CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	BLA
Application Number	761315
PDUFA Goal Date	December 20, 2024
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Reviewer Name(s)	Carla Darling, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
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Review Completion Date	December 19, 2024
Subject	Evaluation of Need for a REMS
Established Name	Concizumab-mtci
Trade Name	Alhemo
Name of Applicant	Novo Nordisk Inc.
Therapeutic Class	Tissue factor pathway inhibitor (TFPI)
Formulation(s)	(b) (4) injection in a prefilled pen
Dosing Regimen	Day 1: Loading dose of 1 mg/kg Day 2: Once-daily dose of 0.20 mg/kg until individualization of maintenance dose After 4 weeks but no later than 8 weeks after initiation of treatment: Individualize maintenance dose based on concizumab-mtci plasma concentration: • <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

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Alhemo (concizumab-mtci) is necessary to ensure the benefits outweigh its risks. Novo Nordisk Inc. submitted a Class 2 resubmission for Biologic Licensing Application (BLA 761315) for concizumab-mtci on June 20, 2024 with the proposed indication of routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with: 1) hemophilia A (congenital factor VIII [FVIII] deficiency) with FVIII inhibitors and 2) hemophilia B (congenital factor IX [FIX] deficiency) with FIX inhibitors. During the review of this submission, the indication was revised to limit the pediatric population to 12 years of age and older. The risks associated with concizumab-mtci include thromboembolic events and hypersensitivity reactions. The applicant did not submit a proposed REMS for this application.

The efficacy of concizumab-mtci was evaluated in one phase 3 trial, which the review team determined provided substantial evidence of effectiveness based on the reduction in the number of bleeding events in patients treated with concizumab-mtci prophylaxis compared to on demand therapy. Additional supportive evidence was provided from a smaller study (study 4310) that demonstrated similar effects and mechanistic support.

Based on the safety and efficacy information available, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of concizumab-mtci. The risks associated with concizumab-mtci include thromboembolic events, hypersensitivity reactions, and bleeding with subtherapeutic concizumab-mtci levels. Similar to other approved treatments for hemophilia, labeling will include the risk of thromboembolic events and hypersensitivity reactions with concizumab-mtci in a Medication Guide and in section 5, Warnings and Precautions of the Prescribing Information (PI). To mitigate the risk of bleeding due to subtherapeutic levels, the importance of adherence to daily dosing will be stressed in section 2, Dosage and Administration of the Prescribing Information, the Medication Guide, and other voluntary education materials. At the time of this review, final labeling, and post-marketing requirements (PMRs) were still under negotiation. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Alhemo (concizumab-mtci, hereafter referred to as concizumab) is necessary to ensure the benefits outweigh its risks. Novo Nordisk Inc. (Applicant) submitted a Biologic Licensing Application (BLA) 761265 for concizumab with the proposed indication for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with: 1) hemophilia A (congenital factor VIII [FVIII] deficiency) with FVIII inhibitors and 2) hemophilia B (congenital factor IX [FIX] deficiency) with FIX inhibitors.[1,2]

This Application is under review in the Division of Non-Malignant Hematology (DNH). The Applicant did not submit a proposed REMS with this application.

2. Background

2.1. Product Information

Concizumab, a new molecular entity (NME)[a], is a tissue factor-pathway inhibitor (TFPI) proposed for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with: 1) HA with FVIII inhibitors and 2) HB with FIX inhibitors.[b,3] During the review of the application, the indication was revised to limit the age of the pediatric population to 12 years of age and older.[4] Through the inhibition of TFPI, concizumab acts to enhance factor Xa (FXa) production during the initiation phase of coagulation which leads to improved thrombin generation and clot formation to achieve hemostasis in patients with Hemophilia A or B with inhibitors. [4] Concizumab is proposed as (b) (4) injection in a prefilled pen for subcutaneous (SC) injection to be self-administered or administered by a caregiver. The proposed concizumab dosing regimen includes:[4]

- Day 1: Loading dose of 1.0 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 plasma concentration by Concizumab Enzyme-Linked Immunosorbent Assay (ELISA) prior to administration of next scheduled dose. An FDA-authorized test for the measurement of concizumab concentration in plasma is not currently available.
    -
- Once the concizumab concentration result is available, individualize the maintenance dose of Alhemo no later than 8 weeks after initiation of treatment based on the following concizumab plasma concentrations:
    - Less than 200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg
    - 200 to 4,000 ng/mL: continue once-daily dose of 0.2 mg/kg
    - Greater than 4,000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg

(b) (4)

Concizumab was granted orphan drug designation for the treatment of hemophilia A (HA) and hemophilia B (HB) and was granted breakthrough therapy designation for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in HB patients with inhibitors. [5-7] If approved, concizumab will be the first non-factor replacement product approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric HB patients with inhibitors and will be an additional non-factor replacement product for routine prophylaxis in adult and pediatric HA patients with inhibitors. Concizumab is currently approved in Canada, Switzerland, Australia, and Japan.[8]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761315 relevant to this review:

- 03/11/2011: Concizumab breakthrough therapy designation granted for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia B patients with inhibitors.[7]
- 10/22/2018: Concizumab was granted orphan drug designation for the treatment of hemophilia A (DRU-2018-6536).
- 07/22/2019: Concizumab was granted orphan drug designation for the treatment of hemophilia B (DRU-2018-6636).
- 03/20/2020: Full Clinical Hold letter issued for unreasonable and significant risk of illness or injury to human subjects concerning the non-fatal thrombotic events in three patients with hemophilia A or B with inhibitors while on treatment with concizumab on the following protocols: NN7415-4311, NN7415-4307, and NN715-4255.[9]
- 05/05/2022: Rolling review request was granted.[10]
- 05/18/2022: BLA 761315 rolling submission portion 1 was received with the proposed indication for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients: hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors and hemophilia B (congenital factor IX deficiency) with factor IX inhibitors.[1]
- 08/24/2022: BLA 761315 rolling submission portion 2 (final portion) was received.[2]
- 10/12/2022: Priority review request was granted.[11]
- 03/15/2023: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no issues related to risk management had been identified to date and that the need for a REMS had not yet been identified.[12]
- 04/24/2023: Complete Response (CR) letter sent to the applicant due to issues with clinical and clinical pharmacology, device (concizumab Enzyme-Linked Immunosorbent Assay [ELISA]), product quality, and facility inspection.[13]
- 06/20/2024: Complete Response received.[3]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Congenital hemophilia A (HA) is an X-linked bleeding disorder characterized by the deficiency or absence of factor VIII (FVIII).[14] Hemophilia A occurs in 1 in 5,000 live male births, without ethnic predominance, which results in an incidence in the United States of about 20,000 people and 400,000 people

worldwide.[15,c] Congenital hemophilia B (HB) is an X-linked bleeding disorder caused by the deficiency of (factor IX (FIX)).[14] The prevalence of the disease is estimated to be 1 in 30,000 males.[16] Deficient factor IX levels results in an increased risk for minor and serious bleeding, including life threatening spontaneous or traumatic bleeding.[14] Patients with hemophilia A or B are at increased risk for minor and serious bleeding including life threatening spontaneous or traumatic bleeding.[14,d] Bleeding can occur in vital organs such as the brain, which can be serious and life-threatening.[17] Adults commonly experience hemophilic arthropathy due to recurrent joint bleeds, which is associated with significant disease morbidity.[17]

3.2. Description of Current Treatment Options

There is no cure for hemophilia. The goal of hemophilia treatment is to prevent and treat bleeding, reduce complications and continue/resume normal activities of daily living. Treatment for HA and HB can either be in response to a bleeding event (episodic or "on demand" treatment) or scheduled treatment to prevent bleeds (prophylactic treatment). Therapeutic options for prophylaxis include plasma-derived or recombinant standard half-life factor, extended half-life factor, and non-factor replacement.[18] One of the most serious complications of HA and HB treatment is the development of neutralizing antibodies (also known as inhibitors) to factor replacement. Approximately 30% of patients with HA and 5-15% of patients with HB will develop inhibitors rendering the factor concentrates ineffective to prevent bleeding events.[19-21] Because their bleeding is more difficult to prevent and treat, patients with inhibitors have an increased risk of serious or fatal bleeding episodes.[22]For patients with a history of high-titer inhibitors, the only hemostatic options currently available are prothrombotic coagulation factors that augment other parts of the coagulation cascade (commonly referred to as "bypassing agents").[14]

Bypassing agents include: factor eight inhibitor bypassing activity (FEIBA), plasma derived activated prothrombin complex concentrate (aPCC), and recombinant activated human FVII (rFVIIa) products such as NovoSeven and SevenFACT.[18] FEIBA is the only bypassing agent that is FDA approved for prophylaxis in patients with HA with inhibitors and HB with inhibitors.[23] Treatment burden is high with the use of bypassing agents as they often require frequent, high-volume, and extended intravenous infusion. Bypassing agents carry a boxed warning stating the risk of thrombotic events as well as warnings and precautions for the risk of hypersensitivity reactions.

There are two non-factor replacement products available for the treatment of hemophilia. Hemlibra (Emicizumab), a humanized, monoclonal, bispecific, factor IXa-and factor X-directed antibody, is the only FDA approved non-factor replacement product for routine prophylaxis in adult and pediatric patients with HA with and without inhibitors.[24] Emicizumab has a boxed warning for the risk of thrombotic

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

microangiopathy and thrombotic events with concomitant use of aPCC. Hympavzi (marstacimab-hncq), another TFPI, was approved on October 11, 2024 for routine prophylaxis in adult and pediatric patients with HA without inhibitors and HB without inhibitors.[25] While the approval of marstacimab-hncq provides the first non-factor replacement therapy for patients with HB without inhibitors and an additional non-factor replacement option for patients with HA without inhibitors, there is still an unmet need for prophylaxis options for patients with HB with inhibitors.

4. Benefit Assessment

The pivotal trial supporting this application, explorer7 trial, NN7415-4311 (NCT04083781), hereafter referred as study 4311, consisted of a multi-center, open-label, randomized controlled study, which evaluated the number of bleeding events in 52 adult and adolescent patients with HA with inhibitors (n=27) and HB with inhibitors (n=25) treated with concizumab prophylaxis compared to no prophylaxis (on demand therapy) for at least 24 weeks. Patients were randomized to concizumab prophylaxis (arm 2; n=33) or no prophylaxis (arm 1; n=19). An additional 81 patients with HA with inhibitors (n=53) and HB with inhibitors (n=28) were assigned to non-randomized concizumab prophylaxis treatment (arms 3 or 4), based on their treatment regimen for hemophilia before entering the study. Arm 3 included 21 patients who were previously enrolled in the concizumab Phase 2 study, explorer4, NN7415-4310 (NCT03196284), hereafter referred as study 4310. Arm 4 included 60 patients previously on prophylaxis with bypassing agents as well as patients receiving on-demand therapy who were screened at a timepoint where the required number of patients in arms 1 and 2 had been randomized. After the initial 24 weeks of the study, all patients were offered to continue in an extension part of the study (ongoing) and receive treatment with concizumab for up to an additional 128 weeks (arms 2-4) or 136 weeks (arm 1).

The primary endpoint was the number of treated spontaneous and traumatic bleeding episodes for at least 24 weeks. The annualized bleeding rate (ABR) was calculated as the number of treated spontaneous or traumatic bleeds divided by the number of days in the analysis set, multiplied by 365. The ABR was 1.7 with 95% CI (1.01, 2.87) for patients on concizumab prophylaxis and 11.8 with 95% CI (7.03, 19.86) for patients on no prophylaxis. The estimated ABR ratio was 0.14 with 95% CI (0.07, 0.29) and 2-sided p-value <0.001, corresponding to an 86% reduction in ABR for patients on concizumab prophylaxis compared to no prophylaxis.

Supportive evidence was provided from the dose escalation phase 2 study 4310, which evaluated the number of bleeding events for at least 24 weeks in adult and adolescent patients with HA with inhibitors and HB with inhibitors treated with concizumab prophylaxis of 0.15 mg/kg, 0.20 mg/kg, and 0.25 mg/kg administered daily SC, compared to no prophylaxis (on demand therapy with eptacog alfa [rFVIIa]). The ABR was significantly lower in patients treated with concizumab prophylaxis compared to no prophylaxis.

The review team concluded that the use of concizumab for prophylaxis in patients with HA with inhibitors and HB with inhibitors resulted in clinically meaningful reduction in bleeding rate.[e,26] The DNH determined that the Applicant provided substantial evidence of effectiveness based on efficacy data from a single, adequate, and well-controlled study (study 4311) that demonstrated a clinical benefit of concizumab in HA with inhibitors and HB with inhibitors with support from a smaller study (study 4310) that demonstrated similar effects and mechanistic support.[26]

5. Risk Assessment & Safe-Use Conditions

Clinical trials supporting the safety analysis of concizumab consists of multiple-dose trials including studies 4307, 4255, 4311, 4310, and 4159 (see **Table 1**1). The safety database includes 320 patients with HA and HB with and without inhibitors that received concizumab.

Serious adverse reactions (SAR)[f] in the clinical trials with concizumab were thromboembolic events, hypersensitivity reactions, and bleeding with subtherapeutic concizumab levels. These risks are further discussed below in section 5.2.

Table 1. Summary of Clinical Trials 4307, 4255, 4311, 4310 and 4159

Trial ID	Trial Description	Population	Concizumab dose	Status
Study 4159 (explorer3, NN7415-4159 [NCT02490787])	Phase 1, Safety, PK and PD Randomized, DB, placebo controlled, multiple-dose 11 weeks	N = 24 HA patients (18–64 years)	SC 0.25, 0.5, and 0.8 mg/kg every 4 days, 12 doses	Completed
Study 4255 (explorer5, NN7415-4255 [NCT03196297])	Phase 2, efficacy and safety OL, multiple-dose Main part: ≥ 24 weeks Extension part: 52-102 weeks (Full trial: ≥76 weeks)	N = 36 HA patients (≥18 years)	Daily SC dose of 0.15 mg/kg with potential dose escalation to 0.20 mg/kg and subsequently to 0.25 mg/kg based on number of spontaneous bleeding episodes within a period of 12 weeks.	Completed

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Trial ID	Trial Description	Population	Concizumab dose	Status
Study 4310 (explorer4, NN7415-4310 [NCT03196284])	Phase 2, efficacy and safety Randomized, OL, controlled, multiple-dose Main part: ≥ 24 weeks Extension part: 52-94 Weeks (Full trial: ≥76 weeks)	N = 25 HAwI: 16 HBwI: 10 (≥18 years)	Day 1: Single SC. loading dose of 0.5 mg/kg concizumab. Day 2 and onwards: Daily SC dose of 0.15 mg/kg with potential dose escalation to 0.20 mg/kg and subsequently to 0.25 mg/kg based on number of spontaneous bleeding episodes within a period of 12 weeks.	Completed
Study 4307 (explorer8, NN7415-4307 [NCT04082429])	Phase 3, efficacy, PK, PD and safety Randomized, OL, controlled, multiple-dose Main part: 24 weeks for arm 1 and 32 weeks for arms 2, 3 and 4. Extension part: up to 265 weeks.	N = 151 HA: 87 HB: 64 (≥12 years)	Day 1: Single SC loading dose of 1 mg/kg concizumab. Day 2 and onwards: Initial daily SC dose of 0.20 mg/kg. Individual maintenance dose will be set to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure after 4 weeks of treatment	CACO and 56-week cut-off reached (extension part ongoing)
Study 4311 (explorer7 trial, NN7415-4311 [NCT04083781])	Phase 3, efficacy, PK, PD and safety Randomized, OL, controlled, multiple-dose Main part: 24 weeks for arm 1 and 32 weeks for arms 2, 3 and 4. Extension part: up to 265 weeks.	N = 127 HAwI: 76 HBwI: 51 (≥12 years)	Day 1: Single SC loading dose of 1 mg/kg concizumab. Day 2 and onwards: Initial daily SC dose of 0.20 mg/kg. Individual maintenance dose will be set to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure after 4 weeks of treatment.	PACO and 56-week cut-off reached (extension part ongoing)

Source: Adapted from Applicant's Clinical Study Report
Abbreviations: CACO, confirmatory analyses cut-off; DB, double-blind; HA, hemophilia A; HAwI, hemophilia A with inhibitors; hemophilia B; HBwI, hemophilia B with inhibitors; OL, open-label; PACO, primary analysis cut-off; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous

5.1. Deaths

There were 5 patient deaths in concizumab treated patients. The original safety pool included 4 of the 5 deaths in concizumab treated patients compared to one patient death reported in arm 1 (no prophylaxis). Reasons for the 4 deaths in the original safety pool include: motor vehicle accident (1), COVID-19 (1), alcoholic coma (1), and intracranial hemorrhage (1). In the motor vehicle accident case, the clinical reviewer commented that it is possible that the patient died due to bleeding related complications. However, as a recent concizumab level was not reported, it is not clear if the patient had

a subtherapeutic level at the time of the event, increasing the risk of fatal bleeding.[27] The fifth case in a concizumab treated patient was an intra-abdominal hemorrhage reported in the 56-week safety update included in the Complete Response submission. The two deaths due to serious bleeding events (intracranial hemorrhage and intra-abdominal hemorrhage) are further discussed in section 5.2.3 of this review.

5.2. Serious Adverse Reaction

5.2.1. Thromboembolic Events

In the clinical development program, 4 patients (1.3%) experienced non-fatal thrombotic events while receiving concizumab compared to 0 patients (0%) in the control group.[g,] The cases of thromboembolic events in 3 of the 4 patients occurred early in clinical trials and an additional case occurred in a fourth patient reported in the 56-week safety update. Thromboembolic events reported in these patients include both arterial and venous thrombotic events (e.g. myocardial infarction, renal infarct, deep vein thrombosis, and cerebral infarction). Notably, all patients had additional risk factors for thrombosis including smoking, history of hypertension, and/or obesity. In addition, two of the three patients with thromboembolic events that occurred early in clinical trials had elevated concizumab levels >4000ng/mL and all three patients received factor or a bypassing agent at the time of the thrombotic event.

The fourth patient was reported in the 56-week safety update with a new case of cerebral infarction in a patient with HA from study 4307. The patient had a medical history of severe hypertension since 2013 and was treated with 2 anti-hypertensive medications. The patient was previously enrolled in the phase 2 trial 4255 and had more than 5 years of concizumab exposure up to the onset of the SAE, including exposure before and after the treatment pause in trial 4307.

Due to the three cases of thromboembolic events that occurred early in clinical trials, the clinical development program was put on a full clinical hold due to the potential for increased risk of thrombosis among patients treated with concizumab. To mitigate the risk for thromboembolic events, the Applicant decreased the concizumab initial daily dosing regimen. Initially, patients randomized to concizumab prophylaxis received a loading dose of 1.0 mg/kg concizumab SC on the first day of treatment, followed by a maintenance dose of 0.25 mg/kg concizumab given as a daily SC injection from the second day onwards. After the study resumed, the Applicant revised the concizumab dosing regimen to retain the loading dose of 1.0 mg/kg and decrease the initial daily dose of 0.20 mg/kg concizumab (instead of 0.25 mg/kg).

In addition to the decrease in initial dosing, other risk mitigation strategies were implemented including:

- Initiate maintenance dose adjustments based on concizumab plasma levels after week 4 as follows:

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

- <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
- >4000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg

- Initiate new guidance for the use of the lowest dose of rescue factor product or bypassing agent while on concizumab prophylaxis.
- Patients were instructed to contact the site when they have a suspected bleed.
- Continuation of previous prophylaxis for up to 2 weeks after initiation of concizumab was no longer allowed (study 4307).
- Elective major surgery was no longer allowed in clinical trials.
- Trial stopping rule requiring urgent evaluation by the Novo Nordisk Safety Committee and consultation with the data monitoring committee in case of one (instead of two) significant thromboembolic event, disseminated intravascular coagulation, thrombotic microangiopathy, or death of study patient which may be related to the study product put in place.

The clinical reviewer determined that thrombosis is a serious adverse reaction associated with concizumab, which is likely due to an exaggerated pharmacologic effect.[27] Additional thrombotic risk factors include receiving concomitant factor or bypassing agent, conditions in which tissue factor is overexpressed (e.g. atherosclerotic disease, crush injury, cancer, disseminated intravascular coagulation, thrombotic microangiopathy, or septicemia), and having concizumab levels >4000 ng/mL. The review team recommends that the Prescribing Information include the revised dosing regimen used after the treatment pause. Additionally, the review team recommends including the risk of thromboembolic events in the Warnings and Precautions section of the Prescribing Information along with a statement to use the lowest effective dose of factor or bypassing agent to decrease the risk of thrombotic events.

5.2.2. Hypersensitivity Reactions

One patient in study 4311 experienced a serious hypersensitivity reaction 12 hours after exposure to concizumab.[h] Symptoms reported in this case included generalized erythema and pruritus with skin rash, persistent dry cough, and abdominal pain, which led to hospitalization. Concizumab was temporarily discontinued, and symptoms improved with antihistamines and steroids. No new events of anaphylaxis were reported in the 56-week safety update. The review team recommends including the risk of hypersensitivity reactions in the Warnings and Precautions section of the Prescribing Information.[27]

5.2.3. Risk of Bleeding with Subtherapeutic Levels

In the clinical development program, most patients with subtherapeutic concizumab levels (<200 ng/mL) had no bleeding or minor bleeding. However; 6 (1.9%) patients had serious bleeding events and 2 (0.6%) patients died with subtherapeutic levels. The fatal case related to intracranial hemorrhage was in a patient that was likely non-compliant with concizumab prophylaxis. This non-compliance, may have

[h] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

caused or at least contributed to the fatal event.[27] The fatal case related to intrabdominal hemorrhage occurred in a patient who was reportedly compliant to treatment, did not have other bleeding episodes, had concizumab levels consistently below the recommended levels of 200 ng/mL, and did not test positive for anti-concizumab antibodies. The clinical reviewer determined that the cause of the intra-abdominal bleeding event is not clear and notes that low concentrations of concizumab (<200ng/mL) can increase the risk of serious and life-threatening bleeding events.

Concizumab levels >200 ng/mL is key to the therapeutic effect of concizumab and levels <4000ng/mL is critical to decrease the risk of thrombosis. The review team determined that a companion diagnostic concizumab assay would be optimal for the effective and safe use of this product; however, the companion diagnostic assay is currently under review by the agency. Due to the unmet need for a non-factor replacement therapy options for patients with HB with inhibitors, concizumab will be approved without the proposed companion diagnostic. While the Applicant completes development of a companion diagnostic assay, an interim assay will be available to assess concizumab levels. The unapproved interim assay was reviewed by the Agency and determined to be adequate for use. Development of a commercially available companion diagnostic assay will be requested in a PMC.

To minimize risk of serious and life-threatening bleeding with subtherapeutic concizumab levels, the clinical reviewer recommends including instructions in labeling to advise prescribers and patients to consider alternative therapies if therapeutic range of concizumab cannot be achieved.[26] Additionally, labeling will include language to stress the importance of adherence.

6. Expected Postmarket Use

The anticipated prescribing population for concizumab will likely be hematologists who specialize in hemophilia treatment and have experience with managing the risks associated with anti-hemophilic therapies and the care of patients with HA and HB with and without inhibitors. Concizumab will likely be used at home by patients or caregivers after patients or caregivers are trained in the outpatient clinics or hemophilia treatment centers. In addition, patients with hemophilia are often knowledgeable about their disease, are able to identify treatment emergent adverse events such as thrombosis, hypersensitivity reactions, and bleeding and are able communicate concerns to their healthcare providers.

7. Risk Management Activities Proposed by the Applicant

The Applicant proposed the following risk management activities beyond routine pharmacovigilance and labeling:

- **Voluntary Distribution of Education Materials:** the Applicant proposed to voluntarily distribute educational materials related to early recognition and management of thrombotic events to healthcare providers and patients. The proposed education materials include a guide for healthcare professionals, guide for patient/caregiver, and a patient alert card.

- **Additional Pharmacovigilance:** the Applicant proposed additional pharmacovigilance (b) (4) (b) (4) to further characterized the risk of thrombosis in patients with hemophilia on concizumab in the real-world setting.

Reviewer's Comments: *We don't object to voluntary educational activities proposed by the applicant; however, we defer to the Office of Prescription Drug Promotion and the Division of Pharmacovigilance for their review and input on these activities.*

8. Discussion of Need for a REMS

The review team recommends approval of concizumab on the basis of the efficacy and safety information currently available.

Congenital HA and HB with and without inhibitors are bleeding disorders characterized by minor and serious bleeding including life threatening spontaneous or traumatic bleeding. As bleeding is more difficult to prevent and treat, patients with inhibitors have an increased risk of serious even fatal bleeding episodes. FDA approved bypassing agents for prophylaxis for HA and HB (both with and without inhibitors) and non-factor replacement products for HA (with and without inhibitors) and HB (without inhibitors) are available to prevent or reduce bleeding in patients. However, there remains an unmet need for non-factor replacement products for patients with HB with inhibitors.

Concizumab offers an additional non-factor replacement option for routine prophylaxis for patients with HB with inhibitors. In study 4311, the use of concizumab prophylaxis in patients with HA with inhibitors and HB with inhibitors, resulted in clinically meaningful reduction in bleeding rate.

Concizumab is associated with increased risk of thromboembolic events, hypersensitivity reactions, and bleeding with subtherapeutic concizumab levels. The risks of thromboembolic events and hypersensitivity reactions have also been observed with other bypassing agents including aPCC and rFVIIa products. Both arterial and venous thrombotic events were reported in clinical trials, and all patients had additional risk factors for thrombosis including smoking, history of hypertension, and/or obesity. Some patients had elevated concizumab levels >4000ng/mL and some patients received factor or a bypassing agent at the time of the thrombotic event. Additionally, patients with prolonged subtherapeutic levels (<200ng/mL) of concizumab are at increased risk of bleeding, which can be serious and life-threatening. For dose optimization, labeling states that concizumab plasma concentration should be measured by Enzyme-Linked Immunosorbent Assay (ELISA) prior to administration of next scheduled dose.

The anticipated prescribing population for concizumab will likely be hematologists who specialize in hemophilia treatment and have experience with managing the risks associated with anti-hemophilic therapies and the care of patients with HA and HB with and without inhibitors. Similar to other approved treatments for hemophilia, the risk of thrombosis including a statement to use the lowest effective dose of factor or bypassing agent to decrease the risk of thrombotic events, will be communicated in section 5: Warnings and Precautions of the Prescribing Information and in the Medication Guide. Prescribers should also be aware of the inherent risk of bleeding due to non-

compliance with prophylaxis therapy to prevent bleeding. The importance of adherence to daily dosing will be stressed in section 2, Dosage and Administration of the Prescribing Information, a Medication Guide, and education materials. Prescribers are likely to be hematologists who specialize in hemophilia treatment and have experience with managing the risks associated with anti-hemophilic therapies and the care of patients with HA and HB with and without inhibitors.

Based on the data available, the seriousness of the disease state, and the prescribing community's likely familiarity with the risks associated with concizumab that do not pose unique REMS considerations compared with the risks associated with other therapies, this reviewer has concluded that should concizumab be approved, a REMS is not necessary to ensure the benefits outweigh the risks of concizumab. At the time of this review, the labeling and PMR negotiations were ongoing. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with concizumab use are similar to other products used for prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with HA with inhibitors and HB with inhibitors. In addition, the likely prescribers are expected to be familiar with and able to appropriately monitor for the risks. At the time of this review, the labeling and PMR negotiations were ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should the Division of Nonmalignant Hematology have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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

Application Type	BLA
Application Number	761315
PDUFA Goal Date	April 24, 2023
OSE RCM #	2022-2316
Reviewer Name(s)	Timothy Bernheimer, PharmD
Team Leader	Carolyn Tieu, PharmD, MPH
Review Completion Date	April 21, 2023
Subject	Defer Comment on Evaluation of Need for a REMS
Established Name	Concizumab-mtci
Trade Name	Alhemo
Name of Applicant	Novo Nordisk
Therapeutic Class	Tissue factor pathway inhibitor (TFPI)-directed antibody
Formulation(s)	Prefilled pen for injection
Dosing Regimen	Day 1: loading dose of 1 mg/kg. Day 2: once-daily dose of 0.2 mg/kg. After 4 weeks but no later than 8 weeks, individualize maintenance dose based on plasma concentration: • <200 ng/ml: adjust to a once-daily dose of 0.25 mg/kg • 200 to 4,000 ng/ml: continue once-daily dose of 0.2 mg/kg • >4000 ng/ml: adjust to a once-daily dose of 0.15 mg/kg

This memorandum by the Division of Risk Management (DRM) defers the review that evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Alhemo (concizumab-mtci) is necessary to ensure the benefits outweigh its risks.

On August 24, 2022, Novo Nordisk (the Applicant) submitted a Biologic Licensing Application (BLA) (b) (4) for Alhemo with the proposed indication 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; and hemophilia B (congenital factor IX deficiency) with factor IX inhibitors.[1,2] The Applicant did not submit a proposed REMS or risk management plan with this application. On March 22, 2023, the Division of Non-Malignant Hematology (DNH) issued a "Deficiencies Preclude Discussion" letter due to deficiencies that were identified during the review of the application that preclude discussion of labeling and postmarketing requirements/commitments at this time.[3]

The review team recommends a complete response (CR) for regulatory action based on issues with clinical and clinical pharmacology, device, product quality, and facility inspection.[4] For clinical and clinical pharmacology, significant fluctuations in concentrations of Alhemo were noted in patients over the treatment period and concentrations can decline steeply to subtherapeutic levels with missed doses. There is a potential risk for a moderate or severe or fatal bleed with subtherapeutic levels of Alhemo. Other CR reasons include failed inspection, inadequate cell bank stability protocols, inadequate reference material stability protocols, inadequate drug substance (DS) and drug product (DP) release and stability specifications and inadequate DS and DP post-approval annual stability protocols, and inadequate interim assay to support the use of the assay in testing clinical specimens. Please refer to the DNH integrated review[2] for a detailed review of identified issues for this BLA and the CR Letter[4] that will be sent to the Applicant.

Based on this information, an evaluation for the need for a REMS for Alhemo will be undertaken by DRM after the Applicant addresses the deficiencies in the CR letter. Please send DRM a new consult request at such time. This memorandum serves to close the existing consult request to DRM for Alhemo under BLA 761315.

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[1] Proposed prescribing information for Alhemo (concizumab-mtci) as currently edited by FDA, Accessed March 10, 2023.

[2] Integrative Review and Evaluation: BLA 761315 Alhemo (concizumab-mtci), injection. Review in progress; accessed March 29, 2023

[3] Deficiencies Preclude Discussion Letter for Alhemo (concizumab-mtci) BLA 761315, dated March 22, 2023. DARRTS Reference ID: 5145706

[4] Draft Complete Response Letter for Alhemo (Concizumab-mtci), injection. Draft in process; accessed April 19, 2023

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