MEMORANDUM

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FDA / CBER / OTAT / DCEPT

BLA 125586/0	
Submission date	August 3, 2017
Review date	April 20, 2018
Applicant	Portola Pharmaceuticals Inc.
Product/Trade Name	Coagulation Factor Xa (Recombinant), Inactivated/ ANDEXXA
Proposed Indication	For patients treated with Factor Xa inhibitors, rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

CMC Review(s)	
• **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 Review(s)	
• **Clinical (product office)**	• Bindu George
• **Postmarketing safety epidemiological review (OBE/DE)**	• Faith Barash
• **BIMO**	• Haecin Chun, Erin McDowell and Dennis Cato
Statistical Review(s)	• Chunrong Cheng and Renee Rees
Pharmacology/Toxicology Review(s)	• Yolanda K. Branch, Anne M. Pilaro, Allen Wensky
Clinical Pharmacology Review(s)	• Mahmood Iftekhar
Labeling Review(s)	
• **APLB (OCBQ/APLB)**	• Kristine Khuc
Regulatory Project Manager	• Jean Gildner
Recommendation	**Complete Response [CR**

Executive Summary

Portola Pharmaceuticals, Inc. submitted a Biologics License Application (BLA) on December 17, 2015 as a rolling review to seek U.S. licensure for Coagulation Factor X (Recombinant), inactivated (ANDEXXA), under the Accelerated Approval Pathway. As significant chemistry, manufacturing, and control and clinical issues were identified during the original review, a Complete Response Letter was issued to Portola on August 17, 2016. Portola responded to the CRL on August 3, 2017.

Following FDA review of the response to the CRL, the CMC issues have been adequately addressed; however, there remain concerns regarding the safety and efficacy of ANDEXXA for the proposed indication of: *the treatment of patients treated with Factor Xa inhibitors, rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.*

Please see primary reviews from the clinical, statistical, and CMC teams for the original BLA submission and the resubmission for specific details of the review.

I concur with the clinical and statistical review teams' recommendation for not approving the BLA at this time. The significant uncertainties as to the surrogate endpoint likely being able to predict clinical benefit as well concerns related to an increased risk of thromboembolic events, indicate an unfavorable benefit risk profile.

Notable Review Issues

Portola originally submitted results from randomized, placebo controlled clinical studies conducted in healthy volunteers who received factor Xa inhibitors–majority received apixaban and rivaroxaban–with the intention of utilizing the change from baseline to nadir anti-fXa activity as a surrogate endpoint in support of an Accelerated Approval. Although, the mean % change from baseline in anti-fXa activity was 92% and 96% for apixaban and rivaroxaban, respectively, the durability of reversibility was short-lived. Portola also provided clinical data from 35 subjects with bleeds (intracranial bleeds [ICH] and gastrointestinal bleeds [GI]) from an ongoing single arm study, ANNEXA 4. However, the clinical review team considered this data to be insufficient to support the correlation of anti-fXa activity to hemostatic efficacy.

Additional challenges in review of the original submission included the lack of agreement on the confirmatory PMR study. Portola had intended that the ANNEXA 4 study would serve as the PMR confirmatory study; however, as the study was not controlled and as such, hemostatic outcomes would be difficult to interpret, Portola proposed a usual care cohort study to provide control data to support the evaluation of the hemostatic outcomes from the ANNEXA 4 study. However, an agreement on the primary endpoint and Statistical Analysis Plan could not be reached prior to the action on the submission.

In response to the CRL, the applicant provided clinical data from 185 subjects from the ANNEXA 4 study. Of the 106 efficacy evaluable subjects who received apixaban or rivaroxaban, the mean % change from baseline in anti-fXa activity was 92% and 87%, respectively. However, correlation between anti-fXa activity and hemostatic efficacy (defined as excellent/good) was difficult to discern because the great majority of responses to treatment were excellent or good, regardless of the reduction of anti-fXa activity from baseline. This raises concerns as to anti-fXa activity being able to serve as

a surrogate endpoint that is reasonably likely to predict clinical benefit. The uncertainties in the surrogate endpoint notwithstanding, the FDA clinical reviewer's safety assessment raised safety concerns with respect to thromboembolic events. In the 185 safety evaluable subjects, the risk of thrombo-embolic/ischemic events was close to 18%. This increased thrombosis risk may directly be tied to ANDEXXA's additional procoagulant activity via its binding to Tissue Factor Pathway Inhibitor (TFPI). In the context of a recent study from Majeed, et al. (Blood 130 (15), 1706-1712. 2017 Aug 23), the risk of thromboembolic events was ~4 % with standard of care, similar to other published literature (see Dr. George's clinical review for additional details). Therefore, this close to 18% rate of thromboembolic events is quite concerning.

Although anti-fXa activity levels changed considerably from baseline, uncertainties as to these changes correlating with hemostatic efficacy, and the risk of thromboembolism in the context of biologic plausibility given ANDEXXA's potential for procoagulant activity, a favorable determination of benefit/risk cannot be made.

Recommendations

Per Section 506(c) of the FD&C Act, FDA may grant accelerated approval to "a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit…."

In the context of a surrogate endpoint, although some uncertainty regarding anticipated clinical benefit is acceptable, the lack of correlation between anti-fXa activity and hemostasis, questions the adequacy of anti-fXa activity as a surrogate endpoint reasonably likely to predict clinical benefit, despite the considerable changes noted in anti-fXa activity from baseline. In addition to this uncertainty with respect to the surrogate endpoint, the risk of thrombosis, especially given the potential procoagulant activity of ANDEXXA, does not support a favorable benefit risk determination. I cannot recommend approval at this time. Discussions are underway with Portola on the design of a randomized controlled study that may be able to provide clinical data that can allow for a better assessment of the safety and efficacy of ANDEXXA for the proposed indication.