

## From The Medical Letter on Drugs and Therapeutics

# Andexxa—An Antidote for Apixaban and Rivaroxaban

**Coagulation factor Xa (recombinant)**, inactivated-zhzo (andexanet alfa; Andexxa – Portola) has received accelerated approval from the FDA for urgent reversal of the anticoagulant effect of the direct factor Xa inhibitors apixaban (Eliquis) and rivaroxaban (Xarelto). Andexanet alfa is the second antidote for a direct oral anticoagulant to become available in the US, and the first for factor Xa inhibitors. Idarucizumab (Praxbind) was approved in 2015 for reversal of the anticoagulant effect of the direct thrombin inhibitor dabigatran etexilate (Pradaxa).<sup>1</sup> Andexanet alfa has not been approved to date for reversal of anticoagulation with the direct factor Xa inhibitors edoxaban (Savaysa)<sup>2</sup> or betrixaban (Bevyxxa).<sup>3</sup>

### Pronunciation Key

**Andexanet alfa:** an dex' a net al' fa      **Andexxa:** an dex' a

The four-letter suffix -zhzo has no pronunciation or meaning; such suffixes are now added to biologic drugs to distinguish reference products from their biosimilars.

### Bleeding With Factor Xa Inhibitors

As with all anticoagulants, severe, potentially fatal bleeding can occur with factor Xa inhibitors, and no specific agent had been available to reverse their anticoagulant effect in the event of life-threatening bleeding or emergency surgery.<sup>4</sup> The results of some studies suggest that the anticoagulant effect of factor Xa inhibitors may be reversed by prothrombin complex concentrates.<sup>5,6</sup>

### Mechanism of Action

Andexanet alfa is a genetically modified variant of human factor Xa (alanine is substituted for serine) produced in the Chinese hamster ovary cell line. It acts as a decoy, binding to factor Xa inhibitors and neutralizing their anticoagulant effect. Based on its mechanism of action, andexanet alfa is expected to reduce the anti-factor Xa activity of all direct (apixaban, betrixaban, edoxaban, and rivaroxaban) and indirect (enoxaparin and fondaparinux) factor Xa inhibitors.

### Clinical Studies

Approval of andexanet alfa was based on the results of two randomized, placebo-controlled trials (ANNEXA-A and ANNEXA-R) that evaluated the mean change from baseline in anti-factor Xa activity following administration of andexanet alfa to healthy volunteers 50-75 years old who had received either apixaban or rivaroxaban.<sup>7</sup>

In ANNEXA-A, 66 healthy subjects received apixaban 5 mg twice daily for 3.5 days. Three hours after the last dose of apixaban, subjects received either andexanet alfa or placebo. Andexanet alfa was given as a 400-mg IV bolus with or without a subsequent 4 mg/minute continuous infusion for 2 hours. Anti-factor Xa activity was reduced within 2-5 minutes by 94% with an andexanet alfa IV bolus, compared to 21% with placebo. Thrombin generation was fully restored within 2-5 minutes in 100% of andexanet-treated patients versus 11%

Table. Pharmacology

	Pharmacology
Route	IV bolus and infusion
Formulation	100 mg single-use vials
Half-life (elimination)	5-7 hours

of placebo-treated patients. These effects were sustained throughout the continuous 2-hour infusion of the drug (Table).

In ANNEXA-R, 80 healthy subjects received rivaroxaban 20 mg once daily for 4 days. Four hours after the last dose of rivaroxaban, subjects received either andexanet alfa or placebo. Andexanet alfa was given as an 800-mg IV bolus with or without a subsequent 8 mg/minute continuous infusion for 2 hours. Anti-factor Xa activity was reduced within 2-5 minutes by 92% with an andexanet alfa IV bolus, compared to 18% with placebo. Thrombin generation was fully restored within 2-5 minutes in 96% of andexanet alfa-treated patients vs 7% of placebo-treated patients. These effects were sustained throughout the continuous 2-hour infusion of the drug.

In an interim analysis of an ongoing single-arm trial (ANNEXA-4) in 238 patients who had acute major bleeding (61% intracerebral, 27% gastrointestinal) within 18 hours after taking a factor Xa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin), administration of andexanet alfa (89% received a low-dose regimen and 11% received a high-dose regimen) reduced anti-factor Xa activity by 91% in patients taking apixaban, by 88% in those taking rivaroxaban, and by 75% in those taking enoxaparin (very few patients were taking edoxaban). Effective hemostasis was achieved in 83% of patients 12 hours after receiving andexanet alfa.<sup>8,9</sup>

No published phase 3 trials demonstrating the efficacy of andexanet alfa in patients taking other direct or indirect factor Xa inhibitors are available, but in phase 2 trials and animal studies, andexanet alfa effectively reduced the anti-factor Xa activity of all of them.<sup>10,11</sup>

The FDA is requiring the manufacturer to conduct a randomized, controlled trial comparing the new product with usual care, which could include prothrombin complex concentrates, in patients taking factor Xa inhibitors who have active bleeding.

### Adverse Effects

The label includes a boxed warning about the risk of thromboembolic, ischemic, and cardiac events, including sudden death, in patients treated with andexanet alfa. In the interim analysis of ANNEXA-4, 11% of patients had a thrombotic event and 12% died within 30 days after administration of the drug; the median time to the first event was 6 days.<sup>9</sup> No thromboembolic events occurred among 223 healthy volunteers who received factor Xa inhibitors and were treated with andexanet alfa. In healthy volunteers, infusion reactions were the only adverse events that occurred more often with andexanet alfa than with placebo.

In ANNEXA-A and ANNEXA-R, no antibodies to factor X or Xa developed in any healthy volunteers, and no neutralizing antibodies against andexanet alfa were detected.

## Dosage, Administration, and Cost

Andexxa is supplied in cartons containing four 100-mg single-use vials. The recommended dosage is based on the factor Xa inhibitor taken, its dose, and the time since the last factor Xa inhibitor dose.

Two dosage regimens are recommended. Patients taking  $\leq 10$  mg of rivaroxaban or  $\leq 5$  mg of apixaban per dose should receive the low-dose regimen, a 400-mg IV bolus dose of andexanet alfa, followed by a 4 mg/minute continuous infusion for up to 120 minutes. Patients taking  $>10$  mg of rivaroxaban or  $>5$  mg of apixaban per dose should receive the high-dose regimen, an 800-mg IV bolus dose of andexanet alfa, followed by an 8 mg/minute continuous infusion for up to 120 minutes if their last dose was  $<8$  hours before starting andexanet alfa; if the last dose was  $\geq 8$  hours before starting andexanet alfa, the low-dose regimen should be used. If the dose and/or timing since the last dose of the factor Xa inhibitor is unknown, the high-dose regimen should be used. The optimal dosage of andexanet alfa for patients taking other factor Xa inhibitors has not been established.

The supply of Andexxa is expected to be limited until early 2019; according to the drug's website (andexxa.com), it is currently available at only ten institutions. Treatment with the high dose would cost \$49 500 for the drug alone.<sup>12</sup> The low-dose regimen would cost half as much.

## Conclusions

Based on an interim analysis of an ongoing single-arm trial, andexanet alfa (Andexxa) can rapidly reverse the anticoagulant effect of apixaban (Eliquis), rivaroxaban (Xarelto), and (off-label) enoxaparin (Lovenox, and generics) in patients with active major bleeding. It should also be effective in reversing the anticoagulant effect of other direct factor Xa inhibitors such as edoxaban (Savaysa) and indirect factor Xa inhibitors such as fondaparinux (Arixtra, and generics), but data are lacking. How andexanet alfa compares with prothrombin complex concentrates, which cost much less, remains to be determined.

### ARTICLE INFORMATION

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