SELECT IMPORTANT SAFETY INFORMATION

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.

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.

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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 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.

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. 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.

Seventy-one subjects were anticoagulated with apixaban and had baseline levels of anti-FXa activity > 150 ng/mL. Nineteen subjects who were anticoagulated with rivaroxaban had elevated baseline anti-FXa activity levels >300 ng/mL. Forty-eight of the 71 apixaban-treated subjects (68%) experienced a > 90% decrease from baseline anti-FXa activity after administration of ANDEXXA. Ten of the 19 rivaroxaban subjects (53%) experienced a > 90% decrease from baseline anti-FXa activity after administration of ANDEXXA.

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.

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 (0/145) or in bleeding patients (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 full Prescribing Information including Boxed Warning on thromboembolic risks, ischemic risks, cardiac arrest, and sudden death. >>