Andexxa® (coagulation factor Xa [recombinant], inactivated-zhzo) – New orphan drug approval

- On May 4, 2018, Portola Pharmaceuticals announced the FDA approval of Andexxa [coagulation factor Xa (recombinant), inactivated-zhzo], for patients treated with Xarelto® (rivaroxaban) and Eliquis® (apixaban), when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
    - Andexxa has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any anti-Factor Xa (FXa) inhibitors other than Xarelto and Eliquis.
    - 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.
- In the U.S. in 2016, there were approximately 117,000 hospital admissions attributable to FXa inhibitor-related bleeding and nearly 2,000 bleeding-related deaths per month.
- Andexxa is a recombinant protein specifically designed to bind to FXa inhibitors and rapidly reverse their anticoagulant effect.
- The safety and efficacy of Andexxa were evaluated in two randomized, placebo-controlled studies, ANNEXA-R and ANNEXA-A. Healthy volunteers were given Eliquis 5 mg twice daily or Xarelto 20 mg once daily. The primary outcome was the mean percent change in anti–FXa activity.
    - Anti-FXa activity was reduced to a greater extent after administration of a bolus of Andexxa vs. placebo, both in the Eliquis study (mean reduction: 94% vs. 21%; $p < 0.001$) and in the Xarelto study (92% vs. 18%, $p < 0.001$).
    - When Andexxa was administered as a bolus plus a 2-hour infusion, it also reduced anti–FXa activity to a greater extent vs. placebo, both in the Eliquis study (92% vs. 33%, $p < 0.001$) and in the Xarelto study (97% vs. 45%, $p < 0.001$).
    - In addition, in an ongoing study, ANNEXA-4, Andexxa was administered to patients taking Eliquis or Xarelto who had acute major bleeding. The median anti-FXa activity decreased by 93% (95% CI: 87, 94) for Eliquis and 89% (95% CI: 58, 94) for Xarelto.
- Andexxa carries a boxed warning for thromboembolic risks, ischemic risks, cardiac arrest and sudden deaths.
- An additional warning and precaution of Andexxa includes re-elevation or incomplete reversal of anti-FXa activity.
- The most common adverse reactions (≥ 5%) for Andexxa use in patients are urinary tract infections and pneumonia.
- The most common adverse reaction (≥ 3%) for Andexxa use in healthy volunteers was infusion-related reactions.
- There are two recommended dosage regimens for Andexxa:

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 has not been evaluated.

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    - 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 Andexxa. Consult Andexxa's drug label for specific recommendations.

- Portola Pharmaceuticals plans to launch Andexxa under an early supply program in early June 2018. Broader commercial launch is expected in early 2019. Andexxa will be available as 100 mg single-use vials.