# MEMORANDUM

**Wilson W. Bryan, M.D.**
**Director, Office of Tissues and Advanced Therapies**
**FDA / CBER / OTAT**

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| **BLA** | 125586/0 |
| **Submission date** | August 3, 2017 |
| **Review date** | May 2, 2018 |
| **Applicant** | Portola Pharmaceuticals, Inc. |
| **Product Name** | coagulation factor Xa (recombinant), inactivated-zhzo |
| **Trade Name** | ANDEXXA |
| **Proposed Indication** | For patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding |

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| **CMC Reviews** | |
| • **CMC (product office)** | • Mikhail V. Ovanesov, Wojciech Jankowski, Ze Peng, Yideng Liang, Andrey G. Sarafanov, and Zuben Sauna |
| • **Facilities review (OCBQ / DMPQ)** | • Christine Harman, Joan Johnson, and Donald Ertel |
| • **Establishment Inspection Report (OCBQ / DMPQ)** | • Joan Johnson, Donald Ertel, Yideng Liang, and Mikhail V. Ovanesov |
| **Clinical Reviews** | |
| • **Clinical (product office)** | • Bindu George and Tejashri Purohit-Sheth |
| • **Postmarketing safety epidemiological review (OBE / DE)** | • Faith Barash |
| • **BIMO** | • Haecin Chun, Erin McDowell, and Dennis Cato |
| **Statistical Reviews** | • Chunrong Cheng and Renee Rees |
| **Pharmacology / Toxicology Review** | • Yolanda K. Branch and Anne M. Pilaro |
| **Clinical Pharmacology Review** | • Iftekhar Mahmood |
| **Labeling Reviews** | |
| • **APLB (OCBQ / APLB)** | • Kristine Khuc and Lisa Stockbridge |
| **Regulatory Project Manager** | • Jean Gildner |

**Regulatory Action** **Approval**

## Background

On December 17, 2015, Portola Pharmaceuticals, Inc. (Portola), submitted a Biologics License Application (BLA) for coagulation factor Xa (recombinant), inactivated-zhzo (ANDEXXA). On August 17, 2016, the FDA issued a Complete Response Letter (CRL) to Portola. On August 3, 2017, Portola resubmitted the BLA.

ANDEXXA's proposed indication is for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. These patients have a substantial risk for morbidity and mortality, and there is no product currently approved to reverse the anticoagulation caused by rivaroxaban and apixaban.

I very much appreciate the reviews of both the original submission and the resubmission. The review team has raised several concerns regarding this BLA, and several members of the review team are recommending against approval of the BLA. Their concerns are appropriate and are well documented in their reviews.

The purpose of this memo is to provide my perspective on the most critical concerns raised by the review team, and to provide the rationale for the approval of this BLA by the Office of Tissues and Advanced Therapies.

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## Review Issues

### Effectiveness

This BLA is under consideration for Accelerated Approval, based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (21 CFR 601.41). Members of the review team appear to agree that the BLA includes substantial evidence that ANDEXXA affects the surrogate endpoint of Factor Xa activity. However, the review team has concerns that the BLA does not contain sufficient data to support that this surrogate is reasonably likely to predict a clinical benefit. Those concerns focus on the following: 1) ANDEXXA has a relatively short-duration (approximately 2 – 4 hours) effect on the surrogate; and 2) the available ANNEXA-4 study data do not show that ANDEXXA's effect on the surrogate correlated with clinical hemostasis in patients. These concerns regarding the surrogate endpoint are critical to the review team recommendations against approval of this BLA.

However, there are reasons to believe that the effect on the surrogate is reasonably likely to predict a clinical benefit. First, there is strong biological plausibility that a decrease in Factor Xa activity, even if for only a few hours, could provide an opportunity for a clot to form that would result in hemostasis, with a resulting improvement in morbidity and mortality. In addition, the magnitude of ANDEXXA's effect on the surrogate was substantial, with a mean decrease in Factor Xa activity of greater than 90% in healthy volunteers who had received either rivaroxaban or apixaban.

The review team notes that ANNEXA-4 does not provide persuasive evidence of a correlation between Factor Xa activity and clinical hemostasis. However, there may be a clinically important correlation that was not detectable in ANNEXA-4, due to the relatively

small number (16) of patients who achieved poor or no hemostasis, among a total of 91 patients with evaluable hemostatic efficacy data.

Therefore, I believe that the observed decrease in Factor Xa activity is reasonably likely to predict a clinical benefit in morbidity and mortality in patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. I agree with the review team that the BLA provides substantial evidence of an effect on this surrogate. Under Accelerated Approval, Portola will be required to conduct a confirmatory clinical trial to confirm the clinical benefit of ANDEXXA.

**Safety**

ANDEXXA is associated with serious and life-threatening events, including arterial and venous thromboembolic events, ischemic events including myocardial infarction and ischemic stroke, cardiac arrest, and sudden death. As noted in the clinical reviews, these events occurred at a higher rate in patients who received ANDEXXA than in literature-based historical controls. In addition, ANDEXXA has a documented procoagulant effect that provides biological plausibility that ANDEXXA caused these adverse events.

However, these adverse events occurred in patients who were receiving anticoagulation and had an underlying disorder with increased risk for such events. In addition, the ANNEXA-4 study population may have important but unidentifiable differences compared to the historical control population. Thus, the comparison to the historical control is problematic. In the absence of a reliable control, it is difficult to discern the actual proportion of these serious and life-threatening events that were probably due to ANDEXXA and the proportion of these that would have occurred even in the absence of ANDEXXA. A randomized clinical trial would provide a much better estimate of the true rate at which ANDEXXA causes these serious adverse events.

Pending such a randomized trial, the presumption is that ANDEXXA may have caused these serious and life-threatening events. Therefore, the product label includes a boxed warning to advise healthcare providers of these risks, and includes advice to mitigate these risks.

**Benefit – Risk Profile**

The BLA clinical reviews conclude that the uncertainty regarding the clinical benefit, in combination with concern about the safety of the product, results in an unfavorable overall benefit-risk profile of ANDEXXA. As discussed above, I believe that the BLA provides substantial evidence of an effect that is reasonably likely to predict a clinical benefit in morbidity and/or mortality. In addition, while the concerns about safety are reasonable, the magnitude of those risks is unclear, and those risks are adequately mitigated by the ANDEXXA label. Therefore, while the overall benefit-risk profile is uncertain, I believe it is favorable.

## Postmarketing Requirement

Under Accelerated Approval, Portola will be required to conduct a randomized, 440-subject clinical trial of ANDEXXA in patients with life-threatening or uncontrolled intracerebral hemorrhage. Relative to the data in the BLA, this postmarketing trial should provide much more reliable data regarding both the benefits and risks of ANDEXXA. The review team has expressed concern about both the feasibility and interpretability of the required postmarketing study. Considering the uncertainty regarding the benefits and risks of ANDEXXA, I believe that there will be substantial equipoise that will facilitate the completion of the required postmarketing study. In addition, the agreed-upon postmarketing study appears to be adequately designed to have the potential to provide interpretable data regarding both the benefits and risks of ANDEXXA. The interpretability of the study will depend on the study conduct and the study data.

## Summary

The nature of Accelerated Approval is that there is expected to be some uncertainty regarding the existence of a clinical benefit. However, the FDA accepts that uncertainty in order to make available products that treat serious conditions with an unmet need. The uncertainties regarding this BLA must be considered in the setting of Accelerated Approval for a serious and life-threatening disorder with an unmet need for a product to reverse anticoagulation due to rivaroxaban or apixaban.

As described above, I have uncertainty regarding both the existence and magnitude of both the benefits and risks of ANDEXXA. However, the BLA meets the regulatory standard of substantial evidence of effectiveness based on a surrogate endpoint that is reasonably likely to predict a clinical benefit. In addition, the serious risks of this product are adequately mitigated through the product label. Therefore, there is an acceptable overall benefit-risk profile for ANDEXXA for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The Office of Tissues and Advanced Therapies will approve this BLA.