Multiple Guidelines Support Use of a Specific Reversal Agent
For FXa Inhibitor–related Life-Threatening or Uncontrolled Bleeding

**ACEP**
American College of Emergency Physicians
Anticoagulant Reversal Strategies in the ED Setting

**ACC**
American College of Cardiology
Guidance for Administering Reversal Agents

**AHA/ACC/HRS**
American Heart Association
American College of Cardiology
Heart Rhythm Society

**CHEST**
American College of Chest Physicians

**ESC/EHRA**
European Society of Cardiology
European Heart Rhythm Association

**NCCN**
National Comprehensive Cancer Network (NCCN)

**ASH**
American Society of Hematology

**ESO**
European Stroke Organisation

**BSG**
British Society of Gastroenterology

**The AC Forum**
The Anticoagulation Forum
Guidance from the Anticoagulation Forum

**SELECT IMPORTANT SAFETY INFORMATION**

**INDICATION**

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

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

**Limitations of Use**

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

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

See full prescribing information for complete boxed warning

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

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

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

Please see additional Important Safety Information on next page and full Prescribing Information including Boxed Warning on thromboembolic risks, ischemic risks, cardiac arrest, and sudden death starting on following page.
Joint Commission Updated National Patient Safety Goal (NPSG) for Anticoagulant Therapy

NOW IN EFFECT


Bleeding is the most common complication of all anticoagulants. In addition to heparin and warfarin, each of the direct oral anticoagulants have different reversal mechanisms. It is important for organizations to use evidence-based practice guidelines when developing protocols to manage bleeding events. For timely and appropriate management, providers need to be aware of the variations in presentation severity (eg, location and severity of bleeding, indication for reversal) and appropriate reversal agents (eg, drug discontinuation, use of concentrated clotting therapy) for each anticoagulation medication used by patients coming to their organization.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thromboembolic and Ischemic Risks

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

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 seven days prior to the bleeding event. The thromboembolic and ischemic risks, cardiac arrest, and sudden death starting on next page.

ADVERSE REACTIONS

The most common adverse reactions (≥ 5%) in bleeding patients receiving ANDEXXA were urinary tract infections and pneumonia. The most common adverse reactions (≥ 3%) in healthy subjects treated with ANDEXXA were infusion-related reactions.

Immunogenicity

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

To report SUSPECTED ADVERSE REACTIONS, call 1-866-777-5947 or contact the FDA by visiting www.fda.gov/medwatch, or calling 1-800-FDA-1088.

Please see additional Important Safety Information on previous page and full Prescribing Information including Boxed Warning on thromboembolic risks, ischemic risks, cardiac arrest, and sudden death starting on next page.

For further information, please visit ANDEXXA.com
ANDEXXA has not been shown to be effective for, and is not indicated for, the change from baseline in anti-FXa activity in healthy volunteers. This indication is approved under accelerated approval based on the improvement in hemostasis in patients.

**INDICATIONS AND USAGE**

ANDEXXA is indicated for patients treated with rivaroxaban or apixaban where reversal of anticoagulation is needed due to life threatening or uncontrolled bleeding. This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon confirmation in patients that demonstrate an improvement in hemostasis in patients.

ANDEXXA has not been shown to be effective for, and is not indicated for, the change from baseline in anti-FXa activity in non-bleeding subjects. A total of 71 subjects were anticoagulated with apixaban and had anti-FXa activity levels >300 ng/mL. Forty-eight of the 71 apixaban-treated subjects experienced arterial or venous thromboembolic events or disseminated intravascular coagulation within two days of antigenic inactivation with ANDEXXA bolus dose. The time to treatment with ANDEXXA may not reflect the rates observed in the clinical trials of a drug cannot predict adverse reaction rates observed in the clinical trials of a drug cannot predict adverse reaction rates observed in the clinical trials of a drug cannot predict adverse reaction rates observed in the clinical trials of a drug cannot predict adverse reaction rates observed in the clinical trials of a drug.
The safety and effectiveness of ANDEXXA during labor and delivery has not been evaluated.

8.1 Pregnancy

There are no adequate and well-controlled studies of ANDEXXA in pregnant women. As with other antithrombotic agents, the potential for miscarriage or abnormalities in pregnancy is not known. ANDEXXA should be avoided in women who are or might become pregnant. If ANDEXXA is used in pregnancy, or if the patient becomes pregnant while taking ANDEXXA, the patient should be apprised of the potential hazard to the fetus.

8.2 Lactation

It is not known whether ANDEXXA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ANDEXXA is administered to a nursing woman.

8.3 Pedi atric Use

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

12.4 Mechanism of Action

The active ingredient in ANDEXXA is a genetically modified variant of recombinant activated protein C (APC). ANDEXXA is derived from human cell lines that have been engineered to specifically secrete recombinant human protein C. This product is produced in human cells to allow for less potential for immunogenicity compared to nonhuman species (primates).

Clinical Pharmacology

The effects of ANDEXXA can be measured using assays for its active ingredient, Coagulation factor Xa (recombinant), inactivated-zhzo exerts its procoagulant effects by binding to the Coagulation factor Xa (recombinant), inactivated-zhzo receptor, Tissue Factor Pathway Inhibitor (TFPI). Inhibition of TFPI activity results in a rapid decrease in anti-FXa activity (within 2 minutes after the completion of the bolus administration) or in bleeding subjects (0/209) to date.

The pharmacokinetics of ANDEXXA in healthy older (≥ 65 years) subjects were similar to those in younger (18-45 years) individuals. The mean baseline ng/mL of ANDEXXA in healthy older (≥ 65 years) subjects was 335.3 (± 25.4) for rivaroxaban and apixaban dose (~ Cmax), ANDEXXA or placebo was administered. A half days to achieve steady-state. At three hours after the last rivaroxaban dose (~ Cmax), ANDEXXA or placebo was administered. The percent changes from baseline at the end of the bolus or infusion, time point, 2-minute points on the graph represent the mean anti-FXa activity level; the x-axis is added to better visualize the immediate, short-term changes in anti-FXa activity following ANDEXXA infusion. The points on the graph represent the mean anti-FXa activity level, and the error bars indicate the standard error of the mean anti-FXa activity level.

13 NONCLINICAL TOXICOLOGY

13.1 Genotoxicity

No mutagenic effects were observed in any of the non-clinical tests performed. The mutagenic effects of ANDEXXA or placebo were monitored using the Escherichia coli/salmonella assay.

13.2 Carcinogenicity

The carcinogenic potential of ANDEXXA was evaluated in 2-year studies in rats and mice. The results of these studies were negative, with no increase in tumor incidence in rats or mice during the course of the study.

13.3 Reproduction

No adverse effects on fertility or reproductive function were observed in rats treated with ANDEXXA or placebo.

13.4 Developmental/Neonatal Toxicology

ANDEXXA has not been shown to be effective for bleeding related to preterm birth. The safety and effectiveness of ANDEXXA have not been evaluated in pregnancy or delivery.

14 CLINICAL STUDIES

14.1 ANDEXXA in Acute Major Bleeding

ANDEXXA was evaluated in two prospective, randomized, placebo-controlled, studies, conducted in the U.S. and Europe. Study 1 (ANNEXA-3) was a large, randomized, double-blind, placebo-controlled trial in patients with severe hemorrhage. The effects of ANDEXXA can be measured using assays for its active ingredient, Coagulation factor Xa (recombinant), inactivated-zhzo exerts its procoagulant effects by binding to the Coagulation factor Xa (recombinant), inactivated-zhzo receptor, Tissue Factor Pathway Inhibitor (TFPI). Inhibition of TFPI activity results in a rapid decrease in anti-FXa activity (within 2 minutes after the completion of the bolus administration) or in bleeding subjects (0/209) to date. The pharmacokinetics of ANDEXXA in healthy older (≥ 65 years) subjects were similar to those in younger (18-45 years) individuals. The mean baseline ng/mL of ANDEXXA in healthy older (≥ 65 years) subjects was 335.3 (± 25.4) for rivaroxaban and apixaban dose (~ Cmax), ANDEXXA or placebo was administered. A half days to achieve steady-state. At three hours after the last rivaroxaban dose (~ Cmax), ANDEXXA or placebo was administered. The percent changes from baseline at the end of the bolus or infusion, time point, 2-minute points on the graph represent the mean anti-FXa activity level; the x-axis is added to better visualize the immediate, short-term changes in anti-FXa activity following ANDEXXA infusion. The points on the graph represent the mean anti-FXa activity level, and the error bars indicate the standard error of the mean anti-FXa activity level.

13.5 Local Tissue Effects

The pharmacokinetics of ANDEXXA in healthy older (≥ 65 years) subjects were similar to those in younger (18-45 years) individuals. The mean baseline ng/mL of ANDEXXA in healthy older (≥ 65 years) subjects was 335.3 (± 25.4) for rivaroxaban and apixaban dose (~ Cmax), ANDEXXA or placebo was administered. A half days to achieve steady-state. At three hours after the last rivaroxaban dose (~ Cmax), ANDEXXA or placebo was administered. The percent changes from baseline at the end of the bolus or infusion, time point, 2-minute points on the graph represent the mean anti-FXa activity level; the x-axis is added to better visualize the immediate, short-term changes in anti-FXa activity following ANDEXXA infusion. The points on the graph represent the mean anti-FXa activity level, and the error bars indicate the standard error of the mean anti-FXa activity level.

13.6 Special Populations

In the U.S. general population, the estimated background risk of the incidence of antibodies to ANDEXXA with the incidence of a given antibody (including neutralizing antibody) positivity in an assay of, Tissue Factor Pathway Inhibitor (TFPI). Inhibition of TFPI activity results in a rapid decrease in anti-FXa activity (within 2 minutes after the completion of the bolus administration) or in bleeding subjects (0/209) to date. The pharmacokinetics of ANDEXXA in healthy older (≥ 65 years) subjects were similar to those in younger (18-45 years) individuals. The mean baseline ng/mL of ANDEXXA in healthy older (≥ 65 years) subjects was 335.3 (± 25.4) for rivaroxaban and apixaban dose (~ Cmax), ANDEXXA or placebo was administered. A half days to achieve steady-state. At three hours after the last rivaroxaban dose (~ Cmax), ANDEXXA or placebo was administered. The percent changes from baseline at the end of the bolus or infusion, time point, 2-minute points on the graph represent the mean anti-FXa activity level; the x-axis is added to better visualize the immediate, short-term changes in anti-FXa activity following ANDEXXA infusion. The points on the graph represent the mean anti-FXa activity level, and the error bars indicate the standard error of the mean anti-FXa activity level.