swissmedic

Date: 19 September 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Alhemo

International non-proprietary name: concizumab

Pharmaceutical form: solution for injection in pre-filled pen

Dosage strength(s): 15 mg/1.5 mL, 60 mg/1.5 mL, 150 mg/1.5 mL, 300 mg/3 mL

Route(s) of administration: subcutaneous

Marketing authorisation holder: Novo Nordisk Pharma AG

Marketing authorisation no.: 68844

Decision and decision date: approved on 8 August 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
rF	Recombinant factor
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TFPI	Tissue factor pathway inhibitor
TMDD	Target-mediated drug disposition
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for concizumab in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 24 November 2022.

Work-sharing procedure
The applicant requested a work-sharing procedure with Canada and Australia.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), and Swissmedic – and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients from 12 years with haemophilia B (congenital factor IX [FIX] deficiency) with FIX inhibitors.

2.2.2 Approved indication

Concizumab is indicated for the treatment of adolescent and adult patients (12 years of age or older) with haemophilia B (congenital factor IX [FIX] deficiency) who have FIX inhibitors and require routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

There is limited clinical experience of concizumab use in patients known to have mild or moderate haemophilia B (FIX activity > 2%).

2.2.3 Requested dosage

Summary of the requested standard dosage:

Initiation of treatment

Day 1: a single initial dose of 1 mg/kg.
Day 2 and until individual adjustment of the maintenance dose: a once-daily dose of 0.20 mg/kg

Maintenance therapy:

The individual maintenance dose is determined based on the plasma concizumab concentration. Determination of the individual maintenance dose should take place as soon as possible and is recommended no later than 8 weeks after initiation of therapy.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	26 August 2022
Formal control completed	22 September 2022
List of Questions (LoQ)	9 February 2023
Response to LoQ	14 February 2023
Preliminary decision	30 March 2023
Response to preliminary decision	16 April 2023
Labelling corrections	17 July 2023
Response to labelling corrections	24 July 2023
Final decision	8 August 2023
Decision	approval

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3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

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4 Nonclinical aspects

4.1 Pharmacology

Concizumab bound to rabbit, cynomolgus monkey, and human tissue factor pathway inhibitor (TFPI) with K_D values of 0.22, 0.06, and 0.04 nM, respectively. It neutralised direct TFPI inhibition of FXa, TFPI inhibition of FVIIa/TF/FXa (i.e. FX activation), and endothelial cell-bound TFPI inhibition of FVIIa/TF-catalysed FX activation with EC_{50} values of 0.8, 1.1, and <0.5 nM, respectively. In plasma, TFPI inhibition of FVIIa/TF-catalysed FX activation was neutralised with an EC_{50} value of approximately 6 nM. In a modified clot assay, concizumab shortened dilute prothrombin time (dPT) in human (normal as well as FVIII- and FIX-deficient), monkey, and rabbit plasma with similar EC_{50} values (approximately 0.5 nM). There was no TFPI inhibition in plasma from other species. In thromboelastography experiments, concizumab improved clotting with EC_{50} values of 0.43 ± 0.14 nM (haemophilia A-like blood) and 0.44 ± 0.13 nM (haemophilia B-like blood) for clotting time; and 2.2 ± 0.7 nM (haemophilia A-like blood) and 2.6 ± 0.9 nM (haemophilia B-like blood) for clot development. Values were similar using haemophilia A-like monkey blood. Concizumab also enhanced thrombin generation and clot formation in platelet-rich plasma at low FVIII concentrations.

In a bleeding model in rabbits made haemophilic with a neutralising FVIII antibody, concizumab (injected intravenously (IV) before induction of bleeding) reduced blood loss in a dose-dependent manner with an ED_{50} value of 0.23 mg/kg. Concizumab also prevented bleeding when administered subcutaneously (SC) and reduced blood loss when injected shortly (5 min) but not 15 min or later after induction of bleeding. In a venous stasis model in non-haemophilic rabbits, IV administration of 2 mg/kg concizumab prior to a standardised crush injury of the ligated facial veins resulted in increased local clot formation. When concizumab dosing was followed by injection of a low molecular weight heparin before the injury, the local clot formation could be prevented.

In conclusion, the *in vitro* and *in vivo* data support the use of concizumab as an antibody against TFPI for prophylactic treatment of haemophilia A and B.

As expected for an IgG4 antibody, concizumab only showed low affinity for various human Fc receptors, did not induce antibody-dependent cellular cytotoxicity *in vitro*, and did not bind to the complement component C4. There was no binding of concizumab to any of the tested human peripheral blood cell subsets. In endothelial cells, concizumab at TFPI-saturating concentrations showed no effect on protein C activation or antithrombin inhibition of thrombin, which was confirmed in the repeat-dose toxicity studies. Concizumab induced no release of TFPI from endothelial cells at concentrations up to 100 nM.

Concizumab did not show any effects on electrocardiograms, blood pressure, neurobehavioural parameters, or respiratory rate at doses up to 50 mg/kg SC and 200 mg/kg IV (C_{max} >1000-fold human C_{max} at clinical dose).

Pharmacodynamic interaction studies *in vitro* and *ex vivo* showed that the effects of concizumab co-administered with recombinant FVIIa (rFVIIa), activated prothrombin complex concentrates (aPCC), rFVIII, or rFIX were mainly additive, with an additional synergistic effect accounting for up to 40% of the total observed effect. *In vivo*, activation of the coagulation system tended to be additive when rFVIIa was administered to monkeys on concizumab. There was no formation of thrombi or other sign of excessive coagulation in that *in vivo* study.

4.2 Pharmacokinetics

In rabbits and monkeys, clearance and volume of distribution of concizumab decreased with increasing dose and, as a result, exposure (AUC) increased over-proportionally with increasing dose.

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This is consistent with target-mediated drug disposition (TMDD). Elimination half-life ($t_{1/2}$) in monkeys when TMDD is saturated approximated 200 h (8 days), which is typical for a monoclonal antibody. There were no sex-related differences in exposure. TMDD was a feature in humans as well.

After repeated daily SC dosing to monkeys, exposure increased proportionally with the dose. Accumulation was considerable, particularly at low dose, but less pronounced after weekly IV administration. These observations are consistent with TMDD.

Increases in concizumab plasma concentration were accompanied by decreases in free TFPI concentrations and TFPI functionality, and increases in total TFPI, and vice versa.

Formation of ADAs reduced the exposure in some of the animals during the repeat-dose toxicity studies. This also affected the functional read-outs. Note that high concizumab serum concentrations may have interfered with the detection of ADAs, potentially resulting in an underestimation of the number of animals with ADAs at higher doses.

The applicant did not conduct any metabolism or excretion studies with concizumab, which is acceptable for a monoclonal antibody, i.e. in line with ICH S6(R1).

In a monkey study, steady-state concentrations of concizumab did not affect exposure to rFVIIa.

4.3 Toxicology

The toxicology programme was conducted in the cynomolgus monkey, a pharmacologically relevant animal species. Concizumab was administered SC once daily, in line with the intended clinical route of administration and frequency of dosing. The duration of the toxicity studies is appropriate for a product targeted for long-term use.

Concizumab did not show any acute toxicity after SC and IV doses up to 200 mg/kg. Serum cytokines remained unaffected at doses up to 50 mg/kg SC and 200 mg/kg IV (C_{max} >1000-fold human C_{max} at clinical dose). Repeat-dose toxicity studies in monkeys revealed thrombi and focal vascular changes as the key findings. Thrombi were considered to result from an exaggerated pharmacological response when administering a procoagulant compound to monkeys with a normal coagulation system (i.e. non-haemophilic animals). A NOAEL was established at 0.5 mg/kg/day SC for 52 weeks, resulting in exposures >70-fold human C_{max} and AUC at clinical dose. Nevertheless, the EU Risk Management Plan (RMP) includes thromboembolic events as an important potential risk.

Based on mechanistic studies, the focal vascular changes were considered to result from local deposition of immune complexes secondary to ADA formation, as observed after administration of other human/humanised proteins to monkeys. Animal studies have limited ability to predict human immune responses to therapeutic proteins.

The applicant did not conduct any genotoxicity studies with concizumab, which is acceptable for a monoclonal antibody, i.e. in line with ICH S6(R1).

No carcinogenicity studies were conducted. In line with ICH S6(R1), the applicant provided an assessment of the carcinogenic potential of concizumab based on a weight of evidence approach considering the mode of action, the literature on TFPI and cancer, as well as the assessment of the completed nonclinical and clinical studies. In conclusion, there is no evidence that concizumab may lead to an increased risk of inducing or enhancing tumour development in humans.

The rationale of the applicant for not conducting any reproductive and developmental toxicity studies with concizumab because the patient population in the haemophilia indication is almost exclusively male is acceptable. Concizumab showed no adverse effects on any of the fertility parameters

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assessed in the 26-week repeat-dose toxicity study at exposures >1000-fold human AUC at clinical dose. In addition, there were no findings in the reproductive organs at histopathology in any of the repeat-dose toxicity studies with durations up to 52 weeks and exposures >1000-fold human AUC at clinical dose. Knockout studies identify TFPI as critical for development, with inactivation of the TFPI-gene in mice shown to result in embryofetal lethality. The implications of blocking TFPI in pregnant women are not clear and use of concizumab during pregnancy is therefore not recommended.

There is no risk for the environment due to the protein nature of concizumab. All relevant nonclinical safety findings are included in the nonclinical part of the safety specification of the RMP. There is no requirement for any nonclinical study in the PIP.

4.4 Nonclinical conclusions

Overall, the submitted nonclinical documentation is considered adequate to support the approval of concizumab for the proposed indications. All safety-relevant nonclinical data are included in the information for healthcare professionals.

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5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Alhemo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Alhemo®, Solution for injection in a ready-to-use pen

Composition

Active substances

concizumab*

*produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

Excipients

L-Arginini hydrochloridum
L-Histidinum
Natrii chloridum
Saccharum
Polysorbatum 80
Phenolum
Acidum hydrochloridum
Natrii hydroxidum
Aqua ad iniectabile

The medicinal product contains a maximum of 0.832 mg/mL sodium.

Pharmaceutical form and active substance quantity per unit

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.

Indications/Uses

Concizumab is indicated for the treatment of adolescent and adult patients (12 years of age or older) with hemophilia B (congenital factor IX [FIX] deficiency) who have FIX inhibitors and require routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

There is limited clinical experience of concizumab use in patients known to have mild or moderate hemophilia B (FIX activity > 2%).

Dosage/Administration

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

- Prior to initiation of concizumab, patients should discontinue prophylactic treatment with bypassing agents
- Treatment with rFVIIa should be discontinued at least 12 hours before starting concizumab and treatment with aPCC should be discontinued at least 48 hours before starting concizumab.
- Hemophilia A patients with FVIII inhibitors should discontinue emicizumab 6 months before starting treatment with Concizumab.

- Concizumab is intended for patients' self-administration or by a caregiver (e.g. parent) after proper training by a health professional.
- Intramuscular injections should be avoided and these may occur inadvertently, particularly in lean and younger patients where it is recommended to inject into a loosely-held skin-fold.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Initiation of treatment

The recommended dosing regimen is a Day 1 loading dose of 1 mg/kg followed by an initial daily dose of 0.2 mg/kg, which is followed by an individualized daily maintenance dose according to the following schedule:

- 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 pre-dose plasma concentration by a validated concizumab enzyme-linked immunosorbent assay (ELISA).
- Once the week 4 concizumab plasma concentration result is available the individual maintenance dose is set as indicated below in Table 1.

Maintenance therapy

Table 1 Individual maintenance dose based on concizumab plasma concentration

concizumab plasma concentration	**Once daily dose Alhemo®**
<200 ng/mL	0.25 mg/kg
200−4000 ng/mL	0.20 mg/kg
>4000 ng/mL	0.15 mg/kg

While concizumab can be administered at any time point of the day, it is recommended to advise patients to inject at the same time each day, in order to prevent doses occurring too close together.

The individual maintenance dose should be established at the earliest convenience (after concizumab plasma concentration week 4 result is available) and no later than 6-8 weeks after initiation of treatment. The individual maintenance dose should only be determined in patients who adhere to their initial everyday dose. Patients who miss consecutive daily doses during this dose finding phase should inform their health professional so that a new 4 week uninterrupted daily dose period is established before plasma concizumab concentrations are measured.

In study NN7415-4311 (explorer7), of the 97 patients who had a week 4 concizumab plasma concentration, 74.2% (n = 72) of patients remained on the 0.20 mg/kg daily dose, 24.7% (n = 24) of patients had their dose increased to 0.25 mg/kg per day, and 1.0% (n = 1) of patients had their dose decreased to 0.15 mg/kg.

For patients with a plasma concizumab concentration > 4000 ng/mL and who required a dose reduction to 0.15 mg/kg, a second concizumab concentration should be considered. Ideally, the second concizumab concentration should be taken 8 weeks after initiation of the lower dose to ensure patients reach steady-state. If the plasma concentration remains above 4000 ng/mL then the benefits of concizumab should be evaluated versus the potential for an increased risk of thromboembolic events.
Additional concizumab plasma concentration measurements can also 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 or acquires a comorbidity, which could affect their coagulation system or drug metabolism/excretion.

In some instances, a more frequent therapeutic type monitoring of plasma concizumab concentrations may be considered appropriate (semi- annual or annual) and this should be discussed in consultation with the patient.

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 Alhemo® to be administered.

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).

The health professionals should assist the patient in rounding off and identifying the appropriate injectable dose on the pen. Ideally, patients should be described and use a pen that can deliver the required daily maintenance dose in one injection.

Duration of treatment

Alhemo® is intended for long-term prophylactic treatment.

Patients with hepatic disorders

No dose adjustments (besides individual maintenance dose setting) are recommended in patients with hepatic impairment, see section ‘Pharmacokinetics’.
Patients with severe hepatic impairment (AST or ALT > 3x ULN combined with total bilirubin > 1.5x ULN) were not included in the clinical trials.

Patients with renal disorders

No dose adjustments (besides individual maintenance dose setting) are recommended in patients with renal impairment, see section ‘Pharmacokinetics’.
Patients with severe renal impairment (eGFR ≤ 30 mL/min/1.73 m2) were not included in the clinical trials.

Elderly patients

No dose adjustments (besides individual maintenance dose setting) are recommended in patients ≥65 years of age, see section ‘Pharmacokinetics’.

Children and adolescents

The efficacy and safety of Alhemo® in children <12 years of age has not yet been established.

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 prophylaxis, including using the lowest possible effective dose to minimize the risk of thromboembolic events for mild and moderate bleeds, which includes a maximum aPCC dose of 100 U/kg within 24 hours.

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 to minimize the risk of thromboembolic events. 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 taking into account the potential for life-threatening thromboembolic events.

Management in the perioperative setting

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

For major surgery, consult a physician experienced in treatment of haemophilia and/or bleeding disorders. As there is no clinical experience in using concizumab during major surgeries because it was not allowed in clinical trial protocols due to a potential for increased risks of thromboembolic events in these patients, it is generally recommended to pause the treatment with concizumab 4 days prior to a major surgery and resume at the normal daily maintenance dose (either 0.15, 0.20 or 0.25 mg/kg) 10-14 days after surgery, considering the overall clinical picture of the patient.

Following a major surgery, a patient may not achieve effective control of bleeds on Alhemo for at least two weeks after resuming therapy since it may take this long for concizumab plasma concentrations to reach the appropriate therapeutic levels. Consult the information for professionals for bypassing agents for their instructions of use in hemophilia patients following major surgeries.

Immune tolerance induction (ITI)

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

Mode of administration

Alhemo® is for subcutaneous use only.

Administer Alhemo® 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.

Alhemo® comes in a ready-to-administer prefilled pen. Needles are not included.

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

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

Always use a new needle for each injection.

Each Alhemo® pen is for use by a single patient. A Alhemo® pen must not be shared between patients, even if the needle is changed.

Intramuscular injections should be avoided and these may occur inadvertently, particularly in lean and younger patients where it is recommended to inject into a loosely-held skin-fold.

For comprehensive instructions on the administration of Alhemo®, see the package leaflet.

Missed dose

It is important that each patient adheres to their daily dosing.

Missed Doses Before the Maintenance Dose has been Determined

Patients who miss doses prior to measurement of their week 4 concizumab plasma concentration are at risk of not having a proper maintenance dose determined. Patiens should resume treatment as soon as possible and inform their health professionals so a new uninterrupted 4-week dosing period is started prior to measuring concizumab plasma concentrations.

Missed Doses After the Maintenance Dose has been Determined

The following dosing guidelines could apply **only** when a patient has forgotten to or neglect to take their once daily maintenance dose. This **does not** apply to patients who have missed doses for other reasons (e.g. surgery).

- 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 contact their health professional right away. While concizumab can be resumed at the maintenance dose, after careful consideration of the clinical picture, the patient may 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. The double dose can be administered under the supervision of a health professional.
- 7 or more missed 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.

For missed doses **due to other reasons** (e.g. surgery), the patient should follow the instructions as described in section ‘Dosage/Administration’ or resume the daily maintenance dose as instructed by their health professionals.

The patient should contact their healthcare provider if in doubt.

Contraindications

Treatment with Alhemo® is contraindicated in subjects with known hypersensitivity to the active substance or any of the excipients listed in section ‘Composition’.

Warnings and precautions

General

Health professionals should discuss with patients at the start of treatment with Alhemo that one or more missed doses of Alhemo may significantly affect the efficacy of the product and that it is important to follow the dosing regimen (see “Dosage/Administration”). Health professionals should discuss alternative treatment options for any patients or caregivers who are unable to or who are unwilling to adhere to this schedule.

Thromboembolic events

Thromboembolic events have been reported in patients treated with concizumab. Prior to initiation of concizumab, patients should discontinue prophylactic treatment with bypassing agents.

Patients treated with concizumab should be informed and monitored for the occurrence of signs and symptoms of thromboembolic events. Patients who experienced thromboembolic events in clinical trials had a combination of different thromboembolic risk factors including the use of high or frequent doses of breakthrough bleed treatment.

The half-life of bypassing agents and emicizumab should be considered when switching to concizumab (see “Dosage/Administration”).

Patients who require additional treatment with bypassing agents for mild or moderate breakthrough bleeds should be administered the lowest possible effective dose of these hemostatic agents (see warning and precautions)

Patients were to be excluded from clinical studies if they were at high risk for developing thromboembolic events and there should be careful consideration whether the potential benefit of Alhemo treatment outweighs the potential risk of thromboembolic complications in these patients. Risk factors include a history or family history of TEEs, obesity, arrhythmias, hypertension, diabetes,

hypercholesterolaemia, smoking, recent major surgeries, and old age taking into consideration the totality of risk factors for the individual patient. In addition, patients in which tissue factor is overexpressed (e.g. advanced atherosclerotic disease, crush injury, cancer or septicaemia), may have further risks of thromboembolic events or disseminated intravascular coagulation (DIC) with Alhemo treatment.

In clinical studies, there was a positive correlation with concizumab plasma concentrations and D-dimer and prothrombin fragment 1+2 plasma levels (see Adverse Reactions [8]).

In case of suspicion of thromboembolic events, concizumab should be discontinued and further investigations and appropriate medical treatment should be initiated.

Hypersensitivity reactions

Allergic-type hypersensitivity reactions have occurred with Alhemo, including hospitalization and permanent discontinuation of therapy. Patients should be informed of the signs of acute hypersensitivity reactions while receiving Alhemo.

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

Immunogenicity

Anti-concizumab antibodies and neutralizing anti-concizumab antibodies have been reported in 25% and 6.5% of patients treated with Alhemo in clinical trials, respectively (see ‘Properties/Efficacy, Further Information). Most patients found to have anti-concizumab antibodies did not experience a change in concizumab plasma concentrations, an increase in bleeding events or any additional safety concerns; however, there were two cases (one in a clinical trial and one in a compassionate use program) where reduction of effectiveness of Alhemo was reported.

In case of clinical signs of loss of efficacy (e.g. increase in breakthrough bleeding events), prompt evaluation by a physician should be sought to assess the etiology and a possible change in treatment should be considered.

Interactions

Pharmacokinetic interactions

No pharmacokinetic drug-drug interaction clinical studies have been conducted.

Pharmacodynamic interactions

Pharmacodynamic interaction studies *in vitro* and *ex vivo* showed that the effects of concizumab co-administered with recombinant FVIIa (rFVIIa), aPCC, rFVIII or rFIX were mainly additive with an additional synergistic effect accounting for up to 40% of the total observed effect.

Effect of Alhemo® on other medicinal products

Laboratory assay interference

In vitro studies showed no relevant interference of concizumab on standard prothrombin and activated partial thromboplastin time assays or FVIII or FIX activity measurement using clot and chromogenic assays. Further, no relevant influence on assays for inhibitory antibodies to FVIII or FIX (Bethesda assay) was observed.

Pregnancy, lactation

Women of childbearing potential

Women of childbearing potential receiving concizumab should use reliable contraceptive method during treatment with concizumab and until 7 weeks after end of treatment. The benefits and 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 reproductiontoxicity studies have not been conducted with concizumab.
The use of concizumab during pregnancy and in women of childbearing potential who are not using contraception is not recommended.

Lactation

It is not known whether concizumab is excreted in human milk. No studies have been conducted to assess the impact of concizumab on milk production or its presence in breast milk. Human IgG is known to be present in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from concizumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

Effects on ability to drive and use machines

concizumab has no influence on the ability to drive and use machines.

Undesirable effects

Adverse drug reactions (ADRs) listed in this section are considered expected with the medicinal product.

Summary of the safety profile

The overall safety profile of concizumab is based on data from NN7415-4311 (phase 3). The safety analysis includes events reported in patients receiving concizumab before a clinical trial treatment pause with a 1.0 mg/kg loading dose on Day 1 followed by a daily 0.25 mg/kg daily dose and events reported in patients treated with the recommended concizumab dosing regimen after the clinical pause.
The most common ADR reported in ≥ 10% of patients treated with at least one dose of concizumab was injection site reactions (22.8%).
Two patients (HBwI) in the clinical trial receiving concizumab prophylaxis withdrew from treatment due to ADRs, which were hypersensitivity reactions.

List of adverse reactions

The following ADRs are based on data from clinical trial NN7415-4311 (phase 3), in which a total of 114 male patients with haemophilia A with inhibitors (71 patients) and haemophilia B with inhibitors (43 patients) received at least one dose of concizumab as routine prophylaxis. 78 of the clinical trial participants were adults and 36 were adolescents (≥ 12 to < 18 years). The patients were exposed for a total of 102.5 exposure years.

Fourteen patients treated with Alhemo® experienced 18 serious adverse events, including one hypersensitivity reaction (0.9%) and one thromboembolic event (0.9%), both led to permanent discontinuation of Alhemo®.

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows:

"very common" (≥1/10)

"common" (≥1/100, <1/10),

"uncommon" (≥1/1,000, <1/100)

"rare" (≥1/10,000, <1/ 1,000)

"very rare" (<1/10,000)

"not known" (frequency cannot be estimated from the available data)

Table 2 Adverse drug reactions from clinical trial NN7415-4311 with Alhemo®.

System Organ Class	**Preferred term**	**Frequency**
Immune system disorders	Hypersensitivity	Common
Investigations	Fibrin D-dimer increased	Common
	Prothrombin fragments 1.2 increased	Common
General disorders and administration site disorders	Injection site reactions*	Very common
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
Vascular disorders	Thromboembolic events	Uncommon

*Injection site reactions: Include 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.

Description of specific adverse reactions and additional information

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 fibrinogen, anti-thrombin and platelets.

Injection site reactions

Injection site reactions were reported in 26 (22.8%) of the patients across the multiple dose clinical trials. The most frequently reported symptoms were injection site erythema (7.9%), injection site bruising (3.5%),. The majority were reported as mild with one event of moderate injection site rash leading to interruption of concizumab therapy.

Undesirable effects from the post-marketing phase

Not applicable.

Paediatric population

The safety profile was similar between adolescent and adult patients and as expected for the age group.
There is limited data in children below 12 years of age.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is limited experience with overdose of concizumab.

Properties/Effects

ATC code

B02BX

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 and the effect of concizumab is not influenced by the presence of inhibitory antibodies to FVIII or FIX.

Concizumab has no structural relationship or sequence homology to FVIII or FIX and, as such, does not induce or enhance the development of direct inhibitors to FVIII or FIX.

Pharmacodynamics

In the study NN7415-4311 (explorer7), geometric mean (CV%) of free TFPI (plasma TFPI not bound to concizumab) for patients on concizumab prophylaxis decreased from 88.3 (20%) ng/mL at baseline to 10.7 (105%) ng/mL at week 24 and mean thrombin peak increased to the range of normal plasma.

Clinical efficacy

Efficacy was evaluated in haemophilia A and B patients with inhibitors when all patients in the on-demand arm and concizumab prophylaxis arms had completed at least 24 or at least 32 weeks, respectively, by comparing the number of treated spontaneous and traumatic bleeding episodes between the treatment arms. The primary outcome was annualised bleeding rate (ABR) comparisons between the treatment arms. The findings are shown in Table 3.

Table 3 Mean Annualised Bleeding Rate with Alhemo® Prophylaxis versus On-demand Treatment in Patients with Hemophilia A with Inhibitors and Hemophilia B with Inhibitors ≥12 Years of Age

	On-demand (Arm 1)	**Alhemo® Prophylaxis (Arm 2)**
N in FAS	19	33
Treated spontaneous and traumatic bleeding episodes ABR estimate 95% CI	 11.8 [7.03; 19.86]	 1.7 [1.01; 2.87]

Median ABRs and number of patients with zero bleeds are shown in the table below.

Table 4 Median Annualised Bleeding Rate with Alhemo® Prophylaxis versus On-demand Treatment in Patients with Hemophilia B with Inhibitors ≥12 Years of Age

	HBwI Alhemo® prophylaxis N=15	**HBwI No prophylaxis N=10**
Median treatment period (weeks) (min; max)	32.3 (3.1;55.9)	34.3 (4.1;54.1)
Treated spontaneous and traumatic bleeds		
Median ABR (IQR)	0.0 (0.0;0.0)	8.5 (3.2;14.3)
# of patients with 0 bleeds during the first 24 weeks of treatment (%[a])	12 (80.0%)	2 (20.0%)
Treated spontaneous bleeds		
Median ABR (IQR)	0.0	6.8

	(0.0;0.0)	(3.2;8.6)
# of patients with 0 bleeds during the first 24 weeks of treatment (%[a])	12 (80.0%)	2 (20.0%)
Treated joint bleeds		
Median ABR (IQR)	0.0 (0.0;0.0)	6.4 (2.9;9.8)
# of patients with 0 bleeds during the first 24 weeks of treatment (%[a])	12 (80.0%)	3 (30.0%)
Treated target joint bleeds		
Median ABR (IQR)	0.0 (0.0;0.0)	0.7 (0.0;2.6)
# of patients with 0 bleeds during the first 24 weeks of treatment (%[a])	13 (86.7%)	5 (50.0%)

Abbreviations: HBwI, hemophilia B with inhibitors; ABR, annualised bleeding rate; IQR, interquartile range (25th percentile to 75th percentile).
Bleed definitions were according to World Federation of Hemophilia criteria.
[a]Including with/without permanent treatment discontinuation within the first 24 weeks of treatment.

Further information

Immunogenicity
In clinical studies, 47 out of 185 treated patients (25%) who were tested developed anti-concizumab antibodies. For 12 out of the 185 patients (6.5%), neutralizing antibodies against concizumab were identified. In one patient who permanently discontinued therapy, free TFPI levels were restored to baseline identifying that the effectiveness concizumab was likely affected by the neutralizing antibodies in this patient.

Treatment of breakthrough bleeds in clinical trials
While using Alhemo® dosing regimen and the breakthrough bleed guidance in section 'Dosage/Administration' bleeds were effectively and safely treated with no thromboembolic events observed.

Pharmacokinetics

Absorption

Following a single-dose s.c. 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).
The bioavailability of concizumab after subcutaneous administration was estimated as 77.7% by population pharmacokinetic modelling.

Distribution

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

Metabolism

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.

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 s.c. dose of 0.25–3 mg/kg was measured in the range from 39 hours (1.6 days) to 195 hours (8.1 days). Due to the non-linear elimination, the half-life is dependent on the concizumab concentration.

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 Ctrough (665 ng/mL) was approximately 38 hours.

Linearity/non-linearity

The pharmacokinetics of concizumab are nonlinear. 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.

The concizumab exposure was similar between haemophilia A and B patients.

Geometric mean steady-state concizumab concentrations in adolescent and adult hemophilia patients (≥ 12 years of age) with inhibitors who received the recommended dosing regimen 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***
Cmax,ss (ng/mL), geometric mean (CV %)	1167.1 (128%)
Ctrough,ss (ng/mL), geometric mean (CV %)	665.4 (221%)
Cmax / Ctrough ratio, mean (SD)	2.2 (5.2)

Cmax,ss = maximum plasma concentration at steady state.

Ctrough,ss = pre-dose (trough) plasma concentration at steady state.
*on Alhemo® dosing regimen.

Kinetics in specific patient groups

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, 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.

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, 5 patients had renal impairment (eGFR <90 mL/min/1.73m^2) at the time when the loading dose was administered. No impact on exposure of concizumab was observed.

Children and adolescents

The mean concizumab exposure was slightly lower in adolescents (≥ 12 years) compared to adults.

Elderly patients

Clinical studies of concizumab did not include sufficient numbers of patients aged 65 and over to determine whether there are differences in exposure compared with younger patients.

Demographic factors

Based on the population pharmacokinetic analysis, the steady-state concizumab exposure increases with increasing body weight.

Preclinical data

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 $AUC_{0\text{-}24h}$).

Genotoxicity / Carcinogenicity

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

Reproductive toxicity

No reproductive toxicity studies have been conducted.

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 3400-fold the human exposure, based on $AUC_{0\text{-}24h}$), concizumab did not affect fertility (testicular size, sperm (number, motility or morphology) or menstrual cycle duration) and did not cause any changes in the male or female reproductive organs.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Shelf life after opening: 4 weeks.

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.
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.
Keep out of the reach of children.

Instructions for handling

Patients are advised to read the Instructions for Use very carefully before using Alhemo® pen.
Instructions for Use of Alhemo® pen are provided within the carton.
Alhemo® should appear clear to slightly opalescent and colourless to slightly yellow. Translucent particles of protein are acceptable. Do not use if the solution is discoloured or contains solid foreign particles.
The flow of the Alhemo® pen should be checked before each injection.
Store the pen without a needle attached. This ensures accurate dosing, and prevents contamination, infection, and leakage.
The Alhemo® pen must not be refilled.
The Alhemo® pen is for use by one person only.

Authorisation number

68844 (Swissmedic)

Packs

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 dose button and the cartridge holder on the pen-injector is 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 sizes containing 1 pen. Not all pack sizes may be marketed. Injection needles are not included.

Alhemo® is recommended to be used with NovoFine® Plus 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

Marketing authorisation holder

Novo Nordisk Pharma AG, Kloten

Domicile : Zürich

Date of revision of the text

March 2023