FILING MEETING SUMMARY

Application type and number:	BLA 125586/0
Product name:	Coagulation Factor Xa (Recombinant), Inactivated
Proposed indication:	Indicated for patients treated with a direct or indirect FXa inhibitor when reversal of anticoagulation is needed.
Applicant:	Portola Pharmaceuticals Inc.
Meeting date & time:	February 1, 2016, 4 pm – 5:30 pm, EST
Meeting Chair/Leader:	Mikhail Ovanesov, PhD
Meeting Recorder:	Thomas J. Maruna, MSc, MLS(ASCP), CPH

Background:
BLA 125586/0 was submitted as a rolling review. The initial modules received on November 6, 2015 included Nonclinical Module 2 (sections 2.4 and 2.6) and Module 4. The remaining modules, i.e., Module 1, Module 2, Module 3 and Module 5, were received on December 17, 2015, starting the review clock. The current action date for this BLA is August 17, 2016.

FDA has determined that an Accelerated Approval pathway is appropriate for a BLA for the reversal of anticoagulation with direct FXa inhibitors. FDA may decide to ask the applicant to name the specific direct FXa inhibitors for which the product would be indicated in patients with severe major bleeding. At this time, there are insufficient data to support an Accelerated Approval pathway for the reversal of anticoagulation with indirect FXa inhibitors, including enoxaparin due to limited or lack of sufficient data. In addition, there are insufficient data to support an indication for (b) (4) (b) (4) in patients receiving either direct or indirect FXa inhibitor anticoagulants.

The product received breakthrough therapy designation on November 22, 2013 under IND 15089. The product also received Orphan designation for the proposed indication of "reversing the anticoagulant effect of direct or indirect factor Xa inhibitors in patients experiencing a serious uncontrolled bleeding event or who require urgent (b) (4) (b) (4) on February 23, 2015. A proprietary name review was conducted under IND 15089; the proprietary name, ANDEXXA, was found to be acceptable. The applicant has been asked to submit a request for proprietary name review under BLA 125586/0.

This application will be reviewed under a priority review schedule and is subject to PDUFA-V requirements.

Table 1: FDA Attendees

Discipline	Name	Present at filing meeting? (Y or N)
Chair	Mikhail Ovanesov, PhD	Y
Regulatory Project Manager (RPM)	Thomas J. Maruna, MSc, MLS(ASCP)	Y
Office Director/Deputy	Jay Epstein, MD	N
Director, DHRR	Basil Golding, MD	Y
Acting Director, DHCR	Howard Chazin, MD, MBA	Y
Deputy Director, DHRR	Mahmood Farshid, PhD	Y
Deputy Director, DHCR	N/A	-
Clinical Reviewer	Lisa Faulcon, MD	Y
Clinical Team Lead	L. Ross Pierce, MD	Y
Clinical Branch Chief	Bindu George, MD	Y
Clinical Pharmacology Reviewer	Iftekhar Mahmood, PhD	Excused
Toxicology Reviewer	Yolanda Branch, PhD	Y
Supervisory Toxicologist	Anne M. Pilaro, PhD	Y
CMC - Immunogenicity Assays	Zuben Sauna, PhD	Excused
CMC - Structural Integrity	Wojciech Jankowski, PhD	Y
CMC - Stability Studies	Yideng Liang, PhD	Excused
CMC - Extractables & Leachables and sterile Water for Injection	Andrey Sarafanov, PhD	Excused
DMPQ Reviewer	Christine Harman, PhD	Excused
DMPQ Reviewer	Joan Johnson, PhD	Y
DMPQ Branch Chief	Ms. Carolyn Renshaw	Y
Statistical Reviewer	Chunrong Cheng, PhD	Y
Statistical Team Lead	Renee Rees, PhD	Y
Postmarketing Safety Epidemiological Reviewer	Faith Barash, MD	Y
OCBQ/APLB Reviewer	Kristine Khuc, PharmD	N
OCBQ/BIMO Reviewer	Ms. Haecin Chun	Y
OCBQ/BIMO Reviewer	Ms. Erin McDowell	Y
OCBQ/DBSQC	Ms. Karen Campbell	Y
OCBQ/DBSQC	Simleen Kaur, PhD	N
OCBQ/DBSQC	Lokesh Bhattacharyya, PhD	N
OCBQ/DBSQC	Ms. Cheryl Hulme	N
Acting Branch Chief, DHRR/LH	Timothy Lee, PhD	Y
OCBQ/DMPQ	Jay Eltermann	Y
RPMS Branch Chief	Iliana Valencia	Y

Filing Meeting Discussion:

- The review committee decided unanimously to file BLA 125516/0
  - The filing action date is February 16, 2016
- Per reviewers, are all parts in English or English translation.
- There are no pending issues concerning the quality of the electronic submission.
- This application is not affected by the Application Integrity Policy (AIP).
- A categorical exclusion for environmental assessment (EA) was requested.
- To date, all late components agreed to in the pre-submission meetings, CRMTS 9913 & 9914, have been received.
- The Mid-Cycle meeting is scheduled for March 24, 2016.
- The Late-Cycle meeting has not been scheduled.

Advisory Committee

The review committee recommends presenting this application to the Blood Products Advisory Committee. The Clinical Review Branch will seek concurrence from the Office management concerning this decision.

Clinical

The application may be filed.

However, the clinical review team identified several potential review issues:

1. The ongoing confirmatory study in subjects with acute major bleeding, ANNEXA-4, is not designed as an "adequate and well-controlled" postmarketing confirmatory trial. FDA has previously advised Portola, and continues to maintain, that an adequately controlled trial is necessary to allow for interpretation of data. Per 21 CFR Part 601, subpart E: "When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence." The guidance on Expedited Programs [1]states that agreement on the design and conduct of the postmarketing confirmatory trials should occur prior to approval. Failure to resolve these outstanding design and control issues with due diligence may adversely impact the regulatory decision taken on this application.
2. There are insufficient data to support the (b) (4) portion of the proposed indication; there are no data for use of the product (b) (4) and the duration of reduction in FXa inhibition (the proposed surrogate endpoint), is short-lived and rebounds rapidly after cessation of the 2 hour product infusion that follows bolus administration. This is of particular concern for (b) (4). In addition, the applicant has not established that reduction in FXa inhibitory activity is reasonably likely to

[1] The Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, Section VII. D. 2

predict clinical benefit in (b) (4) in patients anticoagulated with direct or indirect FXa inhibitors. The applicant had not submitted graphs or tables of (b) (4) incidence/risk as a function of FXa inhibitory activity for any anticoagulant, as they had submitted for bleeding, to establish that the surrogate endpoint would be reasonably predictive of a clinical benefit in (b) (4) (b) (4) The short duration of action, again only suggested by the proposed surrogate endpoint, is also a review issue for the reversal indications in bleeding patients.

3. There is insufficient evidence to support the application of this product for the reversal of coagulopathy with indirect FXa inhibitors, which may be ineligible for the Accelerated Approval pathway. The applicant has not provided an adequate rationale concerning the product's ability to fill an unmet medical need for reversal of indirect FXa inhibitors, particularly enoxaparin, given the availability of protamine. In addition, enoxaparin has a dual mechanism of action not limited to FXa inhibition. Thus, it has not been established that the surrogate endpoint of reduction in FXa inhibitory activity is reasonably like to predict a clinical benefit, a requirement that must be met to utilize the accelerated approval pathway for this indication.

These concerns will be addressed in the filing letter to the applicant. The option of requesting the applicant to withdraw the request for the indications for reversal of indirect FXa inhibitor anticoagulation and for periperative/periprocedural management prior to the filing date was discussed.

Bioresearch Monitoring (BIMO)
The application may be filed.

The BIMO reviewer noted that two clinical sites of healthy volunteer studies in Los Angeles will be inspected. No inspections are planned at this time for the ongoing phase 3-4 confirmatory study in bleeding patients anticoagulated with direct or indirect FXa inhibitors.

Clinical Pharmacology
The application may be filed.

No substantive deficiencies were noted.

Pharmacology/Toxicology
The application may be filed.

No substantive deficiencies were noted.

Chemistry, Manufacturing and Controls (CMC)

The application may be filed.

No substantive deficiencies were noted.

The CMC reviewer noted that additional information concerning the Drug Substance (DS) and Drug Product (DP) final validation for manufacturing " (b) (4) is anticipated to be submitted closer to the action due date as previously agreed upon.

OCBQ/DMPQ
The application may be filed.

No substantive deficiencies were noted.

A pre-license inspection will be scheduled for the DS site only; the DP contract manufacturing site owned by (b) (4) was recently inspected and will be waived. Portola has proposed April 11, 2016. CBER will request a detailed manufacturing schedule from the applicant before confirming the inspection date.

OCBQ/DBSQC
The application may be filed.

No substantive deficiencies were noted.

The product will likely be exempt from Lot Release Testing.

The DBSQC reviewer will schedule an internal meeting in the near future to discuss in-support testing.

Statistical
The application may be filed.

No substantive deficiencies were noted.

Postmarketing Safety Epidemiological
The application may be filed.

A Pharmacovigilance (risk management) Plan was requested on January 25, 2016 via Information Request; a response was originally due on January 29, 2016, however, the applicant requested an extension until February 3, 2016, which was granted.

OCBQ/APLB
The application may be filed.

A proprietary name review was conducted under IND 15089; the proprietary name, ANDEXXA, was found to be acceptable. The applicant has been asked to submit a request for proprietary name review under BLA 125586/0. The request was received on February 1, 2016 under BLA 125586/0.

Post Meeting Notes:

- Office management concurred on February 2, 2016 that the application should proceed to the BPAC. The meeting has been tentatively scheduled for late June 2016.
- On February 3, 2016 CBER contacted the applicant to request a detailed production schedule (with daily activities or process steps and associated room/line #, if possible) for both month April and May to determine a final inspection date.

END