over a period of 30 minutes and the infusion dose was 960 mg. The coprimary outcomes were the percent change in anti–factor Xa activity after andexanet treatment and the percentage of patients with excellent or good hemostatic efficacy at 12 hours after the end of the infusion. The primary safety outcomes were death, thrombotic events, and development of antibodies to andexanet or to native factor X and factor Xa. Efficacy was assessed in the subgroup of patients with confirmed major bleeding and baseline anti–factor Xa activity of at least 75 ng per milliliter (or ≥0.25 IU per milliliter for those receiving enoxaparin). *Results:* Patients had a mean age of 77 years and most had substantial cardiovascular disease. Bleeding was predominantly intracranial (in 227 patients [64%]) or gastrointestinal (in 90 patients [26%]). In patients who had received apixaban, the median anti–factor Xa activity decreased from 149.7 ng per milliliter at baseline to 11.1 ng per milliliter after the andexanet bolus (92% reduction; 95% confidence interval [CI], 91 to 93). In patients who had received

rivaroxaban, the median value decreased from 211.8 ng per milliliter to 14.2 ng per milliliter (92% reduction; 95% CI, 88 to 94). Excellent or good hemostasis occurred in 204 of 249 patients (82%) who could be evaluated. Within 30 days, death occurred in 49 patients (14%) and a thrombotic event in 34 (10%). Of the patients who died 35 were cardiovascular causes, 12 noncardiovascular causes, and 2 of unknown causes. Reduction in anti–factor Xa activity was not predictive of hemostatic efficacy overall but was modestly predictive in patients with intracranial hemorrhage.

Limitations*:* Dosing is dependent on information that is more than likely provided by patient, family, or caregivers. If incorrect information is given, under or over dosing is possible. This could get difficult in a clinical setting where time is and important factor. Anti-factor Xa activities clinical relevance was shown to not be predicative of hemostatic efficacy overall, which makes it hard to apply anti-factor Xa's clinical relevance in practice. It is hard to link the adverse effects reported directly to Andexxa, but serious adverse effects, including death, were reported.

Conclusion: The study hypothesized that a reduction in anti–factor Xa activity was a predictor of clinical response, however in the overall population this was not demonstrated. In patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet markedly reduced anti–factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours, as adjudicated according to prespecified criteria. Serious adverse effects were observed in the study and during follow up. Further studies are needed to evaluate the safety data and proper protocol for restarting anticoagulation therapy to avoid serious health effects.

Contraindications[1,2]: None

Black Box Warning[1,2]**:** 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.

Precautions[1,2]: Arterial and venous thromboembolic events, ischemic events, and cardiac events, including sudden death, have occurred during treatment with Andexxa®. Resume anticoagulant therapy as soon as medically appropriate following treatment with Andexxa®. Re-elevation or incomplete reversal of anticoagulant activity can occur.

Adverse effects[1,2]: In patients receiving Andexxa®, the most common (≥5%) adverse reactions were urinary tract infections and pneumonia. In healthy volunteers being treated with Andexxa®, the most common (≥5%) adverse reactions were infusion related reactions. Some serious adverse effects are acute myocardial infarction (3%), cardiac arrest (0.5%), DVT (6%), ischemic stroke (5%), and pulmonary embolism (3%).

Drug Interactions [1,2]: No known drug interactions

Administration [1,2]:
Adult Dosing: Choose regimen based on specific Factor Xa (FXa) inhibitor used, dose of the FXa inihibitor, and time since the patient's last dose of the FXa inhibitor:

- Rivaroxaban 10 mg or less within less than 8 hours or unknown period of time: Initial, 400 mg IV bolus at target rate of 30 mg/min; follow with 4 mg/min continuous IV infusion for up to 120 minutes.
- Rivaroxaban greater than 10 mg (or unknown dose) within less than 8 hours or unknown period of time: Initial, 800 mg IV bolus at target rate of 30 mg/min; follow with 8 mg/min continuous IV infusion for up to 120 minutes.
- Apixaban 5 mg or less within less than 8 hours or unknown period of time: Initial, 400 mg IV bolus at target rate of 30 mg/min; follow with 4 mg/min continuous IV infusion for up to 120 minutes.
- Apixaban greater than 5 mg (or unknown dose) within less than 8 hours or unknown period of time: Initial, 800 mg IV bolus at target rate of 30 mg/min; follow with 8 mg/min continuous IV infusion for up to 120 minutes.
- Apixaban or rivaroxaban, any dose, greater than 8 hours ago: Initial, 400 mg IV bolus at target rate of 30 mg/min; follow with 4 mg/min continuous IV infusion for up to 120 minutes.

Dose*	Initial IV Bolus	Follow-On IV Infusion
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes

Restart/resume antithrombotic therapy as soon as medically appropriate following treatment with coagulation factor Xa recombinant, inactivated-zhzo.

Renal impairment and hepatic impairment: No dosing adjustments are recommended at this time.

Administration: Start the bolus injection, within 2 minutes of completing the bolus dose administer continuous IV infusion for up to 120 minutes (Infusion requires a 0.2 or 0.22 micron in-line polyethersulfone or equivalent low protein-binding filter).
Preparation/Reconstitution:
IV Bolus

- The reconstituted solution contains coagulation factor Xa (recombinant), inactivated-zhzo at a concentration of 10 mg/mL.
- Reconstitute each 100 mg vial using a 10 mL syringe and a 20 gauge (or higher) needle.
- Reconstitute each 200 mg vial using a 20 mL syringe and a 20 gauge (or higher) needle.

- Slowly add sterile Water for Injection, directing the solution onto the side of the wall of the vial to minimize foaming. You may gently swirl each vial until complete dissolution occurs; however DO NOT SHAKE. This typically takes 3-5 minutes.
- Use a 60 mL or larger syringe with a 20 gauge (or higher) needle to withdraw the solution from each vial until dosing volume is achieved.
- Transfer solution from syringe to an empty polyolefin or polyvinyl chloride IV bag.

IV Continuous Infusion

- Follow the same procedure outlined above 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 proteinbinding filter

Use In Special Populations[2]:
Pediatric dosing[1,2]: Safety and efficacy in pediatric population have not been studied
Elderly[2]: The pharmacokinetics of Andexxa® in older (≥ 65 years; n=10) patients were not different compared to younger (18-45 years; n=10) patients, which was observed in Andexxa-a and –r trials. In the ANNEXA-4 study of Andexxa®, 161 were 65 years of age or older, and 205 were 75 years of age or older. No overall differences in safety or efficacy were observed between these subjects and younger patients, and other reported clinical experience has not identified differences in responses between elderly and younger patients; however, greater sensitivity of some older individuals cannot be ruled out.
Pregnancy&Lactation[1,2]*:* Fetal risk cannot be ruled out

Overdosage: Although no information is given in the package insert pertaining to over dose, it is important to consider when using any reversal agent. Although it may not directly be associated with Andexxa®, putting patients in a hypercoagulable state should be considered and monitored.

Conclusion: There are many factors to consider when using Andexxa®, such as: severity of bleed, last dose of FXa inhibitor, which FXa inhibitor was taken, cardiac status of the patient, etc. Anti-factor Xa activity levels were shown to dramatically decrease quickly and last for roughly 1 to 2 hours. After roughly 5 hours, anti-factor Xa levels were similar to patients treated with placebo, at which point the body may naturally be clearing the anticoagulant drug from the body. Overall, it is unclear what Anti-factor Xa activity clinically means. Anti-factor Xa activities clinical relevance was shown to not be predicative of hemostatic efficacy overall (partially predicative in intracranial bleeds) in Andexxa-4. The studies based a lot of their findings on anti-factor Xa activity. Although more FXa inhibitors were included in the Andexxa-4 study, not all of them were well represented, like edoxaparin. Another huge obstacle this reversal agent faces is cost; depending on which dose is used the cost ranges from $300,000 to $600,000, according to average wholesaler cost (AWC)[6]. There are many complications associated with

serious acute bleeding. It is hard to say if the adverse effects reported in the trials were from those complications or from the reversal agent. Regardless, the adverse effects reported were numerous and serious. With all of that in mind, there are no other options in reversing acute bleeding associated with FXa inhibitors. Andexxa's® use will have to be evaluated on a case-by-case basis. More research is needed to fully understand its criteria and spectrum of use.

Recommended References:

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2. Andexxa®. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed April 1, 2019.
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4. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med. 2015 Dec 17;373(25):2413-24.
5. Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S, Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Goodman S, Leeds J, Wiens BL, Siegal DM, Zotova E, Meeks B, Nakamya J, Lim WT, Crowther M; ANNEXA-4 Investigators. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016 Sep 22;375(12):1131-41.
6. Andexanet alfa: Drug Information. UpToDate. Wolters Kluwer. Topical 117811 Version 17.0. Accessed April 17, 2019.

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