SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Alhemo 150 mg/1.5 mL solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alhemo 150 mg/1.5 mL solution for injection in pre-filled pen

One mL solution contains 100 mg concizumab*.
Each pre-filled pen contains 150 mg of concizumab in 1.5 mL solution (100 mg/mL).

*Concizumab is a humanised IgG4 monoclonal antibody produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear to slightly opalescent, colourless to slightly yellow liquid and practically free from visible particles, that may contain translucent to white particles of protein.

Isotonic solution with pH of approximately 6.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alhemo is indicated for routine prophylaxis of bleeding in patients with:
- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and of 12 years of age or more.

- haemophilia B (congenital factor IX deficiency) with FIX inhibitors and of 12 years of age or more.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in treatment of haemophilia and/or bleeding disorders.

Posology

Treatment should be initiated in a non-bleeding state.

Treatment with rFVIIa should be discontinued at least 12 hours before starting concizumab therapy and treatment with aPCC should be discontinued at least 48 hours before.

The recommended dosing regimen is
- Day 1: a loading dose of 1 mg/kg once.
- Day 2 and until individual maintenance dose setting (see below): once daily dosing of 0.20 mg/kg.
- 4 weeks after initiation of treatment: measurement of concizumab plasma concentration prior to administration of the next scheduled dose. The measurement must be performed using a validated *in vitro* diagnostic test.
- When concizumab plasma concentration result is available: individual maintenance dose is set once based on concizumab plasma concentration as indicated below in Table 1.

Table 1 Individual maintenance dose based on concizumab plasma concentration

Concizumab plasma concentration	Once daily dose Alhemo
< 200 ng/mL	0.25 mg/kg
200−4 000 ng/mL	0.20 mg/kg
> 4 000 ng/mL	0.15 mg/kg

Individual maintenance dose setting should be performed at the earliest convenience (after concizumab plasma concentration result is available) and recommended no later than 8 weeks after initiation of treatment. Additional concizumab plasma concentration measurement(s) can be taken after 8 weeks on the same maintenance dose according to the patient's medical condition. For example, this should be considered if a patient experiences an increased bleeding frequency, a large change in body weight, has missed doses before maintenance dose setting, or acquires a comorbidity, which can lead to an increase in the overall thromboembolic risk.

Since concizumab is dosed per body weight (mg/kg), it is important to recalculate the dose (mg) when the body weight changes.

Calculation of dose

The dose (in mg) is calculated as follows:
Patient body weight (kg) x dose (1, 0.15, 0.20 or 0.25 mg/kg) = total amount (mg) of concizumab to be administered.

The dose is dialled at increments of

- 0.1 mg on the 15 mg/1.5 mL pre-filled pen (blue),
- 0.4 mg on the 60 mg/1.5 mL pre-filled pen (brown), and
- 1.0 mg on the 150 mg/1.5 mL and 300 mg/3 mL pre-filled pens (gold).

The calculated dose is rounded off to the nearest injectable dose on the pen. The physician or nurse must assist the patient in rounding off and identifying the appropriate injectable dose on the pen. Ideally, patients should be prescribed and use a pen that can deliver the required daily maintenance dose in one injection. The nearest injectable dose can be identified by turning the scale drum on the pen or can be calculated as follows:

Divide total dose in mg by dose per increment.
Round off to nearest whole number.
Multiply by dose per increment.

Examples:

A patient's body weight of 42 kg, using a maintenance dose of 0.15 mg/kg.

Day 1 using a loading dose of 1 mg/kg:

- 42 kg x 1 mg/kg = 42 mg of concizumab.

Day 2 and until individual maintenance dose setting using a dose of 0.20 mg/kg:

- 42 kg x 0.20 mg/kg = 8.4 mg of concizumab.

Maintenance dose:

- 42 kg x 0.15 mg/kg = 6.3 mg of concizumab.

A patient is to receive 6.3 mg of concizumab with a 60 mg/1.5 mL pre-filled pen to provide the longest pen duration (days) for this patient's body weight.

To identify the nearest injectable dose:

- 6.3 mg divided by 0.4 mg/increment = 15.75 increments
- 15.75 increments are rounded off to 16 increments
- 16 multiplied by 0.4 mg/increment = 6.4 mg.

6.4 mg is a dose which can be dialled on the 60 mg/1.5 mL pre-filled pen and it is the injectable dose closest to 6.3 mg.

A patient's body weight of 67 kg, using a maintenance dose of 0.20 mg/kg.

Day 1, using a loading dose of 1 mg/kg:

- 67 kg x 1 mg/kg = 67 mg of concizumab.

Day 2 and until individual maintenance dose setting using a dose of 0.20 mg/kg:

- 67 kg x 0.20 mg/kg = 13.4 mg of concizumab

Maintenance dose:

- 67 kg x 0.20 mg/kg = 13.4 mg of concizumab.

The patient is to receive 13.4 mg of concizumab with a 300 mg/3 mL pre-filled pen to provide the longest pen duration (days) for this patient's body weight.

To identify the nearest injectable dose:

- 13.4 mg divided by 1.0 mg/increment = 13.4 increments
- 13.4 increments are rounded off to 13 increments
- 13 increments multiplied by 1.0 mg/increment = 13.0 mg.

13.0 mg is a dose which can be dialled on the 300 mg/3 mL pre-filled pen and it is the injectable dose closest to 13.4 mg.

Choice of product strength and volume

Based on technical features, the Alhemo pre-filled 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**	**Dose increment**	**Maximum dose per injection**
15 mg/1.5 mL	5-53 kg	0.1 mg	8 mg
60 mg/1.5 mL	19-213 kg	0.4 mg	32 mg
150 mg/1.5 mL	47 kg and above	1.0 mg	80 mg
300 mg/3 mL	73 kg and above	1.0 mg	80 mg

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

Product strength	**Body weight**	**Dose increment**	**Maximum dose per injection**
15 mg/1.5 mL	4-40 kg	0.1 mg	8 mg
60 mg/1.5 mL	14-160 kg	0.4 mg	32 mg
150 mg/1.5 mL	35 kg and above	1.0 mg	80 mg
300 mg/3 mL	55 kg and above	1.0 mg	80 mg

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

Product strength	**Body weight**	**Dose increment**	**Maximum dose per injection**
15 mg/1.5 mL	3-32 kg	0.1 mg	8 mg
60 mg/1.5 mL	11-128 kg	0.4 mg	32 mg
150 mg/1.5 mL	28 kg and above	1.0 mg	80 mg
300 mg/3 mL	44 kg and above	1.0 mg	80 mg

If more than one Alhemo pen is relevant based on body weight ranges, the pen with the highest product strength should be chosen. The higher strength pen contains more doses that can be administered, allowing the pen to be used for more days.

Duration of treatment

Alhemo is intended for long-term prophylactic treatment.

Missed dose

Concizumab can be administered any time during the day.

It is important that each patient adheres to their daily dosing. Adherence is particularly important during the initial 4 weeks to ensure a correct maintenance dose is properly established based on the week 4 concizumab plasma concentration (see section 4.2 on posology). Patients who miss doses before the maintenance dose has

been established should resume treatment as soon as possible at the initial 0.2 mg/kg daily dose and inform their healthcare professional.

Missed doses once the maintenance dose has been established

The following dosing guidelines should apply **ONLY** when a patient has forgotten to or neglected to take their once daily maintenance dose.

- 1 missed daily dose: the patient should resume the daily maintenance dose without an additional dose.
- 2 to 6 missed consecutive daily doses: the patient should take the daily dose twice (as two separate injections each corresponding to a daily dose), and then continue taking the daily maintenance dose the next day.
- 7 or more missed consecutive daily doses: The patient should contact their healthcare professional right away. The patient may need to receive a new loading dose before continuing their daily maintenance dose the next day, after careful consideration of the clinical picture.

When in doubt, the patient should contact their healthcare professional.

Management of breakthrough bleeds

No dose adjustment of Alhemo should be done in case of breakthrough bleeds.

Physicians should discuss with the patient and/or caregiver about the dose and schedule of bypassing agents, if required while receiving concizumab prophylaxis.

Treatment with bypassing agents (e.g., rFVIIa or aPCC) can be used for breakthrough bleeds, and the dose and duration will depend on the location and severity of the bleed.

For mild and moderate bleeds that require additional treatment with bypassing agents (e.g., rFVIIa or aPCC), the lowest approved dose and the dose interval as in the approved label is recommended. Furthermore, for aPCC a maximum dose of 100 U/kg body weight within 24 hours is recommended.

For severe bleeds it is recommended to follow the dosing scheme provided in the approved label for the specific product based on clinical judgement.

Management in the perioperative setting

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

Before major surgery, a healthcare professional experienced in treatment of haemophilia and/or bleeding disorders should be consulted. As there is limited clinical experience in using concizumab during major surgeries, it is generally recommended to pause concizumab at least 4 days prior to elective major surgery. Concizumab therapy can be resumed 10-14 days after surgery on the same maintenance dose without a new loading dose, considering the overall clinical picture of the patient.
The criteria for major surgery are any invasive operative procedure that requires ≥ 3 doses of bypassing therapy and/or where any one or more of the following occur:

- A body cavity is entered
- A mesenchyme barrier (e.g. pleura, peritoneum or dura mater) is crossed
- A fascia plane is opened
- An organ is removed
- Normal anatomy is operatively altered.

Immune tolerance induction (ITI)

The safety and efficacy of concomitant use with concizumab in patients receiving ongoing ITI, a desensitisation strategy for eradication of inhibitors, have not been established. No data is available. Careful assessment of potential benefits and risks should be performed if continuation or initiation of concizumab during ITI is considered.

Elderly

No dose adjustments (besides individual maintenance dose setting) are recommended in patients ≥ 65 years of age. No data are available in patients aged 65 years and older. For more information, see section 5.2.

Renal impairment

No dose adjustments (besides individual maintenance dose setting) are recommended in patients with renal impairment. Limited or no data are available in patients with mild, moderate, and severe renal impairment, see section 5.2.

Hepatic impairment

No dose adjustments (besides individual maintenance dose setting) are recommended in patients with hepatic impairment. Limited or no data are available in patients with hepatic impairment, see section 5.2.

Paediatric population

The safety and efficacy of Alhemo in children aged < 12 years has not yet been established. No data are available.

Method of administration

Alhemo is for subcutaneous use only.

Concizumab comes in a ready-to-administer pre-filled pen. Needles are not included, see section 6.5.

Concizumab should be administered daily, at any time point of the day, not necessarily the same time point every day.

Concizumab may be self-administered, or administered by a caregiver, after receiving appropriate training by a health care professional and reading the Instructions for Use.

Concizumab should be administered by subcutaneous injection to the abdomen or thigh with rotation of injection site every day. Subcutaneous injections should not be given in areas where the skin is tender, bruised, red or hard, or areas where there are moles or scars.

A new needle should always be used for each injection.

Each Alhemo pre-filled pen is for use by a single patient. An Alhemo pre-filled pen must not be shared between patients, even if the needle is changed.

For comprehensive instructions on the administration of the medicinal product, see section 6.6 and the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions

Allergic type hypersensitivity reactions have occurred with concizumab within the initial weeks of treatment, including hospitalisation and permanent discontinuation of therapy. Patients should be informed of the signs of acute hypersensitivity reactions.

If symptoms of hypersensitivity occur, the patient should be advised to discontinue the use of Alhemo and contact the physician who should ensure appropriate treatment.

Immunogenicity

Development of neutralising anti-concizumab antibodies, observed in some patients, has not led to loss of efficacy (see section 5.1). However, patients with clinical signs of loss of efficacy (e.g. increase in breakthrough bleeding events) should be evaluated to assess the etiology and other therapeutic options should be considered if neutralising anti-concizumab antibodies are suspected.

Thromboembolic events

Cases of non-fatal arterial and venous thromboembolic events have been reported in the concizumab clinical trials. These cases occurred in patients with multiple risk factors including high or frequent doses of breakthrough bleed treatment (see section 4.8).

Patients treated with concizumab should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events. In case of suspicion of thromboembolic events, concizumab should be discontinued, and further investigations and appropriate medical treatment should be initiated. There should be careful consideration whether the potential benefit of concizumab treatment outweighs the potential risk in patients considered at high risk of thromboembolic events. This consideration should be re-evaluated periodically.

In conditions in which tissue factor is overexpressed (e.g., advanced atherosclerotic disease, crush injury, cancer or septicaemia), there may be a risk of thromboembolic events or disseminated intravascular coagulation (DIC). In these situations, the potential benefit of treatment with concizumab should be weighed against the risk of these complications.

Effects of concizumab on coagulation tests

Concizumab therapy does not produce clinically meaningful changes in standard measures of coagulation including activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

This medicinal product contains 0.25 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction clinical trials have been conducted. A drug-drug interaction toxicity study with rFVIIa in concizumab treated cynomolgus monkeys was conducted. No sign of thrombosis or other adverse findings were observed in normo-coagulant monkeys when adding three consecutive doses of up to 1 mg/kg rFVIIa on top of concizumab at steady state, see section 5.3.

In vitro and *ex vivo* drug-drug interaction studies were performed with rFVIIa, aPCC, rFVIII or rFIX in blood from haemophilia patients who are on prophylactic treatment with concizumab. These studies did not suggest clinically relevant drug-drug interactions.

For guidance on the use of bypassing agents for treatment of breakthrough bleeding episodes in patients receiving concizumab prophylaxis, see section 4.2.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Women of childbearing potential receiving concizumab should use highly effective contraception during treatment with concizumab and until 7 weeks after end of treatment. The benefits and thromboembolic risks of the type of contraceptives used should be evaluated by the treating physician.

Pregnancy

There are no available data on concizumab use in pregnant women. Animal reproduction studies have not been conducted with concizumab. It is not known whether concizumab can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Concizumab should only be used during pregnancy if the potential benefit for the mother outweighs the potential risk to the foetus.

Breast-feeding

It is unknown whether concizumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, concizumab could be used during breast-feeding if clinically needed.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, see section 5.3. No fertility data are available in humans. Thus, the effect of concizumab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Alhemo has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of concizumab is based on data from clinical trials. The most serious adverse reactions in the clinical trials with concizumab were thromboembolic events (0.9%) and hypersensitivity (0.3%).

Tabulated list of adverse reactions

The following adverse reactions are based on pooled data from the clinical trials NN7415-4159 (phase 1b), NN7415-4310 (phase 2), NN7415-4255 (phase 2), NN7415-4311 (phase 3) and NN7415-4307 (phase 3), in which a total of 320 male patients with haemophilia A with and without inhibitors and haemophilia B with and without inhibitors received at least one dose of concizumab as routine prophylaxis. The patients were exposed for a total of 411 exposure years.

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each

frequency grouping, adverse reactions are presented in order of decreasing seriousness, see Table 2.

Table 2 Adverse reactions from pooled clinical trials with concizumab

System Organ Class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity	Common
Vascular disorders	Thromboembolic events	Uncommon
General disorders and administration site disorders	Injection site reactions	Very common

Description of selected adverse reactions

Injection site reactions
Injection site reactions were reported across the multiple dose clinical trials. The most frequently reported symptoms were injection site erythema (5.9%), injection site bruising (4.4%) and injection site haematoma (4.1%). The majority were reported as mild.

Paediatric population

78 of the clinical trial participants were adolescents (≥ 12 to < 18 years). The safety profile was similar between adolescent and adult patients and as expected for the age group.

The safety and efficacy of concizumab in children aged below 12 years have not yet been established. No data are available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via
Yellow Card Scheme
Website: https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is limited experience with overdose of concizumab. Cases of up to 5 times the intended dose have been reported with no clinical consequences. Accidental overdose may result in hypercoagulability and patients should contact their physician for monitoring.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, other systemic haemostatics; ATC code: B02BX10.

Mechanism of action

Concizumab is an anti-tissue factor pathway inhibitor (anti-TFPI) antibody. TFPI is an inhibitor of factor Xa (FXa). Concizumab binding to TFPI prevents TFPI inhibition of FXa. The increased FXa activity prolongs the initiation phase of coagulation and allows sufficient thrombin generation for effective haemostasis. Concizumab acts independently from FVIII and FIX.

Pharmacodynamic effects

In the NN7415-4311 trial, mean free TFPI (plasma TFPI not bound to concizumab) for patients on concizumab prophylaxis decreased by 87% within 24 hours following administration of the concizumab loading dose and remained stable over time. Concizumab re□established thrombin generation capacity reflected by mean thrombin peak within the range of normal plasma, and 94% of patients having thrombin peak values within the range of normal plasma (26–147nM) at the 56-week cut-off. Transiently, moderately elevated thrombin peak levels were reported in 37.6% of patients with no associated safety concerns.

Clinical efficacy and safety

Haemophilia A and B with inhibitors (HAwI and HBwI) aged 12 years and above (NN7415-4311)

The NN7415-4311 trial was a multi-national, multi-centre, open-label phase 3 trial to investigate efficacy and safety of concizumab for prophylaxis of bleeding episodes in 91 adults (58 HAwI and 33 HBwI) and 42 adolescents (22 HAwI and 20 HBwI) male patients with haemophilia A or B with inhibitors.

The trial was comprised of 4 arms, including two non-randomised arms:

- Arms 1 and 2: 52 patients previously treated on-demand, were randomised to no prophylaxis (on-demand treatment with bypassing agents; arm 1) or concizumab prophylaxis (arm 2), with ≥ 6 treated bleeds in the last 24 weeks or ≥ 12 treated bleeds in the last 52 weeks prior to screening, or who were transferred from NN7415-4322
- Arms 3 and 4: 81 additional patients (53 HAwI and 28 HBwI) treated with concizumab prophylaxis

Patients were aged ≥ 12 years of age and body weight > 25 kg, with congenital Haemophilia A or B of any severity with documented history of inhibitor (≥ 0.6 BU), who had been prescribed, or in need of, treatment with bypassing agents in the last 24 weeks prior to screening.
The patients received a dose regimen in line with the SmPC recommendations.

The primary objective of the study 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 haemophilia A or B with inhibitors (see Table 3). Using a negative binomial model, a ratio of the annualised bleeding rates (ABR) was estimated to 0.14 ($p < 0.001$), corresponding to a reduction in ABR of 86% for subjects on concizumab prophylaxis compared to no prophylaxis. An additional analysis including all available information following the ITT principle shows an estimated ABR ratio of 0.20 (95% CI [0.09;0.45], $p<0.001$).

Additionally, the number of patients with zero bleeds has been calculated.

Median ABRs and number of patients with zero bleeds are shown in Table 3.

Efficacy was also assessed when all patients in arm 2, 3 and 4 had completed at least 56 weeks of treatment, and the results were consistent with results presented in Table 3.

Table 3 Annualised bleeding rate with concizumab prophylaxis versus no prophylaxis in patients with haemophilia A with inhibitors and Haemophilia B with inhibitors ≥ 12 years of age (NN7415-4311, arms 1 and 2)

	HAwI and HBwI concizumab prophylaxis N=33	**HAwI and HBwI no prophylaxis N=19**	**ABR ratio [95% CI]**
Treated spontaneous and traumatic bleeds			
Estimated mean ABR [95% CI]	2.1 [1.32; 3.46]	14.8 [8.96; 24.35]	0.14 [0.07; 0.29] P < 0.001
Median (Min; Max) ABR	0.00 (0.0; 66.4)	9.76 (0.0; 94.7)	
# patients with 0 bleeds who completed 24 weeks of treatment (%)	17 (51.5%)	1 (5.3%)	
# patients with 0 bleeds who didn't complete 24 weeks of treatment (%)	4 (12.1%)	1 (5.3%)	
Treated joint bleeds			
Estimated mean ABR [95% CI]	1.7 [1.00; 2.97]	11.4 [6.60; 19.68]	0.15 [0.07; 0.32]
Treated target joint bleeds			
Estimated mean ABR [95% CI]	1.4 [0.40; 4.80]	6.8 [2.00; 22.87]	0.21 [0.04; 1.17]
Treated and untreated bleeds			
Estimated mean ABR [95% CI]	5.2 [3.43; 8.02]	15.8 [9.59; 26.10]	0.33 [0.17; 0.64]

– Number of; HAwI – Haemophilia A with inhibitors; HBwI – Haemophilia B with inhibitors; ABR – Annualised bleeding rate; Bleed definitions were according to World Federation of Haemophilia criteria.

Efficacy was evaluated in haemophilia A and B patients with inhibitors when all patients in arms 1 and 2 had completed the main part of the trial (at least 24 or at least 32 weeks, respectively), by comparing the number of treated bleeding episodes between concizumab prophylaxis (arm 2) and no prophylaxis (arm 1).
Estimated mean ABRs and associated ABR ratios are based on a negative binomial regression with the patient's number of bleeds analysed as a function of the randomised treatment regimen, type of haemophilia (HAwI or HBwI) and bleeding frequency (< 9 or ≥ 9 bleeding episodes during the past 24 weeks prior to screening) and the logarithm of the length of the observation period included as an offset in the model. The estimated mean ABRs are marginal estimates based on the covariate distribution present in the study population. The model is based on all patients randomised and accounts for the use of ancillary therapy. The statistical model for the treated target joint bleeds is only fitted for the patients having target joints at baseline.

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

Increased levels of fibrin D-dimer and fragment 1.2 were reported across the multiple dose trials. 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 fibrinogen, anti-thrombin and platelets.

Treatment of breakthrough bleeds in clinical trials

While using concizumab dosing regimen and the breakthrough bleed guidance in section 4.2 bleeds were effectively and safely treated with no thromboembolic events observed. The safety and efficacy of concomitant use of concizumab prophylaxis dosing regimen and breakthrough bleed treatment were confirmed in trial NN7415-4311. A total of 408 bleeding episodes were treated with rFVIIa (majority) and FEIBA (≥ 56 weeks for concizumab treatment arms).

Immunogenicity

During the treatment periods in trials NN7415-4159 (11 weeks), NN7415-4310 and NN7415-4255 (≥ 76 weeks), NN7415-4311 (≥ 56 weeks for concizumab treatment arms) and NN7415-4307 (≥ 32 weeks for concizumab treatment arms), 68 out of 320 concizumab treated patients (21.3%) tested positive for anti-concizumab antibodies, of which 17 patients (5.3%) tested positive for *in vitro*-neutralising antibodies. In 1 (1.5%) of the 68 patients testing positive for anti-concizumab antibodies, the *in vitro*-neutralising antibodies co-occurred with restoration of free TFPI levels. In the remaining 67 patients (98.5%), there was no identified clinically significant effect of the antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of concizumab.

Paediatric population

The Medicines and Healthcare products Regulatory Agency has deferred the obligation to submit the results of studies with concizumab in one or more subsets of the paediatric population in the treatment of congenital haemophilia A with inhibitors and the treatment of congenital haemophilia B with inhibitors (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetic trials have shown that systemic exposure to concizumab, as measured by 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 at low concizumab concentrations (where the non-linear pathway is dominant) and a slower elimination/lower clearance at higher concizumab concentrations (where the linear pathway is dominant).

The concizumab exposure was similar between haemophilia A and B with inhibitors.

Geometric mean steady state concizumab concentrations at week 24 are shown in Table 4. The pre-dose (trough) plasma concentrations remained stable throughout 56 weeks of treatment.

Table 4 Steady state concizumab concentrations during 24 hours dosing interval at week 24 (NN7415-4311)

Parameters	**All maintenance doses N=99***
$C_{max,ss}$ (ng/mL), geometric mean (CV)	1 167.1 (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 concizumab 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 in the range from 8 hours to 99 hours (4.1 days).

Biotransformation

Concizumab is an antibody and like other large proteins these are mainly catabolised by lysosomal proteolysis into amino acids, which are subsequently excreted or reused by the body. Concizumab is expected to follow this catabolic pathway both for the non-linear elimination pathway via TMDD and for the linear elimination pathway via Fc receptor binding which is common for antibodies.

Elimination

Both linear and non-linear pathways contribute to the elimination of concizumab. A terminal half-life in healthy and haemophilia subjects dosed a single subcutaneous dose of 0.25–3 mg/kg was measured in the range from 39 hours (1.6 days) to 195 hours (8.1 days). At steady state levels, where the linear elimination becomes dominant, the total half-life can be longer.

Special populations

Age
Age had no effect on the concizumab exposure in patients with haemophilia A or B with inhibitors. The study population was within the age range 12−61 years.

Renal impairment
Limited data is available on renal impairment. Of the 112 patients treated with concizumab dosing regimen in NN7415-4311, 4 patients had mild renal impairment (eGFR between 60 and 90 mL/min/1.73 m^2) and 1 patient had moderate renal impairment (eGFR between 30 and 60 mL/min/1.73 m^2) at the time when the loading dose was administered. No impact on exposure of concizumab was observed. No data is available on severe renal impairment.

Hepatic impairment
Limited or no data is available on hepatic impairment. Of the 112 patients treated with concizumab dosing regimen in NN7415-4311, 4 patients had elevated liver enzymes (ALT or AST ≥ 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

Pre-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicology.

Pharmacology mediated formation of thrombi was observed in a 52-week toxicology study in cynomolgus monkeys at subcutaneous doses of ≥ 1 mg/kg/day (corresponding to 300-fold the human exposure based on $AUC_{0\text{-}24h}$).

Carcinogenicity

Studies in animals to evaluate the carcinogenic potential of concizumab, or studies to determine the effects of concizumab on genotoxicity have not been performed.

Fertility

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 3 400-fold the human exposure, based on $AUC_{0\text{-}24h}$), concizumab did not affect fertility (testicular size, sperm functionality or menstrual cycle duration) and did not cause any changes in the male or female reproductive organs.

Teratogenicity

No data are available with respect to potential side effects of concizumab on embryofoetal development.

Drug-drug interaction

In a 28-day drug-drug interaction toxicity study in cynomolgus monkeys with daily dosing of 1 mg/kg concizumab to achieve steady state, three consecutive intravenous doses of up to 1 mg/kg rFVIIa were administered with 2-hour intervals to the concizumab dosed animals. No adverse findings were observed at a concizumab exposure corresponding to 200-fold the human exposure, based on $AUC_{0\text{-}24h}$.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Arginine hydrochloride
L-Histidine
Sodium chloride
Sucrose
Polysorbate 80
Phenol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
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

Before first use

3 years.

After first use

Store for up to 4 weeks at a temperature up to 30 °C or in a refrigerator.

Chemical and physical in-use stability has been demonstrated for 28 days at 30 °C or in a refrigerator. From a microbiological point of view, once opened, the product may be stored for a maximum time of 28 days at 30 °C or in a refrigerator. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Before first use

Store in a refrigerator (2 °C - 8 °C).

Do not freeze. Keep away from the cooling element in the refrigerator.

After first use

Store the pre-filled pen with the cap on to protect the solution from light.

Store the pre-filled pen without a needle attached. This ensures accurate dosing, and prevents contamination, infection, and leakage.

Do not freeze. Keep away from the cooling element in the refrigerator.

Alhemo should be protected from heat and light and should not be stored in direct sunlight.

For storage conditions after first opening of the medicinal product, see section 6.3.

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 pre-filled pen is packed in a carton. Alhemo is available in the following pack sizes, and the dose button and the cartridge holder on the pen-injector is colour–coded according to strength:

- 15 mg/1.5 mL (blue): Unit packs containing 1 pre-filled pen.
- 60 mg/1.5 mL (brown): Unit packs containing 1 pre-filled pen.
- 150 mg/1.5 mL (gold): Unit packs containing 1 pre-filled pen.
- 300 mg/3 mL (gold): Unit packs containing 1 pre-filled pen.

Not all pack sizes may be marketed.

Injection needles are not included. Alhemo is designed 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, e.g. injecting into a loosely held skinfold.

6.6 Special precautions for disposal

For a more comfortable injection, allow the medicinal product to warm up to room temperature if it was stored in the refrigerator. Do not use artificial heating sources.

Inspect the solution visually prior to use. Alhemo in the pen window is a clear to slightly opalescent and colourless to slightly yellow liquid and practically free from visible particles. Translucent to white particles of protein are acceptable.

Do not use if the medicinal product is discoloured.

Comprehensive instructions for the preparation and administration of the medicinal product are provided in the 'Instructions for Use'.

Adolescents and lean patients should be instructed to use injection techniques that minimise the risk of intramuscular injection, e.g. injecting into a loosely held skinfold.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
Denmark

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PL 04668/0458

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