



Our Reference: BL 125582/0

CSL Behring Recombinant Facility AG
Attention: Mr. Kevin D White
February 9, 2016
Sent by email

Dear Mr. White:

We are reviewing your December 5, 2014 biologics license application (BLA) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein. We are providing the following comments and request for additional information to continue our review:

1. Regarding FDA request #1, FDA has determined that the submitted data support the proposed 14-day regimen for the subset of patients ≥ 12 years who are first adequately maintained on a 7-day regimen. Based on these data, a postmarketing commitment study to address concerns of decreased FIX trough levels after repeat dosing is not needed at this time.
2. In response to FDA Request #2b, you state that "Trough FIX activity levels, and efficacy (median AsBR = 0) of IDELVION support the dose range. Therefore both clinical pharmacology and general experience with the product is appropriate for 35-50 IU/kg to control spontaneous bleeds, which is the primary target for prophylaxis therapy under the current WFH treatment guidelines." However, the proposed pediatric dose of 35-50 IU/kg every 7 days was not adequate for 37% (10/27) of the subjects treated in trial 3002; 42% (5/12) of subjects < 6 years and 33% (5/15) of subjects ≥ 6 to 12 years required doses of greater than 50 IU/kg for weekly prophylaxis. Furthermore, according to Listing 16.2.5.3, most of the subjects < 6 years of age who were treated with doses of 35-40 IU/kg required a dose adjustment up to 50 IU/kg. Based on these data, a higher dose range may be needed. Please propose a new dosing regimen for children < 12 years that take into account these findings. You may consider proposing different dosing recommendations for each pediatric age group (< 6 years vs. ≥ 6 years).

Please note that in our response to you we have provided our rationale for the revised recommendations. To expedite the process of the review of additional information requested (item 2) please provide supporting rationale and appropriate summary tables based on clinical data and PK information to justify the revised dose (upper and lower limits of the range) proposed.

2. Section 5.5, Monitoring Laboratory Tests, of the Prescribing Information (PI) warns prescribers that Factor IX in vitro results may vary with the type of activated partial

thromboplastin time reagent used in the assay system. Because overestimation of FIX trough levels is possible and could result in inadequate dosing and increased bleeding events, FDA believes that this warning should be accompanied by communications to health care providers in the form of a Dear Healthcare Provider (DHCP) letter. Please provide a letter of commitment to sending a DHCP and outline:

- a. the issue to be addressed and the action required,
- b. the appropriate audience; and
- c. a timeframe and means of communication of the letter

Please refer to FDA guidance Dear Health Care Provider Letters: Improving Communication of Important Safety Information for recommendations on the content and format of DHCP letters:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM233769.pdf>

In addition, we recommend that you maintain an Information Center with a dedicated phone line that would be available to clinical laboratories to provide guidance with regard to suitability of assays that would be optimal to detect Factor IX levels with the use of your product.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response to this information request as an amendment to this file by February 12, 2016 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is March 5, 2016.

Please send an acknowledgement for receipt of this request.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

Thank you.

If you have any questions, please contact me at (240) 402-8443.

Sincerely,

Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/PPMS

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

Thank you.