

Mid-Cycle Communication Telecon

Application type and number: BLA 125586

Product name: Coagulation Factor Xa (Recombinant), Inactivated

Proposed Indication: For patients treated with a direct or indirect Factor Xa inhibitor when reversal of anticoagulation is needed in situations such as:

- In life-threatening or uncontrolled bleeding
- (b) (4)

Applicant: Portola Pharmaceuticals Inc.

Meeting date & time: April 8, 2016, 12:30 pm – 1:30 pm, ET

Committee Chair: Mikhail Ovanesov, PhD

RPM: Thomas J. Maruna, MSc, MLS(ASCP), CPH

FDA Attendees:

Howard Chazin, MD, MBA, Acting Director, CBER/OBRR/DHCR
John Eltermann, Director, CBER/OCBQ/DMPQ
Bindu George, MD, Branch Chief, CBER/OBRR/DHCR/CRB
Christine Harman, PhD, CMC Facility Reviewer, CBER/OCBQ/DMPQ/BI
Thomas J. Maruna, MSc, MLS(ASCP), CPH, Regulatory Project Manager, CBER/OBRR/IO
Mikhail Ovanesov, PhD, Chair/CMC Product Reviewer, CBER/OBRR/DHRR/LH
Carolyn Renshaw, Branch Chief, CBER/OCBQ/DMPQ/BI
Christopher Sese, Independent Contractor, CDER/OSP

Portola Attendees:

Bill Lis, CEO
John Curnutte, MD, PhD, Executive VP Research and Development
Alex Gold, Senior VP, Clinical Development
Brian Wiens, PhD, Senior Director, Statistics
Michele Bronson, PhD, VP Program Management
Janice Castillo, Senior VP, Regulatory Affairs and Quality Assurance
Stuart Connolly, MD, PHRI, Clinical Consultant and Lead PI of ANNEXA-4 Study

Discussion:

1. Introductions

- a. Acknowledgment of the unmet medical need
- b. Acknowledgment of the ongoing collaborative efforts to identify an adequately designed confirmatory study

2. Status of Review

Our review is ongoing at this time. We continue to review recently received information requests, and several pending IR requests. We continue to develop the features of the confirmatory clinical trial and formalizing our response to the recently received protocol synopsis.

3. Discipline Review Concerns

- a. Chemistry, Manufacturing and Controls
 - i. We have concern for immunotoxicity and potential for ANDEXXA to elicit binding and/or neutralizing antibodies to endogenous Factor X or Factor Xa. We request that you continue to develop your assays to address this potentially significant safety concern.
 - ii. Given that clinical data showed that ANDEXXA reacts differently with the various Factor Xa inhibitors, we ask you to expand the (b) (4) (b) (4) study to include all 4 inhibitors - (b) (4) rivaroxaban, edoxaban and apixaban and representative (b) (4) batches from (b) (4) (b) (4) batches) and (b) (4) batches).
 - iii. We note that your proposed release specifications of (b) (4) DP (DP) for identity and excipients are deficient. ANDEXXA is a mutated coagulation factor product manufactured at large scale, formulated at high concentration and administered at high doses. We need thorough testing of the (b) (4) DP to assure consistency of the manufacturing process and product quality.
 - iv. Similarly, we ask that you enhance the characterization of (b) (4) (b) (4) of andexanet alfa, specifically (b) (4) We need an explanation for the low ratio of (b) (4) of the (b) (4).
 - v. We note that your definition of potency for ANDEXXA “percent of a reference standard” is not suitable for the control of the unitage because there is no assurance of the stability of the reference standard. We ask you to develop a potency unit for ANDEXXA that is traceable to the international reference preparations distributed by the (b) (4) (b) (4) for example (b) (4) (b) (4)

(b) (4)
(b) (4) For example, the unit can be defined as follows: (b) (4)
(b) (4)
(b) (4).”

- vi. Your March 3, 2016, response to our February 17, 2016, request to assess the interference of anti-Factor Xa inhibitory antibody on the pharmacodynamics, pharmacokinetics, and immunogenicity assays is not acceptable. We have sent you a detailed explanation of the deficiency and what you need to do to address it.
- vii. Regarding the (b) (4) thrombin generation assays described in your March 3, 2016, amendment (the original Portola’s method and the currently used commercially available CAT method) used in phase 1, phase 2 and phase 3/4 clinical trials, your justification for assay comparability presented in the March 3, 2016, response is not acceptable. We have sent you a detailed explanation of the deficiency and what you need to do to address it.
- viii. You did not provide sufficient stability data to support the proposed shelf-life of (b) (4) DP manufactured using (b) (4) . Although real-time stability data demonstrated no negative trends, the results from the accelerated stability studies suggest product degradation. We will re-assess the proposed shelf-life when Portola submits additional stability data on Day 120, 16 April 2016.
- ix. The comparability protocols for the proposed manufacturing changes are deficient. You need to provide clear and specific information for the manufacturing changes that should include, but not be limited to, the rationale for the changes, knowledge and understanding of the process the changes are involved in, supporting information, comparability study design and protocol, test methods, justification and validation protocol for the quality attributes to be tested, test methods and acceptance criteria, and data analysis strategy including statistic assessment. Please note that deficiencies in the comparability protocol, if not addressed adequately, will negatively affect the outcome of the BLA review.
- x. We have also identified several less significant deficiencies regarding the validation of the manufacturing process and analytical methods, which we will convey to you via Information Requests. We will probably have additional questions and comments for you after we review the information on process development and validation, which should arrive on April 16, 2016; and the pre-license inspection on April 18-22, 2016.
- xi. The sensitivity of the Container Closure Integrity Testing (CCIT) performed for the primary container is not adequate. Please note that the positive control, in which the stopper was (b) (4) does not adequately simulate a critical leak defect. To support the sensitivity, we recommend that the defect diameter be as small as reasonably possible.

These questions have been communicated to Portola in an IR on April 6, 2016. Portola inquired about a possibility for a teleconference to discuss this IR. Product reviewers agreed to meet with Portola on the basis of reviewers' and Portola's availability.

b. Clinical

- i. We have concerns for insufficient evidence to support the following indications. We have conveyed two of these at the time of filing of the application:

- 1) (b) (4) – there are no data to review to support this indication.
- 2) Enoxaparin and other indirect Factor Xa inhibitors – No healthy volunteers received the proposed bolus followed by an infusion of ANDEXXA, so therefore there is not enough data to support this indication.

After review of the data submitted in the BLA we have also determined that:

- 3) No healthy volunteer subjects were treated with the high dose bolus plus infusion in the phase 3 study of apixaban, therefore there is insufficient data to support this dose.
 - 4) No healthy volunteer subjects received the low dose bolus with the infusion in the phase 2 and 3 studies of rivaroxaban.
 - 5) The observed increases in thrombin generation observed in the healthy volunteer studies suggest that ANDEXXA is a partial agonist with FXa activity. We believe that data are needed to address a potential safety concern of thrombotic risk if infusion of ANDEXXA is continued past the point of clearance of a FXa inhibitor.
- ii. We have concerns with the use of percent reduction in anti-FXa activity (at nadir) as a surrogate endpoint that is reasonably likely to predict for control of bleeding.
- 1) We noted that in the healthy volunteer subjects who received rivaroxaban, apixaban and edoxaban, the decline in anti-FXa activity persisted for only a short interval of time following the end of infusion. This decline was followed by an increase in anti-FXa activity level. In the absence of data to support the level of anti-FXa activity that correlates with a reduced risk of bleeding for each of three direct anticoagulants (rivaroxaban, apixaban and edoxaban), we are uncertain whether the increased levels in the anti-FXa activity shortly following the infusion predispose actively bleeding subjects to risk of continued bleeding. We are concerned that the duration of infusion of ANDEXXA is too short to assure for control of bleeding after treatment.

- 2) We note that in subjects in the healthy volunteer study of edoxaban that the anti-FXa levels following ADNEXXA treatment (high dose bolus + infusion) had higher nadir levels than those noted for subjects in the healthy volunteer studies of apixaban and rivaroxaban. In the absence of data correlating a threshold level of edoxaban with the risk of bleeding, we are uncertain that the demonstrated extent of reversal of edoxaban is sufficient to control bleeding and therefore the ADNEXXA dose given to reduce anti-FXa levels in subjects on edoxaban may not be sufficient. The clinical relevance of percent reduction of anti-FXa levels remains unknown in the absence of a known threshold for control of bleeding and there are no subjects in the ongoing phase 3b/4 study enrolled on edoxaban in which to make any assessments.
- iii. The phase 3b/4 clinical data provided on 35 serious bleeding subjects do not provide sufficient evidence to support the use of the surrogate:
 - 1) The data for apixaban and rivaroxaban are difficult to interpret given a wide range of observed percent reduction in anti-FXa activity.
 - 2) There are no subjects enrolled who are anticoagulated with edoxaban.
 - 3) The submitted data are insufficient to permit independent evaluation of the validity of the final adjudicated outcomes (e.g., results of follow-up CT results are not provided in most cases of ICH).
- iv. Agreement with FDA has yet to be reached on the design of the Prospective Study of the Usual Care Management of patients on Factor Xa inhibitor therapy that is intended to serve as a control for the ongoing Phase 3b/4 study. We acknowledge receipt of the protocol synopsis and plan to provide our preliminary comments to you today, April 8, 2016, in preparation for a teleconference with you on Monday, April 11, 2016.

4. Information regarding major safety concerns

We are continuing our review of safety data.

5. BPAC Update

FDA realizes the importance of this product and the unmet medical need in the target population for treatment with ADNEXXA. Because of the complexity of the scientific issues of FDA concern relevant to the BLA, we wish to obtain external scientific advice from experts in this field. Consequently, we continue to develop our materials for a Blood Products Advisory Committee (BPAC) meeting to be held on June 20-21, 2016, and will communicate with you about your opportunity to provide materials and make presentations to the BPAC.

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