This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ALHEMO® (concizumab)

1.   NAME OF THE MEDICINE

concizumab

2.   QUALITATIVE AND QUANTITATIVE COMPOSITION

Concizumab is a humanised IgG4 monoclonal antibody produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. To retain the high affinity for the Kunitz 2 (K2) domain of tissue factor pathway inhibitor (TFPI), 7 back mutations were included. Additionally, in order to prevent formation of half-antibodies, the serine at position 241 (Kabat annotation) in the heavy chain was replaced with a proline (Ser241Pro).

No raw materials of animal or human origin are used in the concizumab manufacturing process.

Alhemo 15 mg/1.5 mL (10 mg/mL) solution for injection

One mL of solution contains 10 mg of concizumab. One pre-filled pen contains 15 mg concizumab in 1.5 mL solution.

Alhemo 60 mg/1.5 mL (40 mg/mL) solution for injection

One mL of solution contains 40 mg of concizumab. One pre-filled pen contains 60 mg concizumab in 1.5 mL solution.

Alhemo 150 mg/1.5 mL (100 mg/mL) solution for injection

One mL of solution contains 100 mg of concizumab. One pre-filled pen contains 150 mg concizumab in 1.5 mL solution.

Alhemo 300 mg/3 mL (100 mg/mL) solution for injection

One mL of solution contains 100 mg of concizumab. One pre-filled pen contains 300 mg concizumab in 3 mL solution.

For the full list of excipients, see Section 6.1 List of excipients.

3.   PHARMACEUTICAL FORM

Solution for subcutaneous injection.

Alhemo is a clear to slightly opalescent, colourless to slightly yellow liquid, that may contain translucent to white particles of protein.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Alhemo is indicated where prophylaxis is required to prevent or reduce the frequency of bleeding in patients at least 12 years of age who have haemophilia B (congenital factor IX [FIX] deficiency) with FIX inhibitors.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Treatment should be initiated under the supervision of a physician experienced in treatment of haemophilia and/or bleeding disorders. Initiate concizumab in a non-bleeding state, and after discontinuing treatment with bypassing agents. Discontinue rFVIIa at least 12 hours before starting concizumab therapy. Discontinue aPCC at least 48 hours before starting concizumab therapy.

The recommended dosing regimen is summarised in Table 1.

Table 1 Recommended dosing regimen

Treatment day	Dose phase	Concizumab dose
Day 1	Loading dose	1 mg/kg SC once
Day 2 until determination of individual maintenance dose	Initial maintenance dose	0.20 mg/kg SC daily
From determination of individual maintenance dose onwards	Individual maintenance dose	(chosen based on Table 2) SC daily

SC = subcutaneous

Determination of individual maintenance dose:
Measure trough plasma concizumab concentration 4 weeks after initiation of treatment by ELISA (enzyme-linked immunosorbent assay) and use this to determine an individual maintenance dose, based on Table 2. This should take place as soon as possible once the trough plasma concizumab concentration result is available, and no later than 8 weeks after initiation of treatment.

Table 2 Guide for determination of individual maintenance dose

Trough plasma concizumab concentration	Individual maintenance dose (once daily, subcutaneous)
<200 ng/mL	0.25 mg/kg
200−4000 ng/mL	0.20 mg/kg
>4000 ng/mL	0.15 mg/kg

Dose calculation using patient weight

The total dose (in mg) to be administered daily is calculated as follows:

Patient body weight (kg) x dose per kilogram (1, 0.15, 0.20 or 0.25 mg/kg) = total dose (mg) of Alhemo.

The dose is dialled at increments of

- 0.1 mg on the 15 mg/1.5 mL (10 mg/mL) pen (blue),

- 0.4 mg on the 60 mg/1.5 mL (40 mg/mL) pen (brown), and

- 1.0 mg on the 150 mg/1.5 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL) pens (gold).

When commencing treatment, a healthcare professional must assist the patient in rounding off the daily dose calculation and identifying the appropriate injectable dose increment on the pen.

See section 6.5 Nature and contents of container for guidance on the patient body weight range that each of the four product strengths is able to accommodate.

Duration of treatment

Alhemo is intended for ongoing prophylaxis and usage is expected to be long-term.

Dose timing

Alhemo can be administered at any time of day. Administering it at the same time each day is not necessary, however, doing so (as part of a patient's habitual daily routine) may make it easier to keep track of dosing and minimise the risk of missed doses.

Missed doses/dose interruption

When dosing is interrupted, serum levels fall precipitously due to target-mediated drug disposition (see section 5.2 Pharmacokinetic properties). Based on modelling, efficacy is reduced within 1-2 days of stopping for some patients and is abrogated for most patients within a week.

If a dose is missed, do not administer extra Alhemo: instead, resume the maintenance dose. If more than one dose was missed, efficacy may be compromised. Depending on the duration of interruption, it takes up to 2 weeks after resuming for efficacy to be restored. The use of re-loading doses has not been studied. During periods of possible reduced efficacy due to interrupted/missed dosing, patients should avoid activities associated with an increased risk of bleeding.

Management in the perioperative setting

No dose adjustment of Alhemo is needed in case of minor surgeries.

There is no data regarding the use of Alhemo in proximity to major surgery, as patients requiring such had their treatment paused in clinical studies. If major surgery is required, consult a physician experienced in treatment of haemophilia and/or bleeding disorders

AusPAR - Alhemo - concizumab - Novo Nordisk Pharmaceuticals Pty Ltd - PM-2022-03458-1-6
FINAL 8 March 2024. This is the Product Information that was approved with the submission described in this
AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at
<https://www.tga.gov.au/product-information-pi>

regarding concizumab dosing. As there is no experience, it is generally recommended to pause concizumab at least 4 days prior to major surgery, and restart 10-14 days post-surgery at the same maintenance dose as prior to surgery (with no loading dose). Based on PK modelling, concizumab concentration is expected to reach close to pre-pause steady-state levels after approximately 2 weeks. Timing of reintroduction of concizumab should take into account the overall clinical picture of the patient, including presence of post-surgical thromboembolic risk factors, use of other haemostatic products and other concomitant medications.

Method of administration

Alhemo is for subcutaneous use only.

Alhemo comes in a ready-to-administer pre-filled pen. Needles are not included (see section 6.5 Nature and contents of container). Each Alhemo pen is for use by a single patient. An Alhemo pen must not be shared between patients, even if the needle is changed.

Alhemo should appear clear to slightly opalescent, and colourless to slightly yellow. It may contain translucent (colourless) to white particles of protein. The protein particles are less than 0.5 mm in size. Do not use if the solution is discoloured or contains any other solid foreign particles.

The flow of the Alhemo pen should be checked before each injection (see the pen device instructions for use).

Alhemo may be self-administered, or administered by a caregiver, after receiving appropriate training by a healthcare professional and carefully reading the Instructions for Use. Always use a new needle for each injection.

Administer Alhemo by subcutaneous injection to the abdomen or thigh with rotation of injection site every day. Do not inject in areas where the skin is tender, bruised, red or hard, or where there are moles or scars.

Children and very lean patients may be at higher risk of intramuscular injection. Educate patients and caregivers on injection techniques that minimise the risk of intramuscular injection, such as injecting into a loosely-held skinfold.

During treatment with Alhemo, other medicinal products for subcutaneous administration should, preferably, be injected at different anatomical sites.

Dose adjustment in special populations

Intrinsic factors

There are no changes to the recommended dosing regimen (see Table 1) based on renal function, hepatic function or age (see section 5.2 Pharmacokinetic properties).

Management of breakthrough bleeds

Discuss the management of breakthrough bleeds with the patient and/or caregiver prior to commencing concizumab.

Do not adjust the dose of Alhemo if a breakthrough bleed occurs.

AusPAR - Alhemo - concizumab - Novo Nordisk Pharmaceuticals Pty Ltd - PM-2022-03458-1-6
FINAL 8 March 2024. This is the Product Information that was approved with the submission described in this
AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at
<https://www.tga.gov.au/product-information-pi>

Bypassing agents (such as rFVIIa or aPCC) can be used to treat breakthrough bleeds during concizumab therapy: the dose and duration of bypassing agent should be based on the location and severity of the bleed.

For mild and moderate bleeds that require treatment with a bypassing agent, use the lowest possible effective dose to minimise the risk of thromboembolic events. In addition, do not exceed an aPCC dose of 100 U/kg body weight within 24 hours.

For severe bleeds, exercise clinical judgement in the use of bypassing agents according to their Product Information, taking into account the potential for life-threatening thromboembolic events.

4.3. CONTRAINDICATIONS

Treatment with Alhemo is contraindicated in subjects with known hypersensitivity to concizumab or to any of the excipients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Thromboembolic events

Serious thromboembolic events were reported in concizumab phase 3 clinical trials, in context of therapy for breakthrough bleeding that was in excess of standard dosage. In two of three cases, plasma concentrations of concizumab were at the higher end of the observed range of exposure. Dosing for all patients in the trial was subsequently changed to the approved dose regimen (see Table 1), with breakthrough bleed guidance as outlined in 4.2 Dose and method of administration, after which no further thromboembolic events were observed.

Patients at high risk of thromboembolism were excluded from clinical studies. Factors considered in assessing an individual's risk included ta history or family history of thromboembolism, obesity, arrhythmias, hypertension, diabetes, hypercholesterolaemia, smoking, recent major surgeries, and older age. In conditions in which tissue factor is overexpressed (e.g., advanced atherosclerotic disease, crush injury, cancer or septicaemia), there may be a further risk of thromboembolic events or disseminated intravascular coagulation (DIC) with Alhemo treatment.

Inform patients and caregivers that thromboembolism could occur, that to minimise the risk, the lowest effective dose of bypassing agent should be used to treat breakthrough bleeds, and that they should self-monitor for signs and symptoms of thromboembolic events at all times. Discontinue concizumab if thromboembolism is suspected, and initiate further investigations and appropriate medical treatment.

Hypersensitivity reactions

Concizumab can cause allergic-type hypersensitivity reactions. Inform patients and/or caregivers of the signs and symptoms they should monitor for, and to seek emergency medical care if they occur. If hypersensitivity occurs, discontinue concizumab and initiate appropriate treatment.

Immune tolerance induction (ITI)

The safety and efficacy of concizumab in patients receiving ongoing immune tolerance induction have not been established.

Use in patients with low-responding inhibitors

The safety of high doses of factor IX (such as those used in immune tolerance induction or for treatment of bleeds in patients with low-responding inhibitors) in patients receiving concizumab prophylaxis has not been established.

Immunogenicity

Two patients in the clinical development program reported reduced efficacy with anti-concizumab antibodies. See 5.1 Pharmacodynamic properties.

Use in renal impairment

Alhemo has not been studied in patients with severe renal impairment (eGFR $\leq$30 mL/min/1.73 m^2).

Use in hepatic impairment

Alhemo has not been studied in patients with severe hepatic impairment (AST or ALT > 3x ULN combined with total bilirubin > 1.5x ULN).

Use in the elderly

There is limited data regarding the efficacy and safety of Alhemo in patients over the age of 65 years. One such patient was included in the explorer7 clinical study.

Paediatric use

The efficacy and safety of Alhemo in patients under the age of 12 years have not been established.

Effects on laboratory tests

Concizumab can elevate D-dimer and prothrombin fragment 1+2 levels. See section 4.8 Adverse effects (undesirable effects). Concizumab does not cause relevant interference with standard prothrombin and activated partial thromboplastin time assays, FVIII or FIX activity measurement using clot and chromogenic assays, or assays for inhibitory antibodies to FVIII or FIX (Bethesda assay).

4.5.   INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug-drug interaction clinical studies have been conducted. A drug-drug interaction toxicity study in concizumab-treated cynomolgus monkeys receiving three consecutive doses of up to 1 mg/kg rFVIIa was conducted with no adverse findings (including no formation of thrombi or other signs of excessive coagulation).

 In vitro and *ex vivo* drug-drug interaction studies were performed with rFVIIa, aPCC, rFVIII or rFIX in plasma from haemophilia patients who were on prophylactic treatment with concizumab. An additive or minor synergistic effect on thrombin generation was observed

AusPAR - Alhemo - concizumab - Novo Nordisk Pharmaceuticals Pty Ltd - PM-2022-03458-1-6
FINAL 8 March 2024. This is the Product Information that was approved with the submission described in this
AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at
<https://www.tga.gov.au/product-information-pi>

with these agents in the presence of concizumab, supporting their use to manage breakthrough bleeds in patients without interrupting concizumab.

For guidance on the use of bypassing agents in patients receiving concizumab prophylaxis, see section 4.2 Dose and method of administration.

4.6.   FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no available clinical data on the effect of concizumab on fertility, and no specific fertility studies have been conducted with concizumab in animals.

Surrogate endpoints relating to fertility were examined in a general toxicity study in cynomolgus monkeys. In a 26-week toxicity study in sexually mature male and female cynomolgus monkeys with subcutaneous doses up to 9 mg/kg/day (corresponding to 3400-fold the human exposure, based on AUC_{0-24h}), concizumab did not affect testicular size, sperm count, sperm motility, sperm morphology or menstrual cycle duration, and did not cause any microscopic changes in the male or female reproductive organs.

Use in pregnancy – Pregnancy Category D

Based on its mechanism of action and animal data, concizumab could harm a fetus if administered during pregnancy.

TFPI, which concizumab targets, is critical for embryofetal development, and its knockout in mice is associated with embryofetal lethality. As an IgG antibody, placental transfer of concizumab is expected, increasing in a linear fashion as pregnancy progresses. Specific animal reproduction studies have not been conducted with concizumab. There are no available clinical data on concizumab use in pregnancy.

Verify the pregnancy status of females of reproductive potential prior to the initiation of concizumab. Advise patients who are pregnant, and females of reproductive potential, of the potential risk to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with concizumab and until 7 weeks after the last dose.

Use in lactation

There is no data regarding the presence of concizumab in human milk, the effects on the breastfed child, or the effects on milk production. Human IgG is known to be present in human milk and concizumab is an IgG antibody. Because of the potential for adverse effects on a breastfed child, patients should not breastfeed during treatment and for 7 weeks after the last dose of concizumab.

4.7.   EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no evidence that concizumab influences the ability to drive and use machines.

4.8.   ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of concizumab was described based on data from the explorer7 clinical study with a data cut-off date of 27 DEC 2021 (see Section 5.1 Pharmacodynamics, Clinical trials). A total of 114 haemophilia patients with inhibitors received concizumab prophylaxis in this

study (across both the randomised and non-randomised parts), 32% of whom were between the ages of 12 and 17. The median (range) duration of exposure was 9.4 (1.0-20.5) months.

The most common adverse reaction reported in patients who received concizumab was injection site reaction (23%).

Serious adverse events occurred in 12% of patients, including one hypersensitivity reaction (0.9%) and one thromboembolic event (0.9%): both led to permanent discontinuation of concizumab.

Two fatal adverse events occurred during concizumab treatment: the first was due to COVID-19. The second was a sudden death that occurred in hospital, 21 days after a road traffic accident with femoral and humeral fractures requiring surgical intervention.

Concizumab dosing was interrupted for 7% of patients, most commonly due to SARS-COV-2 infection (3 patients). Injection site reaction requiring dose interruption occurred in one patient.

The most common adverse events in explorer7 are presented in Table 3.

Table 3 The most common treatment-emergent adverse events (incidence of at least 5%) in haemophilia patients with inhibitors treated with Alhemo in the explorer7 study

| System Organ Class | Frequency |
Preferred term (MedDRA)	(N=114)
General disorders and administration site disorders	
Injection site reactions*	23%
Pyrexia	5%
Infections and infestations	
Upper respiratory tract infection	7%
Investigations	
Prothrombin fragments 1 & 2 increased	6%
Fibrin D-dimer increased	5%
Musculoskeletal and connective tissue disorders	
Arthralgia	11%
Nervous system disorders	
Headache	5%

*Injection site reactions: this grouped term includes the preferred terms injection site rash, injection site erythema, injection site urticaria, injection site reaction, injection site bruising, injection site haematoma, injection site swelling, injection site pruritus, injection site haemorrhage, injection site hypoaesthesia, injection site induration, and injection site pain.

The following clinically meaningful but less common events also occurred in patients who received Alhemo in the explorer7 study:

Vascular disorders: thromboembolic events (0.9%)
Immune system disorders: hypersensitivity (2.6%)
Skin and subcutaneous tissue disorders: pruritus (0.9%)

Description of selected ADRs

Increased laboratory values of fibrin D-dimer and prothrombin fragment 1.2

Increased levels of fibrin D-dimer were reported in 6 (5.3%) of patients and increased levels of fragment 1.2 were seen in 7 (6.1%) patients. Concizumab plasma concentration is positively correlated with fibrin D-dimer and prothrombin fragments 1.2 indicating haemostatic effect of concizumab.

No clinically significant changes were seen in levels of fibrinogen, anti-thrombin or platelets.

Injection site reactions

Injection site reactions were reported in 26 (22.8%) of the patients. The most frequently reported symptoms were injection site erythema (7.9%) and injection site bruising (3.5%). One event of moderate injection site rash led to interruption of medicinal therapy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9.   OVERDOSE

There is limited experience with overdose of concizumab.

No serious adverse events occurred in a small number of patients who had up to 48 hours of very high exposure to concizumab (around 10-fold the exposures expected with the recommended regimen) during early phase studies. However, this was a small group, and the effect of longer-term high exposures is unknown. A specific exposure-response relationship between concizumab exposure and risk of thromboembolism has not been characterised.

For general information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5.   PHARMACOLOGICAL PROPERTIES

5.1.   PHARMACODYNAMIC PROPERTIES

Antihaemorrhagics – other systemic haemostatics: B02BX

Mechanism of action

Concizumab is an antibody against tissue factor pathway inhibitor (TFPI). Physiologically, TFPI dampens the initiation of coagulation by reducing formation of, and directly inhibiting, activated factor X (FXa). Concizumab binds to the Kunitz 2 (K2) domain of TFPI and inhibits these actions of TFPI. For patients with haemophilia, who have inadequate propagation of coagulation due to deficiency of FVIII or FIX, removing TFPI inhibition may allow adequate formation of FXa to generate sufficient thrombin for haemostasis.

As concizumab acts independently from FVIII and FIX, the effect of concizumab is not expected to be influenced by the presence of inhibitory antibodies to FVIII or FIX.

As concizumab has no structural relationship or sequence homology to FVIII or FIX, it is not expected to induce or enhance the development of direct inhibitors to FVIII or FIX.

Pharmacodynamic data

Concizumab treatment is associated with a dose-related increased capacity for thrombin generation in plasma, as measured by peak thrombin concentration (endogenous thrombin potential (ETP) velocity index), apparent from 6 hours post-dose. In explorer7, concizumab treatment was associated with a mean peak thrombin concentration in the normal plasma range.

Clinical trials

Haemophilia A and B with inhibitors (HAwI and HBwI) aged 12 years and above (explorer7)

The explorer7 trial (NN7415-4311) was an international, multi-centre, open-label, phase 3 study of Alhemo for the treatment of male patients with haemophilia A or B with inhibitors requiring prophylaxis against bleeding. Due to the pro-coagulant nature of Alhemo, patients considered at high risk of thromboembolic events (according to the investigator) were excluded from participating in the trial.

The randomised part of the trial comprised 52 patients (27 HAwI, and 25 HBwI), previously treated on-demand, who were randomised 1:2 to either continue on-demand treatment with bypassing agents (Arm 1, i.e. no prophylaxis) or to receive Alhemo prophylaxis (Arm 2). Randomisation was stratified by haemophilia type (HAwI, HBwI) and categorical[*] number of bleeds in the 24 weeks prior to randomisation (< 9 or ≥ 9).

In addition to the randomised portion of the study, a further 81 patients (53 HAwI and 28 HBwI) received Alhemo prophylaxis on a non-randomised basis in Arms 3 and 4.

Initially, the concizumab dose regimen consisted of a 1 mg/kg loading dose on Day 1 then a once-daily dose of 0.25 mg/kg starting on Day 2. However, the study was paused in March 2020 due to three thromboembolic events in Alhemo-treated patients. The study resumed in August 2020 with 29 of the 33 patients randomised to Alhemo continuing in the study. Following the study pause, patients received concizumab according to the dose regimen described in Table 1 (see 4.2 Dose and method of administration).

The safety profile of Alhemo was described based on data from patients who received concizumab prophylaxis in Arms 2, 3 and 4, under both the pre-pause and post-pause dosing regimens (see 4.8 Adverse effects (undesirable effects)).

The analysis of efficacy was based on data obtained after the study pause with the recommended dose (Table 1) from the randomised portion of the study (Arms 1 and 2).

The primary efficacy endpoint was comparison between the annualised bleeding rate (ABR) during randomised treatment in Arm 1 and that in Arm 2. Bleeding episodes were defined according to World Federation of Haemophilia criteria and were included if they were treated, whether spontaneous or traumatic. Efficacy was evaluated when all patients in Arms

---

[*] The actual (non-categorical) number of bleeds in the 24 weeks prior to randomisation for each patient was not collected.

1 and 2 had completed the main part of the trial (at least 24 or at least 32 weeks, respectively).

Across all four arms of the study, two thirds of patients were adults (including 63% of Arm 1 and 46% of Arm 2), 57% were Caucasian and 30% were Asian. The mean (range) age was 28 (12-67) years. A single patient over the age of 64 was enrolled: they were randomised to Arm 1. Haemophilia B patients made up 53% of Arm 1 and 46% of Arm 2. The majority of patients in Arms 1 and 2 had a documented inhibitor of > 0.6 Bethesda units (BU)/mL reported prior to study entry or at screening. Two patients randomised to Arm 1 did not have any documented inhibitors recorded. Most patients had either severe or moderately severe disease (≤2% FVIII or FIX activity).

The main efficacy findings of explorer7 are shown in Table 4, including descriptive subgroup findings by haemophilia type. Based on comparing the ABRs in Arm 1 and Arm 2, superiority of concizumab over on-demand treatment was concluded.

Table 4 Main efficacy findings of explorer7

	HAwI and HBwI		HAwI		HBwI	
Exposure	**Alhemo** (n=33)	**OnD** (n=19)	**Alhemo** (n=18)	**OnD** (n=9)	**Alhemo** (n=15)	**OnD** (n=10)
Median duration of exposure (months) (range)	9.2 (0.7, 12.9)	7.2 (0.9, 16.8)	11.0 (3.4, 12.9)	5.5 (0.9, 16.8)	7.4 (0.7, 12.8)	7.9 (1.0, 12.5)
Annualised bleeding rate (ABR) - treated spontaneous and traumatic bleeding episodes						
ABR estimate 95% CI	1.7 (1.0, 2.9)	11.8 (7.0, 19.9)	1.6 (0.9, 2.8)	18.3 (10.2, 32.9)	2.2 (0.8, 6.5)	7.2 (2.6, 20.1)
ABR ratio (95% CI), p-value	0.14 (0.07, 0.29), <0.001		0.09 (0.04, 0.18) <0.001*		0.31 (0.07, 1.36), 0.12*	

*nominal p-values (not alpha-controlled)

CI = confidence interval; HAwI = Haemophilia A with inhibitors; HBwI = Haemophilia B with inhibitors; ABR = Annualised bleeding rate; OnD = on-demand treatment (with bypassing agents) i.e. no prophylaxis.

Immunogenicity

In clinical studies, 47 out of 185 of concizumab treated patients (25%) who were tested had developed anti-concizumab anti-drug antibodies (ADA). ADA were neutralising in 12 patients (6.5%). One patient with neutralising antibodies permanently discontinued therapy, as free TFPI levels returned to baseline and it was considered likely that the effectiveness of concizumab was compromised. Reduction of effectiveness of concizumab in association with anti-concizumab antibodies was reported in a second patient in a compassionate use program.

5.2. PHARMACOKINETIC PROPERTIES

Systemic exposure to concizumab (AUC and C_{max}) increased with increasing dose in a greater than dose-proportional manner. This non-linear pharmacokinetic behaviour is caused by target-mediated drug disposition (TMDD) which occurs when concizumab binds to endothelial cell-anchored TFPI with subsequent elimination of the drug-target complex. This is a saturable process and the extent of concizumab elimination by TMDD is determined by

the amount of endothelial cell-anchored TFPI. This results in a fast elimination/high clearance being dominant at low concizumab concentrations (non-linear pathway) and a slower elimination/lower clearance being dominant at higher concizumab concentrations (linear pathway).

Concizumab exposure was similar between haemophilia A and B with inhibitors.

Geometric mean steady state concizumab concentrations are shown in Table 5.

Table 5 Steady-state concizumab concentrations during 24 hours dosing interval at week 24 (explorer7).

Parameters	All maintenance doses N=99*
$C_{max,ss}$ (ng/mL), geometric mean (CV)	1167.1 (1.3%)
$C_{trough,ss}$ (ng/mL), geometric mean (CV)	665.4 (2.2%)
C_{max} / C_{trough} ratio, mean (SD)	2.2 (5.2)

$C_{max,ss}$ = maximum plasma concentration at steady state; $C_{trough,ss}$ = pre-dose (trough) plasma concentration at steady state.

*on Alhemo dosing regimen.

Absorption

Following a single-dose subcutaneous administration of 0.05 – 3 mg/kg concizumab in healthy and haemophilia subjects, the time to maximum plasma concentration of concizumab (t_{max}) was between 8 and 99 hours (4.1 days). Concizumab bioavailability after subcutaneous administration was estimated to be 78% based on population pharmacokinetic modelling.

Distribution

The model-based estimate of steady-state volume of distribution for a typical subject was 5.92 L.

Metabolism

The metabolism of concizumab has not been studied. Large proteins such as IgG antibodies are generally catabolised by lysosomal proteolysis.

Excretion

Linear and non-linear pathways both contribute to the elimination of concizumab. Due to the non-linear elimination, the half-life is dependent on the concizumab concentration. In healthy and haemophilia subjects who received a single subcutaneous dose of 0.25–3 mg/kg, the terminal half-life was 39-195 hours (1.6-8.1 days). At steady state, when linear elimination becomes dominant, the total half-life is expected to be longer. Following multiple subcutaneous injections and based on a population PK analysis, the linear clearance was approximately 0.192 L/day (0.008 L/h), and the estimated half-life at steady-state C_{trough} (665 ng/mL) was approximately 38 hours.

Special populations

Age

Age had no meaningful effect on concizumab exposure. There were insufficient patients over the age of 64 for meaningful assessment of differences in elderly patients.

Renal impairment

No dedicated trials on the effect of renal impairment on the pharmacokinetics of concizumab have been conducted. Of the 112 patients treated with Alhemo dosing regimen in explorer7, five patients had eGFR <90 mL/min/1.73m^2 at the time when the loading dose was administered. No impact on exposure of concizumab was observed.

Hepatic impairment

No dedicated trials on the effect of hepatic impairment on the pharmacokinetics of concizumab have been conducted. Of the 112 patients treated with Alhemo dosing regimen in explorer7, four patients had elevated liver enzymes (ALT or AST $\geq$ 1.5 x ULN) at the time when the loading dose was administered. No impact on exposure of concizumab was observed.

5.3.   PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been performed with concizumab. As a large protein molecule, concizumab is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

Long-term studies in animals to evaluate the carcinogenic potential of concizumab have not been performed.

6.   PHARMACEUTICAL PARTICULARS

6.1.   LIST OF EXCIPIENTS

Arginine hydrochloride
Histidine
Sodium chloride
Sucrose
Polysorbate 80
Phenol
Hydrochloric acid
Sodium hydroxide
Water for injections

6.2.   INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3.   SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After first opening

4 weeks – see below.

6.4.   SPECIAL PRECAUTIONS FOR STORAGE

Before first use: Store in a refrigerator (2-8°C).

After first use: May be stored unrefrigerated for up to 4 weeks at a temperature below 30°C.

Store the pen with the cap on to protect the solution from light. Do not store the pen with the needle attached. This ensures accurate dosing, and prevents contamination, infection, and leakage.

Do not freeze the pen or store it close to a cooling element in a refrigerator. Alhemo should be protected from heat and light and should not be stored in direct sunlight.

6.5.   NATURE AND CONTENTS OF CONTAINER

Alhemo is provided in a portable multi-dose disposable pre-filled pen, which consists of a 1.5 mL or 3 mL glass cartridge sealed in a pen-injector, made of plastic components and metal springs. The cartridge is closed at the bottom with a rubber disc, and at the top with a laminate rubber disc sealed with an aluminium cap. The rubber discs are not made with natural rubber latex.

The Alhemo pen must not be refilled.

The dose button and the cartridge holder on the pen-injector are colour–coded according to strength:

- 15 mg/1.5 mL (10 mg/mL) (blue)

- 60 mg/1.5 mL (40 mg/mL) (brown)

- 150 mg/1.5 mL (100 mg/mL) (gold)

- 300 mg/3 mL (100 mg/mL) (gold)

The pre-filled pen is packed in a carton. Alhemo is available in pack size containing 1 or 5 pens. Not all pack sizes may be marketed in a particular region. Injection needles are not included.

Alhemo is recommended to be used with NovoFine® Plus or NovoFine® needles with a gauge of 32 and a length of 4 mm. If needles longer than 4 mm are used, injection techniques that minimise the risk of intramuscular injection should be used.

Choice of product strength and volume

Based on technical features, the Alhemo pens can accommodate the following body weight ranges:

For patients on a daily dose of 0.15 mg/kg body weight

Product strength	Body weight
15 mg/1.5 mL (10 mg/mL)	5-53 kg
60 mg/1.5 mL (40 mg/mL)	19-213 kg
150 mg/1.5 mL (100 mg/mL)	47 kg and above
300 mg/3 mL (100 mg/mL)	73 kg and above

For patients on a daily dose of 0.20 mg/kg body weight

Product strength	Body weight
15 mg/1.5 mL (10 mg/mL)	5-32 kg
60 mg/1.5 mL (40 mg/mL)	19-128 kg
150 mg/1.5 mL (100 mg/mL)	47 kg and above
300 mg/3 mL (100 mg/mL)	73 kg and above

For patients on a daily dose of 0.25 mg/kg body weight

Product strength	Body weight
15 mg/1.5 mL (10 mg/mL)	3-32 kg
60 mg/1.5 mL (40 mg/mL)	11-128 kg
150 mg/1.5 mL (100 mg/mL)	28 kg and above
300 mg/3 mL (100 mg/mL)	44 kg and above

6.6.   SPECIAL PRECAUTIONS FOR DISPOSAL

Patients are advised to discard injection needles after each injection.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7.   PHYSICOCHEMICAL PROPERTIES

Chemical structure

Concizumab (protein part):

$C_{6462}H_{10004}N_{1712}O_{2046}S_{46}$

CAS number

7.   MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8.   SPONSOR

Novo Nordisk Pharmaceuticals Pty Ltd
Level 10, 118 Mount Street
North Sydney NSW 2060

Australia

www.novonordisk.com.au

9.   DATE OF FIRST APPROVAL

5 July 2023

10.   DATE OF REVISION

N/A

Summary table of changes

Section changed	Summary of new information
N/A	New registration