swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

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: extension of therapeutic indication approved on 15 December 2025

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

ABR	Annualised bleeding rate
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
HA	Haemophilia A
HAwI	Haemophilia A with inhibitors
HB	Haemophilia B
HBwI	Haemophilia B with inhibitors
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
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
PPX	Prophylaxis
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
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)

2 BACKGROUND information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 24 November 2022.

2.2 Indication and dosage

2.2.1 Requested indication

Alhemo is indicated for the treatment of adolescent and adult patients (12 years of age or older) with:
- haemophilia A (congenital factor VIII deficiency) or
- haemophilia A (congenital factor VIII deficiency) with FVIII-inhibitors
- haemophilia B (congenital factor IX deficiency) or
- haemophilia B (congenital factor IX deficiency) with FIX-inhibitors

who 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 A (FVIII activity > 2%) as well as haemophilia B (FIX activity > 2%).

2.2.2 Approved indication

Concizumab is indicated for the treatment of adolescent and adult patients (12 years of age or older) with
- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors,
- severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without FVIII inhibitors,
- haemophilia B (congenital factor IX deficiency) with FIX inhibitors,
- moderate/severe haemophilia B (congenital factor IX deficiency, FIX ≤ 2%) without inhibitors,

and who 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 A (FVIII activity > 2%) or mild haemophilia B (FIX activity > 2%).

2.2.3 Requested dosage

Summary of the requested standard dosage:

No change to the dosage recommendation for Alhemo was requested with the application for extension of indication.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	27 June 2024
Formal control completed	15 July 2024
List of Questions (LoQ)	12 November 2024
Response to LoQ	20 February 2025
Second List of Questions (LoQ II)	1 May 2025
Response to LoQ II	30 June 2025
Preliminary decision	4 September 2025
Response to preliminary decision	3 November 2025
Final decision	15 December 2025
Decision	approval

3 Medical context

Haemophilia A and B are rare, inherited, X chromosome-linked bleeding disorders caused by deficiencies in clotting factors VIII (FVIII) and IX (FIX), respectively. They are life-long diseases that occur predominantly in males. Haemophilia A (HA), the more common of the two disorders, affects approximately 1 in 5,000 live male births; haemophilia B (HB) has a lower incidence of 1 in 30,000 births.

The disease phenotype is similar across haemophilia subtypes, but disease severity and prognosis of the individual patient vary according to the level of the deficient factor. Patients with severe haemophilia experience frequent bleeding episodes into major joints, soft tissue, and muscle, either spontaneously or following even minor trauma. Repeated bleeding can lead to debilitating long-term complications, including haemophilic arthropathy from bleeding into the joints.

Haemophilia is treated primarily by replacing the missing FVIII or FIX.
While there have been advances in therapies to treat HA and HB patients who require regular treatments, additional effective therapies to treat patients with HA and HB are needed.

4 Clinical aspects

4.1 Clinical pharmacology

The dosing regimen investigated in the pivotal trials corresponds to the previously approved dosing regimen. After a loading dose of 1 mg/kg and a maintenance dose of 0.2 mg/kg for 4 weeks, the individual maintenance dose was selected based on the individual plasma concentrations. The majority of patients remained on 0.2 mg/kg.

An updated PopPK model, based on plasma PK data from trial 4311 and trial 4307, was submitted by the applicant. The model adequately describes the exposure in patients, and no new clinically relevant covariates were identified. The most important covariate for predicting concizumab exposure was body weight, with exposure increasing with increasing body weight.

4.2 Dose finding and dose recommendation

A dose finding study was not carried out.

4.3 Efficacy

The efficacy of Alhemo was demonstrated in a pivotal phase 3, open-label, 4-armed study in HA and HB patients. This included a comparison of on-demand treatment with FVIII and FIX products (no prophylaxis) versus concizumab prophylaxis (PPX) in randomised arm 1 and arm 2. The main part of the study had a duration of 24-32 weeks, with the confirmatory analysis cut-off, followed by an open-label, uncontrolled extension treatment phase of 136 weeks. In the randomised part of both arms, patients in arm 1 (no prophylaxis) continued on-demand treatment with their usual factor therapy, and patients in arm 2 received concizumab PPX. Non-randomised arm 3 enrolled patients who had already completed study 4255 prior to treatment pause. Non-randomised arm 4 enrolled patients who had completed study 4255 after the treatment pause as well as patients from non-interventional study (NIS) study 4322. This permitted within-patient comparison with historical annualised bleeding rate (ABR) previously obtained with factor-containing prophylaxis.

The primary efficacy endpoint of a reduction in treated spontaneous and traumatic bleeding episodes with concizumab PPX versus on-demand treatment over 24/32 weeks was demonstrated:

1. For HA patients, the ABR was 3.5 [2.18; 5.54] for concizumab PPX versus 24.5 [14.50; 41.48] for on-demand treatment only; the estimated ABR ratio between concizumab PPX and on-demand treatment was 0.14 (95% CI 0.07-0.29; p<0.001), corresponding to a statistically significant 86% reduction in ABR.
2. For HB patients, the estimated mean ABR was 3.2 [2.00; 5.22] for concizumab PPX versus 14.8 (95% CI 8.14-26.86) for on-demand treatment only; the estimated ABR ratio between concizumab PPX and on-demand treatment was 0.21 (95% CI 0.10-0.45; p<0.001), corresponding to a statistically significant 79% reduction in ABR.

The results of the sensitivity and supplementary analyses were all consistent with the primary endpoint.

The secondary endpoint – intra-patient comparison, non-inferiority of concizumab PPX (trial 4307) versus previous PPX (study 4322) – was not confirmed for either HA or HB patients.

Based on data from the pivotal study, a statistically significant and clinically relevant reduction in bleeding frequency of 86% in HA and 79% in HB as compared to on-demand treatments with FVIII

and FIX was demonstrated in adult and adolescent patients with severe HA (FVIII <1%) or moderate/severe HB (FIX ≤2%).

4.4 Safety

Safety was evaluated on the basis of an updated safety pool for concizumab, containing safety data from the open-label extension (OLE) up to 56-week cut-off point for the pivotal study in HA and HB patients.
Based on the currently available data for HA and HB patients ≥ 12 years of age, concizumab was well tolerated, with 3.1% of patients in the updated safety pool permanently discontinuing the study medication due to AEs and 15.9% of patients in the updated safety pool temporarily discontinuing the study medication due to AEs. The most common treatment-related AEs in HA and HB patients in the pivotal study were injection site reactions, hypersensitivity, increased fibrin D dimer, and prothrombin fragment 1.2, which were mild or moderate in nature. These results were comparable with findings in the total updated safety pool, with generally similar outcomes across the haemophilia subtypes.
An assessment of the initial submission and the recently submitted OLE data for patients with HA and HB did not reveal any change in the already identified risks of thromboembolic events, increased bleeding tendency, or ADAs with concizumab use, and no specific risk was observed in new cases of major surgery in patients who had temporarily interrupted treatment. For more details of the safety profile of concizumab, please refer to the Information for healthcare professionals.

4.5 Final clinical benefit risk assessment

The indication extension for concizumab in patients with HA and HB is based on the results of a phase 3, open-label, 4-armed study. This study is of similar design to the study in patients with HAwI and HBwI that was submitted with the initial application for concizumab, and both studies were considered to have been conducted correctly.

The data provided demonstrated a statistically significant, clinically meaningful reduction in ABR of 86% and 79% in patients with HA and HB, respectively, from baseline to week 24/32 with concizumab PPX compared to on-demand treatment of bleeding with FVIII/FIX replacement treatment.
Furthermore, a higher proportion of patients with no bleeds was observed with concizumab PPX compared to on demand treatment. This effect was sustained over a period of 56 weeks.
The data obtained from both studies provided robust evidence that the effect of concizumab PPX on ABR is similar across haemophilia subtypes and presence or absence of inhibitors.
Although non-inferiority of concizumab PPX compared with previous FVIII/FIX PPX in the same patient was not established, no substantial difference in ABR between both prophylactic treatments was observed.

The updated safety data from the submitted study, which included open-label extension data up to 56 weeks, did not raise prohibitive safety concerns.

Overall, the benefit-risk ratio of concizumab is considered positive for this indication extension to include treatment of severe haemophilia A without inhibitors and moderate/severe haemophilia B without inhibitors.

5 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.

6 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.

▼ 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 pre-filled 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 (for pH adjustment), 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

1 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

1 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

1 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

1 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

- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors,
- severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without FVIII inhibitors,

- haemophilia B (congenital factor IX deficiency) with FIX inhibitors,
- moderate/severe haemophilia B (congenital factor IX deficiency, FIX ≤ 2%) without inhibitors,

and who 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 A (FVIII activity > 2%) or mild haemophilia 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. Treatment with rFVIIa should be discontinued at least 12 hours and treatment with aPCC should be discontinued at least 48 hours before starting concizumab.

- 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. The prophylactic use of factor VIII (FVIII) or factor IX (FIX) products should be discontinued at least two half-lives before starting concizumab therapy. No clinical trial data are available to guide switching patients from non-replacement therapies to concizumab. A wash-out interval of approximately 5 half-lives of the prior therapy, based on the half-life specified in the respective Information for Professional, could be considered before initiating prophylaxis with concizumab. Haemostatic support with factor products or bypassing agents may be needed during the switch from non-factor-based products.
- Hemophilia A patients with and without 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 concizumab***
<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 explorer7, of the 110 patients who had a week 4 concizumab plasma concentration, 71.8 % (n = 79) of patients remained on the 0.20 mg/kg daily dose, 27.3 % (n = 30) of patients had their dose increased to 0.25 mg/kg per day, and 0.9 % (n = 1) of patients had their dose decreased to 0.15 mg/kg.
In study explorer8, of the 138 patients who had a week 4 concizumab concentration, 67.4 % (n = 93) of patients remained on the 0.20 mg/kg daily dose, 25.4 % (n = 35) of patients had their dose increased to 0.25 mg/kg per day, and 7.2 % (n = 10) of patients had their dose decreased to 0.15 mg/kg.
For patients with a plasma concizumab concentration either below 200 ng/ml or above 4000 ng/ml and who required a dose increase to 0.25 mg/kg or reduction to 0.15 mg/kg, respectively, a second measurement of the 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 below 200 ng/ml or above 4000 ng/ml, the benefits of concizumab should be evaluated versus the potential for an increased risk of bleedings or 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. Since concizumab is dosed per body weight (mg/kg), it is important to recalculate the dose (mg) when the body weight changes.
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 concizumab 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),
- 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 use a pen that can deliver the required daily maintenance dose in one injection.

Duration of treatment

Concizumab 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 '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 'Pharmacokinetics'.
Patients with severe renal impairment (eGFR ≤ 30 ml/min/1.73 m^2) 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 'Pharmacokinetics'. Limited data are available in patients aged 65 years and older.

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 or FVIII or FIX (e.g., rFVIIa or aPCC), 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 FVIII or FIX or 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 FVIII or FIX or 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 limited experience in using concizumab during major surgeries, 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 concomitant use with concizumab in patients receiving ongoing ITI, a desensitization 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.

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. An 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

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. 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 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 resume the treatment 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 ‘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 haemostatic 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 haemostatic agents should be considered when switching to concizumab (see ‘Dosage/Administration‘).
Patients who require additional treatment with haemostatic agents for mild or moderate breakthrough bleeds should be administered the lowest possible effective dose (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 concizumab 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 concizumab treatment.
In clinical studies, there was a positive correlation with concizumab concentrations and D-dimer and prothrombin fragment 1+2 plasma levels (see ‘Undesirable effects‘).
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 22.2 % and 5.6 % of patients treated with Alhemo in clinical trials, respectively. Most patients found to have anti-concizumab antibodies did not experience a change in concizumab concentrations, an increase in bleeding events or any additional safety concerns; however, there was one patient in a clinical trial 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.

Sodium

This medicine contains less than 1 mmol of sodium (23 mg) per dose, i.e., it is practically ‘sodium-free.

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 effect of concizumab when co-administered with recombinant FVIIa (rFVIIa), aPCC, rFVIII, or rFIX was primarily additive, with an additional synergistic effect accounting for up to 40 % of the overall 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 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 toxicity 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 ‘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 all concizumab multiple dose trials in patients with haemophilia.
The most common ADR reported in ≥10 % of patients treated with at least one dose of concizumab was injection site reactions (24.7 %).
Serious adverse reactions in the clinical trials with concizumab occurred in 15.9 % of the patients, including hypersensitivity (0.3 %) and thromboembolic events (0.9 %) leading to permanent treatment discontinuation.

List of adverse reactions

The following ADRs are based on pooled data from clinical trials explorer3 (phase 1b), explorer4 (phase 2), explorer5 (phase 2), explorer7 (phase 3) and explorer8 (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 475 exposure years.

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 pooled clinical trials with concizumab

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	Common
Vascular disorders	Thromboembolic events	Uncommon

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 9.1 % of patients and increased levels of fragment 1.2 were seen in 8.1 % of 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 79 (24.7 %) of the patients across the multiple dose clinical trials. The most frequently reported symptoms were injection site erythema (5.9 %), injection site bruising (4.7 %). 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

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.
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. 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.

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 study explorer8, geometric mean (CV%) of free TFPI (plasma TFPI not bound to concizumab) for haemophilia A and B patients on concizumab prophylaxis decreased from 84.2 (18.6 %) ng/ml at baseline to 11.1 (102.4 %) ng/ml at week 24 and mean thrombin peak increased to the range of normal plasma.
In study explorer7, geometric mean (CV%) of free TFPI for haemophilia A and B patients with inhibitors on concizumab prophylaxis decreased from 86.9 (19.5 %) ng/ml at baseline to 10.7 (101.0 %) ng/ml at week 24 and mean thrombin peak increased to the range of normal plasma. In both trials, the reduction in free TFPI occurred within 24 hours following administration of the concizumab loading dose and remained stable over time up to at least 56 weeks.
Concizumab re-established thrombin generation capacity reflected as mean thrombin peak within the range of normal plasma. In study explorer8, pre-dose thrombin peak levels increased from a geometric mean (CV%) value of 21.1 (118.0 %) nmol/l at baseline to 81.3 (70.3 %) nmol/l at week 24 for haemophilia A and B patients on concizumab prophylaxis. In study explorer7, pre-dose thrombin peak levels increased from a geometric mean (CV%) value of 13.0 (97.6 %) nmol/l at baseline to 104.2 (53.3 %) nmol/l at week 24 for haemophilia A and B patients with inhibitors on concizumab prophylaxis. After the initial increase, pre-dose thrombin peak levels remained stable within the range of normal plasma at all visits after baseline for patients on concizumab prophylaxis.

Clinical efficacy

Haemophilia A and B with inhibitors from 12 years onwards (explorer7)

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.
Efficacy was also assessed when all patients in concizumab prophylaxis arms had completed at least 56 weeks of treatment, and the results were consistent with results presented in Table 3.
Median ABRs and number of patients with zero bleeds are shown in the table below.

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 (explorer7, 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]
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.

Severe haemophilia A and moderate/severe haemophilia B without inhibitors (explorer8)

Efficacy was evaluated separately in patients with severe haemophilia A without inhibitors and in patients with moderate/severe haemophilia B without inhibitors when all patients in arms 1, 2 and 4 had completed the main part of the trial (24, at least 32 or at least 32 weeks, respectively), based on the number of treated bleeding episodes, comparing

- Alhemo prophylaxis with no prophylaxis.
- Alhemo prophylaxis with the patient's previous factor prophylaxis.

Superiority of Alhemo prophylaxis over no prophylaxis was confirmed when comparing the reduction in the number of bleeding episodes in arm 1 and arm 2, in adult and adolescent patients with haemophilia A or haemophilia B. Using a negative binomial model, a ratio of the annualised bleeding rates (ABR) was estimated to 0.14 (p< 0.001) for patients with severe haemophilia A, corresponding to a reduction in ABR of 86 % for subjects on Alhemo prophylaxis compared to no prophylaxis. Using the same model for patients with moderate/severe haemophilia B, the ratio was estimated to 0.21 (p< 0.001), corresponding to a reduction in ABR of 79 % for subjects on Alhemo prophylaxis compared to no prophylaxis.
Prophylaxis with concizumab compared to previous prophylaxis with standard half-life or extended half-life FVIII and FIX products did not meet the pre-specified non-inferiority margin of 2. Estimated rate ratio (95% CI) for ABR was 1.39 (0.73; 2.63) for haemophilia A and 1.75 (0.81; 3.78) for haemophilia B.
Median ABRs and number of patients with zero bleeds are shown in Table 4 and 5 (randomised arms 1 and 2) and Table 6 and 7 (intra-patient comparison in arm 4).

Table 4 Annualised bleeding rate with concizumab prophylaxis versus no prophylaxis in patients with haemophilia A without inhibitors ≥ 12 Years of Age (explorer8, arms 1 and 2)

	HA concizumab prophylaxis N=18	***HA no prophylaxis N=9***	***ABR ratio [95% CI]***
Treated spontaneous and traumatic bleeds			
Estimated mean ABR [95% CI]	3.5 [2.18; 5.54]	24.5 [14.50; 41.48]	0.14 [0.07; 0.29]
Median (Min; Max) ABR	2.92 (0.0; 29.5)	19.57 (3.3; 71.7)	
# patients with 0 bleeds, who completed 24 weeks of treatment (%)	6 (33.3%)	0 (0.0%)	
# patients with 0 bleeds, who didn't complete 24 weeks of treatment (%)	0 (0.0%)	0 (0.0%)	
Treated joint bleeds			

Estimated mean ABR [95% CI]	2.8 [1.71; 4.56]	17.6 [10.19; 30.39]	0.16 [0.08; 0.33]
Treated target joint bleeds			
Estimated mean ABR [95% CI]	2.0 [1.19; 3.47]	8.8 [4.84; 15.91]	0.23 [0.11; 0.48]
Treated and untreated bleeds			
Estimated mean ABR [95% CI]	6.2 [4.03; 9.48]	26.8 [15.37; 46.72]	0.23 [0.11; 0.47]

– Number of; HA – Haemophilia A; ABR – Annualised bleeding rate; Bleed definitions were according to World Federation of Haemophilia criteria.

Efficacy was evaluated in haemophilia A patients 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 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.

Table 5 Annualised bleeding rate with concizumab prophylaxis versus no prophylaxis in patients with haemophilia B without inhibitors ≥ 12 Years of Age (explorer8, arms 1 and 2)

	HB concizumab prophylaxis N=24	***HB no prophylaxis N=12***	***ABR ratio [95% CI]***
Treated spontaneous and traumatic bleeds			
Estimated mean ABR [95% CI]	3.2 [2.00; 5.22]	15.4 [8.55; 27.78]	0.21 [0.10; 0.45]
Median (Min; Max) ABR	1.62 (0.0; 11.9)	14.92 (0.0; 50.9)	
# patients with 0 bleeds who completed 24 weeks of treatment (%)	10 (41.7%)	1 (8.3%)	
# patients with 0 bleeds who didn't complete 24 weeks of treatment (%)	1 (4.2%)	0 (0.0%)	

Treated joint bleeds			
Estimated mean ABR [95% CI]	2.7 [1.58; 4.72]	13.1 [6.63; 26.01]	0.21 [0.09; 0.50]
Treated target joint bleeds			
Estimated mean ABR [95% CI]	1.9 [0.95; 3.67]	5.4 [2.22; 13.21]	0.34 [0.11; 1.06]
Treated and untreated bleeds			
Estimated mean ABR [95% CI]	4.2 [2.71; 6.37]	20.2 [11.90; 34.17]	0.21 [0.10; 0.41]

– Number of; HB – Haemophilia B; ABR – Annualised bleeding rate; Bleed definitions were according to World Federation of Haemophilia criteria

Efficacy was evaluated in haemophilia B patients 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 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.

Table 6 Intra-patient comparison of annualised bleeding rate with concizumab prophylaxis versus previous FVIII prophylaxis in patients with haemophilia A without inhibitors ≥ 12 years of age (explorer8, arm 4 versus explorer6)

	HA ***Concizumab prophylaxis*** ***N=29***	***HA*** ***previous FVIII*** ***prophylaxis*** ***N=29***	***ABR*** ***ratio*** ***[95% CI]***
Treated spontaneous and traumatic bleeds			
Estimated mean ABR [95% CI]	5.1 [2.71; 9.65]	3.7 [2.51; 5.42]	1.39 [0.73; 2.63]
Median (Min; Max) ABR	2.33 (0.0; 46.7)	2.17 (0.0; 13.5)	
# patients with 0 bleeds who completed the first 24 weeks of stable treatment (%)	11 (37.9%)	10 (34.5%)	
# patients with 0 bleeds who	0 (0.0%)		

didn't complete 24 weeks of stable treatment (%)			
Treated joint bleeds			
Estimated mean ABR [95% CI]	3.9 [1.35; 7.58]	2.6 [1.80; 3.72]	1.50 [0.69; 3.28]
Treated and untreated bleeds			
Estimated mean ABR [95% CI]	5.5 [3.13; 9.79]	3.9 [2.68; 5.57]	1.43 [0.80; 2.55]

– Number of; HA – Haemophilia A; ABR – Annualised bleeding rate; Bleed definitions were according to World Federation of Haemophilia criteria.

Efficacy was evaluated in haemophilia A patients 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 4) and previous prophylaxis (explorer6).

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 and the logarithm of the length of the observation period included as an offset in the model and a within-patient repeated measurements incorporated using an unstructured covariance matrix. Non-inferiority was confirmed if the upper limit of the 95% CI of the ABR-ratio was below 2.0.

Table 7 Intra-patient comparison of annualised bleeding rate with concizumab prophylaxis versus previous FIX prophylaxis in patients with haemophilia B without inhibitors ≥ 12 years of age (explorer8, arm 4 versus explorer6)

	HB Concizumab prophylaxis N=22	***HB previous FIX prophylaxis N=22***	***ABR ratio [95% CI]***
Treated spontaneous and traumatic bleeds			
Estimated mean ABR [95% CI]	5.4 [2.27; 12.91]	3.1 [2.07; 4.62]	1.75 [0.81; 3.78]
Median (Min; Max) ABR	1.44 (0.0; 50.6)	2.07 (0.0; 10.6)	
# patients with 0 bleeds who completed the first 24 weeks of stable treatment (%)	9 (40.9%)	7 (31.8%)	
# patients with 0 bleeds who didn't complete 24 weeks of stable treatment (%)	1 (4.5%)		
Treated joint bleeds			

Estimated mean ABR [95% CI]	4.2 [1.94; 8.95]	2.6 [1.69; 4.13]	1.58 [0.80; 3.11]
Treated and untreated bleeds			
Estimated mean ABR [95% CI]	6.4 [2.94; 13.68]	3.4 [2.22; 5.10]	1.89 [0.90; 3.95]

– Number of; HB – Haemophilia B; ABR – Annualised bleeding rate; Bleed definitions were according to World Federation of Haemophilia criteria.

Efficacy was evaluated in haemophilia B patients 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 4) and previous prophylaxis (explorer6).
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 and the logarithm of the length of the observation period included as an offset in the model and a within-patient repeated measurements incorporated using an unstructured covariance matrix. Non-inferiority was confirmed if the upper limit of the 95% CI of the ABR-ratio was below 2.0.

Further information

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 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 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 C_{trough} (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. Steady-state concentration was approximately reached at week 4 following once-daily dosing of 0.20 mg/kg with an initial dose of 1 mg/kg on day 1, as estimated by the pharmacokinetic model.
Geometric mean steady-state concizumab concentrations at week 24 in adolescent and adult hemophilia patients (≥12 years of age) with and without inhibitors who received the recommended dosing regimen are shown in Table 8. The pre-dose (trough) plasma concentration remained stable throughout 56 weeks of treatment.

Table 8 Steady-state concizumab concentrations during 24-hour dosing interval at week 24 (explorer7 and explorer8)

Parameters	***Haemophilia A*** ***All maintenance doses*** ***N=73****	***Haemophilia B*** ***All maintenance doses*** ***N=54****	***HAwI and HBwI*** ***All maintenance doses*** ***N=99****
$C_{max,ss}$ (ng/ml), geometric mean (CV%)	1028.7 (129.1%)	721.8 (163.7%)	1167.1 (128%)
$C_{trough,ss}$ (ng/ml), geometric mean (CV%)	724.4 (153.5%)	554.9 (215.6%)	665.4 (221%)
C_{max} / C_{trough} ratio, mean (SD)	1.4 (0.4)	1.6 (0.6)	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.

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 256 patients treated with Alhemo dosing regimen in explorer7 and explorer8, a total of 9 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. No data available for AST and/or ALT >3 x ULN.

Renal impairment

No dedicated trials on the effect of renal impairment on the pharmacokinetics of concizumab have been conducted. Of the 256 patients treated with Alhemo dosing regimen in explorer7 and explorer8, 20 patients had eGFR <90 ml/min/1.73 m^2 at the time when the loading dose was administered. The majority of patients had mild impairment. No data is available on severe renal impairment. 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:

- Alhemo 15 mg/1.5 ml pre-filled pen (10 mg/ml) (blue): pack containing 1 pen. [A]
- Alhemo 60 mg/1.5 ml (40 mg/ml) pre-filled pen (brown): pack containing 1 pen. [A]
- Alhemo 150 mg/1.5 ml (100 mg/ml) pre-filled pen (gold): pack containing 1 pen. [A]
- Alhemo 300 mg/3 ml (100 mg/ml) pre-filled pen (gold): pack containing 1 pen. [A]

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 dosage 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

Dosage 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

Dosage strength	***Body weight***
15 mg/1.5 ml (10 mg/ml)	4-40 kg
60 mg/1.5 ml (40 mg/ml)	14-160 kg
150 mg/1.5 ml (100 mg/ml)	35 kg and above
300 mg/3 ml (100 mg/ml)	55 kg and above

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

Dosage 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

Domizil: Zürich

Date of revision of the text

September 2025