CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761315Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 18, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761315
Product Name, Dosage Form, and Strength:	Alhemo (concizumab-mtci)[a] injection, 60 mg/1.5 mL (40 mg/mL); 150 mg/1.5 mL (100 mg/mL); 300 mg/3 mL (100 mg/mL)
Applicant Name:	Novo Nordisk Inc.
FDA Received Date:	December 2, 2024
TTT ID #:	2022-1204-2
DMEPA 2 Safety Evaluator:	Robbie Kattappuram, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The nonproprietary name, concizumab-mtci, was found conditionally acceptable on August 6, 2024.

1 PURPOSE OF MEMORANDUM

Novo Nordisk Inc. submitted revised container labels and carton labeling received on December 2, 2024 for Alhemo. The revised container labels and carton labeling were in response to the Applicant's transport simulation study supporting that shaking has no negative impact on product quality. As a result, in an Information Request from the Office of Pharmaceutical Quality (OPQ), the Applicant was instructed to revise the storage statement to "Do not freeze" on the container labels and carton labeling.[b] We reviewed the revised container labels and carton labeling for Alhemo (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

Novo Nordisk Inc. implemented all of OPQ's recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[b] Bailey, R. Information Request for "FDA Correspondence: BLA 761315 Carton and Container Labeling" Message to Larry Bai. Silver Spring (MD): FDA, CDER, OND, ORO, DROCHEN (US); 2024 Nov 22. EDR link: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807831da

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/s/

ROBBIE S KATTAPPURAM
12/18/2024 02:58:15 PM

NICOLE F IVERSON
12/19/2024 06:53:14 AM

Consult MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostics and Radiological Health (OIR)

Date: December 12, 2024

To: Courtney Hamilton, Regulatory Project Manager
Division of Regulatory Operations - Cardiology, Hematology, Endocrinology and Nephrology
Office of Regulatory Operations (ORO)
Office of New Drugs (OND)

From: Yan Cai, Ph.D., Reviewer
Hematology Branch (HEMB)
Division of Immunology and Hematology Devices (DIHD)
Office of In Vitro Diagnostics and Radiological Health (OIR/OHT7)
Office of Product Evaluation and Quality (OPEQ)
Center for Devices and Radiological Health (CDRH)

Through: Min Wu, Branch Chief
DIHD/OIR-OHT7/OPEQ/CDRH

Takeesha Taylor-Bell, Deputy Director
DIHD/OIR-OHT7/OPEQ/CDRH

Lea Carrington, Director
DIHD/OIR-OHT7/OPEQ/CDRH

Subject: Validation package for (b) (4) Concizumab ELISA
BLA 761315 Alhemo

Tracking Number: ICCR# 00999664

ICCR Received: 7/8/2024
ICCR Due: 11/11/2024

Background:

Novo Nordisk has developed a recombinant, humanized, anti-IgG4 isotype monoclonal antibody (mAb, concizumab) to treat patients with hemophilia A and hemophilia B. Concizumab is a humanized recombinant mAb of IgG4 isotype with a molecular weight of 149 kilodaltons. Concizumab is directed against the tissue factor pathway inhibitor (TFPI), which is involved in down-regulation of the initiation of the coagulation cascade. Concizumab prevents TFPI from binding to and blocking the active site of the coagulation factor Xa (FXa). This compensates for the limited FXa generation in the absence of a functional FIXa/FVIIIa complex in hemophilia. When the TFPI inhibitory activity is reduced, the FXa produced by the coagulation factor VIIa (FVIIa)/tissue factor (TF) complex will result in sufficient generation of thrombin to achieve hemostasis. Concizumab in a (b) (4) pen-injector is intended to be marketed as a combination product consisting of a drug constituent (concizumab drug product at concentrations of (b) (4) 40 mg/mL and 100 mg/mL) and a device constituent (a (b) (4) pen-injector).

Concizumab is being developed for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with:

- hemophilia A (congenital factor VIII deficiency)
- hemophilia B (congenital factor IX deficiency)
- hemophilia A (congenital factor VIII deficiency) with inhibitors to FVIII
- hemophilia B (congenital factor IX deficiency) with inhibitors to FIX

Intended Use/Indication for Use (IU/IFU) for the (b) (4) Concizumab ELISA in BLA 761315

For in vitro diagnostic use. Rx only.
The Concizumab ELISA (enzyme linked immunosorbent assay) at (b) (4) is intended for the quantitative measurement of concizumab concentration in human 3.2% citrated plasma samples from Haemophilia A and B patients (with and without inhibitors) after 4 weeks from the initiation of treatment with concizumab. The measurement of concizumab concentration is used for dose adjustment decision in accordance with the drug label.

Concizumab concentration (X) at clinical cutoff:	Adjusted concizumab dose:
X < 200 ng/ml	Dose adjustment to 0.25 mg/kg
200 ng/ml < X < 4000 ng/ml	No dose adjustment (dose kept at 0.20 mg/kg)
X > 4000 ng/ml	Dose adjustment to 0.15 mg/kg

figure 1: Dose Adjustment

The Concizumab-ELISA at (b) (4) is a manual assay intended for use by trained laboratory professionals and will be performed at (b) (4) (b) (4)

Study Description:

The Phase 3 clinical trials NN7415-4311 (Explorer 7) and NN7415-4307 (Explorer 8) were initiated in October and November 2019 respectively. Clinical trials were paused by Novo Nordisk and put on clinical hold by the FDA (IND 111691) in March 2020 due to 5 serious non-fatal thrombotic events that occurred in 3 patients in the Phase 3 trials. Following the clinical hold in

March 2020, a Type A meeting was held on June 16, 2020, to reach an agreement on the approach to address the clinical hold issues. A complete response was submitted on July 13, 2020, and the clinical hold was lifted by the FDA on August 11, 2020.

An investigational device exemption (IDE) application (b) (4), was submitted by Novo Nordisk to the CDRH on July 10, 2020 for the Concizumab-ELISA, to quantitate the concentration of Concizumab in citrated human plasma samples for use in the dose adjustment of Concizumab in clinical trials NN7415-4311 and NN7415-4307. The IDE was approved with conditions on August 12, 2020. A meeting (b) (4) was held on September 14, 2020 with CDRH to discuss and reach an agreement on the approaches to address the conditions. The IDE amendment was submitted on September 24, 2020 and the IDE was fully approved on October 22, 2020.

(b) (4)

Novo Nordisk submitted a BLA submission for routine prophylaxis in patients with HBwI and HAwI. The current status of the Concizumab clinical development program is that the primary analysis cut-off has been reached for the phase 3 trial 4311 (HAwI and HBwI patients).

Device Description:

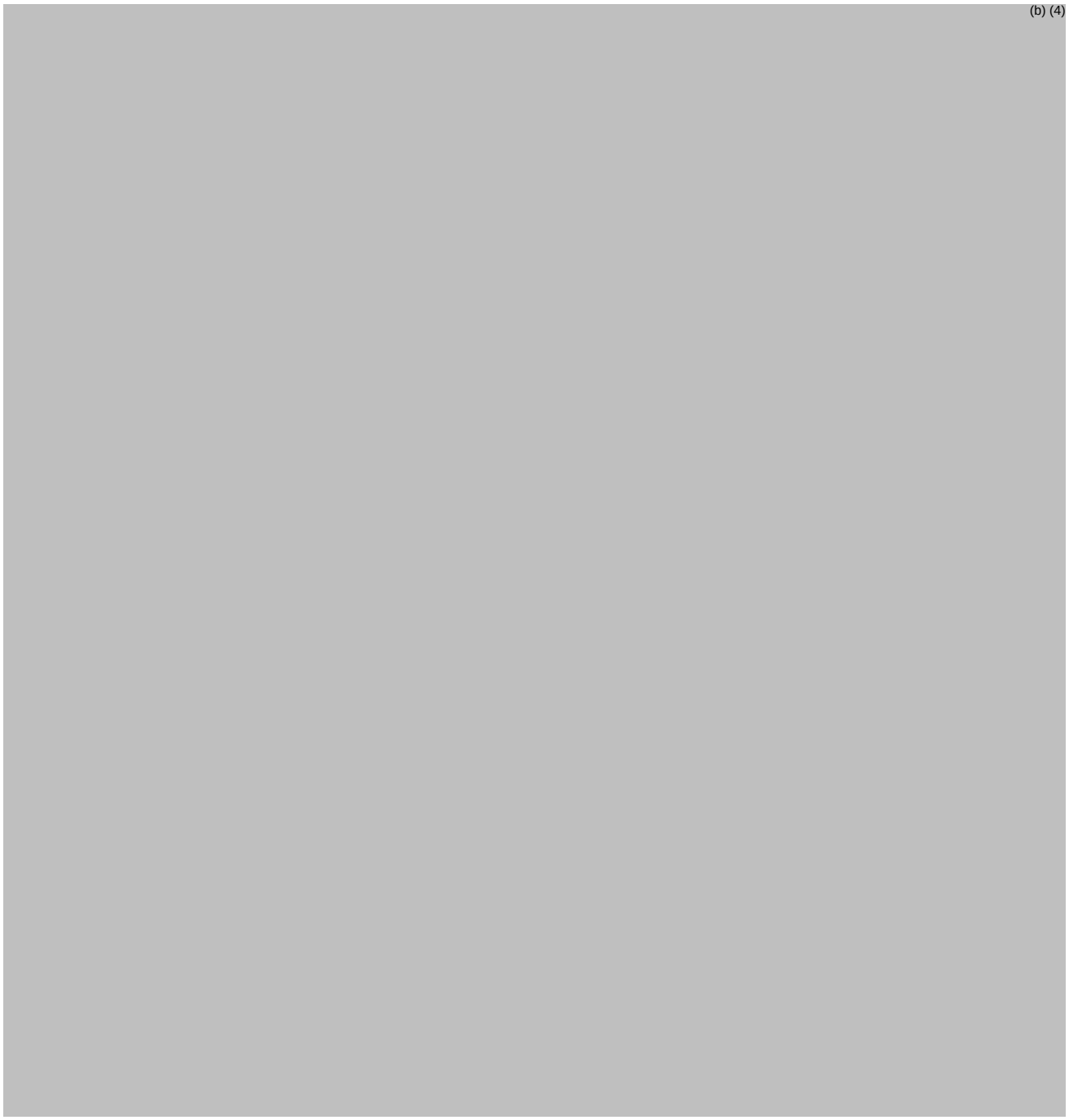
The device is a classical sandwich enzyme-linked immunosorbent assay (ELISA) method, which is used to quantitate the concentration of concizumab (NNC0172-2021) in citrated human plasma samples (b) (4)

(b) (4)

The concizumab-ELISA is a laboratory developed assay and is not an assay kit.

ELISA Methodology/Procedure

(b) (4)



Scope:

CDER provided CDRH with Novo Nordisk's response to the Complete Response Letter sent on April 24, 2023. In this consult request, CDER requested the following of CDRH:

1. Confirmation that the concizumab ELISA assay used in study 4311 is the same as that which would be available clinically in the US broadly. Please provide the regulatory status of the assay since it is DNH understanding that the relevant regulatory/clinical information supporting the assay would be submitted in Q3 of 2023.
2. Confirmation that the adequacy of the concizumab-ELISA test and if they agree with

the sponsors proposal with use of the concizumab-ELISA laboratory test post-approval without full premarket approval of the in vitro diagnostic companion diagnostic device.

3. Complete review of companion diagnostic.

CDRH RESPONSE TO CDER REQUEST #1 and #3

There are three different Concizumab ELISA assays referred to in BLA 761315, and CDRH considers them as three different devices.

Concizumab ELISA performed at (b) (4) (hereinafter as (b) (4) assay): The (b) (4) assay is the Concizumab-ELISA assay manufactured by Novo Nordisk and performed at the (b) (4) site to quantitate the concentration of Concizumab for dose adjustment in clinical trials (NN7415-4311, -4307, -4807 and -4616). The (b) (4) assay was developed for use in the clinical trials and is therefore considered a clinical trial assay (CTA). In an investigational device exemption (IDE), (b) (4) CDRH reviewed the performance of the (b) (4) assay and approved its use in clinical trials (NN7415-4311, -4307, -4807 and -4616).

(b) (4)

Concizumab ELISA manufactured by (b) (4) (hereinafter as (b) (4) assay): The (b) (4) assay is the Concizumab-ELISA assay manufactured and performed by (b) (4) ((b) (4) to quantitate the concentration of Concizumab for Concizumab dose adjustment. This assay has not been used in any clinical trials and is not the subject of a premarket submission; therefore, CDRH is not able to make an assessment of assay performance or validation.

CDRH RESPONSE TO CDER REQUEST #2

Contemporaneous authorization: As per the FDA guidance "In Vitro Companion Diagnostic Devices" (https://www.fda.gov/media/81309/download), "For a novel therapeutic product for which an IVD companion diagnostic device is essential for the safe and effective use of the product, the IVD companion diagnostic device should be developed and approved or cleared contemporaneously so that it will be available for use when the therapeutic product is approved." If CDER determines that the (b) (4) assay (b) (4) is essential to the safe and effective use of

concizumab, we defer to CDER's decision whether Concizumab (BLA 761315) approval will be postponed to ensure the [redacted] assay ([redacted] can be contemporaneously authorized.

Non-contemporaneous authorization: The referred IVD companion diagnostic guidance has discussed two scenarios for non-contemporaneous approvals or approval and clearance under Section IV.B. In this approach that concizumab will be approved without an FDA-authorized companion diagnostic device, we respectfully request CDER to provide CDRH documentation of the benefit-risk assessment to support this non-contemporaneous authorization decision.

If you have any questions or comments regarding this review, please call me at (240) 402-0194 or email me at Yan.Cai@fda.hhs.gov.

Sincerely,

YAN CAI -S

Yan Cai, PhD
Reviewer
Division of Immunology and Hematology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Through

Takeesha Taylor-bell -S

for Lea Carrington
Director
Division of Immunology and Hematology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

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/s/

ROLANDA K BAILEY
12/12/2024 12:12:07 PM
Signing on behalf of Yan Cai

Consult MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostics and Radiological Health (OIR)

Date: December 2, 2024

To: Courtney Hamilton, Regulatory Project Manager
Division of Regulatory Operations - Cardiology, Hematology, Endocrinology and Nephrology
Office of Regulatory Operations (ORO)
Office of New Drugs (OND)

From: Yan Cai, Ph.D., Reviewer
Hematology Branch (HEMB)
Division of Immunology and Hematology Devices (DIHD)
Office of Health Technology VII (OHT7)
Office of Product Evaluation and Quality (OPEQ)
Center for Devices and Radiological Health (CDRH)

Through: Min Wu, Branch Chief
DIHD/OHT7/OPEQ/CDRH

Takeesha Taylor-Bell, Deputy Director
DIHD/OHT7/OPEQ/CDRH

Lea Carrington, Director
DIHD/OHT7/OPEQ/CDRH

Subject: (b) (4) ELISA
BLA (b) (4) Alhemo

Tracking Number: ICCR# 01014797

ICCR Received: 9/4/2024
ICCR Due: 12/02/2024

Background:

Novo Nordisk has developed a recombinant, humanized, anti-IgG4 isotype monoclonal antibody (mAb, concizumab) to treat patients with hemophilia A and hemophilia B. Concizumab is a

humanized recombinant mAb of IgG4 isotype with a molecular weight of 149 kilodaltons. Concizumab is directed against the tissue factor pathway inhibitor (TFPI), which is involved in down-regulation of the initiation of the coagulation cascade. Concizumab prevents TFPI from binding to and blocking the active site of the coagulation factor Xa (FXa). This compensates for the limited FXa generation in the absence of a functional FIXa/FVIIIa complex in hemophilia. When the TFPI inhibitory activity is reduced, the FXa produced by the coagulation factor VIIa (FVIIa)/tissue factor (TF) complex will result in sufficient generation of thrombin to achieve hemostasis. Concizumab in a (b) (4) pen-injector is intended to be marketed as a combination product consisting of a drug constituent (concizumab drug product at concentrations of (b) (4) 40 mg/mL and 100 mg/mL) and a device constituent (a (b) (4) pen-injector).

Concizumab is being developed for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with:

- hemophilia A (congenital factor VIII deficiency)
- hemophilia B (congenital factor IX deficiency)
- hemophilia A (congenital factor VIII deficiency) with inhibitors to FVIII
- hemophilia B (congenital factor IX deficiency) with inhibitors to FIX

Intended Use/Indication for Use (IU/IFU) for (b) (4) ELISA

The intended use for the (b) (4) ELISA in BLA (b) (4) is as follows:

For in vitro diagnostic use. Rx only.
The (b) (4) ELISA (enzyme linked immunosorbent assay) is intended for the quantitative measurement of concizumab concentration in human 3.2% citrated plasma samples from Hemophilia A and B patients (with and without inhibitors) after 4 weeks from the initiation of treatment with concizumab. The measurement of concizumab concentration is used for dose adjustment decision in accordance with the drug label.

Concizumab concentration (X) at clinical cutoff:	Adjusted concizumab dose:
X < 200 ng/ml	Dose adjustment to 0.25 mg/kg
200 ng/ml < X < 4000 ng/ml	No dose adjustment (dose kept at 0.20 mg/kg)
X > 4000 ng/ml	Dose adjustment to 0.15 mg/kg

figure 1: Dose Adjustment

X = Concentration level in patient sample
The (b) (4) ELISA is a manual assay intended for use by trained laboratory professionals.

Study Description:

The Phase 3 clinical trials NN7415-4311 (Explorer 7) and NN7415-4307 (Explorer 8) were initiated in October and November 2019 respectively. Clinical trials were paused by Novo Nordisk and put on clinical hold by the FDA (IND 111691) in March 2020 due to 5 serious non-fatal

thrombotic events that occurred in 3 patients in the Phase 3 trials. Following the clinical hold in March 2020, a Type A meeting was held on June 16, 2020, to reach an agreement on the approach to address the clinical hold issues. A complete response was submitted on July 13, 2020, and the clinical hold was lifted by the FDA on August 11, 2020.

An investigational device exemption (IDE) application ((b) (4) was submitted by Novo Nordisk to the CDRH on July 10, 2020 for the (b) (4) Concizumab-ELISA (clinical trial assay), to quantitate the concentration of Concizumab in citrated human plasma samples for use in the dose adjustment of Concizumab in clinical trials NN7415-4311 and NN7415-4307. The IDE was approved with conditions on August 12, 2020. A meeting ((b) (4)) was held on September 14, 2020, with CDRH to discuss and reach an agreement on the approaches to address the conditions. The IDE amendment was submitted on September 24, 2020, and the IDE was fully approved on October 22, 2020.

(b) (4)

Device Description:

Concizumab is an anti-tissue factor pathway inhibitor (TFPI) antibody for subcutaneous prophylactic therapy for all hemophilia subtypes and acts independently from FVIII and FIX by enhancing the initiation phase of coagulation through increased FXa activity allowing sufficient thrombin generation to prevent bleeds.

The Concizumab-ELISA is based on a standard sandwich enzyme-linked immunosorbent assay (ELISA) method used to quantitate the concentration of concizumab in 3.2% citrated human plasma samples from patients with hemophilia A or B with and without inhibitors (b) (4)

The device is a classical sandwich enzyme-linked immunosorbent assay (ELISA) method, which is used to quantitate the concentration of concizumab in citrated human plasma samples (b) (4) .

(b) (4)

ELISA Methodology/Procedure

(b) (4)

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Scope:

CDER requested CDRH's input for [redacted] ELISA manufactured by [redacted] This is a CDx (companion diagnostic device) used along with concizumab drug label for dose adjustment. In this consult request, CDER included the following requests about CDRH feedback:

1. Please review the ELISA method as it pertains to this Application, [redacted]. This BLA cross-references BLA-761315.

CDRH RESPONSE TO CDER REQUEST #1

Concizumab ELISA performed at [redacted] (hereinafter as [redacted] assay): The [redacted] assay is the Concizumab-ELISA assay manufactured by Novo Nordisk and performed at the [redacted] site to quantitate the concentration of Concizumab for Concizumab dose adjustment in clinical trials (NN7415-4311, -4307, -4807 and -4616). It is a clinical trial assay (CTA), but not a companion diagnostic device. In [redacted] CDRH reviewed its performance and approved its use in clinical trials (NN7415-4311, -4307, -4807 and -4616).

[redacted]

(b) (4)

If you have any questions or comments regarding this review, please call me at (240) 402-0194 or email me at Yan.Cai@fda.hhs.gov.

Sincerely,

YAN CAI -S
Digitally signed by YAN CAI -S
Date: 2024.12.02 15:06:08 -05'00'

Yan Cai, PhD
Reviewer, DIHD/HEMB

Through

Takeesha Taylor-bell -S

for Lea Carrington
Director, DIHD

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/s/

ROLANDA K BAILEY
12/04/2024 03:53:59 PM
On behalf of Dr. Yan Cai

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	9/23/2024		
To:	Melinda Bauerlien		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	OPRO/DRBPMI
From:	Jillian Socea, Infusion Team OPEQ/OHT3/DHT3C		
Through (Division): ***optional**	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: Please review the responses to the CDRH CR device-related comments.		
Recommendation:	The device constituent part of the combination product is **approvable.**		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (optional)**
Jillian N. Socea -S Digitally signed by Jillian N. Socea -S Date: 2024.09.23 08:27:14 -07'00'	Shruti N. Mistry -S 2024.09.23 12:40:21 -04'00'	

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR#01004347
Consult Request Link	01004347 | Case | Salesforce
ICC tracking #	ICC2400657
Submission Number	BLA 761315
Sponsor	Novo Nordisk Inc.
Drug/Biologic	Alhemo (concizumab-xxx injection)
Indications for Use	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with: • hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors • hemophilia B (congenital factor IX deficiency) with factor IX inhibitors
Device Constituent	Pen injector
Related Files	BLA 761315 • ICC2200503, Case 00851224 • ICC2200742, Case 00868052

	• ICC2300487, Case 00923795

2. CDRH REVIEW

ICC Review Request from CDER/OPQ, OPRO/DRBPMI:	Please review the responses to the CDRH CR comments.
Device Presentation(s) being evaluated:	Pen injector
Objective of this Memo:	Review responses to device-related CR comments (responses to Q17 and Q18)
Review **Comments**:	The sponsor's responses to the CR comments are acceptable. The sponsor has incorporated evaluation of EPRs within the post-approval stability protocol and release testing, as requested.
Review **Recommendation**:	The responses to the CDRH CR comments are acceptable. There are no outstanding device-related deficiencies. **The device constituent part of the combination product is approvable.**

Please refer to the previous engineering review ICC2200503 BLA 761315.ALHEMO.concizumab.CDRH-OPEQ Review.ICC2200503-ICC2200742.Case 00851224-00868052.v2 (002).pdf dated March 15, 2023. It appears that CDRH provided CR comments in this final draft due to concerns from CDER (b) (4) in the drug product. CDER requested that CR comments be provided to request evaluation of EPRs to be included in the post-approval stability protocol and release specifications. Therefore, review of the responses to the CR comments provided in this final memo are reviewed below.

An earlier memo was provided to CDER BLA 761315.ALHEMO.concizumab.CDRH-OPEQ Review.ICC2200503-ICC2200742.Case 00851224-00868052.pdf dated February 13, 2023 and was recommended approvable without any CR comments.

Text in *italics* taken from **m1-11-4-response-to-crl-qdf.pdf**

FDA Question 17: Device Constituent

On March 3, 2023, we sent an IR requesting to include the EPRs (i.e., dose accuracy, activation force, hold force, and injection time) of device constituents of the combination product in the DP post-approval stability protocol. In the response received on March 10, 2023, you stated that you are committed to continuing the shelf-life studies for EPRs of the PPQ batches as presented in section 3.2.P.8.2. Although you provided data to support that the device performed as expected up to the claimed shelf-life, the EPRs should also be included in the DP post-approval stability protocol in section 3.2.P.8.2 to ensure the EPRs are monitored post-approval to support batch-to-batch consistency. Therefore, as requested previously, add the EPRs (i.e., dose accuracy, activation force, hold force, and injection time) to the DP post-approval stability protocol.

Sponsor response: *The EPRs (i.e., dose accuracy, activation/hold force and injection time) have been included as a post-approval stability protocol in **3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment for On-going Stability for the** (b) (4) **pen-injector**.*

Table 1 Test programme for [redacted] oncizumab pen-injector long-term testing at 5°C

Storage time (months)	X[2]	12	24	36
Test parameter				
Dose accuracy	x[1]	x	x	x
Activation force[3]	x[1]	x	x	x
Injection time	x[1]	x	x	x

1: The average value for release results is used as time point zero results.
2: The manufacturing date is defined according to [redacted]
3: Hold force is covered by the analytical parameter of Activation force, as explained in 3.2.P.5.6 Justification of Specification for Drug Product.

Reviewer comment: This response is acceptable.

FDA Question 18: Device Constituent

On March 7, 2023, we sent an IR requesting to include the EPRs (i.e., activation force, hold force, and injection time) of device constituents of the combination product in the DP release specifications. In the response received on March 10, 2023, you stated that you implemented controls in the manufacturing process and considered that sufficient. However, in order to align with the DP post-approval stability protocol, the requested EPRs (i.e., activation force, hold force, and injection time) should also be added to the DP release specifications.

Sponsor response: *The EPRs (i.e., dose accuracy, activation/hold force, and injection time) have been included as batch release parameters in 3.2.P.5.1 Specification for Drug Product.*

3.2.P.5.6. Justification of Specification for Drug Product has been updated accordingly.

Analytical procedures, and validations thereof, are provided in 3.2.P.5.2 Analytical Procedure [redacted] for Injection Time, 3.2.P.5.2 Analytical procedure [redacted] for Activation Force, 3.2.P.5.3 Validation of Analytical Procedure for Injection Time and 3.2.P.5.3 Validation of Analytical Procedure for Activation Force.

3.2.P.5.2 Overview of Analytical Procedures for Drug Product and 3.2.P.5.2 Analytical Development for Drug Product have been updated accordingly.

[redacted] *has been added as site for quality control testing of pen-injector performance in 3.2.P.3.1 Manufacturers for Drug Product.*

Furthermore, 3.2.P.2.4 Analysis of Functional Performance and Control Strategy and 3.2.P.3.4 Control of Critical Manufacturing Steps for the Drug-Device Combination Product have been updated to reflect addition of injection time and activation force as batch release parameters.

Table 1 Specification for concizumab drug product in (b) (4) pen-injector

Test parameter	Analytical procedure	Acceptance criteria
Appearance	Visual inspection *USP, Ph. Eur., JP, M216*	Release: Complies[1] Shelf life: Complies[2]
pH	Potentiometry *Ph. Eur., USP, JP*	(b) (4)
Identity	iCIEF (b) (4)	Release: Complies[3]
Specific activity	Coagulation assay/SE-HPLC (b) (4)	Release: (b) (4) Shelf life: (b) (4)
Content	SE-HPLC (b) (4)	*10 mg/mL:* (b) (4) *40 mg/mL:* (b) (4) *100 mg/mL:* (b) (4)
HMWP		Release: (b) (4) Shelf lif
Purity	CE-SDS (b) (4)	Release: (b) (4) Shelf life
Total fragments		Release: (b) (4) Shelf life

Test parameter	Analytical procedure	Acceptance criteria
(b) (4)		
Osmotic pressure	Freezing point depression *Ph. Eur., USP, JP*	Release: (b) (4) mOsmol/kg
Particulate matter ≥ 10 µm ≥ 25 µm	Light obscuration *Ph. Eur., USP, JP*	(b) (4) particles/container ≥ 10µm articles/container ≥ 25µm
Bacterial endotoxins	LAL test *Ph. Eur., USP, JP*	(b) (4) EU/mL
Sterility	(b) (4) *Ph. Eur., USP, JP*	Complies[6]
Dose accuracy	Weighing (b) (4)	Complies[7]
Extractable volume	Weighing *Ph. Eur., USP, JP*	Complies[8]
Injection time	Time measurement (b) (4)	Complies[9]
Activation force	Force measurement (b) (4)	Complies[10]
(b) (4)		

Reviewer comment: This response is acceptable.

---END OF REVIEW---

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/s/

ROLANDA K BAILEY
12/04/2024 03:51:27 PM
On behalf of Jillian N. Socea

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	3/15/2023		
To:	Melinda Bauerlien, FDA/OC/CDER/OPQ/OPRO/DRBPMI/RBPMB2		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Other
From	Florencia Wilson OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761315, Alhemo/concizumab-xxxx		

Engineering consult	Facilities consult
ICC2200503	ICC2200742
Case 00851224	Case 00868052

Recommendation

Filing Recommendation Date: 10/11/2022

☐ CDRH did not provide a Filing Recommendation

X Device Constituent Parts of the Combination Product are acceptable for Filing.

☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A

☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies

Mid-Cycle Recommendation Date: 12/5/2022

☐ CDRH did not provide a Mid-Cycle Recommendation

X CDRH has no approvability issues at this time.

☐ CDRH has additional Information Requests, See Appendix A

☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.

Final Recommendation Date: 2/13/2023

☐ Device Constituent Parts of the Combination Product are Approvable.

☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3

☒ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Florencia T. Wilson -S Digitally signed by Florencia T. Wilson -S Date: 2023.03.15 13:13:56 -04'00'		

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761315
Sponsor	Novo Nordisk Inc.
Drug/Biologic	Alhemo/concizumab-xxxx
Indications for Use	routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients: o hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors o hemophilia B (congenital factor IX deficiency) with factor IX inhibitors
Device Constituent	Pen-Injector
Related Files	

Review Team		
Lead Device Reviewer	*Florencia Wilson*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	1/16/2022
Interim Due Dates	**Meeting/Due Date**
Filing	
74-Day Letter	
Mid-Cycle	12/6/2022 (OND)
Primary Review	11/23/2022
JAM meetings	Labeling – 1/11/2023, 2/6/2023
Internal Meeting(s)	12/5/2022, late cycle – 2/21/2023
Sponsor Meeting(s)	Mid-Cycle – 12/20/2022, Late-cycle - 3/15/2023

Of Note:

- words in *italics* are taken directly from the submission

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:
☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.
☐ Approvable with PMC or PMR, See Section 2.3
☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			Deferred to CDER
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation	X			Deferred to CDER
Human Factors Validation	X			Deferred to DMEPA
Facilities & Quality Systems	X			

2.1. Comments to the Review Team

☒ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
☒ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

1. On March 3, 2023, we sent an interactive information request requesting to include the essential performance requirements (EPRs) (i.e., dose accuracy, activation force, hold force, and injection time) of device constituents of the combination product in the post-approval stability protocol. In the response received on March 10, 2023, you state that you are committed to complete the commitment in continuing the shelf-life studies as presented in 3.2.P.8.2 Stability Commitment for Process Performance Qualification Batches. Although you provided data that the device performed up to the claimed shelf-life, the EPRs should also be included in the post-approval stability protocol with the Drug Product in section 3.2.P.8.2 to ensure the EPRs are monitored post-approval. Therefore, as requested previously, add the EPRs (i.e., dose accuracy, activation force, hold force, and injection time) to the post-approval stability protocol.
2. On March 7, 2023, we sent an interactive information request requesting to include the essential performance requirements (EPRs) (i.e., activation force, hold force, and injection time) of device constituents of the combination product to the DP release specifications. In your response received on March 10, 2023, you stated that you implemented controls in the manufacturing process and considered that sufficient. However, in order to align with the post-approval stability protocol, the requested EPRs (i.e., activation force, hold force, and injection time) should also be added to the DP release specifications.

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	**X**

TABLE OF CONTENTS

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3. PURPOSE/BACKGROUND

3.1. Scope

Novo Nordisk Inc. is requesting approval of Alhemo/concizumab-xxxx . The device constituent of the combination product is a Pen-Injector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

ICC2200503
Case 00851224

This is a rolling BLA submission with the Pharm/tox data and CMC data already submitted. The complete BLA will be submitted July 20, 2022. Please provide assessment of design controls, performance, stability and suitability of the concizumab drug product pen-injector for its intended use when you have the time.

ICC2200742
Case 00868052

Please review the facility for the assembly of the drug device combination product is performed at Novo Nordisk A/S, Kirke Vaerlose Denmark, FEI 3015545250.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device performance, Biocompatibility of the non-drug contacting components, and Facilities review

This review will not cover the following review areas:

Human Factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
Alhemo/concizumab-xxxx	routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients: o hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors o hemophilia B (congenital factor IX deficiency) with factor IX inhibitors
Pen-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
001	1, 3
008	1 (1.14 Labeling)

The product will have a proposed shelf life of 24 months at 36-46°F (2-8°C) including an in-use period of up to 28 days in a refrigerator at 36-46°F (2-8°C) or at room temperature below 86°F (30°C).
All facilities are registered with the FDA and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The production schedules are provided in Module 1.11.1. A complete list of the manufacturing and testing sites with their corresponding FEI numbers is found in Module 3.2.S.2.1 for drug substances and Module 3.2.P.3.1 for the drug product.

Component documents	3. 2. P. 7 3. 2. P. 7 3. 2. P. 7 3. 2. P. 7 3. 2. P. 7	(b) (4)
System document	3. 2. P. 7 3. 2. P. 7	

4. DEVICE DESCRIPTION

4.1. Device Description

(b) (4) concizumab pen-injector
The following are taken from Seq 001, Module 1.2 Reviewer's Guide:

The (b) (4) *concizumab pen-injector is part of a family of devices. The* (b) (4) *pen injector family has a mature pen-injector design used in other approved and marketed combination products. 3.2.P.7 Comparison to other* (b) (4) *Pen-injectors presents a detailed comparison of the characteristics of the pen-injector in the current submission and other* (b) (4) *pen-injectors, as well as the* (b) (4) *concizumab pen-injector used in phase 3 clinical trials.*

(b) (4)

LOA:
DMF: DMF (b) (4)

(b) (4)

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Table 1 Key functional features of the (b) (4) concizumab pen-injector

Feature	Justification for feature
(b) (4)	

The principle of operation of the (b) (4) concizumab pen-injector can be described as two interacting systems: a dial system and a dose system.

- *Dial system: During dose setting, the dial mechanism consisting of dial (b) (4) Please note that 'dial' is also known as 'dose selector'.*
- *Dose system: When the dose button (1) is pushed down, (b) (4) enables delivery of the dose selected. (See section 3.2).*

4.2. Steps for Using the Device

The following are taken from Seq. 008, Module 1.14.1.3 Draft Labeling text, Instruction for Use (IFU) 1.5 mL (b) (4) per mL (this instruction for use applies to all the configuration of the device constituent:

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments The device description is adequate.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	**X**
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities				
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability			X
	Biocompatibility	X		
	Sterility	X		
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors (deferred to DMEPA)	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment
The application is fillable.

5.2. Facilities Information

The following are taken from Seq001, Module 2.3.P.3 Manufacture:

Address Activity

Novo Nordisk A/S
Kirke Værløsevej 30
Værløse
Hovedstaden 3500
Denmark
FEI number: 3015545250
DUNS number: 311359009
Assembly, labelling and secondary packaging of finished product.
Quality control testing of pen-injector (chemical/physical).
Storage of printed packaging materials, bulk drug product and finished product.

Firm Name:	Novo Nordisk A/S
Address:	Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark
FEI:	3015545250
Responsibilities:	Assembly, labelling and secondary packaging of finished product. Quality control testing of pen-injector (chemical/physical). Storage of printed packaging materials, bulk drug product and finished product.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
X Inspection was conducted 1/15/2021 to 1/17/2021. The inspection covered both drug CGMPs and medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

X An inspection is not required because A recent medical device inspection of the firm was acceptable.

LR Comment:

After review of FEI 3015545250, which was last inspected on 01/17/2020 (end date), with an NAI decision. Additionally, the (b) (4) pen-injector family of devices is approved as the device components in several other drug-device combination product. Therefore, only Quality system Documentation will be reviewed.
Below is a list of the approved combination products under this pen injector family:

(b) (4)

Add Additional Facility

5.3. Filing Review Conclusion

FILING REVIEW CONCLUSION
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☐ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance X No Inspection ☐ N/A **Site(s) needing inspection:**
Reviewer Comments The provided Facilities information is adequate.
Refuse to File Deficiencies: ☐ Yes ☐ No X N/A **74-Day Letter Deficiencies:** ☐ Yes ☐ No X N/A

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	Deferred to DMEPA		

Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments
The provided labeling is adequate in the device perspective. The full review of Labeling is deferred to CDER.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes **X No** ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes **X No** ☐ N/A	**Final Deficiencies:** ☐ Yes **X No** ☐ N/A
Reviewer Comments The full review of Labeling is deferred to CDER.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	**X**		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	**X**		
Mitigations are adequate to reduce risk to health	**X**		
Version history demonstrates risk management throughout design / development activities	**X**		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	**X**		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)			X
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
The sponsor provided adequate information.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Dose Accuracy	(b) (4)
Activation force	
Hold Force	
Injection Time	

Reviewer Comments

The totality of the overall design control is adequate. The specifications for the essential performance is acceptable.

(b) (4)

Adequate

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1, "Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems	Y	Y

7.4. Design Control Review Conclusion

Table 1 Process controls for essential functions in the (b) (4) concizumab pen-injector performed during and after final assembly

Assembly step	Process control	Acceptance criteria
During final assembly	(b) (4)	
After final assembly		

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes **X No** ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes **X No** ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments The provided design control information is adequate.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes **X No**		

8. RISK ANALYSIS

8.1. Risk Management Plan

Reviewer Comments

The risk management process used for the concizumab pen injector ((b) (4) complies with ISO 14971. All identified risks have been reduced as far as possible. The residual risks have been evaluated against defined criteria for risk acceptability and were found to be acceptable with respect to the benefit of using the product.
The Risk Management plan is located under 3.2.P.2.4 Product Risk Management Summary. **Adequate**

8.2. Hazard Analysis and Risk Summary Report

Link to Infusion Pump SAC Reviewer Guide

Risk Management plan is located under 3.2.P.2.4 Product Risk Management Summary:
Section 4 (pdf p. 5 of 15)

Risk analysis and evaluation

This section describes the various types of risk analysis and evaluations performed during the development of the (b) (4) concizumab pen-injector, i.e., System Risk Analysis (SRA) (use errors), component Failure Mode Effects and Criticality Analysis (cFMECA) (technical errors), as well as HFE/usability studies and biological evaluation. Results and conclusions from the individual risk analyses and evaluations are provided in section 6.

*An **SRA** on the (b) (4) concizumab pen-injector was performed to identify and analyze reasonably foreseeable misuse and use errors. The SRA lists reasonably foreseeable sequences of events from predicted causes leading to failure of different identified user tasks (from a Task Analysis for the use of the device), consequently resulting in a hazardous situation. Results and conclusions are reported in section 6.1.*

*A **cFMECA** is an analysis of failure modes associated with individual components or subassemblies of components and final assembly of the sub-assemblies in the (b) (4) concizumab pen-injector. Thus, the cFMECA considers failure modes also of the final finished device design, as a failure at the component/sub-assembly level will have an effect on the final finished device. The cFMECA thus evaluates technical errors typically caused by moulding, imprinting, manufacturing of springs, transportation and/or assembly during production, that can lead to malfunction of the final finished device hence potential harm to the intended user. Results and conclusions are reported in section 6.2.*

*An **HFE/usability** study is conducted to demonstrate that the (b) (4) concizumab peninjector is adequately safe and effective for the intended uses, users and use environments and to conclude that the chosen mitigations to address the foreseeable risks are effective as intended in the SRA and that no new use errors have occurred. Results and conclusions are reported in section 6.3.*

*A **Biological Evaluation** of the (b) (4) concizumab pen-injector has been performed in accordance with ISO 10993-1 [4] considering parts which come in direct or indirect contact with users. Results and conclusions are reported in section 6.4.*

Reviewer Comments

The provided Hazard Analysis summary (see above) is **adequate.** As stated above, all identified risks have been reduced as far as possible. The residual risks have been evaluated against defined criteria for risk acceptability and were found to be acceptable with respect to the benefit of using the product.

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments The provided Risk Analysis is adequate.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	(b) (4)	Y	HF	Y	Y
Activation force		Y	HF	Y	Y
Hold Force		Y	HF	Y	Y
Injection Time		Y	HF	Y	Y

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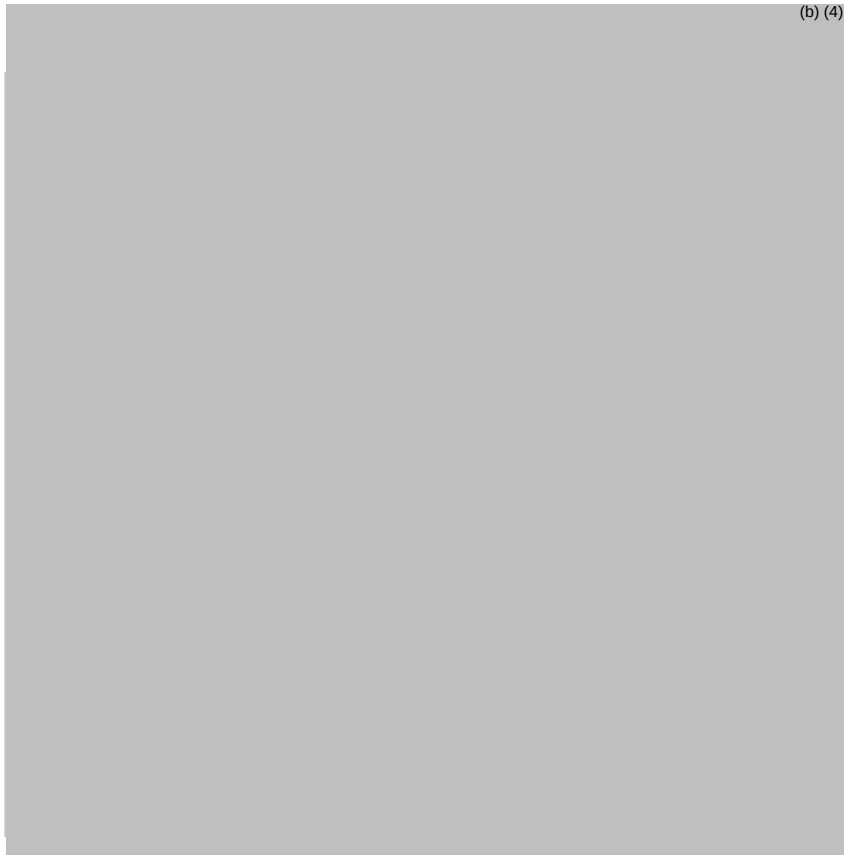


9.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)
Dose Accuracy	(b) (4)	ISO 11608-1	Met the specifications	Y	Y	Y

	(b) (4)					
Activation Force		ISO 11608-1	Met the specifications	Y	Y	Y
Hold force		ISO 11608-1	Met the specifications	Y	Y	Y
Injection Time		ISO 11608-1	Met the specifications	Y	Y	Y

Reviewer Comment

The stability studies are divided into two parts:
- *Long-term testing for up to 36 months at 5°C ± 3°C*
- *Accelerated testing for up to 6 months at 30°C ± 2°C*

The Sponsor performed dose accuracy, activation force, hold force, and injection time at release and after simulated transport. Based on the information provided (see above), the sponsor tested the worst case representative which is the 100 mg/mL in 3 mL and 1.5 mL container closure after transport and at timepoint zero of the accelerated storage for the other essential performance requirements (EPR). The sponsor also provided adequate control strategy to ensure that the combination product meets its EPR at release (see section 11.3). Additionally, this worst case representative was also tested at the 6 months accelerated condition which is equivalent to the proposed shelf-life of 24 months, this is acceptable to in lieu of the long term testing for the worst case concentration (100 mg/mL in 3 mL and 1.5 mL).
A long-term storage stability studies for the other configuration ((b) (4) 40 mg/mL, 100 mg/ml (1.5 ml container closure) of the device was done at 24 months. Although these configurations/concentrations did not have any release testing, the Sponsor's provided testing for the worst case configuration (100 mg/mL (3 mL container closure) after simulated transport, Design Control strategy (Section 11.3) and the family of (b) (4) used in other approved products (different indications for use, but similar volume and viscosity) can be leveraged for release verification testing.
Lastly, the Sponsor provided in-use stability testing to demonstrate that the EPR of the configurations of the combination product following the proposed in-use period of 4 weeks. Testing was done on aged (24 months) devices.
The design verification review of the combination product is adequate.

3/3/2023:

On 3/2/2023, this reviewer received an inquiry regarding the lack of the EPRs in the post-approval stability protocol. An IR will be sent to ensure that the device constituent of the combination product is continuously monitored post-approval and there are no device issues to the end of shelf-life.

3/7/2023:
Additional IR will be sent to the Sponsor for the lack of the EPRs in the release testing. Although the Sponsor provided adequate in-process control and control strategy, the clinical team has concerns with the seen low pk values in the clinical studies and a reported death report of a 13 yo patient. Therefore to ensure that the device performs as expected, the EPRs is requested to be included in the release specifications as well.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments The provided design verification is adequate.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: Yes X No		

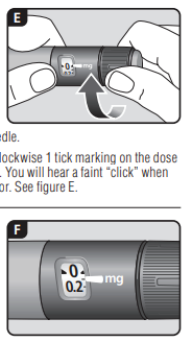
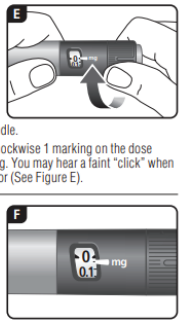
9.3. Discipline Specific Sub-Consulted Review Summary

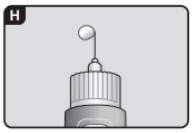
X No Additional Discipline Specific Sub-Consults were requested

☐ The following additional Discipline Specific Sub-Consults were requested:

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted		☐
Human Factors deferred to DMEPA	Review Instructions	X

Norditropin® FlexPro® 15 mg/1.5 mL (10 mg/mL) (human growth hormone)	**Somapacitan (b) (4) peninjector 10 mg/1.5 mL (6.67 mg/mL) (human growth hormone)**	**BLA 761315 (b) (4) concizumab peninjector (b) (4) (for hemophilia)**
⚠ **Always use a new needle for each injection.** This reduces the risk of contamination, infection, leakage of Norditropin®, and blocked needles leading to incorrect dosing. **Step 2. Check the Norditropin® flow with each new Pen** ⓘ **If your Pen is already in use,** go to step 3. **Before using a new Pen,** check the Norditropin® flow to make sure the growth hormone can flow through the Pen and needle. • Turn the dose selector clockwise 1 tick marking on the dose counter to select 0.1 mg. You will hear a faint "click" when you turn the dose selector. See figure E. • **1 marking on the dose counter equals 0.1 mg.** See figure F. 	⚠ **Always use a new needle for each injection.** This reduces the risk of contamination, infection, leakage of SOGROYA®, and blocked needles leading to incorrect dosing. **Step 2. Check the SOGROYA® flow with each new Pen** ⓘ **If your Pen is already in use,** go to Step 3. • **Before using a new Pen,** check the SOGROYA® flow to make sure the growth hormone can flow through the Pen and needle. • Turn the dose selector clockwise 1 marking on the dose counter to select 0.05 mg. You may hear a faint "click" when you turn the dose selector (See Figure E). • **1 marking on the dose counter equals 0.05 mg** (See Figure F). 	(b) (4)

• Check that a drop of Norditropin® appears at the needle tip. See figure H. **If no Norditropin® appears,** repeat step 2 up to 6 times. If you still do not see a drop of Norditropin®, **change the needle:** • Carefully remove the needle from the Pen by turning the needle counterclockwise. Place the needle in a sharps disposal container immediately. See step 5. • and repeat step 2 again. **Do not use the Pen if a drop of Norditropin® still does not appear after changing the needle and repeating step 2. Call Novo Nordisk at 1-888-668-6444 for help.**  https://www.novo-pi.com/norditropin.pdf#page=15	• Check that a drop of SOGROYA® appears at the needle tip (See Figure H). **If no SOGROYA® appears,** repeat Step 2 up to 6 times. If you still do not see a drop of SOGROYA®, **change the needle:** • Carefully remove the needle from the Pen by turning the needle counterclockwise. Place the needle in a sharps disposal container immediately (See Step 5). • Repeat Step 2 again. **Do not use the Pen if a drop of SOGROYA® still does not appear after changing the needle and repeating Step 2. Call Novo Nordisk at 1-888-668-6444 for help.**  https://www.novo-pi.com/sogroya.pdf	(b) (4)

Reviewer Comments

On 12/5/2022, the DMEPA reviewer reached out to CDRH regarding used errors occurring with Step 3 of the Draft instructions for use related to performing a flow check prior to each injection. The errors includes not performing this tasks prior to each injection. The DMEPA team noted, that in the HF results report the Applicant considers this task non-critical because "lack of initial flow check when taking a new pen-injector in use is only a risk for the first dosing with the pen-injector" and because "lack of performed flow check in-between dosing with the same pen-injector that results in an air gap that compromises treatment is only likely to occur in the event of a consecutive change of temperature from one dosing to the next dosing" and that similar products only perform a flow check/test prior to the first injection only. DMEPA has the following questions:

1. From a device perspective, do you agree with the Applicant that it is necessary for users to perform a flow check prior to each injection of the proposed prefilled pen injector?
2. From a device perspective, do you have concerns with DMEPA recommending the Applicant consider whether it is appropriate to revise the IFU to instruct users to perform a flow check prior to the first injection only (not prior to every injection)?

Since the Sponsor also compared the pen-injector to other approved drugs using the same platform pen-injector, I also compared the instructions for use (see above) of approved (b) (4) platform pen-injectors provided by the Sponsor in 3.2.P.7 The other pen-injectors does not have tell the users to test the flow for each injection, only for each new pen-injector. However, this application does. It is not clear on the purpose of this added step. This was discuss with the TL via e-mail on 12/5/2022 with a discussion held on 12/8/2022:

- (#1)
  - We cannot answer this question, because this is outside the purview of the device review
  - Although the DMEPA team stated that other pen-injectors does not state this (perform a flow check to each injection), we can't really refer to those because we don't know what prompted the Sponsor in including this step, for example, this can be a result of a risk assessment performed by the Sponsor
  - CDRH's recommendation to DMEPA is to send an IR to find out why this step is necessary
- (#2)

- For this question, we believe that the clinical team needs to be looped in as this may impact other risks, such as underdosing/overdosing and may depend on what the IR response will be for the rationale on the flow check to each injection

This discussion in the bullet above was sent to the DMEPA reviewer (Ebony Whaley) on 12/8/2022.

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	**X**

Facility Regulatory History Review	
Firm Name:	Novo Nordisk
Address & FEI:	Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark FEI number: 3015545250
Responsibilities:	The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part
Site Inspection Recommendation:	NAI.

Reviewer Comments

A PAI is not recommended. Please see the facilities review under Section 5.2 above.

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	**X** Yes	☐ No

11.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	**X**
CDRH Quality Systems Documentation Review was not conducted	☐

11.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

The following are taken from Seq 001, 3.2.P.3.3:

The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:

Reviewer Comments

The Sponsor provided an adequate summary of manufacturing process/production flow. Adequate

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

11.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:
X Device QSR-based – drug-device streamline approach

☐ Drug cGMP-Based Streamline – Review Instructions
☐ Stream-line Both (**no streamlined approach**)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Novo Nordisk A/S Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark FEI number: 3015545250	**Reviewer Discussion –** (b) (4)

		(b) (4) [redacted]
21 CFR 820.30 Summary of Design Controls	Firm(s): Novo Nordisk A/S Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark FEI number: 3015545250	**Reviewer Discussion –** Reviewed in detail in Section 7 (b) (4) [redacted]
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Novo Nordisk A/S Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark FEI number: 3015545250	**Reviewer Discussion –** (b) (4) [redacted]
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): Novo Nordisk A/S Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark	**Reviewer Discussion –** (b) (4) [redacted]

	FEI number: 3015545250	(b) (4)

Reviewer Comments

For all variants of the (b) (4) *concizumab pen-injector, Novo Nordisk A/S has followed the streamlined approach for drug-device combination products as described in 21 CFR 4.4(b)(1) by complying with the drug cGMP and the applicable device Quality System Regulation (QSR) 21 CFR 820 provisions as well as the 'Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products' [1].*

The Sponsor followed the applicable device Quality System Regulation (QSR) 21 CFR 820. Adequate

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	X Yes	☐ No

11.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:
The following are taken from Seq 001, 3.2.P.2.4 Analysis of Functional Performance and Control Strategy, pdf pp. 44-45 of 63:

Appendix A Summary traceability matrix and control strategy
The matrix in Table 32 collects the information for the performance of activation force, hold force, injection time and dose accuracy of the (b) (4) *concizumab pen-injector, as collected in this document. The table also aligns the performance requirements to these to the evidence of how the control strategy ensures that these same parameters are guaranteed during manufacturing or batch testing.*

Table 32 Performance requirements and control strategy

Requirement	Pen-injector design acceptance criteria	Design Verification according to ISO 11608-1	After transport simulation	After long-term storage	Control strategy		
					Process control	Process validation	Batch release
Activation force	(b) (4)						
Hold force							

Concizumab
3.2.P.2.4 Analysis of Functional

(b) (4)

Requirement	Pen-injector design acceptance criteria	Design Verification according to ISO 11608-1	After transport simulation	After long-term storage	Control strategy		
					Process control	Process validation	Batch release
Injection time	(b) (4)						
Dose accuracy							

(b) (4)

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	(b) (4)	Y
Activation Force		Y

	(b) (4)	
Hold Force		Y
Injection Time		Y

Reviewer Comments

The verification testing for release was performed for dose accuracy. The sponsor provided control strategy for the other essential performance requirements for the (b) (4) concizumab pen-injector to ensure that the performance requirements acceptance criteria are met consistently. The full documentation is located in Sequence 001, 3.2.P.2.4, Analysis of Functional Performance and Control Strategy. The provided control strategy is adequate to ensure that the combination product meets its EPRs at release.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

11.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments		

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No

<<END OF REVIEW>>

12.APPENDIX A (INFORMATION REQUESTS)

12.1. Filing/74-Day Information Requests

N/A

12.2. Mid-Cycle Information Requests

N/A

12.3. Interactive Information Requests

12.3.1. Interactive Information Requests sent on 3/3/2023

In Table 1 of the document Post-approval Stability Protocol and Stability Commitment for On-going Stability for Drug Product in section 3.2.P.8.2, you provided the post-approval stability protocol to be conducted on each variant of concizumab drug product annually under the long-term storage condition (5ºC). The post-approval stability protocol is missing the essential performance requirements (EPRs) of device constituents of the combination product. This is needed to ensure that the device functionality is monitored to the end of shelf-life post approval. Therefore, add the EPRs (i.e., dose accuracy, activation force, hold force, and injection time) to the post-approval stability protocol.

Please provide your response by March 8, 2023, COB.

Sponsor Response:

(b) (4)

Reviewer Comment

(b) (4)

Due to these concerns, the provided response is not acceptable. The team will continue to ask that the EPRs be included in the post-approval protocol. I was also notified that the application will be CR'd, therefore, this request will be provided as a CR deficiency.

CR deficiency:

On March 3, 2023, we sent an interactive information request requesting to include the essential performance requirements (EPRs) (i.e., dose accuracy, activation force, hold force, and injection time) of device constituents of the combination product in the post-approval stability protocol. (b) (4) Although you provided data that the device performed up to the claimed shelf-life, the EPRs should also be included in the post-approval stability protocol with the Drug Product in section 3.2.P.8.2 to ensure the EPRs are monitored post-approval. Therefore, as requested previously, add the EPRs (i.e., dose accuracy, activation force, hold force, and injection time) to the post-approval stability protocol.

12.3.2. Interactive Information Requests sent on 3/7/2023

In section 3.2.P.5.1, dose accuracy is included in the concizumab drug product (DP) release specifications. However, the other essential performance requirements (i.e., activation force, hold force, and injection time) are not included in the DP release specifications. This is needed to ensure that the device functionality is monitored at release. Therefore, add the EPRs (i.e., activation force, hold force, and injection time) to the DP release specifications. In addition, these EPRs should be added to the DP stability specifications to align with the addition of EPRs to the post-approval stability protocol as indicated in the information request sent on March 3, 2023.

Sponsor Response:

(b) (4)

Reviewer Comment

(b) (4)

Therefore, the response is not acceptable. This is wild be added to the CR Deficiency.

CR Deficiency:

On March 7, 2023, we sent an interactive information request requesting to include the essential performance requirements (EPRs) (i.e., activation force, hold force, and injection time) of device constituents of the combination product to the DP release specifications. (b) (4) . However, in order to align with the post-approval stability protocol, the requested EPRs (i.e., activation force, hold force, and injection time) should also be added to the DP release specifications.

13.APPENDIX B (CONSULTANT MEMOS)

N/A

13.1. Human Factors Review Memo – Insert Consultant Name

13.2. Clinical Review Memo – Insert Consultant Name

13.3. Insert Discipline Review Memo – Insert Consultant Name

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROLANDA K BAILEY
12/04/2024 03:45:50 PM
On behalf of Florencia Wilson

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	2/13/2023		
To:	Melinda Bauerlien, FDA/OC/CDER/OPQ/OPRO/DRBPMI/RBPMB2		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Other
From	Florencia Wilson OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761315, Alhemo/concizumab-xxxx		

Engineering consult	Facilities consult
ICC2200503	ICC2200742
Case 00851224	Case 00868052

Recommendation

Filing Recommendation Date: 10/11/2022

☐ CDRH did not provide a Filing Recommendation

X Device Constituent Parts of the Combination Product are acceptable for Filing.

☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A

☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies

Mid-Cycle Recommendation Date: 12/5/2022

☐ CDRH did not provide a Mid-Cycle Recommendation

X CDRH has no approvability issues at this time.

☐ CDRH has additional Information Requests, See Appendix A

☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.

Final Recommendation Date: 2/13/2023

X Device Constituent Parts of the Combination Product are Approvable.

☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3

☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Florencia T. Wilson -S Digitally signed by Florencia T. Wilson -S Date: 2023.02.13 10:38:10 -05'00'		

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761315
Sponsor	Novo Nordisk Inc.
Drug/Biologic	Alhemo/concizumab-xxxx
Indications for Use	routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients: o hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors o hemophilia B (congenital factor IX deficiency) with factor IX inhibitors
Device Constituent	Pen-Injector
Related Files	

Review Team		
Lead Device Reviewer	*Florencia Wilson*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	1/16/2022
Interim Due Dates	**Meeting/Due Date**
Filing	
74-Day Letter	
Mid-Cycle	12/6/2022 (OND)
Primary Review	11/23/2022
JAM meetings	Labeling – 1/11/2023, 2/6/2023
Internal Meeting(s)	12/5/2022, late cycle – 2/21/2023
Sponsor Meeting(s)	Mid-Cycle – 12/20/2022, Late-cycle - 3/15/2023

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			Deferred to CDER
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation	X			Deferred to CDER
Human Factors Validation	X			Deferred to DMEPA
Facilities & Quality Systems	X			

2.1. Comments to the Review Team

X CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

X There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	X

TABLE OF CONTENTS

Update Table of Contents

3. PURPOSE/BACKGROUND

3.1. Scope

Novo Nordisk Inc. is requesting approval of Alhemo/concizumab-xxxx . The device constituent of the combination product is a Pen-Injector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

ICC2200503
Case 00851224

This is a rolling BLA submission with the Pharm/tox data and CMC data already submitted. The complete BLA will be submitted July 20, 2022. Please provide assessment of design controls, performance, stability and suitability of the concizumab drug product pen-injector for its intended use when you have the time.

ICC2200742
Case 00868052

Please review the facility for the assembly of the drug device combination product is performed at Novo Nordisk A/S, Kirke Vaerlose Denmark, FEI 3015545250.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device performance, Biocompatibility of the non-drug contacting components, and Facilities review

This review will not cover the following review areas:

Human Factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
Alhemo/concizumab-xxxx	routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients: o hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors o hemophilia B (congenital factor IX deficiency) with factor IX inhibitors
Pen-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
001	1, 3
008	1 (1.14 Labeling)

The product will have a proposed shelf life of 24 months at 36-46°F (2-8°C) including an in-use period of up to 28 days in a refrigerator at 36-46°F (2-8°C) or at room temperature below 86°F (30°C).
All facilities are registered with the FDA and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The production schedules are provided in Module 1.11.1. A complete list of the manufacturing and testing sites with their corresponding FEI numbers is found in Module 3.2.S.2.1 for drug substances and Module 3.2.P.3.1 for the drug product.

Component documents	(b) (4)	
System document		

4. DEVICE DESCRIPTION

4.1. Device Description

(b) (4) concizumab pen-injector
The following are taken from Seq 001, Module 1.2 Reviewer's Guide:

The (b) (4) *concizumab pen-injector is part of a family of devices. The* (b) (4) *pen injector family has a mature pen-injector design used in other approved and marketed combination products. 3.2.P.7 Comparison to other* (b) (4) *Pen-injectors presents a detailed comparison of the characteristics of the pen-injector in the current submission and other* (b) (4) *pen-injectors, as well as the* (b) (4) *concizumab pen-injector used in phase 3 clinical trials.*

(b) (4)

LOA:
DMF: DMF (b) (4)

(b) (4)

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Table 1 Key functional features of the (b) (4) concizumab pen-injector

Feature	Justification for feature
(b) (4)	

The principle of operation of the (b) (4) concizumab pen-injector can be described as two interacting systems: a dial system and a dose system.

- *Dial system: During dose setting, the dial mechanism consisting of dial (b) (4) Please note that 'dial' is also known as 'dose selector'.*
- *Dose system: When the dose button (1) is pushed down, (b) (4) enables delivery of the dose selected. (See section 3.2).*

4.2. Steps for Using the Device

The following are taken from Seq. 008, Module 1.14.1.3 Draft Labeling text, Instruction for Use (IFU) 1.5 mL (b) (4) per mL (this instruction for use applies to all the configuration of the device constituent:

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments The device description is adequate.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	**X**
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities				
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability			X
	Biocompatibility	X		
	Sterility	X		
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors (deferred to DMEPA)	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment
The application is fillable.

5.2. Facilities Information

The following are taken from Seq001, Module 2.3.P.3 Manufacture:

Address Activity

Novo Nordisk A/S
Kirke Værløsevej 30
Værløse
Hovedstaden 3500
Denmark
FEI number: 3015545250
DUNS number: 311359009
Assembly, labelling and secondary packaging of finished product.
Quality control testing of pen-injector (chemical/physical).
Storage of printed packaging materials, bulk drug product and finished product.

Firm Name:	Novo Nordisk A/S
Address:	Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark
FEI:	3015545250
Responsibilities:	Assembly, labelling and secondary packaging of finished product. Quality control testing of pen-injector (chemical/physical). Storage of printed packaging materials, bulk drug product and finished product.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
X Inspection was conducted 1/15/2021 to 1/17/2021. The inspection covered both drug CGMPs and medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

X An inspection is not required because A recent medical device inspection of the firm was acceptable.

LR Comment:

After review of FEI 3015545250, which was last inspected on 01/17/2020 (end date), with an NAI decision. Additionally, the (b) (4) pen-injector family of devices is approved as the device components in several other drug-device combination product. Therefore, only Quality system Documentation will be reviewed.
Below is a list of the approved combination products under this pen injector family:

(b) (4)

Add Additional Facility

5.3. Filing Review Conclusion

FILING REVIEW CONCLUSION
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☐ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance X No Inspection ☐ N/A **Site(s) needing inspection:**
Reviewer Comments The provided Facilities information is adequate.
Refuse to File Deficiencies: ☐ Yes ☐ No X N/A **74-Day Letter Deficiencies:** ☐ Yes ☐ No X N/A

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	Deferred to DMEPA		

Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments
The provided labeling is adequate in the device perspective. The full review of Labeling is deferred to CDER.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes **X No** ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes **X No** ☐ N/A	**Final Deficiencies:** ☐ Yes **X No** ☐ N/A
Reviewer Comments The full review of Labeling is deferred to CDER.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	**X**		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	**X**		
Mitigations are adequate to reduce risk to health	**X**		
Version history demonstrates risk management throughout design / development activities	**X**		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	**X**		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)			X
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
The sponsor provided adequate information.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Dose Accuracy	(b) (4)
Activation force	
Hold Force	
Injection Time	

Reviewer Comments
The totality of the overall design control is adequate. The specifications for the essential performance is acceptable.

(b) (4)

Adequate

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)

ISO 11608-1, "Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems	Y	Y

7.4. Design Control Review Conclusion

Table 1 Process controls for essential functions in the [redacted] concizumab pen-injector performed during and after final assembly

Assembly step	Process control	Acceptance criteria
During final assembly	(b) (4)	
After final assembly		

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments The provided design control information is adequate.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No		

8. RISK ANALYSIS

8.1. Risk Management Plan

Reviewer Comments

The risk management process used for the concizumab pen injector ((b) (4) complies with ISO 14971. All identified risks have been reduced as far as possible. The residual risks have been evaluated against defined criteria for risk acceptability and were found to be acceptable with respect to the benefit of using the product.
The Risk Management plan is located under 3.2.P.2.4 Product Risk Management Summary. **Adequate**

8.2. Hazard Analysis and Risk Summary Report

Link to Infusion Pump SAC Reviewer Guide

Risk Management plan is located under 3.2.P.2.4 Product Risk Management Summary:
Section 4 (pdf p. 5 of 15)

Risk analysis and evaluation

This section describes the various types of risk analysis and evaluations performed during the development of the (b) (4) concizumab pen-injector, i.e., System Risk Analysis (SRA) (use errors), component Failure Mode Effects and Criticality Analysis (cFMECA) (technical errors), as well as HFE/usability studies and biological evaluation. Results and conclusions from the individual risk analyses and evaluations are provided in section 6.

*An **SRA** on the (b) (4) concizumab pen-injector was performed to identify and analyze reasonably foreseeable misuse and use errors. The SRA lists reasonably foreseeable sequences of events from predicted causes leading to failure of different identified user tasks (from a Task Analysis for the use of the device), consequently resulting in a hazardous situation. Results and conclusions are reported in section 6.1.*

*A **cFMECA** is an analysis of failure modes associated with individual components or subassemblies of components and final assembly of the sub-assemblies in the (b) (4) concizumab pen-injector. Thus, the cFMECA considers failure modes also of the final finished device design, as a failure at the component/sub-assembly level will have an effect on the final finished device. The cFMECA thus evaluates technical errors typically caused by moulding, imprinting, manufacturing of springs, transportation and/or assembly during production, that can lead to malfunction of the final finished device hence potential harm to the intended user. Results and conclusions are reported in section 6.2.*

*An **HFE/usability** study is conducted to demonstrate that the (b) (4) concizumab peninjector is adequately safe and effective for the intended uses, users and use environments and to conclude that the chosen mitigations to address the foreseeable risks are effective as intended in the SRA and that no new use errors have occurred. Results and conclusions are reported in section 6.3.*

*A **Biological Evaluation** of the (b) (4) concizumab pen-injector has been performed in accordance with ISO 10993-1 [4] considering parts which come in direct or indirect contact with users. Results and conclusions are reported in section 6.4.*

Reviewer Comments

The provided Hazard Analysis summary (see above) is **adequate.** As stated above, all identified risks have been reduced as far as possible. The residual risks have been evaluated against defined criteria for risk acceptability and were found to be acceptable with respect to the benefit of using the product.

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments		

The provided Risk Analysis is adequate.
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	(b) (4)	Y	HF	Y	Y
Activation force		Y	HF	Y	Y
Hold Force		Y	HF	Y	Y
Injection Time		Y	HF	Y	Y

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9.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)
Dose Accuracy	(b) (4)	ISO 11608-1	Met the specifications	Y	Y	Y
Activation Force		ISO 11608-1	Met the specifications	Y	Y	Y
Hold force		ISO 11608-1	Met the specifications	Y	Y	Y
Injection Time		ISO 11608-1	Met the specifications	Y	Y	Y

Reviewer Comment

The stability studies are divided into two parts:
- *Long-term testing for up to 36 months at 5°C ± 3°C*
- *Accelerated testing for up to 6 months at 30°C ± 2°C*

The Sponsor performed dose accuracy, activation force, hold force, and injection time at release and after simulated transport. Based on the information provided (see above), the sponsor tested the worst case representative which is the 100 mg/mL in 3 mL and 1.5 mL container closure after transport and at timepoint zero of the accelerated storage for the other essential performance requirements (EPR). The sponsor also provided adequate control strategy to ensure that the combination product meets its EPR at release (see section 11.3). Additionally, this worst case representative was also tested at the 6 months accelerated condition which is

equivalent to the proposed shelf-life of 24 months, this is acceptable to in lieu of the long term testing for the worst case concentration (100 mg/mL in 3 mL and 1.5 mL).
A long-term storage stability studies for the other configuration (b) (4), 40 mg/mL, 100 mg/ml (1.5 ml container closure) of the device was done at 24 months. Although these configurations/concentrations did not have any release testing, the Sponsor's provided testing for the worst case configuration (100 mg/mL (3 mL container closure) after simulated transport, Design Control strategy (Section 11.3) and the family of (b) (4) used in other approved products (different indications for use, but similar volume and viscosity) can be leveraged for release verification testing.
Lastly, the Sponsor provided in-use stability testing to demonstrate that the EPR of the configurations of the combination product following the proposed in-use period of 4 weeks. Testing was done on aged (24 months) devices.
The design verification review of the combination product is adequate.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments The provided design verification is adequate.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: Yes X No		

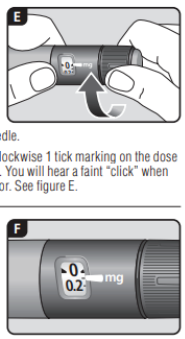
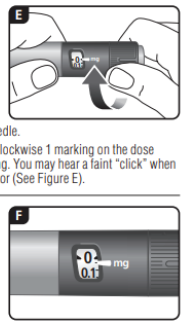
9.3. Discipline Specific Sub-Consulted Review Summary

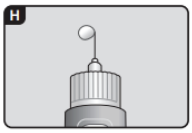
X No Additional Discipline Specific Sub-Consults were requested

☐ The following additional Discipline Specific Sub-Consults were requested:

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA — Review Instructions	X

Norditropin® FlexPro® 15 mg/1.5 mL (10 mg/mL) (human growth hormone)	**Somapacitan (b) (4) peninjector 10 mg/1.5 mL (6.67 mg/mL) (human growth hormone)**	**BLA 761315 (b) (4) concizumab peninjector (b) (4) (for hemophilia)**
⚠ **Always use a new needle for each injection.** This reduces the risk of contamination, infection, leakage of Norditropin®, and blocked needles leading to incorrect dosing. **Step 2. Check the Norditropin® flow with each new Pen** ⓘ **If your Pen is already in use,** go to step 3. **Before using a new Pen,** check the Norditropin® flow to make sure the growth hormone can flow through the Pen and needle. • Turn the dose selector clockwise 1 tick marking on the dose counter to select 0.1 mg. You will hear a faint "click" when you turn the dose selector. See figure E. • **1 marking on the dose counter equals 0.1 mg.** See figure F. 	⚠ **Always use a new needle for each injection.** This reduces the risk of contamination, infection, leakage of SOGROYA®, and blocked needles leading to incorrect dosing. **Step 2. Check the SOGROYA® flow with each new Pen** ⓘ **If your Pen is already in use,** go to Step 3. • **Before using a new Pen,** check the SOGROYA® flow to make sure the growth hormone can flow through the Pen and needle. • Turn the dose selector clockwise 1 marking on the dose counter to select 0.05 mg. You may hear a faint "click" when you turn the dose selector (See Figure E). • **1 marking on the dose counter equals 0.05 mg** (See Figure F). 	(b) (4)

• Check that a drop of Norditropin® appears at the needle tip. See figure H. ⓘ **If no Norditropin® appears,** repeat step 2 up to 6 times. If you still do not see a drop of Norditropin®, **change the needle:** • Carefully remove the needle from the Pen by turning the needle counterclockwise. Place the needle in a sharps disposal container immediately. See step 5. • and repeat step 2 again. **Do not use the Pen if a drop of Norditropin® still does not appear after changing the needle and repeating step 2. Call Novo Nordisk at 1-888-668-6444 for help.**  https://www.novo-pi.com/norditropin.pdf#page=15	• Check that a drop of SOGROYA® appears at the needle tip (See Figure H). ⓘ **If no SOGROYA® appears,** repeat Step 2 up to 6 times. If you still do not see a drop of SOGROYA®, **change the needle:** • Carefully remove the needle from the Pen by turning the needle counterclockwise. Place the needle in a sharps disposal container immediately (See Step 5). • Repeat Step 2 again. **Do not use the Pen if a drop of SOGROYA® still does not appear after changing the needle and repeating Step 2. Call Novo Nordisk at 1-888-668-6444 for help.**  https://www.novo-pi.com/sogroya.pdf	(b) (4)

Reviewer Comments

On 12/5/2022, the DMEPA reviewer reached out to CDRH regarding used errors occurring with Step 3 of the Draft instructions for use related to performing a flow check prior to each injection. The errors includes not performing this tasks prior to each injection. The DMEPA team noted, that in the HF results report the Applicant considers this task non-critical because "lack of initial flow check when taking a new pen-injector in use is only a risk for the first dosing with the pen-injector" and because "lack of performed flow check in-between dosing with the same pen-injector that results in an air gap that compromises treatment is only likely to occur in the event of a consecutive change of temperature from one dosing to the next dosing" and that similar products only perform a flow check/test prior to the first injection only. DMEPA has the following questions:

1. From a device perspective, do you agree with the Applicant that it is necessary for users to perform a flow check prior to each injection of the proposed prefilled pen injector?
2. From a device perspective, do you have concerns with DMEPA recommending the Applicant consider whether it is appropriate to revise the IFU to instruct users to perform a flow check prior to the first injection only (not prior to every injection)?

Since the Sponsor also compared the pen-injector to other approved drugs using the same platform pen-injector, I also compared the instructions for use (see above) of approved (b) (4) platform pen-injectors provided by the Sponsor in 3.2.P.7 The other pen-injectors does not have tell the users to test the flow for each injection, only for each new pen-injector. However, this application does. It is not clear on the purpose of this added step. This was discuss with the TL via e-mail on 12/5/2022 with a discussion held on 12/8/2022:

- (#1)
  - We cannot answer this question, because this is outside the purview of the device review
  - Although the DMEPA team stated that other pen-injectors does not state this (perform a flow check to each injection), we can't really refer to those because we don't know what prompted the Sponsor in including this step, for example, this can be a result of a risk assessment performed by the Sponsor
  - CDRH's recommendation to DMEPA is to send an IR to find out why this step is necessary
- (#2)

- For this question, we believe that the clinical team needs to be looped in as this may impact other risks, such as underdosing/overdosing and may depend on what the IR response will be for the rationale on the flow check to each injection

This discussion in the bullet above was sent to the DMEPA reviewer (Ebony Whaley) on 12/8/2022.

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	**X**

Facility Regulatory History Review	
Firm Name:	Novo Nordisk
Address & FEI:	Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark FEI number: 3015545250
Responsibilities:	The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part
Site Inspection Recommendation:	NAI.

Reviewer Comments

A PAI is not recommended. Please see the facilities review under Section 5.2 above.

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	**X** Yes	☐ No

11.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	**X**
CDRH Quality Systems Documentation Review was not conducted	☐

11.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

The following are taken from Seq 001, 3.2.P.3.3:

(b) (4)

The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:

(b) (4)

Reviewer Comments

The Sponsor provided an adequate summary of manufacturing process/production flow. Adequate

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

11.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:
X Device QSR-based – drug-device streamline approach

☐ Drug cGMP-Based Streamline – Review Instructions
☐ Stream-line Both (**no streamlined approach**)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Novo Nordisk A/S Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark FEI number: 3015545250	**Reviewer Discussion –** (b) (4)

		(b) (4)
21 CFR 820.30 Summary of Design Controls	Firm(s): Novo Nordisk A/S Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark FEI number: 3015545250	**Reviewer Discussion –** Reviewed in detail in Section 7 (b) (4)
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Novo Nordisk A/S Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark FEI number: 3015545250	**Reviewer Discussion –** (b) (4)
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): Novo Nordisk A/S Kirke Værløsevej 30 Værløse Hovedstaden 3500 Denmark	**Reviewer Discussion –** (b) (4)

	FEI number: 3015545250	(b) (4)

Reviewer Comments

For all variants of the (b) (4) *concizumab pen-injector, Novo Nordisk A/S has followed the streamlined approach for drug-device combination products as described in 21 CFR 4.4(b)(1) by complying with the drug cGMP and the applicable device Quality System Regulation (QSR) 21 CFR 820 provisions as well as the 'Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products' [1].*

The Sponsor followed the applicable device Quality System Regulation (QSR) 21 CFR 820. Adequate

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	X Yes	☐ No

11.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:
The following are taken from Seq 001, 3.2.P.2.4 Analysis of Functional Performance and Control Strategy, pdf pp. 44-45 of 63:

Appendix A Summary traceability matrix and control strategy
The matrix in Table 32 collects the information for the performance of activation force, hold force, injection time and dose accuracy of the (b) (4) *concizumab pen-injector, as collected in this document. The table also aligns the performance requirements to these to the evidence of how the control strategy ensures that these same parameters are guaranteed during manufacturing or batch testing.*

Table 32 Performance requirements and control strategy

Requirement	Pen-injector design acceptance criteria	Design Verification according to ISO 11608-1	After transport simulation	After long-term storage	Control strategy		
					Process control	Process validation	Batch release
Activation force	(b) (4)						
Hold force							

Concizumab
3.2.P.2.4 Analysis of Functional

(b) (4)

Requirement	Pen-injector design acceptance criteria	Design Verification according to ISO 11608-1	After transport simulation	After long-term storage	Control strategy		
					Process control	Process validation	Batch release
Injection time	(b) (4)						
Dose accuracy							

(b) (4)

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	(b) (4)	Y
Activation Force		Y

	(b) (4)	
Hold Force		Y
Injection Time		Y

Reviewer Comments

The verification testing for release was performed for dose accuracy. The sponsor provided control strategy for the other essential performance requirements for the (b) (4) concizumab pen-injector to ensure that the performance requirements acceptance criteria are met consistently. The full documentation is located in Sequence 001, 3.2.P.2.4, Analysis of Functional Performance and Control Strategy. The provided control strategy is adequate to ensure that the combination product meets its EPRs at release.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

11.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments		

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No

<<END OF REVIEW>>

12. APPENDIX A (INFORMATION REQUESTS)

12.1. Filing/74-Day Information Requests

N/A

12.2. Mid-Cycle Information Requests

N/A

12.3. Interactive Information Requests

12.3.1. Interactive Information Requests sent on Click or tap to enter a date.

N/A

13. APPENDIX B (CONSULTANT MEMOS)

N/A

13.1. Human Factors Review Memo – Insert Consultant Name
13.2. Clinical Review Memo – Insert Consultant Name
13.3. Insert Discipline Review Memo – Insert Consultant Name

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROLANDA K BAILEY
12/04/2024 03:39:35 PM
On behalf of Florencia Wilson

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 25, 2024

To: Melissa Button, Regulatory Project Manager,
Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, Associate Director for Labeling, DNH

From: Melissa Khashei, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for Alhemo® (concizumab-mtci) injection, for subcutaneous use

BLA: 761315

Background:

In response to DNH's consult request dated June 26, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide/Instructions for Use (IFU) and carton and container labeling for the original BLA submission for Alhemo® (concizumab-mtci) injection, for subcutaneous use.

PI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 15, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide and IFU, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on October 25, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MELISSA KHASHEI
10/25/2024 10:11:05 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 25, 2024
To:	Melissa Button, PharmD Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Maria Nguyen, M.S., B.S.N., RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Melissa Khashei, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFUs)
Drug Name (established name):	ALHEMO (concizumab-mtci)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761315
Applicant:	Novo Nordisk Inc.

1 INTRODUCTION

On June 20, 2024, Novo Nordisk Inc. submitted for the Agency's review a Class 2 resubmission for their original Biologics License Application (BLA) 761315 for ALHEMO (concizumab-mtci) injection. The proposed indication is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with:

- hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors
- hemophilia B (congenital factor IX deficiency) with FIX inhibitors

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on June 26, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for ALHEMO (concizumab-mtci) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on October 10, 2024.

2 MATERIAL REVIEWED

- Draft ALHEMO (concizumab-mtci) injection MG and IFUs received on June 20, 2024 and June 26, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 15, 2024.
- Draft ALHEMO (concizumab-mtci) injection Prescribing Information (PI) received on June 20, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 15, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFUs the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFUs meet the criteria as specified in the Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
10/25/2024 08:46:31 AM
DMPP-OPDP review of concizumab-mtci (ALHEMO) BLA 761315 MG and IFU

MELISSA KHASHEI
10/25/2024 08:48:27 AM

LASHAWN M GRIFFITHS
10/25/2024 01:31:45 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 16, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761315
Product Name, Dosage Form, and Strength:	Alhemo (concizumab-mtci)[a] injection, 60 mg/1.5 mL (40 mg/mL); 150 mg/1.5 mL (100 mg/mL); 300 mg/3 mL (100 mg/mL)
Applicant Name:	Novo Nordisk Inc.
FDA Received Date:	September 27, 2024 and October 4, 2024
TTT ID #:	2022-1204-1
DMEPA 2 Safety Evaluator:	Robbie Kattappuram, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The nonproprietary name, concizumab-mtci, was found conditionally acceptable on August 6, 2024.

1 PURPOSE OF MEMORANDUM

Novo Nordisk Inc. submitted revised container labels and carton labeling received on September 27, 2024 for Alhemo. We reviewed the revised container labels and carton labeling for Alhemo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[b] and revisions requested from the Office of Pharmaceutical Quality (OPQ). An additional request was issued on September 30, 2024, from OPQ requesting revisions to the inactive ingredient name per USP monograph title for all three proposed carton labeling. Thus, Novo Nordisk Inc. submitted revised carton labeling received on October 04, 2024.

2 CONCLUSION

Novo Nordisk Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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[b] Kattappuram, R. Label and Labeling Review for Alhemo (BLA 761315). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 Oct 10. TTT ID: 2022-1204.

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/s/

ROBBIE S KATTAPPURAM
10/16/2024 10:59:23 AM

NICOLE F IVERSON
10/16/2024 04:10:40 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 10, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761315
Product Name, Dosage Form, and Strength:	Alhemo[a] (concizumab-mtci)[b] injection, 60 mg/1.5 mL (40 mg/mL); 150 mg/1.5 mL (100 mg/mL); 300 mg/3 mL (100 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Novo Nordisk Inc.
FDA Received Date:	June 20, 2024, June 26, 2024, and August 23, 2024
TTT ID #:	2022-1204
DMEPA 2 Safety Evaluator:	Robbie Kattappuram, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The proposed proprietary name, Alhemo, was found conditionally acceptable for this BLA 761315 on November 21, 2022 and is pending for this review cycle.

[b] The nonproprietary name, concizumab-mtci, was found conditionally acceptable on August 6, 2024.

1 INTRODUCTION

As part of the approval process for Alhemo (concizumab-mtci) injection, we reviewed the proposed Alhemo Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

Novo Nordisk Inc. previously submitted BLA 761315 on August 24, 2022. We completed a Human Factors (HF) study report and labels and labeling review on July 5, 2023.[c] The review found the results of the HF validation study acceptable; however, our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Our container label and carton labeling recommendations were provided to Novo Nordisk Inc. on March 22, 2023. However, the application received a Complete Response letter on April 24, 2023, due to issues with therapeutic monitoring, product quality, and facility inspections.[d]

Thus, Novo Nordisk Inc. submitted a Class 2 Resubmission on June 20, 2024.[e]

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761315.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C
Information Request	D

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

We performed a risk assessment of the proposed Alhemo Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling to identify deficiencies that may lead to medication errors and other areas of improvement. During our review cycle, we sent an Information Request to the Applicant to request a clean copy of the container labels to assess readability, to which the Applicant responded to on August 23, 2024. We also reached out to the Clinical Pharmacology team to clarify the maximum pediatric dose of Alhemo (b) (4)

[c] Whaley, E. Human Factors Study Report and Labels and Labeling Review for Alhemo (BLA 761315). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 Mar 22. TTT ID No.: 2022-1068 2022-1204.

[d] Hamilton, C on behalf of Lisa Yanoff. Complete Response for BLA 761315. Silver Spring (MD): FDA, CDER, OND, Division of Non-Malignant Hematology (DNH) (US); 2023 Apr 24.

[e] Cover Letter 20240620 BLA 761315 Resubmission Alhemo (concizumab). Plainsboro (NJ): Novo Nordisk Inc.; 2024 Jun 20. Available from: \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-2-cover-letter.pdf.

(b) (4) Clinical Pharmacology confirmed the pediatric patient dose cannot exceed the maximum recommended adult dose (b) (4) We defer to Clinical Pharmacology regarding the acceptability of any proposed changes to these points. We identified areas of the proposed PI, container labels, and carton labeling that could be revised to improve clarity, readability, and availability of important information.

4 CONCLUSION

We evaluated the proposed Alhemo Instructions for Use (IFU) and determined that is acceptable from a medication error perspective.

However, the proposed Alhemo Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Non-Malignant Hematology (DNH) in Section 5 and for Novo Nordisk Inc. in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information

1. General Comments (Highlights of Prescribing Information and Full Prescribing Information)
    a. The plasma concentration is a large number (e.g., 4000) that appears without a comma. We recommend revising the plasma concentration to include a comma to improve readability. For example, revise 4000 to read as 4,000.
    b. As currently presented, the Dosage and Administration section of the Highlights contains the symbols “<” to represent the words less than and “>” to represent the words “greater than”. Error prone symbols may lead to misinterpretation and medication error. We recommend replacing the symbols with their intended meanings.
2. Highlights of Prescribing Information
    a. Dosage Forms and Strengths
        i. The dosage form (b) (4) does not follow the current USP nomenclature which may lead to confusion and could contribute to administration errors. In addition, the package type term is missing. We recommend removing all instances of the dosage form (b) (4) and including the package type term “single-patient use” in the Dosage Forms and Strengths section in the Highlights of Prescribing Information. However, we defer to the Office of Pharmaceutical Quality (OPQ) regarding the acceptability of the dosage form.

3. Full Prescribing Information
    a. Section 2 *Dosage and Administration*
        i. As currently presented in the PI, (b) (4) s such, we recommend you reference the pen label color and not the dose button color in Section 2 and in Section 16 of the PI. For example, the 300 mg/3 mL pen label should be described as “white”.
        ii. The description of the color of the prefilled pen in Section 2.1 *Administration and Use Instructions* can be improved to minimize confusion. For example, we note the 150 mg/1.5 mL prefilled pen is described as (b) (4) (b) (4) (b) (4). Inconsistent descriptions of the appearance of each strength of the prefilled pen may lead to confusion. We recommend removing the term (b) (4) after each color description in Section 2.1. For example, revise (b) (4) to gold”.
        iii. In Section 2.1 *Recommended Dosage*, the dose is presented with a trailing zero (e.g., 1.0 mg). Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 1.0 mg is seen as 10 mg). We recommend revising the rounded dose to remove the trailing zero so that the statement states “150 mg/1.5 mL (100 mg/mL) in increments of 1 mg” and “300 mg/3 mL (100 mg/mL) in increments of 1 mg”.
        iv. Section (b) (4) contains and error prone abbreviation “U”. The abbreviation “U” could be misinterpreted as zero or the number 4, causing a 10-fold overdose or greater. We recommend replacing the abbreviation with their intended meaning (e.g., 100 units/kg).
    b. Section 16 *How Supplied/Storage and Handling*

i. The storage information included the unfamiliar term “cooling element”. Lack of clarity regarding product storage might pose a risk of deteriorated drug medication errors. We recommend defining the term “cooling element” by using the same language found in the Med Guide (e.g., the part that cools the refrigerator).

B. Medication Guide (MG)

1. As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges. The presentation of the storage statement should be clearly stated to mitigate the risk of incorrect storage of the product. We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges.

6 RECOMMENDATIONS FOR NOVO NORDISK INC.

A. General Comments (Container Label(s) and Carton Labeling)

1. As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges. The presentation of the storage statement should be clearly stated to mitigate the risk of incorrect storage of the product. We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Alhemo received on June 20, 2024 from Novo Nordisk Inc.

Table 2. Relevant Product Information for Alhemo	
Product Name	Alhemo
Initial Approval Date	N/A
Nonproprietary Name	concizumab-mtci
Indication	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with: • hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors • hemophilia B (congenital factor IX deficiency) with FIX inhibitors
Dosage Form	injection
Strength	60 mg/1.5 mL (40 mg/mL); 150 mg/1.5 mL (100 mg/mL); 300 mg/3 mL (100 mg/mL)
Route of Administration	Subcutaneous
Dose and Frequency	Day 1: Loading dose of 1 mg/kg Day 2: Once-daily dose of 0.20 mg/kg until individualization of maintenance dose (see below) • 4 weeks after initiation of treatment: For dose optimization, measure concizumab mtci plasma concentration by Concizumab Enzyme-Linked Immunosorbent Assay (ELISA) prior to administration of next scheduled dose After concizumab-mtci plasma concentration result is available but recommended no later than 8 weeks after initiation of treatment: Individualize maintenance dose of Alhemo based on the following concizumab mtci plasma concentrations: • <200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg • 200 to 4000 ng/mL: continue once-daily dose of 0.20 mg/kg • >4000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg
How Supplied	60 mg/1.5 mL (40 mg/mL) (b) (4) prefilled pen 150 mg/1.5 mL (100 mg/mL) (b) (4) prefilled pen 300 mg/3 mL (100 mg/mL) (b) (4) prefilled pen

Table 2. Relevant Product Information for Alhemo	
Product Name	Alhemo
Storage	Before use: Store in a refrigerator at 36° to 46°F (2° to 8°C) for up to 24 months. After first use: Store for up to 4 weeks in a refrigerator at 36˚ to 46˚F (2˚ to 8˚C) or at room temperature below 86˚F (30˚C). Write the date of first use in the space provided on the carton. Store unused Alhemo with the cap on and in the original carton to protect from light. Alhemo should not be stored in direct sunlight, and the Alhemo pen should be kept away from direct heat. Do not freeze or store it close to a cooling element in a refrigerator. Do not use Alhemo if it has been frozen or stored at temperatures above 86˚F (30˚C).
Container Closure	1.5 mL cartridge made of (b) (4) glass, colorless, with (b) (4) rubber plunger.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Alhemo labels and labeling submitted by Novo Nordisk Inc.

- Prescribing Information received on June 20, 2024, available from \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-14-1-3-alhemo-uspi-resub-with-inhibitors.pdf
- Medication Guide received on June 26, 2024, available from \\CDSESUB1\EVSPROD\bla761315\0057\m1\us\m1-14-1-3-medication-guide.docx
- Instructions for Use received on June 20, 2024, available from
    - \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-14-1-3-ifu-60-mg-1-5-ml-40-mg-ml-mock-up.pdf,
    - \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-14-1-3-ifu-150-mg-1-5-ml-100-mg-ml-mock-up.pdf
    - \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-14-1-3-ifu-300-mg-3-ml-100-mg-ml-mock-up.pdf
- Container labels received on June 20, 2024
- Carton labeling received on June 20, 2024
- Container labels without tinting received on August 23, 2024

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[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On August 13, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, “Alhemo”, “concizumab” and “761315”. Our search identified 1 previous review[g] since the date of our last search on March 22, 2023, and we considered our previous recommendations to see if they are applicable for this current review.

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[g] Whaley, E. Human Factors Study Report and Labels and Labeling Review for Alhemo (BLA 761315). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 Mar 22. TTT ID No.: 2022-1068 2022-1204.

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NICOLE F IVERSON
10/10/2024 03:56:49 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 25, 2023

To: Courtney Hamilton, PharmD, BCPS, Senior Regulatory Project Manager
Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling
(DNH)

From: Melissa Khashei, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader
(OPDP)

Subject: OPDP Labeling Comments for **TRADENAME** (concizumab-xxxx) injection, for subcutaneous use

BLA: 761315

This memo is in response to DNH's labeling consult request dated August 26, 2022. OPDP defers comment on the proposed labeling at this time and requests that DNH submit a new consult request during the subsequent review cycle. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or Melissa.Khashei@fda.hhs.gov.

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/s/

MELISSA KHASHEI
04/25/2023 10:52:18 AM

Consult MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostics and Radiological Health (OIR)

Date: March 2, 2023

To: Courtney Hamilton, Regulatory Project Manager
Division of Regulatory Operations - Cardiology, Hematology, Endocrinology and Nephrology
Office of Regulatory Operations (ORO)
Office of New Drugs (OND)

From: Yan Cai, Ph.D., Reviewer
Hematology Branch (HEMB)
Division of Immunology and Hematology Devices (DIHD)
Office of In Vitro Diagnostics and Radiological Health (OIR/OHT7)
Office of Product Evaluation and Quality (OPEQ)
Center for Devices and Radiological Health (CDRH)

Through: Takeesha Taylor-Bell, Deputy Director
DIHD/OIR-OHT7/OPEQ/CDRH

Lea Carrington, Director
DIHD/OIR-OHT7/OPEQ/CDRH

Subject: Validation package for (b) (4) Concizumab ELISA
BLA 761315 Alhemo

Tracking Number: ICCR# 00892502

ICCR Received: 1/20/2023
ICCR Due: 3/27/2023

Background:

Novo Nordisk has developed a recombinant, humanized, anti-IgG4 isotype monoclonal antibody (mAb, concizumab) to treat patients with hemophilia A and hemophilia B. Concizumab is a humanized recombinant mAb of IgG4 isotype with a molecular weight of 149 kilodaltons. Concizumab is directed against the tissue factor pathway inhibitor (TFPI), which is involved in down-regulation of the initiation of the coagulation cascade. Concizumab prevents TFPI from

binding to and blocking the active site of the coagulation factor Xa (FXa). This compensates for the limited FXa generation in the absence of a functional FIXa/FVIIIa complex in hemophilia. When the TFPI inhibitory activity is reduced, the FXa produced by the coagulation factor VIIa (FVIIa)/tissue factor (TF) complex will result in sufficient generation of thrombin to achieve hemostasis. Concizumab in a [redacted] pen-injector is intended to be marketed as a combination product consisting of a drug constituent (concizumab drug product at concentrations of [redacted] 40 mg/mL and 100 mg/mL) and a device constituent (a [redacted] pen-injector).

Concizumab is being developed for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with:

- hemophilia A (congenital factor VIII deficiency)
- hemophilia B (congenital factor IX deficiency)
- hemophilia A (congenital factor VIII deficiency) with inhibitors to FVIII
- hemophilia B (congenital factor IX deficiency) with inhibitors to FIX

Intended Use/Indication for Use (IU/IFU) for Concizumab ELISA

The intended use for the [redacted] Concizumab-ELISA in this BLA submission is as follows:

The Concizumab-ELISA (enzyme linked immunosorbent assay) is intended for the quantitative measurement of concizumab concentration in human 3.2% citrated plasma samples from Hemophilia A and B patients (with inhibitors) at a single time point after 4 weeks from the initiation of treatment with concizumab. The measurement of concizumab concentration is used for a one-time dose adjustment decision based on the Concizumab-ELISA result as follows, in accordance with the drug label.

Concizumab concentration (X) at clinical cutoff:	Adjusted concizumab dose:
X < 200 ng/ml	Dose adjustment to 0.25 mg/kg
200 ng/ml < X < 4000 ng/ml	No dose adjustment (dose kept at 0.20 mg/kg)
X > 4000 ng/ml	Dose adjustment to 0.15 mg/kg

figure 1: Dose Adjustment

Reviewer Comment: The IU in the BLA package is the same as the one in [redacted].

IU/IFU under IDE [redacted]
Concizumab-ELISA is intended to quantitate the concentration of concizumab in citrated human plasma samples for use in dose adjustment of concizumab for treatment of patients with hemophilia A and B with or without inhibitors in Phase 3 clinical trials.

[redacted]

(b) (4)

The Concizumab-ELISA device is for use in determining the concentration of the drug concizumab in 3.2% citrated plasma from patients with hemophilia A & B, with and without inhibitors, who are undergoing treatment with concizumab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Concizumab is an anti-TFPI antibody for subcutaneous prophylaxis across all hemophilia subtypes that acts independently from FVIII and FIX by enhancing the initiation phase of coagulation through increased FXa activity allowing sufficient thrombin generation to prevent bleeds.

Study Description:

The Phase 3 clinical trials NN7415-4311 (Explorer 7) and NN7415-4307 (Explorer 8) were initiated in October and November 2019 respectively. Clinical trials were paused by Novo Nordisk and put on clinical hold by the FDA (IND 111691) in March 2020 due to 5 serious non-fatal thrombotic events that occurred in 3 patients in the Phase 3 trials. Following the clinical hold in March 2020, a Type A meeting was held on June 16, 2020, to reach an agreement on the approach to address the clinical hold issues. A complete response was submitted on July 13, 2020, and the clinical hold was lifted by the FDA on August 11, 2020.

An investigational device exemption (IDE) application ((b) (4) was submitted by Novo Nordisk to the CDRH on July 10, 2020 for the Concizumab-ELISA, to quantitate the concentration of Concizumab in citrated human plasma samples for use in the dose adjustment of Concizumab in clinical trials NN7415-4311 and NN7415-4307. The IDE was approved with conditions on August 12, 2020. A meeting (b) (4) was held on September 14, 2020 with CDRH to discuss and reach an agreement on the approaches to address the conditions. The IDE amendment was submitted on September 24, 2020 and the IDE was fully approved on October 22, 2020.

(b) (4)

Novo Nordisk submitted a BLA submission for routine prophylaxis in patients with HBwI and HAwI. The current status of the Concizumab clinical development program is that the primary analysis cut-off has been reached for the phase 3 trial 4311 (HAwI and HBwI patients).

Device Description:

The device is a classical sandwich enzyme-linked immunosorbent assay (ELISA) method, which is used to quantitate the concentration of concizumab (NNC0172-2021) in citrated human plasma samples (b) (4)

(b) (4)

The concizumab-ELISA is a laboratory developed assay and is not an assay kit.

ELISA Methodology/Procedure

(b) (4)

Scope:

CDER provided CDRH with BLA validation package from the sponsor (Novo Nordisk). CDER requested CDRH's input on the validation studies regarding the (b) (4) Concizumab-ELISA. CDRH identified the deficiencies and points of consideration for the Lead Reviewer, as indicated below.

CDRH RECOMMENDATIONS TO CBER ON STUDIES/STUDY DESIGNS

The comments and recommendations below are from review of the studies and study designs that (b) (4) ((b) (4) conducted to support validation of the (b) (4) Concizumab ELISA kit for post market sample analysis at (b) (4) The (b) (4) ELISA will be used for a limited period for post market sample analysis. (b) (4) . These studies and study designs were provided in submission (b) (4) and in materials provided interactively by Novo Nordisk to CDRH on December 14, 2022. CDRH has reviewed the proposed studies and study results and has the following recommendations to CDER to communicate to Novo Nordisk through (b) (4) as CDER deems appropriate.

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(b) (4)

Additional Comment: In summary, it is lack of sufficient data in some studies (e.g., cross-validation study, interference study, sample stability study and precision study if applicable) to support the adequacy use of (b) (4) Concizumab ELISA for the clinical samples under the BLA application. (b) (4)

CDRH would like to convey to CDER that the level of analytical validation that the sponsor proposes to perform, and which we are commenting on with this consult memo, is not sufficient or adequate to support a post market analysis of samples by using the (b) (4) assay. CDRH is only providing review and recommendations regarding the analytical validation for the (b) (4) Concizumab ELISA that should be sufficiently validated for use in the clinical study outlined in BLA application.

CDRH QUESTIONS TO SPONSOR (already communicated these questions to sponsor)

Questions sent on 1/27/2023:

(b) (4)

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(b) (4)

If you have any questions or comments regarding this review, please call me at (240) 402-0194 or email me at Yan.Cai@fda.hhs.gov.

Sincerely,

Yan Cai -S (Affiliate)

Digitally signed by Yan Cai -S (Affiliate)
Date: 2023.03.02 16:25:48 -05'00'

Yan Cai, PhD
Reviewer, DIHD/HEMB

Through

Takeesha Taylor-bell -S

for

Lea Carrington
Director, DIHD

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/s/

COURTNEY V HAMILTON
04/18/2023 10:11:18 AM
Signing on behalf of Dr. Yan Cai

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	April 5, 2023
To:	Courtney Hamilton, PharmD, BCPS Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ALHEMO (concizumab-mtci)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761315
Applicant:	Novo Nordisk Inc.

1 INTRODUCTION

On August 24, 2022, Novo Nordisk Inc. submitted for the Agency's review the final part of their rolling submission of an original Biologics License Application (BLA) 761315 for ALHEMO (concizumab-mtci) injection. The proposed indication for ALHEMO (concizumab-mtci) injection is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with:

- hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
- hemophilia B (congenital factor IX deficiency) with factor IX inhibitors.

On August 26, 2022, the Division of Non-Malignant Hematology (DNH) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ALHEMO (concizumab-mtci) injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFUs for ALHEMO (concizumab-mtci) injection.

2 CONCLUSIONS

Due to identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time, DNH issued a Deficiencies Preclude Discussion letter on March 22, 2023 and plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JESSICA M CHUNG
04/05/2023 02:22:32 PM

SHARON R MILLS
04/05/2023 02:30:56 PM

LASHAWN M GRIFFITHS
04/05/2023 02:34:26 PM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 22, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761315
Drug Constituent Name and Strength	Alhemo[a] (concizumab-mtci)[b] injection, (b) (4) (b) (4) 60 mg/1.5 mL (40 mg/mL), 150 mg/1.5 mL (100 mg/mL), and 300 mg/3 mL (100 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Device Constituent:	prefilled pen
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novo Nordisk Inc.
FDA Received Date:	8/24/22; 9/16/22; 10/31/22; 2/8/23; 2/27/23
TTT ID #:	2022-1068; 2022-1204
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Deputy Director:	Chi-Ming (Alice) Tu, PharmD, BCPS, FISMP

[a] The proposed proprietary name, Alhemo was found conditionally acceptable for this BLA 761315 on November 21, 2022.

[b] The nonproprietary name "concizumab-mtci" was found conditionally acceptable for this BLA 761315 on February 14, 2023.

1 REASON FOR REVIEW

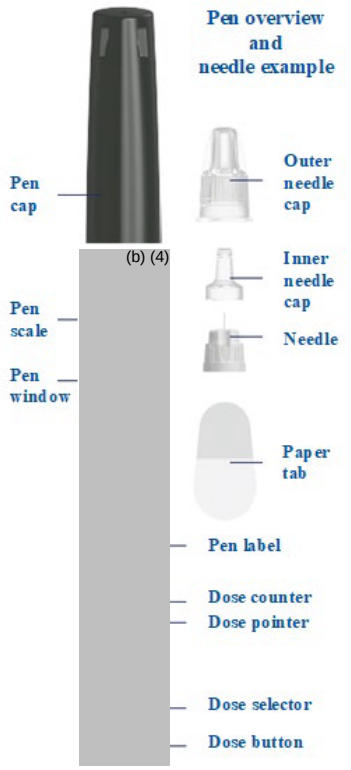
This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761315 for Alhemo (concizumab-mtci) injection.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed prefilled pen device constituent that is intended for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors or hemophilia B (congenital factor IX deficiency) with FIX inhibitors.

The proposed combination product is a multidose prefilled pen that can deliver variable doses and is intended for subcutaneous administration. The proposed combination product is intended for use by lay caregivers, adult and pediatric patients, and healthcare professionals (HCPs) including physicians, nurses, and pharmacists. See Appendix A and Figure 1 for more information.

Figure 1 : Proposed prefilled pen device constituent



1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On December 12, 2019, the Applicant requested preliminary feedback on the proposed training of patient participants in the HF study under IND 111691. On January 27, 2020, we responded to the Applicant and indicated the proposed approach of providing a brief introduction to the use of the prefilled pen in the HF formative study was reasonable. We also recommended that the Applicant submit their HF validation study protocol for Agency review. [c]
- On November 9, 2020, the Applicant submitted a HF validation study protocol under IND 111691 for the proposed combination product. We completed our review of the HF validation study protocol and issued comments to the Applicant on January 6, 2021.[d]
- On August 24, 2022, the Applicant submitted the results of the HF validation study under BLA 761315, which is the subject of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous DMEPA HF Reviews	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the user interface has been optimized to support the safe and effective use of the proposed product.

[c] Wu, L. Advice/Information Request for concizumab IND 111691. Silver Spring (MD): FDA, CDER, OSE, OMEPRM (US); 2020 JAN 27. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8053af3b.
[d] Wu, L. Human Factors Validation Study Protocol Advice for concizumab. Silver Spring (MD): FDA, CDER, OSE (US); 2021 JAN 6. IND 111691. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805c2c0d.

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details

Participants	• Children/adolescent patients (aged 9 – 17 years, accompanied by a parent/caregiver to assist if needed)
	  ○ n = 15
	• Adult patients
	  ○ n = 15
	• Adult lay caregivers
	  ○ n = 15
	• Healthcare professionals (HCPs) with experience administering to patients in and out of hospitals and/or teach others to give injections and who may or may not have specific knowledge of hemophilia
	  ○ n = 15

Training	Participants were not trained.
Test Environment and Materials	Testing occurred in a controlled usability lab environment that included a table, chairs, a child-sized manikin, injection pad, and supplies. Participants were asked to simulate use of the concizumab prefilled pen by injecting into an injection pad attached to their body (patients) or by injecting directly into a mannikin (lay caregivers and HCPs). Test materials included: • Concizumab prefilled pens and cartons • Concizumab prefilled pen IFU • Pen needles For example, participant assigned to administer the 1 mg dose would be presented with the (b) (4) 1.5 mL prefilled pens and cartons, prefilled pen IFU, and pen needles.
Sequence of Study	Simulated use • First injection scenario (without splitting the dose) - participants were assigned to administer one of the following doses: ○ (b) (4)

	○ 60 mg/1.5 mL: 4 mg ○ 150 mg/1.5 mL: 10 mg ○ 300 mg/3 mL: 10 mg • Second injection scenario (Participants were supplied with a used/end-of-content [EOC] prefilled pen that did not contain enough medication to administer the intended dose in one injection. As such, participants were to either split the dose between the EOC pen and a full/unused pen [for a total of 2 injections] or inject with only a full/unused pen) - participants were assigned to administer one of the following doses: ○ (b) (4) ○ 60 mg/1.5 mL: 32 mg ○ 150 mg/1.5 mL: 80 mg ○ 300 mg/3 mL: 80 mg Root cause analysis (RCA) Knowledge tasks • Knowledge check using open-ended questions • IFU readability assessment where participants were directed to a specific IFU section and asked to interpret the IFU text. This assessment was conducted if the participant did not respond correctly during the aforementioned knowledge check portion. Post-test interview/RCA

3.2 DISCUSSION OF METHODOLOGY

The Applicant did not implement all the Agency's HF validation study protocol recommendations.

- Proprietary name: The Applicant did not implement our recommendation to revise the proposed proprietary name on the user interface (i.e., carton labeling, instructions for use [IFU]) tested the HF validation study from (b) (4) to either "TRADENAME" or the conditionally accepted proprietary name, "Alhemo". We do not find that the difference in proprietary name negatively impacted user performance in the HF validation study. However, we provided a recommendation for the Applicant to revise their proposed labels and labeling to include the conditionally accepted proprietary name (see Table 7 in Appendix E).

- IFU: The Applicant did not revise the IFU graphic depicting the appropriate injection sites to include labels for the appropriate injection sites (i.e., abdomen, front of thighs). We find that the lack of implementation of the aforementioned recommendation does not preclude our review of the HF validation study results.

4 RESULTS AND ANALYSES

Table 3 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations. Additionally, we provide our review of the label and labeling for areas of vulnerability that may lead to medication errors in Tables 4 and 5.

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

<table>
<tr><th></th><th>Identified Issue</th><th>DMEPA's Analysis and Findings</th></tr>
<tr><td colspan="3">Simulated use</td></tr>
<tr><td>1.</td><td>For the attach the needle task, see the table and list below for a summary of use-related events.

<table>
<tr><th></th><th>1st injection scenario</th><th>2nd injection scenario (EoC pen)</th><th>2nd injection scenario (full pen)</th></tr>
<tr><td>Total number of UE, CC, UD</td><td>UE, n = 2</td><td>UE, n = 1</td><td>UE, n = 1</td></tr>
<tr><td>Type of participants</td><td>P10, C15</td><td>C15</td><td>C15</td></tr>
</table>

Use-related events included:
• UE
  ○ Did not attach the needle
  ○ Did not twist the needle to secure it

Based on the URRA, if this task is omitted or not performed correctly, there is risk of reduced protection against bleeds.

Relevant subjective data and the Applicant's root cause analysis (RCA) stated:
• Habit of not using the IFU
• IFU information not salient –1 participant skipped over the second sentence of the first bullet point in IFU Step 2 and recommended including "turn until tight" as a separate bullet point.

The Applicant stated the carton labeling instructs users to read the IFU. Additionally, the Applicant stated IFU Step 2 instructs users how to attach the needle and that there is a tactile click when the needle is turned and attached correctly to the pen. The Applicant did not propose mitigations in response to participants' performance on this task.</td><td>The subjective feedback indicated that a participant identified that the second bullet in IFU Step 2 could be revised for improved prominence.

Step 2 of the IFUs instructs users regarding how to attach the needle and includes a corresponding graphic. However, we find the location of the graphics can be improved to increase the visibility and prominence of the key sub-steps (i.e., attaching the needle and removing the needle caps [see the row below for detail regarding participant performance on the removing the needle caps task]). As such, we provide an IFU recommendation in the Identified Issues and Recommendations table below. We determined this revision is a clarification of the instructions that can be implemented without the submission of additional HF validation data.</td></tr>
</table>

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

<table>
<tr><th></th><th>Identified Issue</th><th>DMEPA's Analysis and Findings</th></tr>
<tr><td>2.</td><td>For the remove needle caps task, see the table and list below for a summary of use-related events.

<table>
<tr><th></th><th>1st injection scenario</th><th>2nd injection scenario (EoC pen)</th><th>2nd injection scenario (full pen)</th></tr>
<tr><td>Total number of UE, CC, UD</td><td>UE, n = 3
CC, n = 7</td><td>UE, n = 3
Use difficulty, n = 1</td><td>UE, n = 2</td></tr>
<tr><td>Type of participants</td><td>UE: A11, C1, H12
CC: C2, C5, C7, C15, P16, H3, H13</td><td>UE: A11, P10, H12,
UD: P11</td><td>UE: P10, H12</td></tr>
</table>

Use-related events included:
• UE
  ○ Performed the injection with the inner needle cap still on
  ○ Did not remove the outer or inner needle caps
• CC
  ○ Performed the flow check with the inner needle cap on. However, they removed the inner cap before performing the injection.
  ○ Perform the injection with the inner needle cap still on. Once they realized the medication was not coming out, they removed the inner cap and performed the injection correctly.
• UD
  ○ Struggled to remove the outer needle cap because their father was holding it down. The participant said they would ask their mother (who normally helps with treatment) for help. Their father then suggested removing the needle and reattaching a new needle. After reattaching a new needle their father held the device lower down and the participant was able to remove both needle caps.</td><td>The subjective feedback indicated unclear IFU information (i.e., unclear and unlabeled graphic) contributed to the use-related events with this task.

Step 2 of the IFUs instructs users to remove the outer and inner needle caps and includes a corresponding graphic. See row #1 above for additional discussion and recommendation regarding removal of the needle caps.</td></tr>
</table>

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

<table>
<tr><th></th><th>Identified Issue</th><th>DMEPA's Analysis and Findings</th></tr>
<tr><td></td><td>Based on the URRA, if this task is omitted or not performed correctly, there is risk of reduced protection against bleeding events (if needle cap is not removed) or discomfort or loss of nonsignificant functionality or quality (if the needle cap is not removed during flow check).

Relevant subjective data and the Applicant's RCA:
• Negative transfer – experience with products with one needle cap, with no needle cap, or where the needle is not visible and does not appear until a button/plunger is pushed down
• IFU Step 2 is not clear or salient –
○ Overlooked part of IFU Step 2 regarding removing the inner cap or did not understand Figure B due to lack of labeling
○ Did not understand IFU Step 2 graphic B due to the lack of hand placement

The Applicant stated the needles that are intended for use with the prefilled pen are a well-known marketed product and no new use errors were identified. The Applicant did not propose mitigations in response to participants' performance on this task.</td><td></td></tr>
<tr><td>3.</td><td>For the test the flow task, see the table and list below for a summary of use-related events.

<table>
<tr><th></th><th>1st injection scenario</th><th>2nd injection scenario (EoC pen)</th><th>2nd injection scenario (full pen)</th></tr>
<tr><td>Total number of UE, CC, UD</td><td>UE, n = 14
CC, n = 2
UD, n = 1</td><td>UE, n = 15
CC, n = 2</td><td>UE, n = 22</td></tr>
<tr><td>Type of participants</td><td>UE: A1, C5, C6, C11, C13, C14, P2, P4, P10, P11, H3, H8, H11, H12
CC: C4, C7
UD: P3</td><td>UE: A1, A4, A13, P2, P4, P10, P11, P16, C1, C5, C6, C7, C13, C14, H12
CC: A6, P12</td><td>A1, A4, A5, A13, C1, C4, C6, C8, C13, C14, P1, P4, P7, P8, P10, P11, P16, H3, H8, H10, H12, H15,</td></tr>
</table></td><td>We acknowledge the Applicant categorized this task as non-critical; however, based on the potential harm that may occur if this task is omitted or not performed correctly (i.e., underdose), we consider this task critical. We defer to the clinical review team for their assessment of the Applicant's assertion that underdose caused by failure to test the flow has no medical consequence, and we note the assessment of the clinical impact of a single underdose is currently under review.

Additionally, we defer to the Center for Devices and Radiologic Health (CDRH) for their</td></tr>
</table>

Table 3. Identified Issues and DMEPA's Analysis and Findings **Legend: A** = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error		
	Identified Issue	**DMEPA's Analysis and Findings**

	Use-related events included:
	• UE
	  ○ Did not perform the task
	  ○ Pressed the dose button without dialing first
	  ○ Dialed the incorrect flow check volume (i.e., higher than 0.1 mL)
	• CC
	  ○ Initially dialed the incorrect flow check volume but self-corrected
	  ○ Initially skipped the step and then adjusted the dose to correct or self-corrected
	• UD
	  ○ Pressed the dose button when dialed to "0", referred to the IFU when they did not see any medication, and then self-corrected
	
	Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose (no medical consequence per Applicant).
	
	Relevant subjective data and the Applicant's RCA:
	• IFU information not salient:
	  ○ Overlooked Part (a) in IFU Step 3 and/or the second bullet in IFU Step 6 ("Test the flow before each injection")
	  ○ Did not notice the second sentence in IFU Step 4 ("You can adjust your dose by turning the dose selector in either direction…")
	  ○ Did not notice the first sentence in IFU Step 3 ("A drop may appear at the needle tip, but you should still test the flow before each injection to avoid underdosing")
	• IFU information not clear:
	  ○ Believed IFU Step 3 could be skipped as long as the pen works
	  ○ Believed the step was not necessary (e.g., in the 2nd injection scenario, a participant believed this step was unnecessary and noted they already performed the task with 1st injection)
		assessment of the Applicant's claims regarding the occurrence and impact of an air gap or air in the prefilled pen in instances where the user does not test the flow.
		The subjective feedback indicated participants overlooked portions of IFU Steps 3 and 4 or found aspects of the IFU unclear. Additionally, negative transfer contributed to the use-related events.
		
		Step 3 of the IFUs instructs users to test the flow and includes corresponding graphics. However, we find the title of IFU Step 3 can be improved to clarify that users should test the flow of the prefilled pen prior to each injection. **As such, we provide an IFU recommendation in the Identified Issues and Recommendations table below**. We determined this revision is a clarification of the instructions that can be implemented without the submission of additional HF validation data. Additionally, we defer to the clinical and CDRH review teams regarding whether the residual risk associated with this task is a review issue.

Table 3. Identified Issues and DMEPA's Analysis and Findings **Legend: A** = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error		
	Identified Issue	**DMEPA's Analysis and Findings**
	○ Use of similar graphics for two separate steps (i.e., IFU Steps 3 and 4); the participant skipped over IFU Step 3 after acknowledging the graphic depicting a hand dialing what they believed was the dose which is similar to the graphic used in IFU Step 4 • Habit of not using the IFU • Negative transfer: experience with products that don't require priming or that require priming that is done differently Regarding the justification for categorizing this task as non-critical, the Applicant stated that failure to test the flow would result in no medical consequence and provided the following justification for the categorization: • Failure to test the flow initially when taking a new prefilled pen in use is only a risk for the first dosing with the prefilled pen. The first dosing with the prefilled pen, potentially resulting in a single underdose, will replace the required step of initial flow check and thereby the next dosing with that same prefilled pen will only require flow check in-between dosing • Failure to test the flow in-between dosing with the same prefilled pen resulting in an air gap that compromises treatment is not reasonably foreseeable to occur for consecutive occasions. An air gap that compromises treatment is only likely to occur in the event of a consecutive change of temperature from one dosing to the next dosing – e.g., a user should consecutively perform dosing at cold temperatures on uneven days and at hot temperatures on even days • Failure to test the flow in-between dosing with the same prefilled pen resulting in air in cartridge not removed will only result in slower dosing that would not result in an underdose that compromises treatment The Applicant stated that information about the flow check is included in IFU Step 3 and in the Important Information section. The Applicant did not propose mitigations in response to participants' performance on this task.	
4.	For the set the intended dose task, see the table and list below for a summary of use-related events.	We note the Applicant categorized A15's performance as a close call; however, because

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

	Identified Issue	DMEPA's Analysis and Findings

	1st injection scenario	2nd injection scenario (EoC pen)	2nd injection scenario (full pen)
Total number of UE, CC, UD	UE, n = 3 CC, n = 1	UE, n =5	UE, n = 1
Type of participants	A15, P7, P10, P15	A11, A15, P2, P11, and C5	C15

Use-related events included:

- UE
  - Set the incorrect dose
  - Set the dose depicted in the IFU instead of the dose stated on the prescription
  - Incorrectly set the dose to 24 mg (dose depicted in the 300 mg IFU) instead of 10 mg
- CC
  - Incorrectly set the dose to 9.6 mg (dose depicted in the 60 mg IFU) instead of 4 mg; when the moderator reminded them that the dose was indicated on their prescription they dialed to the correct amount

Based on the URRA, if this task is omitted or not performed correctly, there is risk of thromboembolism or reduced protection against bleeds.

Relevant subjective data and the Applicant's RCA stated:

- IFU
  - IFU depicts a dose amount that may not match the patient's specific prescription
- Device/device design
  - Misread the numbers on the dial
  - Insufficient design — decimal point on pen is very small and participants might have overlooked it
- Believed the maximum dose was 1 mg so they dialed to 0.8 mg (instead of 8 mg)

of moderator intervention, we consider this a use error. Specifically, the moderator reminded A15 to dial the dose on the mock prescription (i.e., 4 mg) after A15 set the dose to 9.6 mg.

The subjective feedback indicated that misinterpretation of the decimal point in the dosing window may have contributed to some participants setting an incorrect dose and that some participants referred to the dose in the IFU instead of the dose on the prescription.

We acknowledge a participant in the 2nd injection scenario set the dose to 3.2 mg instead of 32 mg because they overlooked the decimal point. However, based on our independent review of the product sample, we did not identify areas of improvement for the prefilled pen device design and find that the constituent parts of the prefilled pen related to dialing the dose (e.g., dose counter, dose pointer, dose selector, and dose button) are similar to other currently marketed products.

Step 4 of the IFUs instructs users to set the dose. However, Step 4 can be improved to minimize the risk of users confusing the dose depicted in the graphic as the prescribed dose. **As such, we provide an IFU recommendation in the Identified Issues and Recommendations table**

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

<table>
<tr><th></th><th>Identified Issue</th><th>DMEPA's Analysis and Findings</th></tr>
<tr><td></td><td>

Negative transfer — experience with vial and syringe

Did not realize the pen did not contain enough medication or that they would require an additional pen to receive a full dose due to previous experience.

Thought they "gave up" 1 mg to test the flow twice so they should set the dial higher than the intended dose.

The Applicant stated IFU Step 4 instructs users to select their prescribed dose. The Applicant also stated IFU Step 6 guides users on how to handle an EoC pen. Additionally, the Applicant stated the carton labeling instructs users to read the IFU and states "Dials in x increments and contains y mg total". The Applicant did not propose mitigations in response to participants' performance on this task.
</td><td>below. We determined this revision is a clarification of the instructions that can be implemented without the submission of additional HF validation data.</td></tr>
<tr><td>5.</td><td>
For the select an injection location task, see the table and list below for a summary of use-related events.
<table>
<tr><th></th><th>1st injection scenario</th><th>2nd injection scenario (EoC pen)</th><th>2nd injection scenario (full pen)</th></tr>
<tr><td>Total number of UE, CC, UD</td><td>UE, n = 11</td><td>UE, n = 7</td><td>UE, n = 7</td></tr>
<tr><td>Type of participants</td><td>P2, P4, P6, P8, P10, P11, A3, A15, H3, H8, H12</td><td>P2, P4, P10, P11, A3, A15, H12</td><td>P4, P6, P8, P10, P11, H8, H12</td></tr>
</table>
Use-related events included:

UE

Injected into the arm as if administering intravenously
Injected into the back of the arm

</td><td>The subjective feedback indicated negative transfer due familiarity with other injection sites contributed to several of the use-related events with this task. We also acknowledge that participants demonstrated an understanding of the correct injection locations after referring to the IFU.

We note the carton labeling and container label indicate the product should be used administered subcutaneously. Additionally, the "Where on my body should I inject my dose?" section of the IFUs includes text and a corresponding graphic to describe the acceptable injection site locations.</td></tr>
</table>

<table>
<tr><th colspan="3">Table 3. Identified Issues and DMEPA's Analysis and Findings
Legend: A = adult patient participant, C = caregiver participant, CC = close call, EoC = end-of-content, H = healthcare professional participant, IFU = instructions for use, P = pediatric patient participant, UD = use difficulty, UE = use error</th></tr>
<tr><th></th><th>Identified Issue</th><th>DMEPA's Analysis and Findings</th></tr>
<tr><td></td><td>Based on the URRA, if this task is omitted or not performed correctly, there is risk of thromboembolism or intramuscular bleed.

Relevant subjective data and the Applicant's RCA stated:
• Negative transfer
○ Patient participants were experienced self-administering intravenous injections
○ HCP participants were familiar with administering subcutaneous injections in the back of arm

The Applicant stated the IFU and carton labeling specify the product should be administered subcutaneously. The Applicant did not propose mitigations in response to participants' performance on this task.</td><td>We did not identify additional areas of improvement and have no recommendations at this time..</td></tr>
<tr><td>6.</td><td>For the insert needle in subcutis task, see the table and list below for a summary of use-related events.

<table><tr><th></th><th>1st injection scenario</th><th>2nd injection scenario (EoC pen)</th><th>2nd injection scenario (full pen)</th></tr><tr><td>Total number of UE, CC, UD</td><td>UE, n = 2</td><td>UE, n =1</td><td>N/A</td></tr><tr><td>Type of participants</td><td>A11, P6</td><td>A11</td><td>N/A</td></tr></table>
Use-related events included:
• UE:
○ Inserted the needle at an approximately 45-degree angle

Based on the URRA, if this task is omitted or not performed correctly, there is risk of pain or injection site reaction.</td><td>The subjective feedback from 1 participant indicated IFU Step 5 contributed to a use-error.

The "Where on my body should I inject my dose?" section of the IFUs indicates users should inject at a 90-degree angle. However, the injection site graphic in IFU Step 5 is unclear which makes it difficult to determine the depicted injection angle. As such, we provide an IFU recommendation in the Identified Issues and Recommendations table below. We determined this revision is a clarification of the instructions that can be implemented without the submission of additional HF validation data.</td></tr>
</table>

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

<table>
<tr><th></th><th>Identified Issue</th><th>DMEPA's Analysis and Findings</th></tr>
<tr><td></td><td>Relevant subjective data and the Applicant's RCA stated:
IFU information not clear: injected sideways because "the picture in the instructions should be at a different angle" and noted that IFU Step 5 graphic appeared to show the pen being injected from the side.
Test artifact: 1 participant said they knew to inject a 90-degree angle, but it was difficult to do because the injection pad was on their dominant wrist.
The Applicant stated the IFU specifies the product should be administered subcutaneously in both text and a graphic. The Applicant did not propose mitigations in response to participants' performance on this task.</td><td></td></tr>
<tr><td>7.</td><td>For the inject the dose task, see the table and list below for a summary of use-related events.<table><tr><th></th><th>1st injection scenario</th><th>2nd injection scenario (EoC pen)</th><th>2nd injection scenario (full pen)</th></tr><tr><td>Total number of UE, CC, UD</td><td>UE, n = 9</td><td>UE, n = 8</td><td>UE, n = 10</td></tr><tr><td>Type of participants</td><td>C1, C7, C8, C14, P2, P10, P15, H11, H12</td><td>A11, A15, P10, P15, C7, C14, H11, H12</td><td>P4, P10, P14, P15, C7, C8, C13, H8, H11, H12</td></tr></table>Use-related events included:
UE
Held the prefilled pen down for less than 6 seconds after the click (when the pen dial reached 0).
Did not hold the prefilled pen down
Injected the dose and held correctly but did not think that all the medication went through, so the participant then attached another needle and injected again (this was their third injection during the scenario)</td><td>We note that some participants did not hold the prefilled pen down for 6 seconds after the click (when the dial reached 0) or did not hold prefilled pen down at all. However, we note the inject the dose task and the 6 second hold time is not unique to the proposed product and are consistent with other currently marketed products from the Applicant (i.e., Tresiba FlexTouch and Norditropin FlexPro).

As previously noted, the assessment of the clinical impact of a single underdose is currently under review.

The subjective feedback indicated that participants who referred to the IFU found certain use steps in IFU Step 5 lacked prominence or clarity.</td></tr>
</table>

Table 3. Identified Issues and DMEPA's Analysis and Findings **Legend: A** = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error		
	Identified Issue	**DMEPA's Analysis and Findings**
	Based on the URRA, if this task is omitted or not performed correctly, there is risk of reduced protection against bleeding events due to underdose. Additionally, in Table 13 Extract of non-critical risk scenarios, the Applicant also states that if a user removes the prefilled pen from the skin before injection is completed, there is risk of a single underdose that does not have medical consequence. Relevant subjective data and the Applicant's RCA stated: • IFU information not salient: o Overlooked part of IFU Step 5, substep (e) o IFU does not explicitly state that the pen is intended for multi-use • IFU information not clear: o Did not understand when they should count to 6 and the wording in IFU Step 5, substep (e) was unclear • Insufficient feedback: o Believe the injection task was complete after hearing the click and seeing the dial return to 0 • Negative transfer: o Previous experience with EpiPen, insulin pen, single-use devices (i.e., Humira) and different devices o Experience with young child: did not hold for full 6 seconds because of their experience injecting into a young child who often pulls away In a Response to Information Request (IR) dated October 31, 2022, the Applicant stated "the use errors observed for the injection task were solely related to the holding time ("count slowly to 6 after the dose counter has returned to <0>"). All participants understood to hold the dose button pressed down until the dose counter returned to <0>, which means that the active phase of injection for their intended doses was completed. During debrief, the participants that had not counted slowly to 6 after end of dose, admitted to not reading as closely the IFU as they would in	IFU Step 5 includes several use steps for injecting the proposed product. However, the prominence and wording and substep (e) could be improved. **As such, we provide an IFU recommendation in the Identified Issues and Recommendations table below**. We determined this revision is a clarification of the instructions that can be implemented without the submission of additional HF validation data.

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

<table>
<tr><th></th><th>Identified Issue</th><th>DMEPA's Analysis and Findings</th></tr>
<tr><td></td><td>real practice due to the artificial test environment. They read the IFU and then understood the instruction to hold the prefilled pen after the dose counter has returned to <0>.
In real-life, Novo Nordisk strongly encourages physicians to use the IFU prior to initiating treatment and expects that the treatment is initiated under the guidance of a healthcare provider". The Applicant also noted that during the 6 second hold time, the user is expected to hold the needle inserted into the skin but is not required to maintain pressure on the dose button. Additionally, the Applicant noted that the instruction to "count slowly to six" after the scale drum returns to <0> is present for all the (b) (4) pen-injector variants from Novo Nordisk (Applicant) such as Norditropin FlexPro (NDA 21148) and Tresiba FlexTouch (NDA 203314).

The Applicant also stated the IFU Step 5 and the Important Information section informs users about withdrawing the pen after 6 seconds. The Applicant did not propose mitigations in response to participants' performance on this task.</td><td></td></tr>
<tr><td>8.</td><td>For the remove and dispose of the used needle task, see the table and list below for a summary of use-related events.

<table>
<tr><th></th><th>1st injection scenario</th><th>2nd injection scenario (EoC pen)</th><th>2nd injection scenario (full pen)</th></tr>
<tr><td>Total number of UE, CC, UD</td><td>UE, n =3
CC, n = 2</td><td>UE, n = 3</td><td>UE, n =3
UD, n = 1</td></tr>
<tr><td>Type of participants</td><td>A1, A11, P10, H4, H9</td><td>A1, C2, P10</td><td>A1, A8, P10, P11</td></tr>
</table>

Use-related events included:
• UE
○ Disposed of the entire pen in the sharps container
○ Did not remove and dispose of the used needle
○ Needlestick injury (poked with the back of needle)
○ Did not remove the needle and put the cap on top the needle.</td><td>The subjective feedback indicated that some participants did not understand the pen is multidose and thus disposed of the entire prefilled pen (instead of only disposing of the used needle) or almost disposed of the pen until they read IFU Step 7. However, we anticipate that patients and caregivers would be dispensed 1—2 pens for a one-month supply with actual use, which would likely signal that the prefilled pen is multidose especially given the product is administered daily.

Although one participant (i.e., P11) stated they would store the pen with the used needle and then perform the task prior to their next dose; P11 performed this task correctly in the previous simulated use scenarios.</td></tr>
</table>

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

<table>
<tr><th></th><th>Identified Issue</th><th>DMEPA's Analysis and Findings</th></tr>
<tr><td></td><td>

CC

Initially stated they would place entire pen in the sharps container, then noticed IFU Step 7 which indicates the pen is used for multiple doses

UD

Initially unsuccessful when trying to pull the needle off but then was able to remove the needle by squeezing and pulling.

Based on the URRA, if this task is omitted or not performed correctly there is risk of discomfort, loss of nonsignificant functionality or quality, puncture wound or skin abrasion, and reduced protection against bleeding events (if the user fails to remove needle after use).

Relevant subjective data and the Applicant's RCA stated:

IFU information not salient or clear

Overlooked parts of IFU that indicate the pen is multidose
The concept that the pen is multidose is not explicitly stated
Overlooked the second sentence of IFU Step 6 "Do not touch the back end of the needle"
Focused on picture B in IFU Step 2 instead of the graphic in IFU Step 6

Unfamiliar with reusing a device
Did not expect the needle would be on both sides

The Applicant stated the IFU Steps 6 and 7 and the Throwing Away and Storing sections of the IFU provide information regarding removing the needle and correct pen disposal and storage between uses. The Applicant did not propose mitigations in response to participants' performance on this task.
</td><td>Additionally, 1 participant (i.e., C2) experienced a needlestick injury because they did not expect the needle would be on both sides and did not notice the part of IFU step 6 that mentioned not touching the back end of the needle. We note the prefilled pen will be used with standard commercially available pen needles (i.e., Novofine Plus). Therefore, the risk of needle stick injury while performing this task is not unique to the proposed product.

Step 6 in the IFUs includes text and a graphic to depict removing the used needle. However, we find a statement regarding the needle cap can be improved to mitigate the risk of needle stick injury. As such, we provide IFU recommendations in the Identified Issues and Recommendations table below. We determined these revisions are clarifications of the instructions that can be implemented without the submission of additional HF validation data.</td></tr>
<tr><td>9.</td><td>For the put on the pen cap task, see the table and list below for a summary of use-related events.
<table>
<tr><th></th><th>1st injection scenario</th><th>2nd injection scenario (EoC pen)</th><th>2nd injection scenario (full pen)</th></tr>
</table>
</td><td>The subjective feedback indicated that the IFUs do not prominently convey that the pen is multidose. However, we also note the participants who experienced use-related events in the 1st injection scenario performed the task correctly in subsequent injection scenarios.</td></tr>
</table>

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

	Identified Issue	DMEPA's Analysis and Findings

	<table><tr><td>Total number of UE, CC, UD</td><td>UE, n = 2
	UD, n = 1</td><td>N/A</td><td>N/A</td></tr><tr><td>Type of participants</td><td>A15, C2, P4</td><td>N/A</td><td>N/A</td></tr></table>
	Use-related events included:
	• UE
	  ○ Did not put the pen cap on
	• UD
	  ○ Initially tried to put the outer needle cap back on but then corrected and put the pen cap on
	
	Based on the URRA, if this task is omitted or not performed correctly, there is risk of discomfort or loss of nonsignificant functionality or quality.
	
	Relevant subjective data and the Applicant's RCA stated:
	• IFU information not salient:
	  ○ Overlooked parts of IFU that indicate the pen is multidose
	  ○ The concept that the pen is multidose is not explicitly stated
	• Unfamiliar with reusing a device
	
	The Applicant stated the IFU Step 7 and the Important Information, Throwing Away, and Storing sections of the IFU provide information regarding correct disposal. The Applicant did not propose mitigations in response to participants' performance on this task.
		Additionally, refer to our assessment in row #8 above regarding participants' understanding that the pen is multidose.
		
		We find the title of IFU Step 7 can be improved to better convey to the task the step describes. **As such, we provide an IFU recommendation in the Identified Issues and Recommendations table below**. We determined this revision is a clarification of the instructions that can be implemented without the submission of additional HF validation data.

Knowledge check/comprehension questions		
10.	For the knowledge check/comprehension question regarding frequency of administration (How often should a patient take a dose?), see the table and list below for a summary of use-related events.	The subjective feedback indicated the pediatric participant had difficulty understanding terms "prescribed" and "healthcare provider" due to

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

	Identified Issue	DMEPA's Analysis and Findings
	<table><tr><td>Total number of UE, CC, UD</td><td>UD, n = 1</td></tr><tr><td>Type of participants</td><td>P1</td></tr></table> Use-related event included: • UD ○ Said they would ask their mom how often to take the medication Based on the URRA, if the corresponding task is omitted or not performed correctly, there is risk of reduced protection against bleeding events due to incorrect frequency of injections. Relevant subjective data and the Applicant's RCA stated: • Read "take your dose at frequency prescribed by your healthcare provider" and had difficulty with the word "prescribed" and was unsure what "healthcare provider" meant • Test artifact: participant did not understand some of the IFU due to their age (9 years old) The Applicant stated the IFU Step 4 ensures the patient selects the prescribed dose and that they expect that a caregiver would assist the participant in understanding the task. The Applicant did not propose mitigations in response to participants' performance on this knowledge task.	their age. However, we find that it is likely a pediatric patient would seek assistance from a caregiver regarding the frequency of administration. We note all caregiver participants provided a correct response. The introductory and Important Information sections of the IFUs instruct users to administer the proposed product at the frequency prescribed by their doctor. We also note that the frequency of administration information would likely appear on the prescription label. We did not identify areas of improvement and have no recommendations at this time.
11.	For the knowledge check/comprehension question regarding the product expiration (How many days can a pen be used for?), see the table and list below for a summary of use-related events. <table><tr><td>Total number of UE, CC, UD</td><td>UE, n = 7 UD, n =1 CC, n = 1</td></tr><tr><td>Type of participants</td><td>A6, A9, A14, C6, P6, P7, P16, H11, H14</td></tr></table>	The subjective feedback indicated that several participants misinterpreted or were confused by the IFU statement regarding how many days the pen can be used after first use. (b) (4) . However, based on

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

	Identified Issue	DMEPA's Analysis and Findings

	Use-related events included:
	• UE
	  ○ Did not interpret the IFU information correctly. They believed the IFU indicated the pen would not be used more than once per month or that they should first use the pen and then wait a 28-day period to use again.
	• CC
	  ○ Initially believed the IFU indicated the pen should be used once a month. After rereading the IFU, they interpreted the information correctly.
	• UD
	  ○ Needed to read and interpret the IFU information a few times before they understood.
	
	Based on the URRA, if the corresponding task is omitted or not performed correctly, there is risk of reduced protection against bleeding events due to exceeding in-use time.
	
	Relevant subjective data and the Applicant's RCA stated:
	• IFU information not clear: participants did not understand the statement "(b) (4) Participants provided suggestions for rephrasing the statement such as (non all inclusive):
	  ○ "use the pen no more than 28 days after first use", "if opened, discard after 28 days", "pen is only good for 28 days", "discard after 28 days", "once opened, do not use after 28 days", "once you take the first dose do not use your pen for more than 28 days",", and "after 28 days do not use your pen".
	
	The Applicant stated the Important Information and Storing sections of the IFU include information to ensure the usage time does not exceed 28 days. The Applicant did not propose mitigations in response to participants' performance on this knowledge task.
		subjective feedback, we find the labeling statements related to the in-use period can be improved. **As such, we provide IFU and carton labeling recommendations in the Identified Issues and Recommendations table below**. We determined these revisions are clarifications of the instructions that can be implemented without the submission of additional HF validation data.

Table 3. Identified Issues and DMEPA's Analysis and Findings

Legend: A = adult patient participant, **C** = caregiver participant, **CC** = close call, **EoC** = end-of-content, **H** = healthcare professional participant, **IFU** = instructions for use, **P** = pediatric patient participant, **UD** = use difficulty, **UE** = use error

	Identified Issue	DMEPA's Analysis and Findings

12.	For the knowledge check/comprehension question regarding the storage task (What is important to consider when storing pen in refrigerator?), see the table and list below for a summary of use-related events.
	
	Total number of UE, CC, UD: UE, n = 3
	Type of participants: C12, P2, P6
	
	Use-related events included:
	• UE
	  ○ Believed the product should not be stored next to other items in the refrigerator
	  ○ Stated "store it in something and then put it in the fridge"
	
	Based on the URRA, if the corresponding task is omitted or not performed correctly, there is risk of (a) thromboembolism or (b) discomfort or loss of nonsignificant functionality or quality.
	
	Relevant subjective data and the Applicant's RCA stated:
	• IFU information not clear— unfamiliar language: participants were not familiar with the term "cooling element".
	
	The Applicant stated the Storing section of the IFU includes information to ensure that the prefilled pen is stored correctly in the fridge. The Applicant did not propose mitigations in response to participants' performance on this knowledge task.
		We note the phrasing of the knowledge task question may not have elicited the intended response from participants.
		
		The subjective feedback indicated that the term "cooling element" in the IFU could be clarified to minimize confusion.
		
		The Storing section of IFUs instructs users on how to store the product. However, we find the statement "When stored in the refrigerator, do not store the pen directly next to the cooling element" can be improved. **As such, we provide an IFU recommendation in the Identified Issues and Recommendations table below.** We determined this revision is a clarification of the instructions that can be implemented without the submission of additional HF validation data.

4.1 ANALYSIS OF NON-CRITICAL TASKS

The HF validation study showed use errors and use difficulties with the non-critical tasks listed below. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis, and Applicant's proposed risk mitigation strategy we

determined the residual risk is acceptable. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the following non-critical tasks:

- Unpack system elements

4.2 LABELS AND LABELING

The proposed prescribing information (PI), container labels, carton labeling, and instructions for use (IFU) may be improved to promote the safe use of this product from a medication error perspective.

Tables 4 and 5 below include the identified medication error issues with the submitted PI and IFU, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

On January 25, 2023, the Agency provided our container labels and carton labeling recommendations in an IR (see Appendix E). Then, on February 8, 2023, the Applicant submitted revised carton labeling and container labels in response to the January 25, 2023 IR (see Appendix F.4). Subsequently, on February 14, 2023, the nonproprietary name "concizumab-mtci" was found conditionally acceptable. As such, we issued an IR on February 24, 2023 requesting the Applicant revise the carton labeling and container labels to include the nonproprietary name suffix "-mtci" (see Appendix E). On February 27, 2023, the Applicant submitted revised carton labeling and container labels (see Appendix F.6).

Table 4: Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Prescribing Information – General Recommendation			
1.	The dosage form "(b) (4) is not correct.	The dosage form should be consistent with USP nomenclature.	We recommend revising all instances of "(b) (4) in the Highlights of Prescribing Information and Full Prescribing Information to "injection", as appropriate. However, we defer to the Office of Pharmaceutical Quality (OPQ) regarding the acceptability of the dosage form.
2.	The Dosage and Administration section in Highlights of PI and in Full PI contains trailing zeroes (e.g., 1.0 mg)	To avoid ten-fold misinterpretation, trailing zeroes should be eliminated from dose expressions.[e]	We recommend removing all instances of trailing zeroes in the Dosage and Administration section in Highlights of PI and in Full PI (e.g., 1 mg).
Full Prescribing Information			
1.	(b) (4) contains an error prone abbreviation (i.e., "U").	The abbreviation "U" could be misinterpreted as zero or the number 4, causing a 10-fold overdose or greater.[f]	We recommend revising "U" to "units".

[f] Error-Prone Abbreviations, Symbols, and Dose Designation: ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2022 DEC 29]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 4: Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
2.	The description of the color of the prefilled pen (b) (4) can be improved to minimize confusion. (b) (4)	Inconsistent descriptions of the appearance of each strength of the prefilled pen may lead to confusion.	We recommend removing the term (b) (4) .
3.	As currently presented in the PI, (b) (4)	We expect your proposed strengths to be adequately differentiated. (b) (4)	(b) (4) (b) (4) we recommend the PI describe color differentiation (b) (4) (b) (4) (b) (4) As such, we recommend you reference the pen label color in Section 2 (b) (4) of the PI (see recommendation immediately above) and in Section 16 of the PI. For example, the 300 mg/3 mL pen label should be described as “white”.

Table 4: Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
	(b) (4)		
4.	The storage information in Section 16 How Supplied/Storage and Handling includes the unfamiliar term “cooling element” that might not be readily understood.	Lack of unclarity regarding product storage might pose of risk of deteriorated drug medication errors.	We recommend defining or clarifying the term “cooling element”.

Table 5: Identified Issues and Recommendations for Novo Nordisk Inc.			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instructions for Use (IFU) – all strengths – PDF versions			
1.	The location of the graphics in Step 2 can be improved to increase the visibility and prominence of the key sub-steps (i.e., attaching the needle and removing the needle caps).	In the HF validation study, there were use-related events (i.e., use errors, close calls, and a use difficulty) with the attach the needle and remove the needle caps tasks. Based on the URRA, if the remove the needle caps tasks are omitted or not performed correctly, there is risk of reduced protection against bleeds.	Relocate Step 2 graphic A to appear directly below the first bullet (i.e., "…See A."). Additionally, relocate Step 2 graphic B to appear directly below the third bullet ("…See B."). For example, we refer to the formatting used in your Tresiba FlexTouch Pen IFU and your Norditropin FlexPro Pen IFU.
2.	The title of Step 3 can be improved to clarify that users should test the flow of the prefilled pen (i.e., prime the prefilled pen) prior to each injection.	In the HF validation study, the subjective feedback and root cause analysis information that indicated some participants overlooked the instruction to the test the flow before each injection or did not know the task was necessary for each subsequent injection after the 1st injection. Lack of prominence of a use task might result in the task being omitted due to being overlooked.	Revise the title of Step 3 from "(b) (4) to "Prime before each dose. Dial to '1' and test the flow before each dose."

Table 5: Identified Issues and Recommendations for Novo Nordisk Inc.			
	Identified Issue	**Rationale for Concern**	**Recommendation**
3.	Users may confuse the Step 4 graphic depicting an example dose with their prescribed dose.	In the HF validation study, there were use-related events (i.e., use errors) in which participants incorrectly dialed the dose depicted in the IFU instead of the prescribed dose. Based on the URRA, if the set the intended dose task is not performed correctly, there is risk of thromboembolism or reduced protection against bleeds.	Revise the Step 4 graphic to include two dose examples. We find this revision might prompt users to identify the graphics as examples and not the intended dose. For example, we note the Tresiba FlexTouch Pen IFU and the Norditropin FlexPro Pen IFU include graphics containing two dose examples. Also, consider zooming in on the dose counter and dose pointer part of the prefilled pen for the two dose examples to improve readability.
4.	The injection angle depicted in the Step 5 graphic is unclear due to the perspective view used. Specifically, the graphic appears to depict the prefilled pen being injected into the right portion of the injection site with the left hand, and the injection angle is difficult to discern. Additionally, the placement of the hand in the graphic can be improved.	In the HF validation study, there were use-related events (i.e., use errors) with the insert needle in subcutis task. We specifically note subjective feedback which indicate the IFU graphic appears to show the pen being injected from the side. Based on the URRA, if the insert the needle task is omitted or not performed correctly, there is risk of pain or injection site reaction.	Revise the Step 5 graphic to more clearly depict the prefilled pen being injected into the injection site at a 90-degree.

Table 5: Identified Issues and Recommendations for Novo Nordisk Inc.			
	Identified Issue	**Rationale for Concern**	**Recommendation**
5.	Step 5 can be improved to increase the visibility and prominence of the key sub-steps (i.e., press and hold the button, count slowly to 6 after the dose counter has returned to <0>).	In the HF validation study, there were use-related events (i.e., use errors) with the inject the dose task. We specifically note subjective feedback which indicated participants overlooked part of IFU Step 5 sub-step (e) and found the wording of IFU Step 5 sub-step (e) unclear. Based on the URRA, if the inject the dose task is omitted or not performed correctly, there is risk of reduced protection against bleeding events due to underdose.	Increase the prominence of Step 5 substep (b) (4) by dividing Step 5 into separate steps (e.g., revise Step 5 substep (b) (4) to Step 6 [and renumber subsequent steps accordingly]) or into separate groups of steps (e.g., revise Step 5 substeps (b) (4) to Step 5 and revise Step 5 substeps (b) (4) to Step 6 [and renumber subsequent steps accordingly]). Include a graphic directly below Step 5 substep (b) (4) that depicts the step of counting slowly to 6 after the dose counter has returned to <0> (similar to Figure P in the Tresiba FlexTouch Pen IFU). Additionally, consider revising Step 5 substep (b) (4) (b) (4) to "Once the needle has returned to <0>, count slowly to 6 while the needle is still in your skin".
6.	Step 6 can be improved to more prominently convey the risk associated with touching inside of the bottom of the pen needle (e.g., needle stick injury).	In the HF validation study, 1 participant experienced a needle stick injury due to being poked with the back of the needle.	Consider replacing the term "(b) (4) with a more adequate term and label the appropriate location in the Step 6 graphic of the pen needle with your newly selected term.

Table 5: Identified Issues and Recommendations for Novo Nordisk Inc.			
	Identified Issue	**Rationale for Concern**	**Recommendation**
	Additionally, the term "(b) (4) in the IFU may not clearly convey the location of the exposed needle on the inside of the bottom of the pen needle. (b) (4)	Based on the URRA, if a user experiences a needle stick injury (via the needle front or back-end or a contaminated needle), there is risk of a puncture wound or skin abrasion/infection.	Additionally, revise the Step 6 statement (b) (4) to a statement similar to "Do not touch the [newly selected term] of the needle to avoid sticking yourself with the needle".
7.	The title of Step 7 can be improved to mitigate the risk of users not recapping the pen.	In the HF validation study, there were use-related events (i.e., use errors and a use difficulty) with the put on the pen cap task. Based on the URRA, if the put on the pen cap task is omitted or not performed correctly, there is risk of	Revise the title of Step 7 from "(b) (4)" to "Recap the pen".

Table 5: Identified Issues and Recommendations for Novo Nordisk Inc.			
	Identified Issue	**Rationale for Concern**	**Recommendation**
		discomfort or loss of nonsignificant functionality or quality.	
8.	The post-opening expiration date information in the Important information about your pen section is unclear.	In the HF validation study, there were use-related events (i.e., use errors, a use difficulty, and a close call) with the knowledge check/comprehension question "How many days can a pen be used for?" in which participants misinterpreted the post-opening expiration date information or had difficulty interpreting the post-opening expiration date information. Based on the URRA, if users do not correctly interpret the post-opening expiration date, there is risk of reduced protection against bleeding events due to exceeding in-use time.	Revise the statement "(b) (4) to "After 28 days, you must throw away (discard) your pen in an FDA-cleared sharps disposal container".
9.	The storage information in the Storing section of the IFU can be improved to increase the prominence of the storage conditions.	Lack of prominence of the product storage information might pose of risk of deteriorated drug medication errors.	Revise the headers "Before first use" and "After first use" to appear in bold font.

Table 5: Identified Issues and Recommendations for Novo Nordisk Inc.			
	Identified Issue	**Rationale for Concern**	**Recommendation**
10.	The storage information includes an unfamiliar term, “cooling element”, that might not be readily understood by lay users.	Lack of unclarity regarding product storage might pose of risk of deteriorated drug medication errors.	Define and clarify the term “cooling element” in the Storing section of the IFU to improve lay user understanding. Please note you may consider including examples of a cooling element, if appropriate.
11.	The presentation of Step 6 in the PDF version of the draft IFUs submitted in the October 31, 2022 Response to Information Request is different from the Word versions submitted on August 24, 2022. Specifically, the PDF version of the IFUs includes information related to “Do you need a larger dose than you can dial”. However, the Word version of the IFUs includes this information below a blank box to the right of the graphic depicting a sharps container.	We need to understand the proposed Word IFU format to provide a comprehensive review of the IFUs.	Clarify whether “Do you need a larger dose than you can dial” will appear in the box in Step 6 in the commercial IFUs.

Table 5: Identified Issues and Recommendations for Novo Nordisk Inc.			
	Identified Issue	**Rationale for Concern**	**Recommendation**
12.	The IFUs do not include the conditionally acceptable proprietary name (PN) Alhemo.	The proposed proprietary name, Alhemo, was found conditionally acceptable on November 21, 2022.[g]	Revise the IFU to include the PN Alhemo.

[g] Wu, L. Proprietary Name Granted Letter for concizumab. Silver Spring (MD): FDA, CDER, OSE (US); 2022 NOV 21. BLA 761315. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8069a7ed.

5 CONCLUSION AND RECOMMENDATIONS

Our review of the results of the human factors (HF) validation study identified use errors with critical tasks which indicates that there are additional mitigations that should be implemented to address use errors that occurred. We have determined that these mitigations can be implemented without submitting additional data from an HF validation study for Agency review.

Additionally, our evaluation of the proposed packaging, label, and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 4 for the Division of Non-Malignant Hematology (DNH).

The carton labeling and container labels submitted on February 27, 2023 are acceptable from a medication error perspective. We are continuing to collaborate on labeling negotiations for the IFU (see Table 5 above) with DNH in a collaborative document at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 6 presents relevant product information for Alhemo that Novo Nordisk submitted on 8/24/2022.

Table 6. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Hemostatic agent/ tissue factor pathway inhibitor (TFPI)-directed antibody
Active Ingredient (Drug or Biologic)	concizumab-mtci
Indication	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with: • hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors • hemophilia B (congenital factor IX deficiency) with FIX inhibitors
Route of Administration	subcutaneous
Dosage Form	injection
Strength	(b) (4) 60 mg/1.5 mL (40 mg/mL), 150 mg/1.5 mL (100 mg/mL), and 300 mg/3 mL (100 mg/mL)

Dose and Frequency	TRADENAME® should be administered once-daily, (b) (4)
	
	Recommended dosing regimen:
	• Day 1: Loading dose of 1 mg/kg
	• Day 2: Once-daily dose of 0.2 mg/kg until individualization of maintenance dose (see below)
	  ○ 4 weeks after initiation of treatment: For dose optimization measure concizumab-mtci plasma concentration once by Concizumab Enzyme-Linked Immunoassay (ELISA) prior to administration of next scheduled dose
	• After concizumab-mtci plasma concentration result is available but recommended no later than 8 weeks after initiation of treatment: Individualize maintenance dose of TRADENAME® once based on the following concizumab-mtci plasma concentrations:
	  ○ <200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg
	  ○ 200 to 4000 ng/mL: continue once-daily dose of 0.2 mg/kg

<table>
<tr><td></td><td>
>4000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg
The calculated dose is rounded off to the nearest injectable dose as follows:

60 mg/1.5 mL (40 mg/mL) in increments of 0.4 mg (brown)
150 mg/1.5 mL (100 mg/mL) in increments of 1 mg (gold)
300 mg/3 mL (100 mg/mL) in increments of 1 mg

</td></tr>
<tr><td>How Supplied</td><td>
TRADENAME® (concizumab-mtci) injection is a clear to slightly opalescent, colorless to slightly yellow liquid, that may contain translucent to white particles of proteins. TRADENAME® is available as one single-patient use prefilled pen per carton in the following presentations:
<table>
<tr><th>Presentation</th><th></th></tr>
<tr><td>60 mg/1.5 mL (40 mg/mL)</td><td>brown</td></tr>
<tr><td>150 mg/1.5 mL (100 mg/mL)</td><td>gold</td></tr>
<tr><td>300 mg/3 mL (100 mg/mL)</td><td></td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>

Before use: Store in a refrigerator at 36°F to 46°F (2°C to 8°C)
After first use: Store for up to 4 weeks in a refrigerator at 36˚F to 46˚F (2˚C to 8˚C) or at room temperature below 86˚F (30˚C). Write the date of first use in the space provided on the carton.
Store TRADENAME® with the cap on and in the original carton to protect from light. TRADENAME® should not be stored in direct sunlight, and the TRADENAME® pen should be kept away from direct heat. Do not freeze or store it close to a cooling element in a refrigerator. Do not use TRADENAME® if it has been frozen or stored at temperatures above 86˚F (30˚C).

</td></tr>
</table>

	(b) (4) [redacted]
Container Closure/Device Constituent	Prefilled prefilled pen with a variable dose setting mechanism • During dose delivery, the dose counter on the prefilled pen moves towards “0” and produces clicks to confirm that the injection is occurring and to indicate when the dose counter has returned to "0". The full dose is delivered when the needle has been kept in the skin while counting slowly to 6 after the dose counter has returned to "0". • The prefilled pen contents are delivered in two phases: o The active phase (b) (4) [redacted] o The relaxation phase follows the active phase. In this phase, (b) (4) [redacted]

	(b) (4)
Intended Users	Adult and pediatric patients, caregivers, HCPs
Intended Use Environment	Home, healthcare facilities (e.g., physician's office, pharmacy, or hospital)

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On November 18, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, concizumab and IND 111691.

B.1.2 Results

Our search identified 1 previous review[h], and we considered our previous recommendations to see if they are applicable for this current review.

Additionally, in a Type B pre-BLA meeting under IND 111691[i], we recommended the Applicant submit the HF validation study results report within 30 days of the BLA submission.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessed in EDR via:

\\CDSESUB1\EVSPROD\bla761315\0014\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hawi-hbwi\5354-other-stud-rep\human-factors-engineering-report-ut266\study-report-body.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessed in EDR via:
\\CDSESUB1\EVSPROD\bla761315\0008\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hawi-hbwi\5354-other-stud-rep\hfe-engineering\hfe-engineering.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On September 12, 2022, we sent an Information Request (IR) to the Applicant to request a description of the HF validation study protocol revisions implemented after the Applicant received Agency feedback and the intend-to-market carton labeling and container labels. The Applicant provided an adequate response to the IR on September 16, 2022. See EDR link:

\\CDSESUB1\EVSPROD\bla761315\0014\m1\us\m1-11-3-resp-fda-ir-20220912.pdf

On October 25, 2022, we sent an IR to the Applicant to request clarification regarding the second and third injection scenarios in the HF validation study results report, detail on the

[h] Wu, L. Human Factors Validation Study Protocol Advice for concizumab. Silver Spring (MD): FDA, CDER, OSE (US); 2021 JAN 6. IND 111691. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805c2c0d.

[i] Matthews, M. Type B Meeting Minutes for concizumab. Silver Spring (MD): FDA, CDER, OCHEN, DNH (US); 2022 MAY 26. IND 111691. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80662a59

injection times of the proposed device, and PDF versions of the IFUs. The Applicant provided an adequate response to the IR on October 31, 2022. See EDR link:

\\CDSESUB1\EVSPROD\bla761315\0020\m1\us\m1-11-3-clinical-information-amendment.pdf

On January 25, 2023, the Agency sent an IR[j] to the Applicant that included our container label and carton labeling recommendations in Table 7 below.

Table 7: Identified Issues and Recommendations for Novo Nordisk

	Identified Issue	Rationale for Concern	Recommendation
Container Labels and Carton Labeling			
1.	The container labels and carton labeling include the placeholder, "Tradename".	The proposed proprietary name, Alhemo, was found conditionally acceptable on November 21, 2022.[k]	Replace "Tradename" with the conditionally acceptable proprietary name Alhemo.
2.	As currently presented the established name is not at least half the size of the proprietary name on the container labels.	The size of the established name does not comply with 21 CFR 201.10(g)(2).	Ensure the established name is at least half the size of the proprietary name as required per 21 CFR 201.10(g)(2). Additionally, refer to container labels and carton labeling recommendation #1 above.
3.	The expiration date format is missing.	To minimize confusion and reduce the risk for deteriorated drug medication errors, clarify the format you intend to use.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a

[j] Hamilton, C. Information Request for Alhemo (BLA 761315). Silver Spring (MD): FDA, CDER, OND, DNH (US); 2023 JAN 25. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806ac9f3.

[k] Wu, L. Proprietary Name Granted Letter for concizumab. Silver Spring (MD): FDA, CDER, OSE (US); 2022 NOV 21. BLA 761315. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8069a7ed.

Table 7: Identified Issues and Recommendations for Novo Nordisk			
	Identified Issue	**Rationale for Concern**	**Recommendation**
			year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.[l]
Container Labels			
1.	It is unclear if the submitted container labels reflect the intend-to-market color scheme. Specifically, the proposed container labels include a yellow background color to represent the background tint.	Confusion regarding the appearance of the intend-to-market labels and labeling impact's the Agency's ability to complete a comprehensive review.	Confirm the background color of your intend-to-market labels and labeling. Ensure your submission of revised container labels reflects the actual intended colors of the intend-to-market labels and labeling.
2.	The "Rx only" statement is bolded and has equal prominence with the established name and strength.	Key information, such as the established name and strength, should be prominently displayed.	Reduce the prominence of the "Rx only" statement by debolding.
3.	The strength statement is not prominent and can be improved for readability.	Key information such as the product strength should be prominently displayed.	Increase the prominence of the strength statement. Additionally, consider relocating and/or reducing the size of graphic on the label to allow additional space for increasing the font size of key information including the product strength.

[l] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2021. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

Table 7: Identified Issues and Recommendations for Novo Nordisk			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Carton Labeling			
1.	The carton labeling does not include a space for users to write the post-opening expiration date.	We are concerned that confusion regarding the post-opening expiration date might result in deteriorated drug medication errors.	Include the following statements on the carton labeling: Include the statements "Date of first opening __/__/__. Discard unused portion of the pen 28 days after first opening." in bold font under the storage information on the back panel of the carton labeling. Additionally, the "__/__/__" statement will alert the users to write a complete date (month, day, and year).
2.	The storage information can be improved for clarity.	Lack of unclarity regarding product storage might pose of risk of deteriorated drug medication errors.	Revise the storage information from "(b) (4) (b) (4)" to: **Before first use:** Store refrigerated at 36°F to 46°F (2°C to 8°C). **After first use:** Store refrigerated or at room temperature up to 86˚F (30˚C) for up to 28 days. Store pen in the carton to protect from light. Do not Freeze (b) (4) **Date of first opening __/__/__. Discard unused portion of the pen 28 days after first opening.** Do not store with needles attached. Additionally, refer to carton labeling recommendation #1 above.

Table 7: Identified Issues and Recommendations for Novo Nordisk			
	Identified Issue	**Rationale for Concern**	**Recommendation**
3.	The carton labeling does not include a usual dose statement.	A usual dose statement is required per 21 CFR 201.55.	Revise the carton labeling to include the statement "Dosage: See prescribing information" on the back panel.
4.	It is unclear whether your carton labeling includes a machine-readable (2D data matrix barcode) product identifier.	In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act.[m] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling.
5.	The "(b) (4)" statement on the principal display panel (PDP) underneath the strength statement is redundant.).	Redundant information may clutter the PDP.	Remove the "(b) (4)" statement as it is mentioned already as part of the net quantity on the PDP.

On February 24, 2023, we sent an IR to the Applicant to request submission of revised carton labeling and container labels that incorporate the nonproprietary name suffix "-mtci". The Applicant provided a response on February 27, 2023. See EDR link: \\CDSESUB1\EVSPROD\bla761315\0039\m1\us\cover.pdf

[m] The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling (received on August 24, 2022 and September 16, 2022)

Using the principles of human factors and Failure Mode and Effects Analysis,[n] along with postmarket medication error data, we reviewed the following Alhemo labels and labeling submitted by Novo Nordisk Inc.

- Container labels received on 9/16/22
- Carton labeling received on 9/16/22
- Instructions for Use (image not shown) received on 8/24/22, available from:

(b) (4)

  - 60 mg/1.5 mL
    - \\CDSESUB1\EVSPROD\bla761315\0008\m1\us\ifu-60mg.doc
    - \\CDSESUB1\EVSPROD\bla761315\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hawi-hbwi\5354-other-stud-rep\human-factors-engineering-report-ut266\ifu-ut266-31-010-1.pdf
  - 150 mg/1.5 mL
    - \\CDSESUB1\EVSPROD\bla761315\0008\m1\us\ifu-150mg.doc
    - \\CDSESUB1\EVSPROD\bla761315\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hawi-hbwi\5354-other-stud-rep\human-factors-engineering-report-ut266\ifu-ut266-31-020-1.pdf
  - 300 mg/3 mL
    - \\CDSESUB1\EVSPROD\bla761315\0008\m1\us\ifu-300mg.doc
    - \\CDSESUB1\EVSPROD\bla761315\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hawi-hbwi\5354-other-stud-rep\human-factors-engineering-report-ut266\ifu-ut266-31-030-1.pdf
- Prescribing Information (image not shown) received on 8/24/22, available from: \\CDSESUB1\EVSPROD\bla761315\0008\m1\us\uspi.doc

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[n] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EBONY A WHALEY
03/22/2023 04:58:33 PM

COLLEEN L LITTLE
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LOLITA G STERRETT
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CLINICAL INSPECTION SUMMARY

Date	March 1, 2023
From	Anthony Orencia, M.D., Ph.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Andrew Dmytrijuk, M.D., Medical Officer Carrie Diamond, M.D., Medical Team Leader Ann Farrell, M.D., Division Director Courtney Hamilton, Pharm.D., Regulatory Health Project Manager Division of Nonmalignant Hematology (DNH) Office of Cardiovascular, Hematology, Endocrinology and Nephrology Drugs (OCHEN)
BLA	BLA 761315
Applicant	Novo Nordisk Inc.
Drug	Alhemo (concizumab-mtci) ™
NME	Yes
Division Classification	Tissue factor pathway inhibitor (TFPI)-directed antibody
Proposed Indications	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors (HAwI) or hemophilia B (congenital factor IX deficiency) with factor IX inhibitors (HBwI)
Review Type	Priority Review
Consultation Request Date	September 28, 2022
Summary Goal Date	March 31, 2023
Action Goal Date	April 24, 2023
PDUFA Date	April 24, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study NN7415-4311 were submitted to the Agency in support of a biologics license application (BLA) for the drug concizumab, proposed as for routine prophylaxis to prevent or to reduce the frequency of bleeding episodes in adult and pediatric patients with (1) hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors or (2) hemophilia B (congenital factor IX deficiency) with factor IX inhibitors. Two foreign clinical investigators, Joanna Zdziarska, M.D. and Ana Boban, M.D., as well as the sponsor were inspected for Study NN7415-4311.

Based on the inspections, the study appears to have been conducted adequately and the study data derived from these clinical investigator sites are considered reliable. The data from Study NN7415-4311 submitted to the Agency for assessment appear acceptable in support of the proposed indication.

II. BACKGROUND

Concizumab is a subcutaneously injected, monoclonal antibody, anti-tissue factor pathway inhibitor (TFPI). Concizumab acts independently from coagulation factor VIII (FVIII) and coagulation factor IX (FIX) by enhancing the initiation phase of coagulation through increased activated coagulation factor X (FXa) production. This therapeutic monoclonal antibody is being developed for preventing and reducing the frequency of bleeding episodes in hemophilia A (HA) and hemophilia B (HB) with and without inhibitors.

Concizumab is intended to address a life-threatening medical need in hemophilia patients by offering a subcutaneous (s.c.) route administered bleeding prophylaxis in a pen-injector. Concizumab is not expected to be effective in the acute treatment of bleeding episodes, and breakthrough bleeds would require treatment with a coagulation factor or bypassing agent (e.g., plasma-derived activated prothrombin complex concentrate).

The proposed indication of concizumab is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with (1) hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors (HAwI) or (2) hemophilia B (congenital factor IX deficiency) with factor IX inhibitors (HBwI).

Of the multiple clinical trial investigations submitted to the Agency, the Division of Nonmalignant Hematology (DNH) requested that Study NN7415-4311 be examined closely, in support of the current applicant's BLA. Reference is also made to the Investigational New Drug (IND) Application 111691 for concizumab submitted on May 19, 2015.

Study NN7415-4311

Study NN7415-4311 was a an interventional, multi-national (primarily ex-US), multi-center, randomized, open-label, designed to compare the efficacy of concizumab in patients on stable prophylaxis (PPX) administered daily subcutaneously to no PPX (on demand treatment with bypassing agents) in reducing the number of bleeding episodes in adult and adolescent patients (age at least 12 years) with HAwI or HBwI.

Patients were randomized 2:1 to concizumab PPX or no PPX. The study consisted of a three-week screening period, a main part (24−32 weeks treatment period), an extension part (128−136 weeks treatment period), and a 7-week follow-up period.

The trial includes the following four arms:
Arm 1 - on demand administration.
Arm 2 - concizumab PPX treatment.

Arms 3 and 4 consisted of patients allocated to concizumab PPX treatment, namely:
Arm 3- transferred from the Phase 2 trial 4310.
Arm 4- previously treated on PPX or on demand.

The primary objective for Study NN7415-4311 was to compare the effect of concizumab prophylaxis to no prophylaxis (on-demand treatment with bypassing agents) in reducing the number of bleeding episodes in adult and adolescent patients with hemophilia A or B with inhibitors.

The main part of the trial was considered completed for a patient when the patient had completed at least 24 weeks of participation (screening period not included) for patients on no PPX (Arm 1), or 32 weeks of participation (screening period not included) for patients on concizumab PPX (Arms 2, 3 and 4).

The primary efficacy endpoint involved the number of treated spontaneous and traumatic bleeding episodes. Efficacy assessments focused on the randomized treatment arms, i.e., Arms 1 and 2. For on demand (Arm 1): from randomization (Week time zero) up until start of concizumab treatment (at least 24 weeks). For concizumab (Arm 2): from start of the new concizumab dosing regimen (Week time zero) up until the primary analysis cut-off (at least 32 weeks).

The main safety endpoint of concern was bleeding or thromboembolism. Previously, concizumab treatment was paused while five thromboembolic events reported in three patients in two Phase III trials. Risk mitigation measures were implemented, and trial protocols were updated before resuming the trials.

To mitigate the risk for thromboembolic events the applicant initiated a new guidance for treatment of mild and moderate breakthrough bleeding episodes with specific guidance for use of the lowest dose of factor product or bypassing agent while on concizumab PPX. Also, the applicant revised the concizumab dosing regimen consisting of a loading dose of 1.0 mg/kg (unchanged from the initial dosing regimen) and an initial daily dose of 0.20 mg/kg concizumab (instead of 0.25 mg/kg). The applicant also revised the criteria for an increase or decrease in the daily maintenance dose to 0.25 mg/kg or 0.15 mg/kg, respectively based on concizumab exposure levels at the Week four visit after initiating treatment. No thromboembolic events were reported after the treatment restart.

The trial was conducted in 27 countries. The study initiation date was on October 27, 2019, and primary completion date on December 27, 2021.

III. RESULTS (by site)

1. **Joanna Zdziarska, M.D./ Site 480**
   ul. Mikolaja Kopernika 17
   Krakow, Malopolskie, 31-501
   Poland

   Inspection dates: December 12-14, 2022

A total of six study subjects were screened (one subject was a rescreen); five study subjects were enrolled. Three of the five enrolled subjects completed the study. Two subjects who discontinued were transferred to alternative therapies during the study pause. The study is ongoing.

Regulatory and source documents were reviewed. The audit involved a review of records and procedures related to the clinical trial protocol and its amendments; subject selection criteria and consenting; test article controls, including accountability; source data evaluation, including primary efficacy endpoint of bleeding events; adverse event reporting, including assessment of under-reporting of serious adverse events, and laboratory testing.

Source records for all enrolled study subjects were examined and verifiable. Records were noted to be complete, legible, and organized. Study activities were conducted in compliance with the protocol. The primary efficacy endpoint was verifiable. There was no evidence of under-reporting of adverse events (e.g., no lapses in approvals or failure to file required reports) were noted). No discrepancies were noted.

No significant objectionable findings were found during the inspection. A list of inspectional observations (Form FDA 483) was not issued by FDA at the close-out of the inspection.

2. Ana Boban, M.D./Site 385
Kispaticeva 12, University Hospital Centre
Zagreb 10000 HRV
Croatia

Inspection dates: December 5-8, 2022

Dr. Boban is the head of the hemophilia unit. As principal investigator, she conducts investigational clinical trials for this hemophilia patient population.

Five study subjects were screened; four study subjects were enrolled and randomized. Three subjects discontinued (withdrew from the study). A single subject is still on treatment in this ongoing study.

Ethics committee approvals, study correspondence, drug accountability, facility adequacy, staff qualifications, and monitoring procedures were reviewed. This inspection covered the safety of study subjects along with serious adverse event reporting, protocol deviations, subject eligibility, overall protocol compliance, and the verification of source documentation related to study endpoint criteria.

Adverse event and serious adverse reporting appeared adequate and consistent with the study protocol requirement and the case report form reports. The primary efficacy endpoint (bleeding events) was verifiable. There was no evidence of under-reporting of adverse events (e.g., no lapses in approvals or failure to file required reports were noted).

No list of inspectional observations (FDA Form 483) was issued by FDA at the close-out of the site inspection.

3. Novo Nordisk Inc./Sponsor
800 Scudders Mill Rd
Plainsboro, NJ 08536

Inspection dates: December 12 -21, 2022

The sponsor inspection involved comprehensive onsite review of study monitor selection, site and clinical investigator selection, clinical site monitoring, form FDA 1572s, financial disclosures, safety reporting and handling, data monitoring committee activities, study documents, standard operating procedures, data collection and handling, protocol deviations, and investigational product disposition. Monitoring actions taken for those clinical investigators who did not comply with the investigational plan appeared to be adequate.

Procedure documents for Novo Nordisk's review and processing of serious adverse events (SAEs), such as (b) (4) were assessed during the inspections. FDA's inspection also assessed safety oversight performed by medical monitors and safety advisors in addition to the data monitoring committee (DMC). No discrepancies were observed for adverse event reporting.

At the end of the sponsor inspection, no FDA Form 483 was issued. However, some of the following relevant discussion items at the close out meeting with sponsor deserve mention: (a) Ensure adequate oversight of drug product disposition at clinical sites to track and to evaluate investigative drug products, for example, with temperature deviations, prior to subject dispensing. Sites had no additional checkpoints preventing dispensing of the investigative drug product after initial assignment by interactive web response systems. For example, the audit found that the investigational drug product was administered to Subject (b) (6) (treatment arm not specified) after undergoing a temperature deviation at the clinical site. However, no consequential adverse events were reported following temperature excursions, and (b) Complete query resolution and clarifications between affiliates (that is, affiliate trial managers and monitors) and clinical investigators should be documented allowing for appropriate handling and follow-up. For example, clarification received from a clinical investigator, for the timely reporting of the onset dates of a serious adverse event, via e-mail was not captured in the queries or updated in the electronic data capture data.

In general, the sponsor's oversight and monitoring of this clinical study appear to be acceptable.

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