ANDEXXA- andexanet alfa injection, powder, lyophilized, for solution
AstraZeneca Pharmaceuticals LP

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

Warnings and Precautions (5.1, 5.2) 03/2024

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

DOSAGE AND ADMINISTRATION

For intravenous (IV) 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 IV bolus, with a target rate of 30 mg/min, followed by continuous infusion for 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 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for 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 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 bleeding subjects receiving ANDEXXA were urinary tract infections and pneumonia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
* 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 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.

2 DOSAGE AND ADMINISTRATION

For intravenous (IV) use only.

2.1 Dose

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

Table 1: ANDEXXA Dosing Regimens

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

* The safety and effectiveness of more than one dose have 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 Last Dose of FXa Inhibitor before ANDEXXA Initiation)

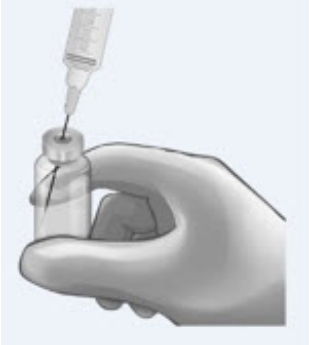
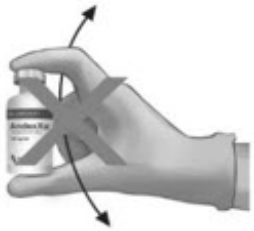
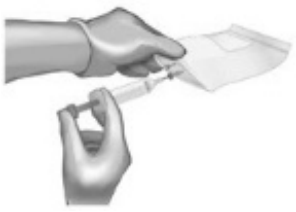
FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg or Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg or Unknown	High Dose	

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 (36°F to 46°F)
- 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). 200 mg vials:	

Reconstitute the 200 mg vial of ANDEXXA with 20 mL of Sterile Water for Injection (SWFI). Use a 20-mL (or larger) syringe and 20-gauge (or smaller in diameter, e.g. 21-gauge) 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 three to five 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 40-mL (or larger) syringe with a 20-gauge (or smaller in diameter, e.g. 21-gauge) 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/min.
- Within two minutes following the bolus dose, administer the continuous IV infusion for 120 minutes.

2.4 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.

3 DOSAGE FORMS AND STRENGTHS

ANDEXXA is available as a white to off-white lyophilized powder in single-use vials of 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 419 bleeding subjects in the ANNEXA-4 study who received ANDEXXAand were treated with apixaban or rivaroxaban. There were

45/419 (10.7%) subjects who experienced a thrombotic event. The median time to first event was

10 days, and 17 subjects experienced the event within three days of treatment. Of the 419 subjects

who received ANDEXXA, 266 received at least one anticoagulation dose within 30 days after

treatment as a prophylactic measure. Of these 266 subjects, 14 subjects (5.3%) had a thrombotic

event after resumption *[see Adverse Reactions (6.1)].*

Monitor subjects 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 subjects 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 subjects 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 subjects *[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.

A total of 114 subjects from ANNEXA-4 were anticoagulated with apixaban or rivaroxaban and

had elevated baseline levels of anti-FXa (>150 ng/mL for apixaban and >300 ng/mL for

rivaroxaban). After administration of ANDEXXA, these subjects experienced decreased anti-FXa

activity levels, with median reductions of 96% for rivaroxaban and 92% for apixaban.

5.3 Use of Heparin Following Administration of ANDEXXA

ANDEXXA may interfere with the anticoagulant effect of heparin.

Use of ANDEXXA as an antidote for heparin has not been established. Avoid use of

ANDEXXA for the reversal of direct FXa inhibitors (apixaban and rivaroxaban) prior to heparinization as ANDEXXA may cause unresponsiveness to heparin. If anticoagulation is needed, use an alternative anticoagulant to heparin.

6 ADVERSE REACTIONS

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

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 directly compared to rates in the clinical trials of

another drug and may not reflect the rates observed in clinical practice.

The ANNEXA-4 study was a multinational, prospective, open-label study using ANDEXXA in

subjects presenting with acute major bleeding and who have recently received an FXa inhibitor.

Four hundred and seventy-seven subjects were enrolled and received ANDEXXA. Of these 477

subjects, 419 subjects were treated with apixaban (245/419; 58.5%) or rivaroxaban (174/419;

41.5%). Most subjects had received apixaban or rivaroxaban as anticoagulation treatment for atrial

fibrillation (348/419; 83%) or venous thromboembolism (65/419; 16%). In the majority of subjects,

ANDEXXA was used to reverse anticoagulant therapy following either an intracranial hemorrhage

(289/419; 69%) or a gastrointestinal bleed (95/419; 23%), with the remaining subjects (35/419;

8.4%) experiencing bleeding at other sites. Subjects were assessed at a Day 30 follow-up visit

following infusion with ANDEXXA.

Deaths

In the ANNEXA-4 study, of the 419 subjects in the safety population who were treated with

apixaban or rivaroxaban, there were 75 deaths (18%). There were 37 cardiovascular deaths related

to bleeding, 19 deaths that were cardiovascular and not related to bleeding, 14 that were non-cardiovascular,

and 5 deaths had an uncertain or unknown cause. The average time to death was 15

days after treatment. All subjects died prior to Day 45. Of the 75 subjects who died, the initial

bleeding event was intracranial bleeding in 55 (73%), gastrointestinal bleeding in 14 (19%), and

other bleeding types in 6 (8%) subjects.

Thromboembolic and Ischemic Events

In the ANNEXA-4 study, 45/419 (10.7%) subjects experienced one or more of the following

thromboembolic events: cerebrovascular accident (CVA) (19/45; 42%), deep venous thrombosis

(11/45; 24%), myocardial infarction (9/45; 20%), pulmonary embolism (5/45; 11%), and transient

ischemic attack (1/45; 2%). The median time to event was ten days. A total of 38% of subjects

with thromboembolic events (17/45) experienced the thromboembolic event during the first three

days. Of the 419 subjects who received ANDEXXA, 282 (67.3%) received any form of re-anticoagulation

within 30 days after treatment. Of these 282 subjects, 16 received anticoagulation

in response to a thrombotic event, while 266 received the anticoagulation as a prophylactic. Of

these 266, 14 subjects (5.3%) had a thrombotic event after resumption of anticoagulation; while of

the 153 subjects who did not receive anticoagulation as a prophylactic, 31 (20.3%) had a

thrombotic event. No patient had a thrombotic event after resumption of oral anticoagulation *[see*

Warnings and Precautions (5.1)].

Infusion-Related Reactions

In the ANNEXA-4 study, 2/419 (0.5%) subjects experienced an infusion-related reaction, neither

of which were assessed as severe (1 moderate; 1 mild). Reported signs and symptoms were

transient and included rigors, chills, hypertension, oxygen desaturation, agitation and confusion.

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 developmental 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.

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 419 subjects in the ANNEXA-4 study of ANDEXXA, 381 (91%) were 65 years of age or

older, and 278 (66%) were older than 75 years of age. No overall differences in safety or efficacy

were observed between these subjects and younger subjects, and other reported clinical experience

has not identified differences in responses between elderly and younger subjects; however, greater

sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

ANDEXXA (coagulation factor Xa (recombinant), inactivated-zhzo) is a sterile, white to off-white lyophilized powder available in single-use vials.

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 SWFI for 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 FXa. 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 anticoagulant 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 (TF)-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 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 two-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 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 the sustained elevation over placebo were not observed in a contact-activated thrombin generation assay (an assay that is not affected by TF-TFPI interaction).

Laboratory assessment of coagulation does not necessarily correlate with or predict the hemostatic effectiveness of ANDEXXA.

12.2.1 Therapeutic Monitoring

Current commercial clinical anti-FXa-activity assays are unsuitable for measuring FXa activity following administration of ANDEXXA. Due to the reversible binding of ANDEXXA to the FXa inhibitor, the high sample dilution currently used in commercial clinical assays promotes dissociation of the inhibitor from ANDEXXA, resulting in detection of erroneously elevated anti-FXa activity levels, thereby causing a substantial underestimation of the reversal activity of ANDEXXA.

12.3 Pharmacokinetics

A summary of the pharmacokinetic (PK) properties of ANDEXXA in healthy subjects is shown in the table below (see Table 3).

Table 3: Summary of PK Parameters with High and Low Doses

	Low Dose	**High Dose**
n	11	10
$AUC_{0-\infty}$ (hr*µg/mL)	200.5 (16.3) [153.4; 255.6]	572.9 (16.0) [467.1; 783.9]
C_{max} (µg/mL)	76.6 (17.5) [61.1; 100.1]	206.6 (18.8) [158.9; 280.5]
Clearance (L/hr)	4.4 (16.3) [3.4; 5.7]	3.1 (16.0) [2.3; 3.8]
$T_{1/2}$ (hr)	3.3 (15.0) [2.3; 4.0]	2.7 (20.0) [1.9; 3.4]
V_{ss} (L)	4.4 (17.6) [3.3; 5.7]	3.0 (23.3) [2.2; 5.0]

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).

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and

specificity of the assay. Differences in assay methods preclude meaningful comparisons of the

incidence of ADAs in the studies described below with the incidence of ADAs in other studies,

including those of ANDEXXA.

Using electrochemiluminescence (ECL)-based assays, 417 ANDEXXA-treated healthy subjects

were tested for antibodies to ANDEXXA as well as for antibodies cross-reacting with

factor X

(FX) and FXa. The analysis of available samples up to Day 48 from pooled healthy subjects

revealed low incidence of anti-ANDEXXA (≤ 8.7%) and anti-FXa (≤ 0.8%) at all timepoints and

no anti-FX antibody was detected at any timepoint. The pattern of immunogenicity in subjects with

acute major bleeding in the ANNEXA-4 study was similar to that observed in healthy subjects. Of

the 277 ANDEXXA-treated subjects in ANNEXA-4 who had available samples at Day 30 or 45,

7.9% (22/277) had antibodies against ANDEXXA, 0.4% (1/277) subjects had antibodies against

FXa and no subjects had antibodies against FX. No neutralizing antibodies against ANDEXXA or

cross-reacting with FX or FXa were detected in healthy subjects or in bleeding subjects.

Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the

pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of ANDEXXA have not been

fully characterized.

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 (Study 1 ANNEXA-A; Study 2 ANNEXA-R).

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 five minutes after the end of the continuous infusion.

The safety and efficacy of ANDEXXA were evaluated in a multinational, prospective, single-arm,

open-label study (Study 3 ANNEXA-4) in subjects presenting with acute major bleeding and who

have recently received an FXa inhibitor. This study examined the percent change in anti-FXa

activity from baseline to the nadir between five minutes after the end of the bolus up until the end of the infusion and the rate of effective hemostasis within 12 hours after infusion, as rated by an independent endpoint adjudication committee.

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 three and a half 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 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

In Study 1 and Study 2, 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 below (see Table 4).

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

Table 4 - 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*	-160.6 (49.3)	-63.2 (18.1)
Mean % (± SD) change from baseline at the nadir*	-92.3 (2.8)	-32.7 (5.6)
Median difference and associated 95% confidence interval (CI)†	-59.5 (-64.1; -55.2)	not applicable

p-value	< 0.0001‡	not applicable

* 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.
† The CI is for the Hodges-Lehman estimate of shift.
‡ p-value obtained from a 2-sided exact Wilcoxon rank-sum test.

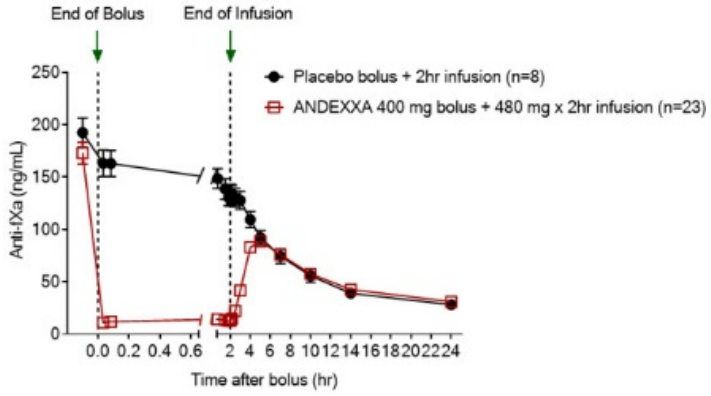
Table 4 - B: Change in Anti-FXa Activity/Study 2 (rivaroxaban)

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*	-324.5 (89.2)	-143.4 (58.8)
Mean % (± SD) change from baseline at the nadir*	-96.7 (1.8)	-44.6 (11.8)
Median difference and associated 95% confidence interval (CI)†	-51.9 (-58.0; -47.0)	not applicable
p-value	< 0.0001‡	not applicable

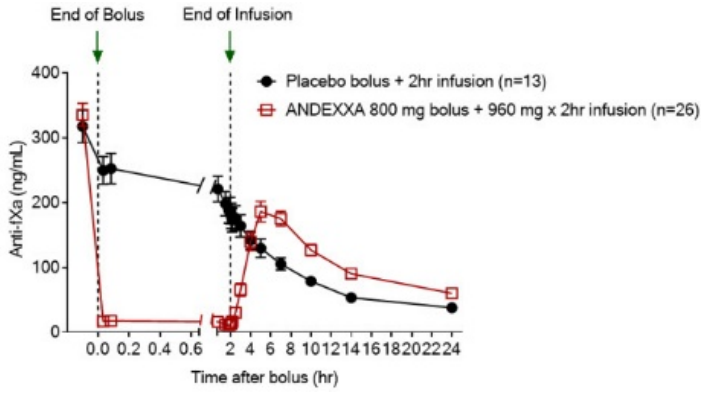
SD = Standard deviation.
Note: Baseline is the last assessment obtained prior to the first dose of ANDEXXA or placebo.

* 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.
† The CI is for the Hodges-Lehman estimate of shift.
‡ 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 two 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.

Study 3 ANNEXA-4 (NCT02329327)

In a multinational, prospective, single-arm, open-label study, ANDEXXA was administered to 477

subjects taking FXa inhibitors who presented with acute major bleeding.

The co-primary endpoints are: (a) percent change in anti-FXa activity from baseline to the nadir

between five minutes after the end of the bolus up until the end of the infusion; and (b) rate of

effective hemostasis within 12 hours after infusion, as rated by an independent endpoint

adjudication committee.

For the 477 subjects dosed with ANDEXXA, 302 were efficacy-evaluable defined as subjects (1)

on treatment with apixaban or rivaroxaban; (2) who 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 (95% CI) decrease from baseline to nadir in anti-FXa activity for

apixaban was -93% (-94%; -92%) and for rivaroxaban was -94% (-95%; -93%).

An improvement in hemostasis has not been established. 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 single-use vials in a carton. ANDEXXA is not made with natural rubber latex.

ANDEXXA vials are provided as follows (see Table 5):

Table 5: Presentation of ANDEXXA

NDC	Carton Configuration	Vial Cap Color	Packaging Color
NDC 0310-3200-04	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 "200 mg/vial" in a blue graphic on the front panel.
NDC 0310-3200-05	5 single use vials in a carton, each vial containing 200 mg of ANDEXXA		

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)]*.

Manufactured by:

AstraZeneca AB

Södertälje, Sweden SE-15185

Distributed by:

AstraZeneca Pharmaceuticals LP

Wilmington, DE 19850

U.S. License No. 2059

Product of Spain

ANDEXXA is a registered trademark of the AstraZeneca group of companies.

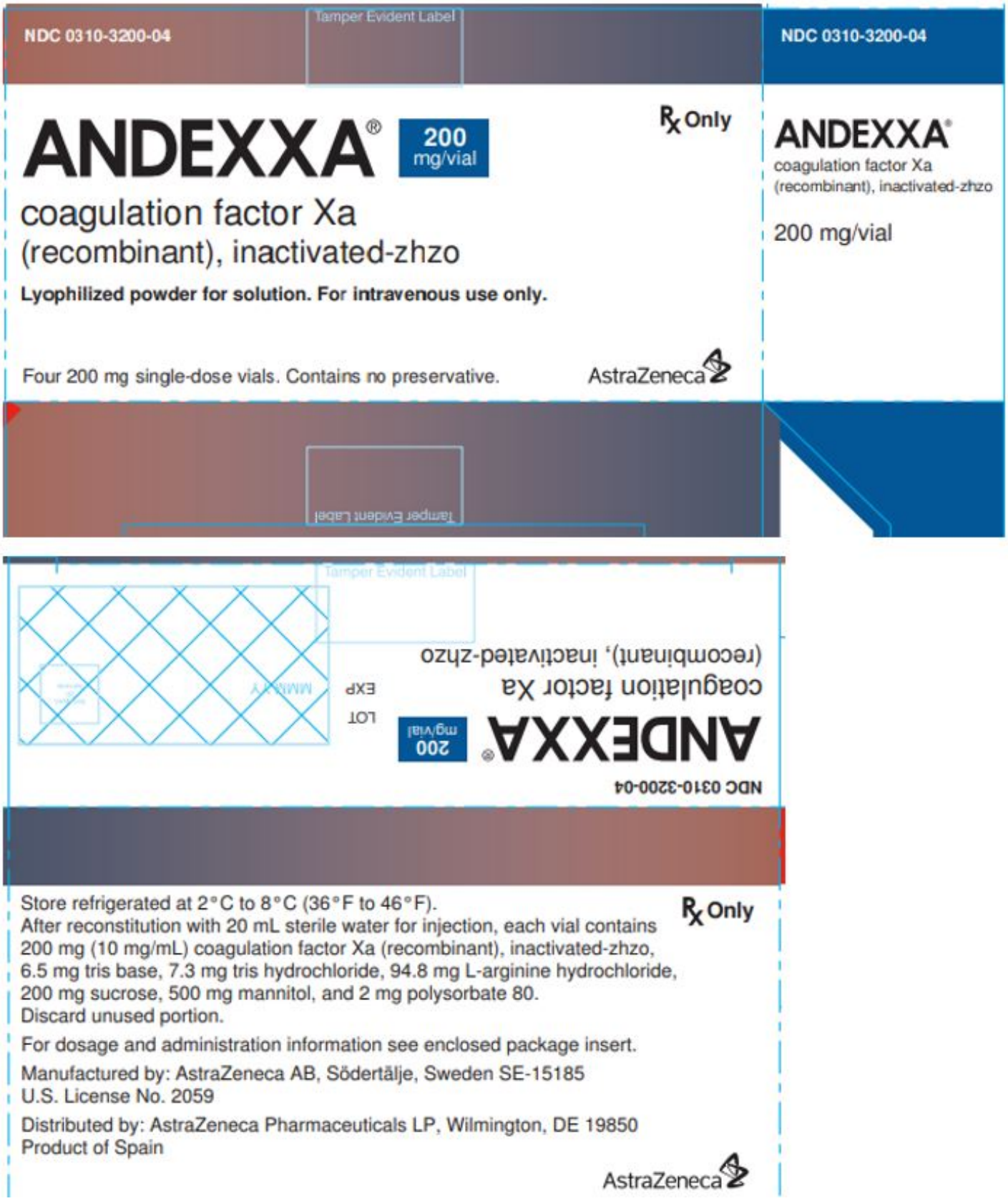
PRINCIPAL DISPLAY PANEL - 200 mg Vial Carton

NDC 0310-3200-04 Rx Only

ANDEXXA® 200mg/vial
coagulation factor Xa
(recombinant), inactivated-zhzo

Lyophilized powder for solution. For intravenous use only.

Four 200 mg single-dose vials. Contains no preservative. AstraZeneca



ANDEXXA

andexanet alfa injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0310-3200
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
andexanet alfa (UNII: BI009E452R) (andexanet alfa - UNII:BI009E452R)	andexanet alfa	200 mg in 20 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0310-3200-04	4 in 1 CARTON	07/12/2022	
1	NDC:0310-3200-01	20 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		
2	NDC:0310-3200-05	5 in 1 CARTON	07/03/2023	
2	NDC:0310-3200-01	20 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125586	07/12/2022	

Labeler - AstraZeneca Pharmaceuticals LP (054743190)

Registrant - AstraZeneca PLC (230790719)

Revised: 3/2024 AstraZeneca Pharmaceuticals LP