HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANDEXXA safely and effectively. See Full Prescribing Information for ANDEXXA.

ANDEXXA® (coagulation factor Xa (recombinant), inactivated-zhzo)
Lyophilized powder for solution for intravenous injection
Initial U.S. Approval: 2018

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: (5.1)

- **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.

RECENT MAJOR CHANGES

Dosage and Administration (2) 12/2018

INDICATIONS AND USAGE

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. (1)

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 to demonstrate an improvement in hemostasis in patients. (1, 14)

Limitation 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. (1)

DOSAGE AND ADMINISTRATION

For intravenous use only.

- Dose ANDEXXA based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor. (2)
- Administer as an intravenous (IV) bolus, with a target rate of 30 mg/min, followed by continuous infusion for up to 120 minutes. (2.3)
- There are two dosing regimens:

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

* The safety and effectiveness of more than one dose have not been evaluated. (2.1)

DOSAGE FORMS AND STRENGTHS

ANDEXXA is available as a lyophilized powder in single-use vials of 200 mg or 100 mg of coagulation factor Xa (recombinant), inactivated-zhzo. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- 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. (5.1)
- Re-elevation or incomplete reversal of anticoagulant activity can occur. (5.2)

ADVERSE REACTIONS

The most common adverse reactions (≥ 5%) in patients receiving ANDEXXA were urinary tract infections and pneumonia. (6.1)

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

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*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

***** Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

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

Treatment with ANDEXXA has been associated with serious and life-threatening adverse events, including: (5.1)

- **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.

1 INDICATIONS AND USAGE

ANDEXXA is 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 *[see Clinical Studies (14)]*. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies to demonstrate an improvement in hemostasis in patients.

Limitation 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.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dose

There are two dosing regimens (see Table 1). The safety and efficacy of an additional dose has not been established.

Table 1: ANDEXXA Dosing Regimens

Dose *	Initial IV Bolus	Follow-On IV Infusion	Total Number of 200 mg Vials	Total Number of 100 mg Vials
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes (480 mg)	5 (2 vials bolus + 3 vials infusion)	9 (4 vials bolus + 5 vials infusion)
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes (960 mg)	9 (4 vials bolus + 5 vials infusion)	18 (8 vials bolus + 10 vials infusion)

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

The recommended dosing of ANDEXXA is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor (see Table 2).

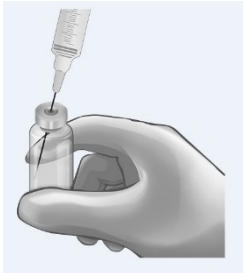
Table 2: ANDEXXA Dose Based on Rivaroxaban or Apixaban Dose (Timing of FXa Inhibitor Last Dose before ANDEXXA Initiation)

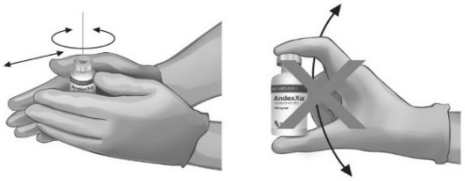
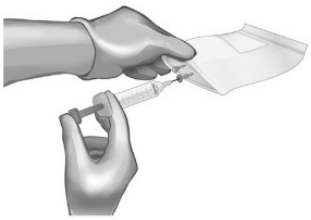
FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg or Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg or Unknown	High Dose	

2.2 Reconstitution

- The reconstituted solution contains coagulation factor Xa (recombinant), inactivated-zhzo at a concentration of 10 mg/mL.
- Reconstituted ANDEXXA in vials is stable at room temperature for up to Eight hours, or may be stored for up to 24 hours at 2°C to 8°C.
- Reconstituted ANDEXXA in IV bags is stable at room temperature for up to Eight hours.

IV Bolus Preparation

Determine total number of vials required (see Table 1). 100 mg vials: Reconstitute the 100mg vial of ANDEXXA with 10 ml of Sterile Water for Injection USP (SWFI) Or 200 mg vials: Reconstitute the 200 mg vial of ANDEXXA	

with 20 mL of SWFI. Use 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 (A). Do not shake (B); shaking could lead to foaming. Typical dissolution time for each vial is approximately 3 to 5 minutes. If dissolution is incomplete, discard the vial and do not use the product. Upon reconstitution, the parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration	(A)_ (B) 
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.	

Discard the syringe and needle.

Discard the vials, including any unused portion.

Continuous IV Infusion Preparation

- 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 protein-binding filter.

2.3 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/minute.
- Within two minutes following the bolus dose, administer the continuous IV infusion for up to 120 minutes.

2.4 Restarting Antithrombotic 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.

3 DOSAGE FORMS AND STRENGTHS

ANDEXXA is available as a white to off-white lyophilized powder in single-use vials of 100 mg or 200 mg of coagulation factor Xa (recombinant), inactivated-zhzo.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic and Ischemic Risks

The thromboembolic and ischemic risks were assessed in 185 patients who received the Generation 1 product and in 124 patients who received the Generation 2 product. The median time to first event was six days, and patients were observed for these events for 30 days following the ANDEXXA infusion. Of the 86 patients who received Generation 1 product and were re-anticoagulated prior to a thrombotic event, 11 (12.7%) patients experienced a thromboembolic, ischemic event, cardiac event or death.

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.

5.2 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 *[see Clinical Studies (14)]*. 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.

Thirty-eight patients who received the Generation 1 product were anticoagulated with apixaban and had baseline levels of anti-FXa activity >150 ng/mL. Nineteen of these 38 (50%) patients experienced a > 93% decrease from baseline anti-FXa activity after administration of ANDEXXA. Eleven patients who were anticoagulated with rivaroxaban had baseline anti-FXa activity levels > 300 ng/mL. Five of the 11 patients experienced a > 90% decrease from baseline anti-FXa activity after administration of ANDEXXA. Anti-FXa activity levels for patients who received the Generation 2 product were not available.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared directly to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the pooled safety analysis of clinical trials of ANDEXXA, 223 healthy volunteers received FXa inhibitors followed by treatment with ANDEXXA. The frequency of adverse reactions was similar in the ANDEXXA-treated group (120/223; 54%) and the placebo-treated group (54/94;

57%). Infusion-related adverse reactions occurred in 18% (39/223) of the ANDEXXA-treated group, and were the only adverse reaction that occurred more frequently than in the placebo group. No serious or severe adverse reactions were reported.

The ANNEXA-4 study is an ongoing multinational, prospective, open-label study using ANDEXXA in patients presenting with acute major bleeding and who have recently received an FXa inhibitor. To date, safety data are available for 185 patients who received the Generation 1 product and 124 subjects who received the Generation 2 product. Fifty-nine percent of 185 patients who received the Generation 1 product and 69% of 124 patients who received the Generation 2 product were older than 75 years. Patients had received either apixaban (98/185, 53%) or rivaroxaban (72/185, 40%), as anticoagulation treatment for atrial fibrillation (143/185, 77%) or venous thromboembolism (48/185, 26%). In the majority of patients, ANDEXXA was used to reverse anticoagulant therapy following either an intracranial hemorrhage (106; 57%) or a gastrointestinal bleed (58; 31%), with the remaining 21 patients (11%) experiencing bleeding at other sites. Patients were assessed at a 30-day follow-up visit following infusion of ANDEXXA.

Deaths

In the ongoing ANNEXA-4 study, there were 25 deaths (14%) amongst the 185 patients receiving the Generation 1 product. These deaths occurred prior to the Day 30 follow-up visit. Eight patients died within ten days after the ANDEXXA infusion. The percentage of patients, by bleeding type, who died prior to the Day 30 follow-up visit was: 14% for intracranial bleeding, 10% for gastrointestinal bleeding, and 19% for other bleeding types. There were 23 deaths (18%) amongst the 124 patients who received Generation 2 that occurred prior to the Day 30 follow-up visit.

Thromboembolic Events

In the ongoing ANNEXA-4 study, 33/185 (17.8%) patients receiving the Generation 1 product experienced one or more of the following overall thromboembolic events: deep venous thrombosis (11/33; 33%), ischemic stroke (9/33; 24%), acute myocardial infarction (5/33; 15%), pulmonary embolism (5/33; 15%), cardiogenic shock (3/33; 9%), sudden death (2/33; 6%), congestive heart failure (2/33; 6%), acute respiratory failure (2/33; 6%), cardiac arrest (1/33; 3%), cardiac thrombus (1/33; 3%), embolic stroke (1/33; 3%), iliac artery thrombosis (1/33; 3%), and non-sustained ventricular tachycardia (1/33; 3%). The median time to the first event in these 33 subjects was six days. Eleven of 33 (33%) patients were on antithrombotic therapy at the time of the event. Patients who received the Generation 2 product experienced a similar rate of overall thromboembolic events (17.7%) as the Generation 1 product. *[see Warnings and Precautions (5.1)]*.

No thromboembolic events were observed in 223 healthy volunteers who received FXa inhibitors and were treated with ANDEXXA.

Infusion-related Reactions

Infusion-related reactions occurred in 18% (39/223) of ANDEXXA-treated healthy volunteers vs. 6% (6/94) of placebo-treated subjects. These reactions were characterized by a range of symptoms including flushing, feeling hot, cough, dysgeusia, and dyspnea. Symptoms were mild to moderate in severity, and 90% (35/39) did not require treatment. One subject with a history of hives prematurely discontinued ANDEXXA after developing mild hives.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Using an electrochemiluminescence (ECL)-based assay, 145 Generation 1 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 who received the Generation 1 product has been similar to that observed in healthy volunteers with 6% (6/98) of the patients having antibodies against ANDEXXA. None of these anti-ANDEXXA antibodies were neutralizing. No antibodies cross-reacting with FX or FXa were detected in healthy subjects (0/145) or in bleeding patients (0/98) to date. There is insufficient data to assess for the presence of anti-ANDEXXA antibodies for subjects received the Generation 2 product.

Detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ANDEXXA with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of ANDEXXA in pregnant women to inform patients of associated risks. Animal reproductive and development studies have not been conducted with ANDEXXA.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Labor or Delivery

The safety and effectiveness of ANDEXXA during labor and delivery have not been evaluated.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ANDEXXA in human milk, the effects on the breastfed child, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ANDEXXA and any potential adverse effects on the breastfed child from ANDEXXA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy of ANDEXXA in the pediatric population have not been studied.

8.5 Geriatric Use

Of the 185 patients who received the Generation 1 product in the ANNEXA-4 study of ANDEXXA 161 were 65 years of age or older and 113 were 75 years of age or older. Of the 124 subjects who received Generation 2 product, 92 subjects 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 the elderly and younger patients; however, greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of ANDEXXA in older (≥ 65 years; n=10) patients were not different compared to younger (18-45 years; n=10) patients.

11 DESCRIPTION

ANDEXXA (coagulation factor Xa (recombinant), inactivated-zhzo) is a sterile, white to off-white lyophilized powder available in single-use vials. The Generation 2 product is produced using a modified Generation 1 manufacturing process.

Each 100 mg vial delivers 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.

Each 200 mg vial delivers 200 mg of coagulation factor Xa formulated with the inactive ingredients tromethamine (Tris base), Tris hydrochloride, L-arginine hydrochloride, sucrose (1% w/v), mannitol (2.5% w/v), and polysorbate 80 (0.01% w/v) at pH 7.8.

After reconstitution of the lyophilized powder with sterile Water for Injection for intravenous (IV) administration, the product is a clear, colorless to slightly yellow solution. ANDEXXA contains no preservatives.

The active ingredient in ANDEXXA is a genetically modified variant of human Factor Xa. The active site serine was substituted with alanine, rendering the molecule unable to cleave and activate prothrombin. The gamma-carboxyglutamic acid (Gla) domain was removed to eliminate the protein's ability to assemble into the prothrombinase complex, thus removing the potential anti-coagulant effects.

No additives of human or animal origin are used in the manufacture of ANDEXXA. The recombinant protein is produced in a genetically engineered Chinese Hamster Ovary (CHO) cell expression system and has a molecular weight of approximately 41 kDa. The manufacturing process incorporates two validated virus clearance steps.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Coagulation factor Xa (recombinant), inactivated-zhzo exerts its procoagulant effect by binding and sequestering the FXa inhibitors, rivaroxaban and apixaban. Another observed procoagulant effect of the ANDEXXA protein is its ability to bind to, and inhibit the activity of Tissue Factor Pathway Inhibitor (TFPI). Inhibition of TFPI activity can increase tissue factor-initiated thrombin generation.

12.2 Pharmacodynamics

The effects of ANDEXXA can be measured using assays for its anti-FXa activity, free fraction of FXa inhibitor and thrombin generation. In addition to its ability to sequester the FXa inhibitors, rivaroxaban and apixaban, ANDEXXA has been shown to inhibit the Tissue Factor Pathway Inhibitor (TFPI) activity.

The dose and dosing regimen of ANDEXXA that are required to reverse anti-FXa activity and to restore thrombin generation were determined in dose-ranging studies on healthy volunteers. Dosing of ANDEXXA, as a bolus followed by a 2-hour continuous infusion, resulted in a rapid decrease in anti-FXa activity (within two minutes after the completion of the bolus administration) followed by reduced anti-FXa activity that was maintained throughout the duration of the continuous infusion *[see Clinical Studies (14)]*. The anti-FXa activity returned to the placebo levels approximately two hours after completion of a bolus or continuous infusion. Whereas, TFPI activity in plasma returned to the pretreatment levels approximately 96 hours following ANDEXXA administration.

Elevation of Tissue Factor (TF)-initiated thrombin generation above the baseline range (prior to anticoagulation) occurred within two minutes following a bolus administration of ANDEXXA and was maintained throughout the duration of the continuous infusion. The TF-initiated thrombin generation was elevated above placebo for at least 22 hours. The sustained elevation of thrombin generation over the baseline range, and sustained elevation over placebo were not

observed in a contact-activated thrombin generation assay (an assay that is not affected by TF-TFPI interaction). A PK/PD study compared the change in anti-FXa activity for the low and high dose regimens for both Generation 1 and Generation 2 ANDEXXA. The results are shown in the table below.

Table 3: Summary of Comparisons of change in anti FXa activity between Generation 1 and Generation 2 ANDEXXA with High and Low Doses

	Low Dose		High Dose	
PD Result	Gen1	Gen2	Gen1	Gen2
n	11	11	11	10
% Decrease in Anti-FXa Activity	90.31 (10.5) [59.2, 95.7]	92.9 (0.94) [91.4,94.2]	96.7 (1.32) [93.9, 98.4]	96.2 (1.32) [94.0, 98.7]

Data presented are mean (Standard Deviation), [range]

12.3 Pharmacokinetics

A PK/PD study in healthy subjects compared the PK parameters for the Generation 1 and Generation 2 ANDEXXA. The results are shown in the table below.

Table 4: Summary of PK parameters between Gen 1 and Gen 2 with High and Low Doses

	Low Dose		High Dose	
PK parameter	Generation 1	Generation 2	Generation 1	Generation 2
n	10	11	11	10
$AUC_{0-\infty}$ (hr*µg/mL)	205.2 (20.8) [137.0, 265.9]	200.5 (16.3) [153.4, 255.7]	441.9 (24.8) [329.5, 737.6]	572.9 (16.0) [467.1, 783.9]
Cmax (µg/mL)	79.8 (24.4) [51.3, 114.9]	76.6 (17.5) [61.1, 100.1]	149.5 (22.5) [114.4, 239.0]	206.6 (18.8) [158.9, 280.5]
Clearance (L/hr)	4.3 (20.8) [3.6, 6.4]	4.4 (16.3) [3.4, 5.7]	4.0 (24.7) [3.4, 5.7]	3.1 (16.0) [2.3, 3.8]
$T_{1/2}$ (hr)	4.3 (38.5) [3.3, 11.9]	3.3 (15.0) [2.3, 4.0]	4.0 (28.7) [2.0, 5.7]	2.7 (20.0) [1.9, 3.4]
Vss (L)	5.1 (43.4) [3.2, 13.8]	4.4 (17.6) [3.3, 5.7]	4.1 (26.7) [2.4, 5.7]	3.0 (23.3) [2.2, 5.0]

From Table 14.2.1.2A of Clinical Study Report 16-512
Data presented are geometric mean (Geometric Mean %Coefficient of Variation), [range]

Drug-Drug Interaction

The pharmacokinetics of ANDEXXA were not affected by apixaban (5 mg orally BID for six days) or rivaroxaban (20 mg orally once daily for six days).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies were performed to evaluate the effects of ANDEXXA on carcinogenesis, mutagenesis, or impairment of fertility.

14 CLINICAL STUDIES

The safety and efficacy of ANDEXXA were evaluated in two prospective, randomized, placebo-controlled studies, conducted in healthy volunteers. Both studies examined the percent change in anti-FXa activity, from baseline to nadir, for the low-dose and high-dose regimens of bolus followed by continuous infusion. Nadir is defined as the smallest value measured within 5 minutes after the end of the continuous infusion.

Study 1 ANNEXA-A (NCT02207725) – apixaban reversal

In Study 1, healthy subjects (median age: 57 years; range: 50 to 73 years) received apixaban 5 mg twice daily for 3.5 days to achieve steady-state. At three hours after the last apixaban dose (~C_{max}), ANDEXXA or placebo was administered. Eight subjects received placebo and 24 received ANDEXXA, administered as a 400 mg intravenous (IV) bolus followed by a 4 mg per minute continuous infusion for 120 minutes (total 480 mg).

Study 2 ANNEXA-R(NCT02220725) – rivaroxaban reversal

In Study 2, healthy subjects (median age: 57 years; range: 50 to 68 years) received rivaroxaban 20 mg once per day for four days to achieve steady-state. At four hours after the last rivaroxaban dose (~ C_{max}), ANDEXXA or placebo was administered. Thirteen subjects received placebo and 26 received ANDEXXA, administered as an 800 mg IV bolus followed by an 8 mg per minute continuous infusion for 120 minutes (total 960 mg).

Reduction in Anti-FXa Activity

The percent change from baseline in anti-FXa activity at its nadir was statistically significant ($p < 0.0001$) in favor of the ANDEXXA groups compared to placebo in both Studies 1 and 2. The results of Study 1 and Study 2 are provided in Table 5(see below).

The time courses of anti-FXa activity before and after ANDEXXA administration are shown in Figure 1.

Table 5 - A: Change in Anti-FXa Activity/Study 1 (apixaban)

Anti-FXa Activity	**ANDEXXA** n=23	**Placebo** n=8
Mean baseline ng/mL (± SD)	173.0 (50.5)	191.7 (34.4)
Mean ng/mL (± SD) change from baseline at the nadir[a]	-160.6 (49.3)	-63.2 (18.1)
Mean % (± SD) change from baseline at the nadir[a]	-92.3 (2.8)	-32.7 (5.6)
95% Confidence interval (CI)[b]	-59.5 (-64.1, -55.2)	Not Applicable
p-value	< 0.0001 [c]	Not Applicable

Table 5 - B: Change in Anti-FXa Activity/Study 2 (rivaroxaban)

Anti-FXa Activity	**ANDEXXA** n=26	**Placebo** n=13
Mean baseline ng/mL (± SD)	335.3 (91.0)	317.2 (91.0)
Mean ng/mL (± SD) change from baseline at the nadir[a]	-324.5 (89.2)	-14.4 (58.8)
Mean % (± SD) change from baseline at the nadir[a]	-96.7 (1.8)	-44.6 (11.8)
95% Confidence interval (CI)[b]	-51.9 (-58.0, -47.0)	Not Applicable
p-value	< 0.0001[c]	Not Applicable

SD = Standard deviation

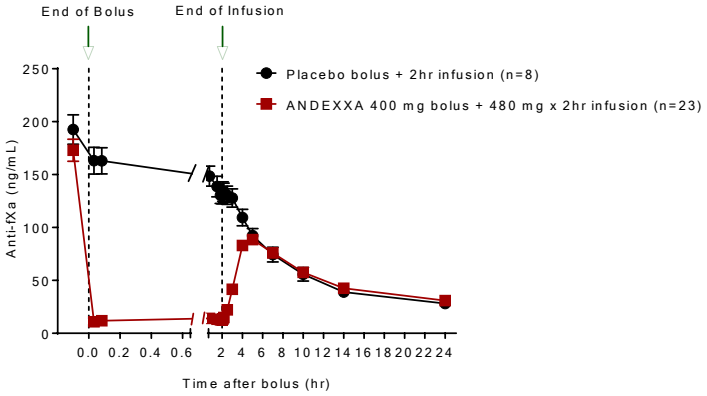
Note: Baseline is the last assessment obtained prior to the first dose of ANDEXXA or placebo.

[a]Nadir is the smallest value for anti-FXa activity at the 110 minute (ten minutes prior to the end of the infusion) time point, 2-minute time point before completion of the infusion, or the 5-minute time point after the completion of the infusion for each subject.

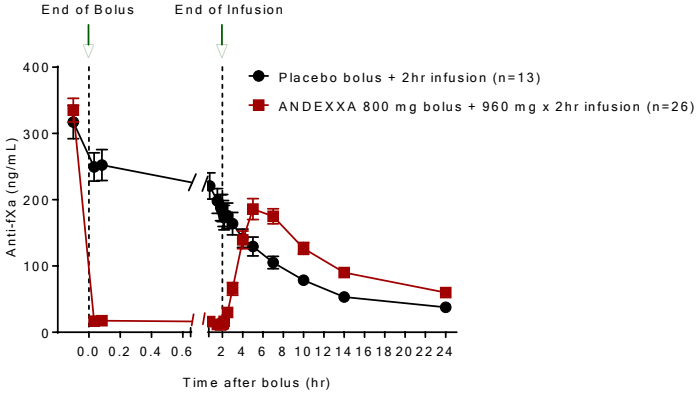
[b]The CI is for the Hodges-Lehman estimate of shift.

[c]p-value obtained from a 2-sided exact Wilcoxon rank-sum test.

Figure 1: Change in Anti-FXa Activity (ng/mL) in Subjects Anticoagulated with Apixaban (A – Study 1) and Rivaroxaban (B – Study 2)



(A)



(B)

Anti-FXa activity was measured prior to and after ANDEXXA or placebo administration.
Dashed lines indicate the end of the bolus or infusion. A break in the x-axis is added to better visualize the immediate, short-term dynamics of anti-FXa activity following ANDEXXA treatment. The points on the graph represent the mean anti-FXa activity level; error bars illustrate standard error. There was a statistically significant difference ($p < 0.05$) in the percent change of anti-FXa activity normalized to pre-bolus between ANDEXXA and placebo until 2 hours after administration of infusion.
A. Apixaban – with ANDEXXA 400 mg IV bolus plus 4 mg/min infusion for 120 minutes.
B. Rivaroxaban – with ANDEXXA 800 mg IV bolus plus 8 mg/min infusion for 120 minutes

ANNEXA-4 (NCT02329327)

In an ongoing multinational, prospective, single-arm, open-label study, ANDEXXA was administered to patients taking FXa inhibitors who presented with acute major bleeding.

Interim results of the study include data for 185 patients who received the Generation 1 product. The anti-FXa levels for 116 patients who received the Generation 2 product were not available.

Of the 185 patients who received the Generation 1 product, 129 were considered efficacy-evaluable and defined as patients who: 1) were dosed with ANDEXXA; 2) had a baseline anti-FXa activity above 75 ng/mL; and 3) were adjudicated as meeting eligibility criteria for acute major bleeding. *[also see Adverse Reactions (6)]*.

For anti-FXa activity, the median decrease from baseline to nadir was -93% for apixaban and -90% for rivaroxaban. ANDEXXA has not been shown to be effective for bleeding related to any FXa inhibitors other than apixaban or rivaroxaban.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ANDEXXA, coagulation factor Xa (recombinant), inactivated-zhzo is a white to off-white lyophilized cake or powder supplied as 4 single-use vials in a carton.

ANDEXXA vials are provided as follows:

Table 6: Presentation of ANDEXXA

NDC	Carton Configuration	Vial Cap Color	Packaging Color
NDC 69853-0101-1	4 single use vials in a carton, each vial containing 100 mg of ANDEXXA	Vials have a blue flip-off cap	1. Carton and vial label have a red colored stripe across the front. 2. Carton and vial label have "100mg/vial" in a red graphic on the front panel.
NDC 69853-0102-1	4 single use vials in a carton, each vial containing 200 mg of ANDEXXA	Vials have a red flip-off cap	1. Carton and vial label have a red to blue transition colored stripe across the front. 2. Carton and label have "200mg/vial" in a blue graphic on the front panel.

Storage and Handling

Unopened vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

Inform patients that reversing FXa inhibitor therapy increases the risk of thromboembolic events. Arterial and venous thromboembolic events, ischemic events, cardiac events, and sudden death were observed within 30 days following ANDEXXA administration.
[see Warnings and Precautions (5.1)].

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