

Late Cycle Meeting Background Package, July 11, 2013 - Novoeight

DEPARTMENT OF HEALTH & HUMAN
SERVICES

Public Health Service

Food and
Drug Administration

1401 Rockville Pike

Rockville, MD 20852-1448

BLA 125466/0
MEETING BACKGROUND PACKAGE
Novo Nordisk Inc.
Attention: Mr. Robert B. Clark
P.O. Box 846
Plainsboro, NJ 08536

LATE CYCLE

Dear Mr. Clark:

Please refer to your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act for Antihemophilic Factor (Recombinant) [Novoeight], Lyophilized Powder for Solution for Intravenous Injection (250, 500, 1000, 1500, 2000, and 3000 IU/vial).

We also refer to the Late-Cycle meeting (LCM) scheduled for July 11, 2013. 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, MD

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, July 11, 2013; 1 p.m. - 2:30 p.m. EDT

Meeting Location: Woodmont Office Complex I
Room 200S
1401 Rockville Pike
Rockville, MD 20852

Application Number: STN 125466/0

Product Name: Antihemophilic Factor (Recombinant) [Novoeight]

Indication: Control and prevention, perioperative management, and routine prophylaxis of bleeding episodes in adults, adolescents and children with hemophilia A

Applicant Name: Novo Nordisk 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. The application has not yet been fully reviewed by the signatory authority, division director, or chairperson and 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 may be needed to address the identified issues, whether it will be reviewed by the Agency in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. If you submit any new information in

response to the issues identified in this background package before this LCM or the Advisory Committee meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

Substantive Issues to be discussed at the Late Cycle Meeting:

Chemistry, Manufacturing and Controls

1. Specifications

- Information Request regarding the specification parameters and acceptance criteria was sent on June 24, 2013. Specifically, the currently used parameter, -----
--(b)(4)----- the content of (b)(4) product-related impurities in Drug Substance and Drug Product. It should be re-defined to include -----(b)(4)-----
-----, and the acceptance criteria should be revised accordingly. To better control the manufacturing process and product quality, parameters *Specific Activity* and *Excipients* should be added to Drug Product specification. To better ensure product safety, the limits for *Bacterial Endotoxin* in Drug Product and for -----(b)(4)----- in Drug Substance should be revised based on the results of Batch Analyses and Stability data.
- The potency, i.e., Factor VIII activity, of the product should be defined by the One-Stage Clotting Assay and included in the Drug Product Specification.

2. Stability

- Available data appear to support the proposed shelf-life of Novoeight of 24 months when stored at 2 – 8 °C (36 – 48 °F), or 6 months at room temperature (up to 30 °C or 96 °F). The in-use stability of the reconstituted product needs to be addressed since an out-of-specification result for --- (b)(4) --- was reported for batch ----- (b)(4) -----, compared to Specification limit: (b)(4)) at the 4-hour time point when stored at 30 °C after reconstitution.
- An additional Information Request regarding Stability Protocol, Shelf-life Specifications, and the data to support the in-use stability was sent on June 24, 2013.
- PMC to include at least one commercial batch each of 500 IU, 1000 IU, and 1500 IU strengths in the stability study is requested in the June 24, 2013 Information Request.

3. Adventitious Agents Safety Evaluation

Viral clearance data were deemed incomplete. In response, Novo Nordisk performed validation studies for clearance of ----- (b)(4) -----, model virus for enveloped DNA viruses) which has a higher resistance to physico-chemical treatment. Two Study Reports – for turoctocog alfa and Anti-FVIII monoclonal antibody, were submitted to FDA on June 25, 2013, and are currently under review.

4. Analytical Methodology

In response to FDA request, Novo Nordisk performed a verification study for the Sterility test to address the new requirements of the final rule of 21 CFR 610.12 (with challenge microorganisms to be added ----- (b)(4) -----)

-----, instead of adding the bacteria to the -----(b)(4)-----). The *Verification Report* was received and is currently under review.

5. In-support Testing

During the determination of *Content and* ---(b)(4)---, strong interaction was observed between the -----(b)(4)-----, which affected the outcome of the assay. With limited number of -----(b)(4)-----, the (b)(4) failed to meet the System Suitability Criteria (----- (b)(4)----- of rFVIII reference material). This observation was communicated to the Applicant who acknowledged that -----(b)(4)----- should be continued until the System Suitability Criteria are met. However, multiple -----(b)(4)----- have also led to failures in meeting the criterion for -----(b)(4)-----.

The assay needs to be further validated to establish a number of -----(b)(4)----- required for the assay to meet the criteria for both System Suitability ----- (b)(4)----- of rFVIII reference material) and -----(b)(4)----- . Alternatively, different method(s) may need to be developed to measure these quality attributes.

6. Facilities and Equipment

CBER performed a Pre-License Inspection at Novo Nordisk A/S facility in --- (b)(4)--- Denmark during --(b)(4)---. A Form FDA 483 containing four observations was issued to the firm on -----(b)(4)-----. Novo Nordisk submitted the documentation of their corrective actions on June 21, 2013, which is currently under review. Responses to other Information Requests are either under review (Amendments 18, 21, 22) or forthcoming (June 18, 2013 Information Request).

Non-clinical pharmacology / toxicology

There are no substantive review issues at this time.

Clinical pharmacology

There are no substantive review issues at this time.

Clinical

There are no substantive review issues at this time.

Bioresearch Monitoring

BIMO inspections of two clinical sites in the United States were performed on March 11 – 25, 2013 and March 25 - April 1, 2013. Inspections of two sites in Brazil are pending.

Pharmacovigilance

There are no substantive review issues at this time.

Human Factors Study

There are no substantive review issues at this time.

Labeling

- APLB will perform a secondary review of the proprietary name within 90 days of the Action Due Date.
- Recommendations to the *Prescribing Information* and the vial and carton labels will be provided as part of the labeling review.

Advisory committee meeting

Presentation of the BLA at 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.

Protocols for the following Postmarketing Commitment (PMC) studies have been submitted:

1. Safety and Efficacy of turoctocog alfa (rFVIII) in Prevention and Treatment of Bleeds in Pediatric Previously Untreated Patients with Hemophilia A
2. A Multi-centre Non-interventional Study of Safety and Efficacy of turoctocog alfa (rFVIII) during Long-Term Treatment of Severe and Moderately Severe Haemophilia A (FVIII < 2%)

PMC/PMR

A milestone schedule for the two planned PMC studies (trials NN7008-3553 and NN7008-3809) listed in the Pharmacovigilance Plan (PVP) should be submitted.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/Chairs)
Welcome, Introductions, Ground rules, Objectives of the Meeting
2. Discussion of Substantive Review Issues – 50 minutes

- a. Discussion on the --(b)(4)-- assay for the determination of Content and -----
----- (b)(4) ----- Drug Product
- b. Discussion on the assignment of potency by one-stage clotting assay
- c. Overview of pending Information Requests (June 18 & 24, 2013), any clarifications (if needed), and current status of responses (whether any delay of responses is anticipated)
- d. FDA may have comments on Novo Nordisk's responses to Information Requests (Amendments # 17, 18, 21, 22, 23)
- e. FDA may have comments on Novo Nordisk's responses to Form FDA 483 (received on June 21, 2013)

3. Current Assessment of the need for REMS or other risk management actions

No issues were identified that would require a REMS.

4. Major Labeling Issues – 15 minutes

FDA Overview of identified labeling issues and proposed revisions to the labeling

5. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

A milestone schedule for the two planned PMC studies (trials NN7008-3553 and NN7008-3809) listed in the PVP should be submitted.

6. Potential questions from Novo Nordisk – 5 minutes

7. Wrap up and Action Items – 10 minutes

Page Last Updated: 11/15/2013

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