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To: STN: 125671/0

Through: Lokesh Bhattacharyya, Ph.D., Lab Chief, CBER/OCBQ/DBSQC
Maryna C. Eichelberger, Ph.D., Director, CBER/OCBQ/DBSQC

Subject: Review Memo for Biological License Application for Antihemophilic Factor (Recombinant), GlycoPEGylated, from Novo Nordisk

Recommendation: Approval

Summary of Review:

The BLA, STN125671, was submitted by Novo Nordisk to seek approval for its Antihemophilic Factor (Recombinant), GlycoPEGylated, also referred to as turoctocog alfa pegol. The drug product is a recombinant human factor VIII with a 40 kDa polyethylene glycol (PEG) moiety covalently attached to its O-linked glycan moiety; and it is intended to treat adults and children with hemophilia A.

In the memo, the analytical methods and their validations, as used for the release testing of both turoctocog alfa pegol drug substance and drug product, were reviewed. The methods include:

- 1) for the drug substance: (b) (4)
- 2) for the drug product: visual inspection, identity by (b) (4), Particulate matter, (b) (4), methionine (b) (4), Polysorbate 80 (b) (4), Calcium content by AAS (Atomic Absorption Spectroscopy), and sucrose (b) (4)

Based on the information provided in this submission, the above-mentioned assays have been validated adequately for their intended uses; approval is recommended for these assays.

Submitted Information reviewed:

- 125671
- 1.2 Cover letters
 - 0001 Cover Letter – 20180227 Original Application
 - 3.2.S. Drug Substance [Substance – Manufacturer]
 - 3.2.S. turoctocog alfa pegol-nnas
 - 3.2.S.4. Control of Drug Substance
 - 3.2.S.4.1. Specification
 - Specification for Turoctocog Alfa Pegol

- 3.2.S.4.2. Analytical Procedures
 - (b) (4) [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- 3.2.S.4.3. Validation of Analytical Procedures
 - (b) (4) [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- 3.2.S.4.5. Justification of Specification
 - Justification of Specification for Drug Substance
- 3.2.S. Drug Product [Product-Dosage Form-Manufacturer]
 - 3.2.P. turoctocog alfa pel – powder for sol for inj - nnas
 - 3.2.P.5. Control of Drug Product
 - 3.2.P.5.1. Specification
 - Specification for drug product
 - Control Strategy for Drug Substance
 - 3.2.P.5.2. Analytical Procedures
 - Analytical Development for drug product
 - Analytical Procedure (b) (4) – Appearance of Powder and Reconstitution Time
 - Analytical Procedure (b) (4) [REDACTED]
 - Analytical Procedure (b) (4) – Quantitative Determination of Polysorbate 80 (b) (4) [REDACTED]
 - Analytical Procedure (b) (4) – Quantitative Determination of Calcium (b) (4) [REDACTED]
 - Analytical Procedure (b) (4) – Quantitative Determination of Sucrose (b) (4) [REDACTED]
 - 3.2.P.5.3. Validation of Analytical Procedures
 - Verification of Repeatability for Drug Product Analytical Procedure
 - Validation of Analytical Procedure (b) (4) – Appearance of Powder and Reconstitution Time

- Verification of Compendial Procedure – (b) (4)
- Validation of Analytical Procedure (b) (4) – Quantitative Determination of Polysorbate 80 (b) (4)
- Validation of Analytical Procedure (b) (4) – Quantitative Determination of Calcium (b) (4)
- Validation of Analytical Procedure (b) (4) – Quantitative Determination of Sucrose (b) (4)
- 3.2.P.5.6. Justification of Specifications
 - Justification of Specification for Drug Product
 - Control Strategy for Drug Product

125671/0.14 (Amendment) – Recd 07/09/2018 – DATS#745399

- 1.11.1 Quality Information Amendment
 - Response to FDA Information Request dated June 01, 2018

125671/0.15 (Amendment) –Recd 07/20/2018-DATS#748894

- 1.11.1 Quality Information Amendment
 - Response to FDA Information Request dated July 6, 2018

125671/0.31 (Amendment) -Recd 10/05/2018-DATS#763483

- 1.11.1 Quality Information Amendment
 - Response to FDA CMC IR dated September 7, 2018

125671/0.51 (Amendment) -Recd 12/20/2018-DATS#780814483

- 1.11.1 Quality Information Amendment
 - Follow Up Response to FDA CMC Information Request dated September 7, 2018
- 3.2.S.4.2. Analytical Procedures
 - Analytical Procedure (b) (4)
- 3.2.S.4.3. Validation of Analytical Procedures
 - Verification of Repeatability for Drug Substance Analytical Procedure
 - Validation of Analytical Procedure (b) (4)

Review Narrative:

1. Drug Substance

(b) (4)

i) (b) (4)

. No description of this analytical method has been provided in the BLA, and an IR was submitted on June 1, 2018.

IR question

(b) (4)

however, no detailed description of the assay procedures was provided in the BLA. Please provide the SOP or a detailed description of the test.

Review of the response from the sponsor

In response, the sponsor provided a detailed description of the analytical method, including the execution of the method, material and equipment, and the generation of reportable result in Amendment, STN125671/0.14. The information provided is adequate, and the response to the IR is acceptable.

Method Validation

This method is a simple and well established method and was not validated. This is acceptable because of its simplicity. Based on the review of the information from both the original BLA and Amendment 14, this method is approvable for the lot release of (b) (4)

(b) (4)

Based on the information provided in the verification report, the method for the determination of (b) (4) has been verified for the release testing of (b) (4) turoctocog alfa pegol (b) (4) reconstituted drug product.

(b) (4)

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(b) (4)

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(b) (4)

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2nd IR questions

The following IR questions were submitted on September 7, 2018 to seek further information from the sponsor regarding the validation of the identity/purity by (b) (4) method for turoctocog alfa pegol (b) (4) drug product:

- 1) You validated the linearity of the method for the lower part of the range with the drug product, and the upper part of the range with the (b) (4), indicating that the linearity was validated for drug product and (b) (4) over the entire range of the assay. Please provide linearity results for the drug product (b) (4) over the respective applicable ranges of the assay.
- 2) Your acceptance criterion for linearity is (b) (4). This is not acceptable. The acceptance criteria of a quantitative assay should be quantitative. Please revise the

validation report to express the linearity validation criterion in terms of statistically meaningful parameters, such as R or R² values.

- 3) Different acceptance criteria for precision, including both repeatability and intermediate precision were listed for different components in (b) (4) as drug product. Please provide justifications.

Review of the response

In Amendment 31, Novo Nordisk provided responses to the three IRs, and the responses were reviewed in the following sections.

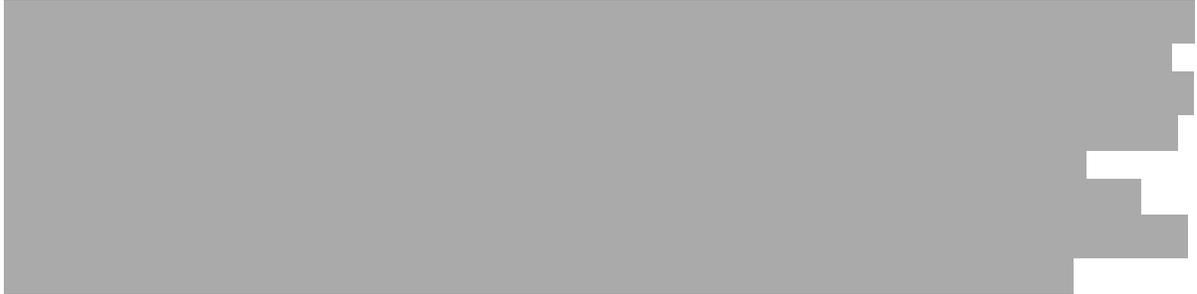
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(b) (4)

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(b) (4)



Based the validation data provided in the original BLA, as well as Amendment 14 and Amendment 31, all the validation characteristics have been evaluated, and all outstanding issued raised in the IRs related to the method have been adequately addressed, and this method has been validated for its intended purpose.

(b) (4)



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(b) (4)

(b) (4)

IR question

The following IR was submitted on September 7, 2018, to seek further information on this method:

In your submission, (b) (4) was validated partly as an identity and partly as a characterization method. However, this is a critical lot-release test with numerical release specification. Therefore, it is essential that you fully validate the method as a quantitative assay. Please provide additional validation data for accuracy, linearity, and range of the method. You indicated that you could not perform accuracy because of the difficulty to “establish a true or accepted value with respect to (b) (4)”. We suggest that you evaluate accuracy using an (b) (4) method such as (b) (4), or evaluated by (b) (4) studies using well characterized (b) (4) reference materials (many of which are available commercially).

Review of the response

In Amendment 31, Novo Nordisk acknowledged FDA’s request for the validation of the method as a quantitative assay, and asked to delay the response to the IR until December 19, 2018, to which FDA agreed. On December 20, Novo Nordisk submitted Amendment 51 as a complete response to the IR.

(b) (4)

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(b) (4)

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(b) (4)

2. Drug Product

The turoctocog alfa pegol drug product is a lyophilized powder that can be reconstituted in (b) (4) 0.9% NaCl solution for intravenous injection; the drug product is presented in five different strengths: 500 IU/vial, 1000 IU/vial, 1500 IU/vial, 2000 IU/vial, and 3000 IU/vail. The following analytical methods for the lot release testing of turoctocog alfa pegol drug product were reviewed in this memo: visual inspection, (b) (4) particulate matter, (b) (4), methionine (b) (4), Polysorbate 80 content (b) (4), Calcium content by (b) (4), and sucrose (b) (4)

i) Visual inspection

The appearance of the lyophilized drug product powder, the reconstitution time/solubility of the lyophilized drug product, and the appearance of reconstituted drug product were determined by visual inspection (b) (4)

Appearance of powder and reconstitution time). When examined against a black and a white back ground, the lyophilized drug product appears as a white to off-white powder; once reconstituted in (b) (4) 0.9% NaCl solution, the lyophilized powder dissolves within (b) (4)

Method

A brief description of analytical procedures for visual inspection was provided (b) (4), including information on the execution of the method, assay validity criteria, and the generation of reportable result. The provided information is adequate.

Method Validation

This method is a simple and well established method, and was not validated. This is acceptable because of its simplicity. This assay is approvable for the lot release of turoctocog alfa pegol drug product.

(b) (4)

(b) (4)

iv) Particulate matter

The particulate matter in turoctocog alfa pegol drug product is determined (b) (4)

The specification for the reconstituted drug product vial is: (b) (4)

This corresponds to an acceptable

(b) (4)

Method

As indicated in the verification report (b) (4)

the analytical method is in accordance with the method described in (b) (4). However, no description of this analytical method has been provided in the BLA, and an IR was submitted to seek further information.

Method Validation

The analytical method for the determination of particulate matter of turoctocog alfa pegol drug product, is in close accordance with the method, (b) (4) [redacted], therefore, a verification study was performed to verify the suitability of the method for the release testing of drug product (b) (4) [redacted]

(b) (4) [redacted]

the drug product test verified, the analytical method was verified for the lot release testing of reconstituted turoctocog alfa pegol drug product.

IR questions and the response from the sponsor

The following IR was submitted on July 6, 2018, to seek further information on this method:

In Section 3.2.5 of the submission, a (b) (4) method was used to determine the particulate matter of the drug product; however, no detailed description of the assay procedures was provided in the BLA. Please provide the SOP or a detailed description of the test by July 20, 2018.

Review of the response

In Amendment 15, the sponsor provided a detailed description of the analytical method, including the execution of the method, the preparation of the samples, assay validity criteria, and the generation of reportable result. The information provided is adequate, and the response to the IR is acceptable.

Base on the review of the information from both the original BLA and Amendment 0.15, this method is approvable for the lot release testing of turoctocog alfa pegol drug product.

(b) (4) [Redacted]

[Redacted]

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(b) (4)

(b) (4)

IR question

The following IR was submitted on September 7, 2018, to seek further information on this method:

In the validation report, your acceptance criterion for linearity is (b) (4). This is not acceptable. The acceptance criteria of a quantitative assay should be quantitative. Please provide statistically meaningful data associated with the validation of linearity, such as Coefficient of Correlation (R) or Coefficient of Determination (R²); and make adjustments to the current acceptance criterion of (b) (4) based on the statistical result.

(b) (4)

vii) Polysorbate 80 content (b) (4)

Method
(b) (4)

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(b) (4)



IR question

The following IR was submitted on September 7, 2018, to seek further information on this method:

The validation acceptance criterion for linearity (b) (4) is vague and not statistically meaningful, please use statistically meaningful data, such as Coefficient of Correlation (R) or Coefficient of Determination (R^2), as acceptance criterion, and provide justification.

(b) (4)



viii) Calcium content (b) (4)



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(b) (4)

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(b) (4)

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In the validation of analytical procedure (b) (4), the linearity of the method should be validated by (b) (4). Please provide the (b) (4) and statistically meaningful results, including R or R² values.

Review of the response

As response to the IR question, Novo Nordisk indicated in Amendment 31 that “the relationship between (b) (4)

(b) (4)

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ix) Sucrose by (b) (4)
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(b) (4)

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