

Late Cycle meeting, April 3, 2014 - Eloctate

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Our STN: BL 125487/0

LATE CYCLE MEETING BACKGROUND PACKAGE

Biogen Idec, Inc.
Attention: Nadine D. Cohen, PhD
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Antihemophilic Factor (Recombinant), Fc Fusion Protein, ELOCTATE®.

We also refer to the Late Cycle meeting (LCM) scheduled for April 3, 2014. Attached is our background package, to include a review status update and an agenda for this meeting.

If you have any questions, please contact Leigh Pracht at (301)827-6116.

Sincerely,

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

ENCLOSURE:

Late Cycle Meeting Background Package

LATE CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Thursday, April 3, 2014; 1:30 - 3:00 PM

Meeting Location: Woodmont Office Complex I

Room 200S

1401 Rockville Pike

Rockville, MD 20852

Application Number: STN BL 125487/0

Product Name: Antihemophilic Factor (Recombinant), Fc Fusion Protein, ELOCTATE®

Indication: Control and prevention, routine prophylaxis, and perioperative management (surgical prophylaxis) of bleeding episodes in adults and children (≥ 12 yrs.) with Hemophilia A

Applicant Name: Biogen Idec, Inc.

INTRODUCTION

The purpose of a Late Cycle meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. Final review of the application has not been completed by the signatory authority, division director, or chairperson; 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 needed to address identified issues. 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 the new information at this meeting.

BACKGROUND

The FDA received the original biologics license application (BLA), STN BL 125487/0, from Biogen Idec, Inc. on March 7, 2013, to request licensure for Antihemophilic Factor (Recombinant), Fc Fusion Protein. The BLA was filed on April 28, 2013. Amendment 27, received on November 15, 2013 was designated as a major amendment; thereby, extending the review clock by 3 months. The proposed proprietary name, ELOCTATE®, was found acceptable on March 10, 2014. The action due date is June 7, 2014. The final drug product is manufactured as a lyophilized powder to be reconstituted with b(4) NaCl diluent provided with the product. The product is available at the following nominal dosage strengths expressed as international units (IU) per vial: 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU or 3000 IU. The proposed indications are:

- Control and prevention of bleeding episodes in adults and children (≥ 12 yr.) with Hemophilia A
- Routine prophylaxis to prevent or reduce the frequency of bleeding in adults and children (≥ 12 yr.)
- Perioperative management (surgical prophylaxis) in adults and children (≥ 12 yr.)

OVERVIEW OF DISCIPLINE REVIEWS AND PENDING ISSUES TO DATE

The current substantive review issues are as follows:

CMC/PRODUCT:

Please respond to the following deficiencies.

1. Your response in amendment 30 to item 18b from the September 11, 2013 information request was inadequate. Please revise the drug substance release specification for ----b(4)-----.
2. Your response in amendment 30 to item 19 from the September 11, 2013 information request was inadequate. Please align in-process specifications (IPS) for microbial control with those listed in Table CMC-1.

[b(4)]

3. Process validation reports submitted to amendment 37 indicated that established process hold time limits far exceeded manufacturing experience for the validated process. Please align process hold time limits during drug product manufacture with conformance lot manufacturing experience.
4. --b(4)----- for an out-of specification (OOS) result for Factor VIII potency, associated with process validation report, --b(4)----- revealed the practice of averaging an OOS result with a result meeting specification to generate a reportable result within specification. Please be advised that this practice is unacceptable under any circumstances.

CMC/FACILITY, EQUIPMENT:

5. During empty chamber thermal mapping of the lyophilizer, the ----b(4)----- located on the top shelf, rear corner positions failed to meet the acceptance criteria of ---b(4)-----) in all three runs performed. We have concerns that operation of the lyophilizer is not well controlled during the initial portion of the lyophilization cycle and may therefore not be able to provide temperature uniformity throughout the chamber. Please comment.
6. Please note that we are waiting for the re-qualification report for container closure integrity testing of the diluent syringe as committed in amendment 25.
7. Please note that the Final Rule for 21 CFR Part 4 – Regulation of Combination Products became effective July 22, 2013. The pre-filled diluent syringe is considered a combination product [21 CFR 3.2(e)]. It appears that you have chosen to demonstrate compliance with the drug CGMPs. Please ensure you have complied with the following provisions of the Quality System (QS) regulation for the pre-filled diluent syringe:

- a) 21 CFR § 820.20. Management responsibility
- b) 21 CFR § 820.30. Design controls
- c) 21 CFR § 820.50. Purchasing controls
- d) 21 CFR § 820.100. Corrective and preventive action

CLINICAL:

There are no substantive review issues at this time.

CLINICAL PHARMACOLOGY:

There are no substantive review issues at this time.

NON-CLINICAL PHARMACOLOGY/TOXICOLOGY:

There are no substantive review issues at this time.

BIOSTATISTICAL:

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

HUMAN FACTORS:

There are no substantive review issues at this time.

In-support Testing:

There are no substantive review issues at this time.

LABELING:

Recommendations for the Prescribing Information and the vial and carton labels will be provided as part of the labeling review.

ADVISORY COMMITTEE MEETING:

Presentation of STN BL 125487/0 to the Blood Products Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS:

No issues were identified that would require a Risk Evaluation Mitigation Strategy (REMS) or a Post-marketing Requirement (PMR) study. The following studies are considered post-marketing commitment studies:

- Pediatric study 8HA02PED, *An Open-Label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein, BIIB031, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A*
- Safety extension study 8HA01EXT, *An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIII-Fc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia A*
- Future study to evaluate safety and efficacy of ELOCTATE® in previously untreated patients

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/SL)
 - Welcome, Introductions, Ground rules, Objectives of the Meeting
2. Discussion of Substantive Review Issue(s) – 50 minutes
 - a. Overview of pending information requests, any clarifications, and current status of responses (whether any delay of responses is anticipated)
 - b. FDA comments on Biogen's responses to information requests
3. Labeling Discussion – 15 minutes
 - a. Any labeling issues for discussion
 - b. Questions from Biogen
4. Wrap up and Action Items – 10 minutes
 - a. Summary of discussion points
 - b. Questions and comments from Biogen