



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125582/0

CSL Behring Recombinant Facility AG
Attention: Mr. Kevin D. White
CSL Behring
1020 First Avenue, P.O. Box 61501
King of Prussia, PA 19406-0901

Dear Mr. White:

Please refer to your biologics license application (BLA) submitted under the Public Health Service Act for Coagulation Factor IX (Recombinant), Albumin Fusion Protein [IDELVION]. The proposed indications are in children and adults with hemophilia B (congenital Factor IX deficiency) for: (1) On-demand treatment and control of bleeding episodes, (2) Perioperative management of bleeding, and (3) Routine prophylaxis to reduce the frequency of bleeding episodes.

Attached are our briefing materials, including our agenda, for the Late-Cycle Meeting (LCM) scheduled for August 25, 2015.

If you have any questions, please contact Edward Thompson, Regulatory Project Manager, at (240) 402-8443.

Sincerely,

Basil Golding, MD
Director
Division of Hematology Research and Review
Office of Blood Research and Review
Center for Biologics Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Materials

Late-Cycle Meeting Materials

Meeting Date and Time: August 25, 2015, 1:30 to 3:30 p.m., EDT

Meeting Location: Building 2, Room 2047 W
Federal Research Center
10903 New Hampshire Avenue
Silver Spring, MD 20993

Application Number: BL 125582/0

Product Name: Coagulation Factor IX (Recombinant), Albumin Fusion Protein [IDELVION]

Indications: In children and adults with hemophilia B (congenital Factor IX deficiency) for: (1) On-demand treatment and control of bleeding episodes, (2) Perioperative management of bleeding, and (3) Routine prophylaxis to reduce the frequency of bleeding episodes.

Applicant Name: CSL Behring Recombinant Facility AG (CSL)

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues and major deficiencies that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authorities, division directors, and application chair. Therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that could be submitted that may be needed to address the identified issues. We may also discuss whether the submission of such information would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle.

If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

1. DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

2. SUBSTANTIVE ISSUES TO BE DISCUSSED AT THE LATE-CYCLE MEETING

Chemistry, Manufacturing and Controls

a. Deficiencies in method validation

Review of method validation identified multiple deficiencies that could be traced back to deficiencies in the standard operating procedures (SOPs) identified during the facility inspection. CSL proposed to submit four amendments to address these deficiencies in method validation on July 15, August 15, September 15 and September 30. These deficiencies are critical in that they have negative impact on several CMC aspects, including process validation, manufacturing controls, process development, and comparability studies.

b. Insufficient control of the albumin moiety

The proposed release assays are inadequate to control the quality of the albumin moiety. Specifically, analysis of Albumin by (b) (4) is not validated as a quantitative assay. FDA acknowledges CSL's 23 June 2015 proposal to re-validate the analysis of Albumin by (b) (4) and evaluate other approaches to develop release assays for the Albumin moiety. The data analysis of albumin (b) (4) is not valid and needs to be redone. This information was communicated in an information request on 23 July 2015.

c. Deficiencies in justifications of specifications

In general, the specifications are not adequately justified, for example, the acceptance criteria for the specifications for Albumin by (b) (4) (b) (4) (b) (4) are not adequate to control product quality. The validations of many analytical methods are also deficient. These issues were communicated to CSL in information requests (IRs) on 12 June and 20 July 2015, and CSL has committed to submit the responses by 30 September 2015. The adequacy of the information to fully resolve these deficiencies will be determined upon review of CSL's responses, and additional information may be required during the review.

d. Deficiencies in comparability studies

Inconsistencies in the comparability studies of product lots manufactured at pilot and commercial scales in (b) (4) Marburg, Germany, were identified. Specifically, the results from (b) (4) indicate qualitative differences between the lots produced at the (b) (4) and those produced at the (b) (4). These issues were communicated to CSL in an IR on 23 July 2015.

e. Deficiencies in extractable and leachable studies

High amounts of the following impurities were found in the product: (b) (4)

For these compounds, assessments of the risks to patients should be provided. These issues were communicated to CSL in an IR on 17 July 2015.

Facility inspection

During the inspection of the CSL facilities in Marburg, Germany on 28 May – 5 June 2015, FDA reviewers identified several deficiencies in the manufacture of IDELVION, which were detailed in a Form FDA 483 issued to CSL on 5 June 2015. CSL provided responses to these inspectional observations on 26 June 2015. Final recommendation is pending a complete review of these responses. If we identify any issues related to the facility inspection, we will bring them up during the LCM.

Clinical

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70

During the review four subjects were noted to have proteinuria. FDA requests discussing CSL's plans if any, to further evaluate the association between the proteinuria and r-FIX

Non-clinical pharmacology / toxicology

There are no substantive review issues at this time.

Clinical pharmacology

There are no substantive review issues at this time.

Biostatistics

There are no substantive review issues at this time.

Bioresearch Monitoring

There are no substantive review issues at this time.

Pharmacovigilance

There are no substantive review issues at this time.

Labeling

In a request dated 16 July 2015, FDA requested that CSL conform to the Agency's efforts to harmonize labeling for blood coagulation factors, which removed the word "prevent" to avoid confusion between the "on demand treatment and control" indication and the "routine prophylaxis" indication. CSL responded with a proposal to retain the word "prevent" in the on-demand and prophylaxis indications. We continue to recommend that CSL change the label as requested on 16 July, 2015.

Amendments

We acknowledge the receipt of your amendments listed below:

- a. 29 July 2015 amendment #25 (response to FDA IR dated 15 July 2015 regarding residual moisture (b) (4)).
- b. 30 July 2015 amendment #26 (response to FDA IR dated 16 July 2015 regarding the language for indication and usage claims).
- c. 31 July 2015 amendment #27 (**partial** response to FDA IR dated 17 July 2015 regarding method revalidation studies).
- d. 31 July 2015 amendment #28 (response to FDA IR dated 17 July 2015 regarding leachables).
- e. 7 August 2015 amendment #29 (response to FDA IR dated 23 July 2015 regarding characterization of post translational modifications).
- f. 10 August 2015 amendment #30 (response to FDA IR dated 20 July 2015 regarding method validation and specifications and post-approval stability protocol and commitment).
- g. 10 August 2015 amendment #31 (response to FDA IR dated 13 July 2015 regarding proteinuria).

These amendments are under active review, and additional information may be requested should the need arises.

Outstanding Information Requests

The pending IRs with their status are listed below:

- a. An IR for the controls of critical steps and intermediates; quality control assays for the drug substance and drug product, their validation reports and release specifications was sent on 12 June 2015 with responses due by 23 July 2015. Partial responses were submitted on 23 June and 15 July 2015; complete responses are still pending.
- b. An additional IR regarding quality control assays for the drug substance and drug product and their validation reports was sent on 17 July 2015. Partial responses were submitted on 31 July 2015; complete responses are still pending.

3. ADVISORY COMMITTEE MEETING

Presentation of the BLA at the *Blood Products Advisory Committee* is not planned.

4. REMS OR OTHER RISK MANAGEMENT ACTIONS

FDA determined that additional information is needed to further evaluate the possible association between proteinuria and rIX-FP and requested that CSL revise the extension study 3003 to include additional monitoring for proteinuria. CSL was advised that the revised extension study would be considered a postmarketing commitment study. CSL's response to obtain follow-up data for three out of the four subjects who developed proteinuria during the pivotal trial, instead of revising the extension study, is under review.

End

Drafted by Edward Thompson on 7/17/15
Revised by Mikhail Ovanesov on 8/10/15
Revised by Tim Lee on 8/10/15
Revised by Bindu George on 8/11/15
Revised by Wayne Hicks on 8/11/15
Revised by Paul Mintz on 8/11/15
Reviewed by Basil Golding on 8/11/15
Revised by Trevor Pendley on 8/12/15

Template number: T 910.11: Late-cycle Meeting Summary

Template effective date:

Template POC: Linda Dixon