ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Alhemo 15 mg/1.5 mL solution for injection in pre-filled pen
Alhemo 60 mg/1.5 mL solution for injection in pre-filled pen
Alhemo 150 mg/1.5 mL solution for injection in pre-filled pen
Alhemo 300 mg/3 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alhemo 15 mg/1.5 mL solution for injection in pre-filled pen

One mL solution contains 10 mg concizumab*.
Each pre-filled pen contains 15 mg of concizumab in 1.5 mL solution (10 mg/mL).

Alhemo 60 mg/1.5 mL solution for injection in pre-filled pen

One mL solution contains 40 mg concizumab*.
Each pre-filled pen contains 60 mg of concizumab in 1.5 mL solution (40 mg/mL).

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

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

Alhemo 300 mg/3 mL solution for injection in pre-filled pen

One mL solution contains 100 mg concizumab*.
Each pre-filled pen contains 300 mg of concizumab in 3 mL solution (100 mg/mL).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

Isotonic solution with pH of approximately 6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

Treatment should be initiated in a non-bleeding state.

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

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

Table 1 Individual maintenance dose based on concizumab plasma concentration

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

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

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

Calculation of dose

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

The dose is dialled at increments of
- 0.1 mg on the 15 mg/1.5 mL pre-filled pen (blue),

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

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

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

Examples:

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

Day 1 using a loading dose of 1 mg/kg:
- 42 kg x 1 mg/kg = 42 mg of concizumab.

Day 2 and until individual maintenance dose setting using a dose of 0.20 mg/kg:
- 42 kg x 0.20 mg/kg = 8.4 mg of concizumab.

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

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

To identify the nearest injectable dose:
- 6.3 mg divided by 0.4 mg/increment = 15.75 increments
- 15.75 increments are rounded off to 16 increments
- 16 multiplied by 0.4 mg/increment = 6.4 mg.

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

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

Day 1, using a loading dose of 1 mg/kg:
- 67 kg x 1 mg/kg = 67 mg of concizumab.

Day 2 and until individual maintenance dose setting using a dose of 0.20 mg/kg:
- 67 kg x 0.20 mg/kg = 13.4 mg of concizumab

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

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

To identify the nearest injectable dose:
- 13.4 mg divided by 1.0 mg/increment = 13.4 increments
- 13.4 increments are rounded off to 13 increments
- 13 increments multiplied by 1.0 mg/increment = 13.0 mg.

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

Choice of product strength and volume

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

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

Product strength	**Body weight**	**Dose increment**	**Maximum dose per injection**
15 mg/1.5 mL	5-53 kg	0.1 mg	8 mg
60 mg/1.5 mL	19-213 kg	0.4 mg	32 mg
150 mg/1.5 mL	47 kg and above	1.0 mg	80 mg
300 mg/3 mL	73 kg and above	1.0 mg	80 mg

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

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

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

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

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

Duration of treatment

Alhemo is intended for long-term prophylactic treatment.

Missed dose

Concizumab can be administered any time during the day.

It is important that each patient adheres to their daily dosing. Adherence is particularly important during the initial 4 weeks to ensure a correct maintenance dose is properly established based on the week 4 concizumab plasma concentration (see section 4.2 on posology). Patients who miss doses before the maintenance dose has been established should resume treatment as soon as possible at the initial 0.2 mg/kg daily dose and inform their healthcare professional.

Missed doses once the maintenance dose has been established

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

- 1 missed daily dose: the patient should resume the daily maintenance dose without an additional dose.

- 2 to 6 missed consecutive daily doses: the patient should take the daily dose twice (as two separate injections each corresponding to a daily dose), and then continue taking the daily maintenance dose the next day.
- 7 or more missed consecutive daily doses: The patient should contact their healthcare professional right away. The patient may need to receive a new loading dose before continuing their daily maintenance dose the next day, after careful consideration of the clinical picture.

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

Management of breakthrough bleeds

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

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

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

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

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

Management in the perioperative setting

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

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

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

Immune tolerance induction (ITI)

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

Elderly

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

Renal impairment

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

Hepatic impairment

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

Paediatric population

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

Method of administration

Alhemo is for subcutaneous use only.

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

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

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

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

A new needle should always be used for each injection.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Hypersensitivity reactions

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

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

Immunogenicity

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

Thromboembolic events

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

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

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

Effects of concizumab on coagulation tests

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

Excipients

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

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

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness, see Table 2.

Table 2 Adverse reactions from pooled clinical trials with concizumab

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

Description of selected adverse reactions

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

Paediatric population

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

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

Clinical efficacy and safety

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

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

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

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

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

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

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

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

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

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

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

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

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

Increased levels of fibrin D-dimer and fragment 1.2 were reported across the multiple dose trials. Concizumab plasma concentration is positively correlated with fibrin D-dimer and prothrombin fragments 1.2 indicating haemostatic effect of concizumab.
No clinically significant changes were seen in fibrinogen, anti-thrombin and platelets.

Treatment of breakthrough bleeds in clinical trials

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

Immunogenicity

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

Paediatric population

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

5.2 Pharmacokinetic properties

Pharmacokinetic trials have shown that systemic exposure to concizumab, as measured by AUC and C_{max}, increased with increasing dose in a greater than dose-proportional manner. This non-linear pharmacokinetic behaviour is caused by target-mediated drug disposition (TMDD) which occurs when concizumab binds to endothelial cell-anchored TFPI with subsequent elimination of the drug-target complex. This is a saturable process and the extent of concizumab elimination by TMDD is determined by the amount of endothelial cell-anchored TFPI. This results in a fast elimination/high clearance at low concizumab concentrations (where the non-linear pathway is dominant) and a slower elimination/lower clearance at higher concizumab concentrations (where the linear pathway is dominant).

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

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

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

Parameters	**All maintenance doses N=99***
$C_{max,ss}$ (ng/mL), geometric mean (CV)	1 167.1 (1.3)
$C_{trough,ss}$ (ng/mL), geometric mean (CV)	665.4 (2.2)
C_{max} / C_{trough} ratio, mean (SD)	2.2 (5.2)

$C_{max,ss}$ = maximum plasma concentration at steady state.
$C_{trough,ss}$ = pre-dose (trough) plasma concentration at steady state.
*on concizumab dosing regimen.

Absorption

Following a single-dose subcutaneous administration of 0.05–3 mg/kg concizumab in healthy and haemophilia subjects, the time to maximum plasma concentration of concizumab (t_{max}) was in the range from 8 hours to 99 hours (4.1 days).

Biotransformation

Concizumab is an antibody and like other large proteins these are mainly catabolised by lysosomal proteolysis into amino acids, which are subsequently excreted or reused by the body. Concizumab is

expected to follow this catabolic pathway both for the non-linear elimination pathway via TMDD and for the linear elimination pathway via Fc receptor binding which is common for antibodies.

Elimination

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

Special populations

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

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

Hepatic impairment
Limited or no data is available on hepatic impairment. Of the 112 patients treated with concizumab dosing regimen in NN7415-4311, 4 patients had elevated liver enzymes (ALT or AST ≥ 1.5 x ULN) at the time when the loading dose was administered. No impact on exposure of concizumab was observed.

5.3 Preclinical safety data

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

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

Carcinogenicity

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

Fertility

In a 26-week toxicity study in sexually mature male and female cynomolgus monkeys with subcutaneous doses up to 9 mg/kg/day (corresponding to 3 400-fold the human exposure, based on $AUC_{0\text{-}24h}$), concizumab did not affect fertility (testicular size, sperm functionality or menstrual cycle duration) and did not cause any changes in the male or female reproductive organs.

Teratogenicity

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

Drug-drug interaction

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Before first use

3 years.

After first use

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

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

6.4 Special precautions for storage

Before first use

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

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

After first use

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

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

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

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

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

6.5 Nature and contents of container

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

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

- 15 mg/1.5 mL (blue): Unit packs containing 1 pre-filled pen and multipacks containing 5 (5 packs of 1) pre-filled pens.
- 60 mg/1.5 mL (brown): Unit packs containing 1 pre-filled pen and multipacks containing 5 (5 packs of 1) pre-filled pens.
- 150 mg/1.5 mL (gold): Unit packs containing 1 pre-filled pen and multipacks containing 5 (5 packs of 1) pre-filled pens.
- 300 mg/3 mL (gold): Unit packs containing 1 pre-filled pen.

Not all pack sizes may be marketed.

Injection needles are not included. Alhemo is designed to be used with NovoFine Plus or NovoFine needles with a gauge of 32 and a length of 4 mm. If needles longer than 4 mm are used, injection techniques that minimise the risk of intramuscular injection should be used, e.g. injecting into a loosely held skinfold.

6.6 Special precautions for disposal and other handling

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

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

Do not use if the medicinal product is discoloured.

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

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

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/001
EU/1/24/1881/002
EU/1/24/1881/003
EU/1/24/1881/004
EU/1/24/1881/005
EU/1/24/1881/006
EU/1/24/1881/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Patheon Biologics LLC
4766 LaGuardia Drive,
St. Louis, MO 63134
USA

Name and address of the manufacturer responsible for batch release

Novo Nordisk A/S
Novo Alle 1
2880 Bagsvaerd
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The educational material for healthcare professionals shall include:

- The Summary of Product Characteristics.

- Guide for healthcare professionals with the following key elements:
  - Brief introduction to concizumab and the risk of thromboembolic events.
  - Guidance on the use of concizumab incl. the following information:
    - Physicians should discuss with the patient and/or the caregiver about the dose and schedule of bypassing agents, if required while receiving concizumab prophylaxis.
    - Caution should be exercised when the patient is at high risk of developing thromboembolic events.
    - Patients should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events.
    - In case of suspicion of thromboembolic events, concizumab should be discontinued, and further investigations and appropriate medical treatment should be initiated.
  - Reminder to distribute the educational material to all patients and ensure they read and understand these materials.
  - Reminder that all patients receiving treatment with concizumab should be given a Patient alert card and reminded to carry it at all times and show it to healthcare professionals who may treat them.
  - Reminder to report any adverse events associated with the use of concizumab.

The educational material for patients/carers shall include:

- The package leaflet.
- Guide for patients/carers with the following key messages:
  - Brief introduction to concizumab and the risk of thromboembolic events.
  - Description of signs and symptoms of thromboembolic events.
  - Reminder to stop using concizumab if symptoms occur and contact the physician immediately.
  - Reminder to always carry their patient card and show it to healthcare professionals who may treat them.
  - Reminder to report any adverse events to their treating doctor.
- Patient alert card with the following key elements:
  - Reminder to carry the card at any time and to show it to HCPs to inform on concizumab treatment and the risk of thromboembolic events.
  - Contact details of the patient’s concizumab prescriber.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Alhemo 15 mg/1.5 mL solution for injection in pre-filled pen
concizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 15 mg concizumab in 1.5 mL solution (10 mg/mL)
1 mL solution contains 10 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alhemo 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON MULTIPACK (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Alhemo 15 mg/1.5 mL solution for injection in pre-filled pen
concizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 15 mg concizumab in 1.5 mL solution (10 mg/mL)
1 mL solution contains 10 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multipack: 5 (5 packs of 1) pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alhemo 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON MULTIPACK (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Alhemo 15 mg/1.5 mL solution for injection in pre-filled pen
concizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 15 mg concizumab in 1.5 mL solution (10 mg/mL)
1 mL solution contains 10 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Alhemo 15 mg/1.5 mL injection
concizumab
SC

2. METHOD OF ADMINISTRATION

subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 mL

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Alhemo 60 mg/1.5 mL solution for injection in pre-filled pen
concizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 60 mg concizumab in 1.5 mL solution (40 mg/mL)
1 mL solution contains 40 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alhemo 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON MULTIPACK (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Alhemo 60 mg/1.5 mL solution for injection in pre-filled pen
concizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 60 mg concizumab in 1.5 mL solution (40 mg/mL)
1 mL solution contains 40 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multipack: 5 (5 packs of 1) pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alhemo 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON MULTIPACK (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Alhemo 60 mg/1.5 mL solution for injection in pre-filled pen
concizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 60 mg concizumab in 1.5 mL solution (40 mg/mL)
1 mL solution contains 40 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Alhemo 60 mg/1.5 mL injection
concizumab
SC

2. METHOD OF ADMINISTRATION

subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 mL

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 150 mg concizumab in 1.5 mL solution (100 mg/mL)
1 mL solution contains 100 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alhemo 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON MULTIPACK (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 150 mg concizumab in 1.5 mL solution (100 mg/mL)
1 mL solution contains 100 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Multipack: 5 (5 packs of 1) pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alhemo 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON MULTIPACK (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 150 mg concizumab in 1.5 mL solution (100 mg/mL)
1 mL solution contains 100 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Alhemo 150 mg/1.5 mL injection
concizumab
SC

2. METHOD OF ADMINISTRATION

subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 mL

6. OTHER

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Alhemo 300 mg/3 mL solution for injection in pre-filled pen
concizumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 300 mg concizumab in 3 mL solution (100 mg/mL)
1 mL solution contains 100 mg concizumab,

3. LIST OF EXCIPIENTS

L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen

5. METHOD AND ROUTE OF ADMINISTRATION

subcutaneous use
Needles are not included
Read the package leaflet before use
Read the instructions
Find the leaflet under the pen

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

After first use: Use within 4 weeks
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Before use: Store in a refrigerator. Do not freeze.
After first use: Store in refrigerator or outside refrigerator but keep below 30 °C.
Do not freeze or store in direct sunlight.
Keep the cap on the pen to protect from light.
Do not store the pen with a needle attached.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBERS

EU/1/24/1881/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alhemo 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Alhemo 300 mg/3 mL injection
concizumab
SC

2. METHOD OF ADMINISTRATION

subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Alhemo 15 mg/1.5 mL solution for injection in pre-filled pen
concizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alhemo is and what it is used for

What Alhemo is

Alhemo contains the active substance concizumab, which belongs to a group of medicines called ‘monoclonal antibodies’. Concizumab is a protein that recognises and binds to a target in the blood involved in the coagulation process.

What Alhemo is used for

Alhemo is used to prevent or reduce the frequency of bleeds in adults and adolescents from 12 years with:
- haemophilia A with inhibitors.
- haemophilia B with inhibitors.

Haemophilia A is inborn blood clotting factor VIII deficiency and haemophilia B is inborn blood clotting factor IX deficiency.

How Alhemo works

Concizumab blocks a natural factor in your blood that prevents blood from clotting. This factor is called tissue factor pathway inhibitor. This blocking makes the clotting of your blood more effective and therefore helps prevent or reduces bleeds when you are lacking a clotting factor.

Alhemo acts independently of factor VIII and factor IX and independently of inhibitors to these.

2. What you need to know before you use Alhemo

Do not use Alhemo
- If you are allergic to concizumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Allergic reactions
There is a risk that you may experience an allergic reaction. Stop the treatment and contact your doctor if you have symptoms of allergic reactions such as rash, redness, hives and itching. You could also experience symptoms of severe allergic reactions such as:
- Itching on large areas of skin
- Redness and/or swelling of lips, tongue, face or hands
- Difficulty in swallowing
- Shortness of breath
- Wheezing
- Tightness of the chest
- Pale and cold skin
- Fast heartbeat
- Dizziness due to low blood pressure.

Stop using Alhemo and immediately seek emergency help if you have symptoms of severe allergic reactions.

Blood clots
Blood clots can form anywhere in the body.

Stop using Alhemo and contact your doctor immediately, if you have symptoms of blood clots such as:
- Swelling, warmth, pain, or redness of the skin – these could be symptoms of a blood clot in your legs or arms.
- Feeling short of breath, severe chest pain – these could be symptoms of blood clots in your heart or lungs.
- Headache, feeling confused, trouble with speech or movement, numbness in face, eye pain or swelling, or problems with your vision – these could be symptoms of a blood clot in your brain or eyes.
- Sudden pain in stomach or lumbar area – these could be symptoms of blood clots in your gut or kidneys.

Children and adolescents

Alhemo is not recommended for children under 12 years with haemophilia A with inhibitors or haemophilia B with inhibitors.

Other medicines and Alhemo

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

Use a highly effective method of contraception during treatment with Alhemo and for 7 weeks after your last injection. Talk to your doctor about the type of contraceptive to use.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines

Alhemo is unlikely to affect your ability to drive or use machines.

Alhemo contains sodium and polysorbates

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

This medicine contains 0.25 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Alhemo

See the detailed **Instructions for use** on the other side of this leaflet before using your Alhemo pre-filled pen. Ask your doctor if you need to use alternative injection techniques, e.g. lean patients and adolescents may need to inject into a loosely held fold of skin to avoid injecting too deep (into the muscle).

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

Management of breakthrough bleeds

Before you start using Alhemo talk with your doctor about how to handle a potential bleed.

The recommended dose for adults and adolescents is
- Starting dose on day 1: 1 mg per kg body weight.
- From day 2 until the maintenance dose is set: 0.20 mg per kg body weight once daily.
- Individual maintenance dose as decided by the doctor: 0.15, 0.20 or 0.25 mg per kg body weight once daily.

Alhemo is injected under the skin of your abdomen or thigh and can be used any time of the day.

If you use more Alhemo than you should

Contact your doctor immediately.

If you forget to use Alhemo

Alhemo can be used any time of the day.
One or more missed doses of Alhemo affects how well the medicine works. It is important to take Alhemo every day.

If you miss your daily dose of Alhemo:

If you miss a dose during the first 4 weeks of treatment, contact your doctor to discuss how to resume.

If you miss a dose after dose maintenance setting:
- If you missed 1 daily dose, resume your daily dose.
- If you missed 2 to 6 daily doses, take your daily dose twice (as two separate injections each corresponding to a daily dose), and then continue taking your daily dose the next day.
- If you missed 7 or more daily doses, contact your doctor right away as you will need to receive a new loading dose before continuing your daily dose the next day.

If you are in doubt, contact your doctor.

If you stop using Alhemo

You may no longer be protected against bleeding. Do not stop using Alhemo without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Alhemo and immediately contact your doctor if you have any symptoms of **severe allergic reactions or symptoms of blood clots.** See "Warnings and precautions" in section 2.

Other side effects
Very common: may affect more than 1 in 10 people
- Injection site reactions such as redness, bleeding, itching, hives, swelling, pain, numbness.

Common: may affect up to 1 in 10 people
- Allergic reaction

Uncommon: may affect up to 1 in 100 people
- Blood clots

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Alhemo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and carton after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice that the solution is discoloured.

Before use
- Store unused Alhemo pens at 2 °C - 8 °C in a refrigerator.
- Store your new, unused pen with the pen cap on.
- When stored in the refrigerator, do not store the pen directly next to the cooling element.
- Do not use Alhemo if it has been frozen or stored at temperatures above 30 °C.

After first use
- Store the Alhemo pen you are currently using without a needle attached for up to 28 days (4 weeks), either:
  - In the refrigerator at 2 °C - 8 °C.
    Do not store the pen directly next to the cooling element. Do not use Alhemo if it has been frozen.

  or
  - At room temperatures below 30 °C.
    Discard the pen if it has been stored above 30 °C. Do not store the pen in direct sunlight.
- Store your in-use Alhemo pen with the pen cap on.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Alhemo contains

- The active substance is concizumab.
  One millilitre Alhemo 15 mg/1.5 mL contains 10 mg concizumab.
- The other ingredients are L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment) and water for injections. See also section 2 “Alhemo contains sodium and polysorbates”.

What Alhemo looks like and contents of the pack

Alhemo is a clear to slightly unclear and colourless to slightly yellow solution for injection in pre-filled disposable pen. Transparent to white particles of protein are acceptable.

Alhemo 15 mg/1.5 mL is available as a unit pack containing 1 pre-filled pen or a multipack of 5 (5 packs of 1) pre-filled pens. Not all pack sizes may be marketed.

Needles for injection are not included.

Marketing Authorisation Holder and Manufacturer

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

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Instructions for use
Alhemo 15 mg/1.5 mL solution for injection in pre-filled pen
concizumab

What is in this package?

- 1 Alhemo pre-filled pen
- Package leaflet

Needles are not included.

Read the instructions and make sure you have received training from your doctor or nurse before you use the pen.

Follow the instructions from your doctor or nurse on how to use Alhemo and how often you should inject Alhemo.

The pen is pre-filled with 15 mg of Alhemo for subcutaneous use only (injection in the skin). The pen contains several doses of Alhemo.

The pen can deliver a maximum of 8 mg in one injection. The interval on the dose counter is 0.1 mg. If you need more than 8 mg, you need to inject multiple times. Other pens are available that can deliver your daily dose in one injection. Ask your doctor or nurse.

⚠ **Information for safety**

The pen is for single patient use only and must not be shared. Sharing your pen or needles may lead to infection and transmission of disease.

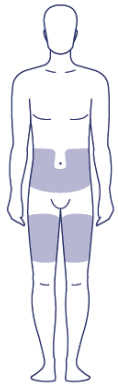
Always use a new needle for each injection. Do not re-use needles as this may lead to needle blockage, infection and incorrect dosing.

The needle is covered by two caps. You must remove both caps. If you forget to remove both caps, you will not inject any solution.

Where on my body should I inject my dose?

You can inject in the skin of:
- Your stomach (abdomen) OR
- Your thigh.

Inject at a 90°angle. The grey areas on the picture to the right show the injection sites. For every injection, select a new injection site at least 5 centimetres away from where you last injected.



Check your pen 1

Check pen label
Look at the name and colour to make sure you have the correct medicine.

Inspect medicine
Pull off the pen cap and check that Alhemo in the pen window is a clear to slightly unclear and colourless to slightly yellow solution. Transparent to white particles of protein are acceptable. If Alhemo looks discoloured do not use the pen.

Check expiry date
Check the expiry date on the pen label to make sure it has not passed. If the expiry date has passed, do not use the pen.

If your pen is cold
You can inject Alhemo right from the refrigerator or let it reach room temperature before you inject. You can warm the pen in the palms of your hands. Do not use any other heating sources.

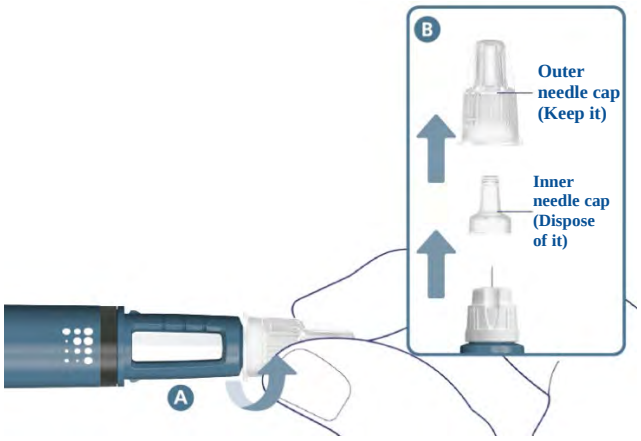
Attach a new needle 2

Take a new needle and tear off the paper tab.

- Push the needle straight onto your pen. Turn until it is on tight. See A.
- Pull off the outer needle cap and keep it. See B.
- Pull off the inner needle cap and dispose of it. See B.

Never use a bent or damaged needle.

Use only needles recommended by your doctor or nurse. This pen is designed to be used with NovoFine Plus 32G x 4 mm or NovoFine 32G x 4 mm injection needles. If you use needles longer than 4 mm, talk to your doctor or nurse about how to perform your injection.

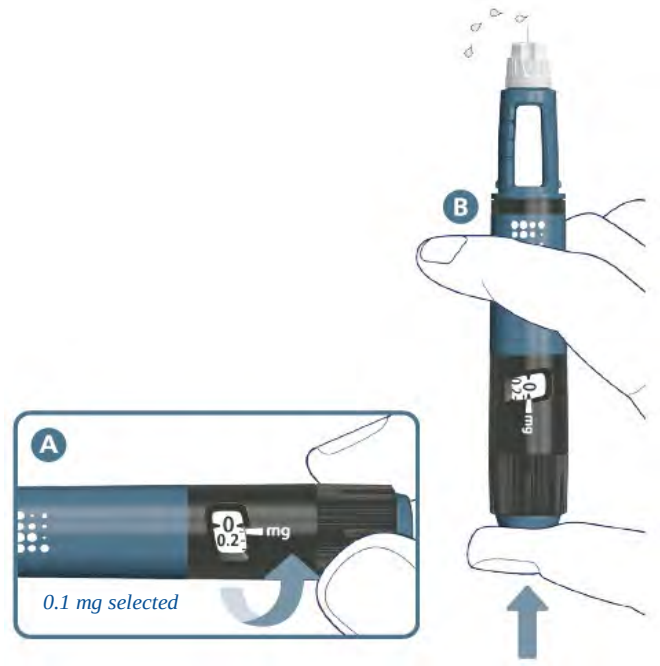


Test the flow **3**

A drop of Alhemo may appear at the needle tip, but you should still test the Alhemo flow before **each injection** to avoid underdosing:

a. Turn the dose selector one marking to select 0.1 mg. See A in the Figure below. Hold the pen with the needle pointing upwards.
b. Press the dose button. See B.
c. Watch for a stream of Alhemo leaving the needle tip. See B.

If no stream appears, go to *Troubleshooting if no stream appears when testing the flow.*



Select your dose **4**

Turn the dose selector to select your prescribed dose.

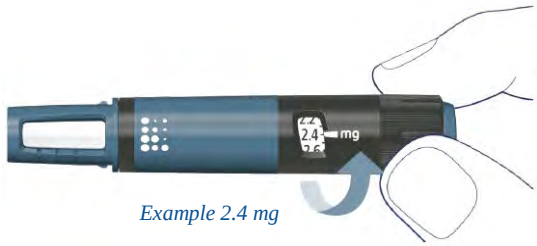
Confirm that you have selected the correct dose.

You can adjust your dose by turning the dose selector in either direction.

If you need a larger dose than you can dial, you must inject yourself multiple times to get your full dose. Other pens are available that can deliver your daily dose in one injection. Ask your doctor or nurse. For more information, see step 6.

The pen contains 15 mg of Alhemo.

The pen can deliver a maximum of 8 mg in one injection.



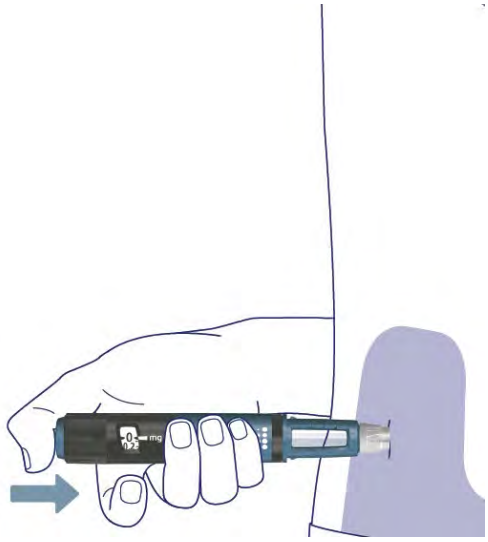
Example 2.4 mg

Inject your dose **5**

Read through steps a. to e. before you start injecting.
This is to make sure you get your full dose.

a. Select the injection site. See *Where on my body should I inject my dose?*
b. Insert the needle straight into your stomach (abdomen) or thigh at a 90°angle.
c. Press and hold the dose button down until the dose counter returns to **<0>**.
d. While the needle is still in your skin, **count slowly to 6, after the dose counter has returned to <0>.**
e. Retract the needle from your skin.

The pen clicks during dosing and you might also hear or feel a click when the dose counter returns to **<0>**.

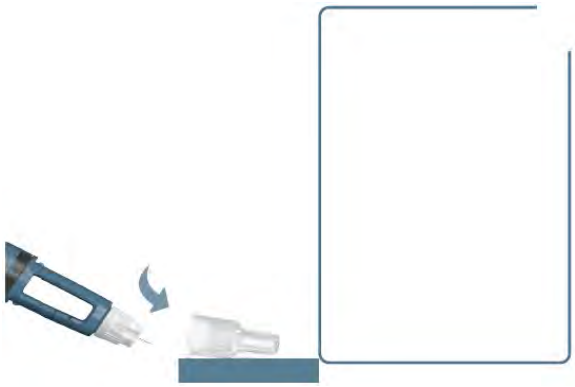


Remove the needle **6**

Remove the needle from your pen after each injection by inserting the needle tip into the outer needle cap without touching the needle or the cap.

When the needle is covered, carefully push the outer needle cap completely on. Unscrew the needle. Do not touch the back end of the needle.

Dispose of the needle as instructed by your doctor, nurse, pharmacist or local authorities.



Do you need a larger dose than you can dial?
Your doctor should give you a pen that can deliver your daily dose in one injection. If you need a larger dose than you can dial, you must inject yourself more than once to get your full dose.
Repeat steps 1 to 6 until you have received your full dose. When you have received your full dose go to step 7.

- Use a new needle for each injection.
- Test the Alhemo flow before each injection.
- Accurately calculate how much to inject in each injection to receive your full dose.

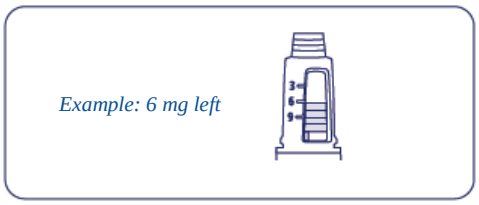
After your dose **7**

Put the pen cap back on your pen to protect Alhemo from light.

Now your pen is ready for storage until you need it next time.

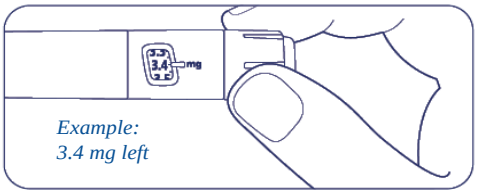
After first use do not use your pen for more than 28 days.

How much Alhemo is left in your pen?
The pen scale shows approximately how much Alhemo is left in your pen.



If you want to see more accurately how much Alhemo is left in your pen, turn the dose selector until it stops. The dose pointer will line up with the number of milligrams left in the pen. The number shown on the dose counter is the number of milligrams left in your pen.

If the dose counter shows 8, there are 8 mg or more left in the pen. The example below shows 3.4 mg of Alhemo left in the pen.



Troubleshooting if no stream appears when testing the flow (step 3)

- If no stream appears, repeat step 3 up to six times until you see a stream.
- If still no stream appears, prepare a new needle (step 2) and test again (step 3).
- If still no stream appears after using a new needle, do not use the pen. Use a new pen.

Storage
See section 5 “How to store Alhemo” on the reverse side of this leaflet.

Take good care of your pen
Treat your pen with care. Rough handling or misuse may cause inaccurate dosing. If this happens you might not get the intended effect of this medicine.

Do not expose your pen to dust, dirt or liquid.

Do not wash, soak or lubricate your pen. If necessary, clean it with mild detergent on a moistened cloth.

Keep your pen out of sight and reach of others, especially children.

Disposing of Alhemo pens, needles and packaging material
When your pen is empty you must dispose of it according to your local regulations.

You cannot refill your pen.

To reduce the risk of a needle stick, dispose of used needles immediately as instructed by your doctor, nurse, pharmacist or local authorities.

[Text for the front page of the folded leaflet]
Package leaflet and Instructions for use

Package leaflet: Information for the user

Alhemo 60 mg/1.5 mL solution for injection in pre-filled pen
concizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alhemo is and what it is used for

What Alhemo is

Alhemo contains the active substance concizumab, which belongs to a group of medicines called ‘monoclonal antibodies’. Concizumab is a protein that recognises and binds to a target in the blood involved in the coagulation process.

What Alhemo is used for

Alhemo is used to prevent or reduce the frequency of bleeds in adults and adolescents from 12 years with:
- haemophilia A with inhibitors.
- haemophilia B with inhibitors.

Haemophilia A is inborn blood clotting factor VIII deficiency and haemophilia B is inborn blood clotting factor IX deficiency.

How Alhemo works

Concizumab blocks a natural factor in your blood that prevents blood from clotting. This factor is called tissue factor pathway inhibitor. This blocking makes the clotting of your blood more effective and therefore helps prevent or reduces bleeds when you are lacking a clotting factor.

Alhemo acts independently of factor VIII and factor IX and independently of inhibitors to these.

2. What you need to know before you use Alhemo

Do not use Alhemo
- If you are allergic to concizumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Allergic reactions
There is a risk that you may experience an allergic reaction. Stop the treatment and contact your doctor if you have symptoms of allergic reactions such as rash, redness, hives and itching. You could also experience symptoms of severe allergic reactions such as:
- Itching on large areas of skin
- Redness and/or swelling of lips, tongue, face or hands
- Difficulty in swallowing
- Shortness of breath
- Wheezing
- Tightness of the chest
- Pale and cold skin
- Fast heartbeat
- Dizziness due to low blood pressure.

Stop using Alhemo and immediately seek emergency help if you have symptoms of severe allergic reactions.

Blood clots
Blood clots can form anywhere in the body.

Stop using Alhemo and contact your doctor immediately, if you have symptoms of blood clots such as:
- Swelling, warmth, pain, or redness of the skin – these could be symptoms of a blood clot in your legs or arms.
- Feeling short of breath, severe chest pain – these could be symptoms of blood clots in your heart or lungs.
- Headache, feeling confused, trouble with speech or movement, numbness in face, eye pain or swelling, or problems with your vision – these could be symptoms of a blood clot in your brain or eyes.
- Sudden pain in stomach or lumbar area – these could be symptoms of blood clots in your gut or kidneys.

Children and adolescents

Alhemo is not recommended for children under 12 years with haemophilia A with inhibitors or haemophilia B with inhibitors.

Other medicines and Alhemo

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

Use a highly effective method of contraception during treatment with Alhemo and for 7 weeks after your last injection. Talk to your doctor about the type of contraceptive to use.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines

Alhemo is unlikely to affect your ability to drive or use machines.

Alhemo contains sodium and polysorbates

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

This medicine contains 0.25 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Alhemo

See the detailed **Instructions for use** on the other side of this leaflet before using your Alhemo pre-filled pen. Ask your doctor if you need to use alternative injection techniques, e.g. lean patients and adolescents may need to inject into a loosely held fold of skin to avoid injecting too deep (into the muscle).

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

Management of breakthrough bleeds

Before you start using Alhemo talk with your doctor about how to handle a potential bleed.

The recommended dose for adults and adolescents is
- Starting dose on day 1: 1 mg per kg body weight.
- From day 2 until the maintenance dose is set: 0.20 mg per kg body weight once daily.
- Individual maintenance dose as decided by the doctor: 0.15, 0.20 or 0.25 mg per kg body weight once daily.

Alhemo is injected under the skin of your abdomen or thigh and can be used any time of the day.

If you use more Alhemo than you should

Contact your doctor immediately.

If you forget to use Alhemo

Alhemo can be used any time of the day.
One or more missed doses of Alhemo affects how well the medicine works. It is important to take Alhemo every day.

If you miss your daily dose of Alhemo:

If you miss a dose during the first 4 weeks of treatment, contact your doctor to discuss how to resume.

If you miss a dose after dose maintenance setting:
- If you missed 1 daily dose, resume your daily dose.
- If you missed 2 to 6 daily doses, take your daily dose twice (as two separate injections each corresponding to a daily dose), and then continue taking your daily dose the next day.
- If you missed 7 or more daily doses, contact your doctor right away as you will need to receive a new loading dose before continuing your daily dose the next day.

If you are in doubt, contact your doctor.

If you stop using Alhemo

You may no longer be protected against bleeding. Do not stop using Alhemo without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Alhemo and immediately contact your doctor if you have any symptoms of **severe allergic reactions or symptoms of blood clots.** See "Warnings and precautions" in section 2.

Other side effects
Very common: may affect more than 1 in 10 people
- Injection site reactions such as redness, bleeding, itching, hives, swelling, pain, numbness.

Common: may affect up to 1 in 10 people
- Allergic reaction

Uncommon: may affect up to 1 in 100 people
- Blood clots

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Alhemo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and carton after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice that the solution is discoloured.

Before use
- Store unused Alhemo pens at 2 °C - 8 °C in a refrigerator.
- Store your new, unused pen with the pen cap on.
- When stored in the refrigerator, do not store the pen directly next to the cooling element.
- Do not use Alhemo if it has been frozen or stored at temperatures above 30 °C.

After first use
- Store the Alhemo pen you are currently using without a needle attached for up to 28 days (4 weeks), either:
  - In the refrigerator at 2 °C - 8 °C.
    Do not store the pen directly next to the cooling element. Do not use Alhemo if it has been frozen.

  or
  - At room temperatures below 30 °C.
    Discard the pen if it has been stored above 30 °C. Do not store the pen in direct sunlight.
- Store your in-use Alhemo pen with the pen cap on.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Alhemo contains

- The active substance is concizumab.
  One millilitre Alhemo 60 mg/1.5 mL contains 40 mg concizumab.
- The other ingredients are L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment) and water for injections. See also section 2 “Alhemo contains sodium and polysorbates”.

What Alhemo looks like and contents of the pack

Alhemo is a clear to slightly unclear and colourless to slightly yellow solution for injection in pre-filled disposable pen. Transparent to white particles of protein are acceptable.

Alhemo 60 mg/1.5 mL is available as a unit pack containing 1 pre-filled pen or a multipack of 5 (5 packs of 1) pre-filled pens. Not all pack sizes may be marketed.

Needles for injection are not included.

Marketing Authorisation Holder and Manufacturer

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

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Instructions for use

Alhemo 60 mg/1.5 mL solution for injection in pre-filled pen
concizumab

What is in this package?

- 1 Alhemo pre-filled pen
- Package leaflet

Needles are not included.

Read the instructions and make sure you have received training from your doctor or nurse before you use the pen.

Follow the instructions from your doctor or nurse on how to use Alhemo and how often you should inject Alhemo.

The pen is pre-filled with 60 mg of Alhemo for subcutaneous use only (injection in the skin). The pen contains several doses of Alhemo.

The pen can deliver a maximum of 32 mg in one injection. The interval on the dose counter is 0.4 mg. If you need more than 32 mg, you need to inject multiple times. Other pens are available that can deliver your daily dose in one injection. Ask your doctor or nurse.

⚠ Information for safety

The pen is for single patient use only and must not be shared. Sharing your pen or needles may lead to infection and transmission of disease.

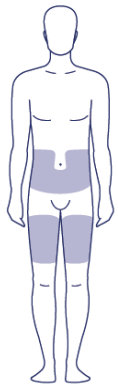
Always use a new needle for each injection. Do not re-use needles as this may lead to needle blockage, infection and incorrect dosing.

The needle is covered by two caps. You must remove both caps. If you forget to remove both caps, you will not inject any solution.

Where on my body should I inject my dose?

You can inject in the skin of:
- your stomach (abdomen) OR
- your thigh.

Inject at a 90°angle. The grey areas on the picture to the right show the injection sites. For every injection, select a new injection site at least 5 centimetres away from where you last injected.



Check your pen 1

Check pen label
Look at the name and colour to make sure you have the correct medicine.

Inspect medicine

Pull off the pen cap and check that Alhemo in the pen window is a clear to slightly unclear and colourless to slightly yellow solution. Transparent to white particles of protein are acceptable. If Alhemo looks discoloured do not use the pen.

Check expiry date
Check the expiry date on the pen label to make sure it has not passed. If the expiry date has passed, do not use the pen.

If your pen is cold
You can inject Alhemo right from the refrigerator or let it reach room temperature before you inject. You can warm the pen in the palms of your hands. Do not use any other heating sources.

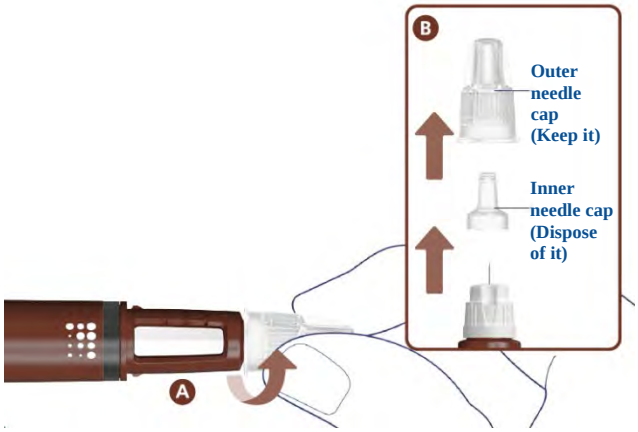
Attach a new needle 2

Take a new needle and tear off the paper tab.

- Push the needle straight onto your pen. Turn until it is on tight. See A.
- Pull off the outer needle cap and keep it. See B.
- Pull off the inner needle cap and dispose of it. See B.

Never use a bent or damaged needle.

Use only needles recommended by your doctor or nurse. This pen is designed to be used with NovoFine Plus 32G x 4 mm or NovoFine 32G x 4 mm injection needles. If you use needles longer than 4 mm, talk to your doctor or nurse about how to perform your injection.

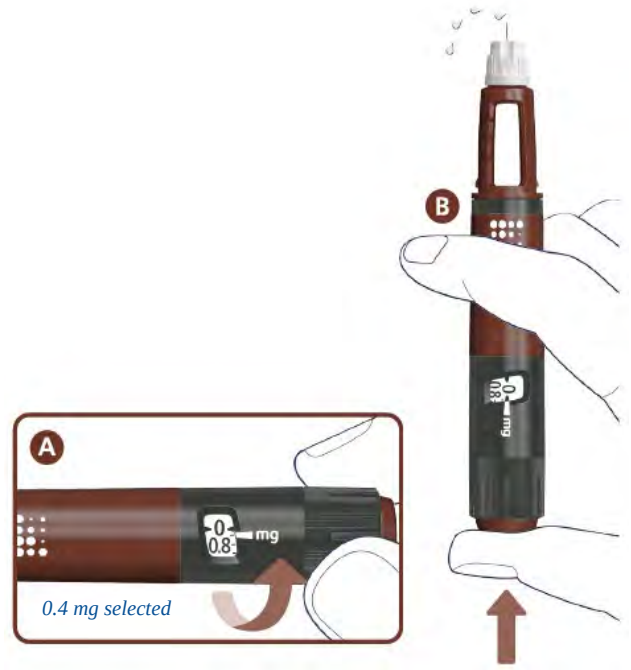


Test the flow 3

A drop of Alhemo may appear at the needle tip, but you should still test the Alhemo flow before **each injection** to avoid underdosing:

a. Turn the dose selector one marking to select 0.4 mg. See A in the Figure below. Hold the pen with the needle pointing upwards.
b. Press the dose button. See B.
c. Watch for a stream of Alhemo leaving the needle tip. See B.

If no stream appears, go to *Troubleshooting if no stream appears when testing the flow.*



Select your dose 4

Turn the dose selector to select your prescribed dose.

Confirm that you have selected the correct dose.

You can adjust your dose by turning the dose selector in either direction.

If you need a larger dose than you can dial, you must inject yourself multiple times to get your full dose. Other pens are available that can deliver your daily dose in one injection. Ask your doctor or nurse. For more information, see step 6.

The pen contains 60 mg of Alhemo.

The pen can deliver a maximum of 32 mg in one injection.

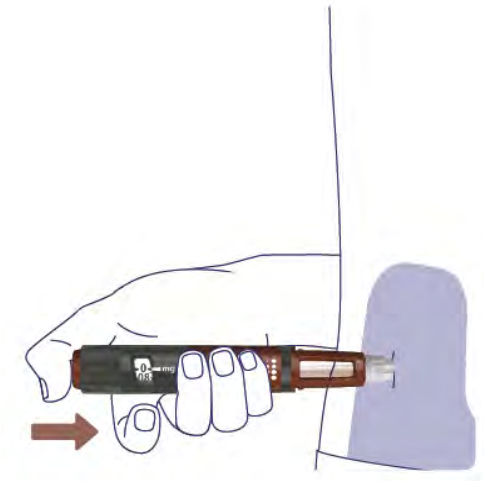
Example 9.6 mg

Inject your dose 5

Read through steps a. to e. before you start injecting.
This is to make sure you get your full dose.

a. Select the injection site. See *Where on my body should I inject my dose?*
b. Insert the needle straight into your stomach (abdomen) or thigh at a 90°angle.
c. Press and hold the dose button down until the dose counter returns to **<0>**.
d. While the needle is still in your skin, **count slowly to 6, after the dose counter has returned to <0>.**
e. Retract the needle from your skin.

The pen clicks during dosing and you might also hear or feel a click when the dose counter returns to **<0>**.

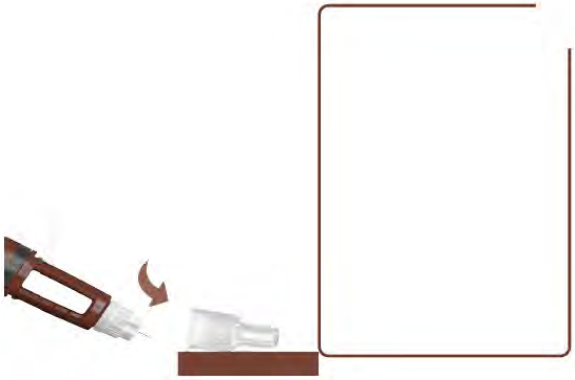


Remove the needle 6

Remove the needle from your pen after each injection by inserting the needle tip into the outer needle cap without touching the needle or the cap.

When the needle is covered, carefully push the outer needle cap completely on. Unscrew the needle. Do not touch the back end of the needle.

Dispose of the needle as instructed by your doctor, nurse, pharmacist or local authorities.



Do you need a larger dose than you can dial?
Your doctor should give you a pen that can deliver your daily dose in one injection. If you need a larger dose than you can dial, you must inject yourself more than once to get your full dose.
Repeat steps 1 to 6 until you have received your full dose. When you have received your full dose go to step 7.

- Use a new needle for each injection.
- Test the Alhemo flow before each injection.
- Accurately calculate how much to inject in each injection to receive your full dose.

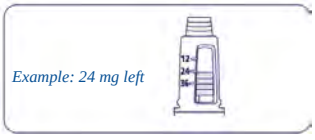
After your dose 7

Put the pen cap back on your pen to protect Alhemo from light.

Now your pen is ready for storage until you need it next time.

After first use do not use your pen for more than 28 days.

How much Alhemo is left in your pen?
The pen scale shows approximately how much Alhemo is left in your pen.



If you want to see more accurately how much Alhemo is left in your pen, turn the dose selector until it stops. The dose pointer will line up with the number of milligrams left in the pen. The number shown on the dose counter is the number of milligrams left in your pen.

If the dose counter shows 32, there are 32 mg or more left in the pen. The example below shows 13.6 mg of Alhemo left in the pen.

Troubleshooting if no stream appears when testing the flow (step 3)

- If no stream appears, repeat step 3 up to six times until you see a stream.
- If still no stream appears, prepare a new needle (step 2) and test again (step 3).
- If still no stream appears after using a new needle, do not use the pen. Use a new pen.

Storage
See section 5 “How to store Alhemo” on the reverse side of this leaflet.

Take good care of your pen
Treat your pen with care. Rough handling or misuse may cause inaccurate dosing. If this happens you might not get the intended effect of this medicine.

Do not expose your pen to dust, dirt or liquid.

Do not wash, soak or lubricate your pen. If necessary, clean it with mild detergent on a moistened cloth.

Keep your pen out of sight and reach of others, especially children.

Disposing of Alhemo pens, needles and packaging material
When your pen is empty you must dispose of it according to your local regulations.

You cannot refill your pen.

To reduce the risk of a needle stick, dispose of used needles immediately as instructed by your doctor, nurse, pharmacist or local authorities.

[Text for the front page of the folded leaflet]
Package leaflet and Instructions for use

Package leaflet: Information for the user

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alhemo is and what it is used for

What Alhemo is

Alhemo contains the active substance concizumab, which belongs to a group of medicines called ‘monoclonal antibodies’. Concizumab is a protein that recognises and binds to a target in the blood involved in the coagulation process.

What Alhemo is used for

Alhemo is used to prevent or reduce the frequency of bleeds in adults and adolescents from 12 years with:
- haemophilia A with inhibitors.
- haemophilia B with inhibitors.

Haemophilia A is inborn blood clotting factor VIII deficiency and haemophilia B is inborn blood clotting factor IX deficiency.

How Alhemo works

Concizumab blocks a natural factor in your blood that prevents blood from clotting. This factor is called tissue factor pathway inhibitor. This blocking makes the clotting of your blood more effective and therefore helps prevent or reduces bleeds when you are lacking a clotting factor.

Alhemo acts independently of factor VIII and factor IX and independently of inhibitors to these.

2. What you need to know before you use Alhemo

Do not use Alhemo
- If you are allergic to concizumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Allergic reactions
There is a risk that you may experience an allergic reaction. Stop the treatment and contact your doctor if you have symptoms of allergic reactions such as rash, redness, hives and itching. You could also experience symptoms of severe allergic reactions such as:
- Itching on large areas of skin
- Redness and/or swelling of lips, tongue, face or hands
- Difficulty in swallowing
- Shortness of breath
- Wheezing
- Tightness of the chest
- Pale and cold skin
- Fast heartbeat
- Dizziness due to low blood pressure.

Stop using Alhemo and immediately seek emergency help if you have symptoms of severe allergic reactions.

Blood clots
Blood clots can form anywhere in the body.

Stop using Alhemo and contact your doctor immediately, if you have symptoms of blood clots such as:
- Swelling, warmth, pain, or redness of the skin – these could be symptoms of a blood clot in your legs or arms.
- Feeling short of breath, severe chest pain – these could be symptoms of blood clots in your heart or lungs.
- Headache, feeling confused, trouble with speech or movement, numbness in face, eye pain or swelling, or problems with your vision – these could be symptoms of a blood clot in your brain or eyes.
- Sudden pain in stomach or lumbar area – these could be symptoms of blood clots in your gut or kidneys.

Children and adolescents

Alhemo is not recommended for children under 12 years with haemophilia A with inhibitors or haemophilia B with inhibitors.

Other medicines and Alhemo

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

Use a highly effective method of contraception during treatment with Alhemo and for 7 weeks after your last injection. Talk to your doctor about the type of contraceptive to use.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines

Alhemo is unlikely to affect your ability to drive or use machines.

Alhemo contains sodium and polysorbates

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

This medicine contains 0.25 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Alhemo

See the detailed **Instructions for use** on the other side of this leaflet before using your Alhemo pre-filled pen. Ask your doctor if you need to use alternative injection techniques, e.g. lean patients and adolescents may need to inject into a loosely held fold of skin to avoid injecting too deep (into the muscle).

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

Management of breakthrough bleeds

Before you start using Alhemo talk with your doctor about how to handle a potential bleed.

The recommended dose for adults and adolescents is
- Starting dose on day 1: 1 mg per kg body weight.
- From day 2 until the maintenance dose is set: 0.20 mg per kg body weight once daily.
- Individual maintenance dose as decided by the doctor: 0.15, 0.20 or 0.25 mg per kg body weight once daily.

Alhemo is injected under the skin of your abdomen or thigh and can be used any time of the day.

If you use more Alhemo than you should

Contact your doctor immediately.

If you forget to use Alhemo

Alhemo can be used any time of the day.
One or more missed doses of Alhemo affects how well the medicine works. It is important to take Alhemo every day.

If you miss your daily dose of Alhemo:

If you miss a dose during the first 4 weeks of treatment, contact your doctor to discuss how to resume.

If you miss a dose after dose maintenance setting:
- If you missed 1 daily dose, resume your daily dose.
- If you missed 2 to 6 daily doses, take your daily dose twice (as two separate injections each corresponding to a daily dose), and then continue taking your daily dose the next day.
- If you missed 7 or more daily doses, contact your doctor right away as you will need to receive a new loading dose before continuing your daily dose the next day.

If you are in doubt, contact your doctor.

If you stop using Alhemo

You may no longer be protected against bleeding. Do not stop using Alhemo without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Alhemo and immediately contact your doctor if you have any symptoms of **severe allergic reactions or symptoms of blood clots.** See "Warnings and precautions" in section 2.

Other side effects
Very common: may affect more than 1 in 10 people
- Injection site reactions such as redness, bleeding, itching, hives, swelling, pain, numbness.

Common: may affect up to 1 in 10 people
- Allergic reaction

Uncommon: may affect up to 1 in 100 people
- Blood clots

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Alhemo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and carton after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice that the solution is discoloured.

Before use
- Store unused Alhemo pens at 2 °C - 8 °C in a refrigerator.
- Store your new, unused pen with the pen cap on.
- When stored in the refrigerator, do not store the pen directly next to the cooling element.
- Do not use Alhemo if it has been frozen or stored at temperatures above 30 °C.

After first use
- Store the Alhemo pen you are currently using without a needle attached for up to 28 days (4 weeks), either:
  - In the refrigerator at 2 °C - 8 °C.
    Do not store the pen directly next to the cooling element. Do not use Alhemo if it has been frozen.

  or
  - At room temperatures below 30 °C.
    Discard the pen if it has been stored above 30 °C. Do not store the pen in direct sunlight.
- Store your in-use Alhemo pen with the pen cap on.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Alhemo contains

- The active substance is concizumab.
  One millilitre Alhemo 150 mg/1.5 mL contains 100 mg concizumab.
- The other ingredients are L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment) and water for injections. See also section 2 “Alhemo contains sodium and polysorbates”.

What Alhemo looks like and contents of the pack

Alhemo is a clear to slightly unclear and colourless to slightly yellow solution for injection in pre-filled disposable pen. Transparent to white particles of protein are acceptable.

Alhemo 150 mg/1.5 mL is available as a unit pack containing 1 pre-filled pen or a multipack of 5 (5 packs of 1) pre-filled pens. Not all pack sizes may be marketed.

Needles for injection are not included.

Marketing Authorisation Holder and Manufacturer

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

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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

What is in this package?

- 1 Alhemo pre-filled pen
- Package leaflet

Needles are not included.

Read the instructions and make sure you have received training from your doctor or nurse before you use the pen.

Follow the instructions from your doctor or nurse on how to use Alhemo and how often you should inject Alhemo.

The pen is pre-filled with 150 mg of Alhemo for subcutaneous use only (injection in the skin). The pen contains several doses of Alhemo.

The pen can deliver a maximum of 80 mg in one injection. The interval on the dose counter is 1 mg. If you need more than 80 mg, you need to inject multiple times.

⚠ **Information for safety**

The pen is for single patient use only and must not be shared. Sharing your pen or needles may lead to infection and transmission of disease.

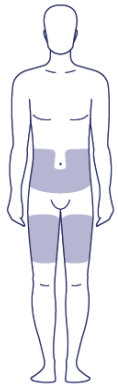
Always use a new needle for each injection. Do not re-use needles as this may lead to needle blockage, infection and incorrect dosing.

The needle is covered by two caps. You must remove both caps. If you forget to remove both caps, you will not inject any solution.

Where on my body should I inject my dose?

You can inject in the skin of:
- your stomach (abdomen) OR
- your thigh.

Inject at a 90°angle. The grey areas on the picture to the right show the injection sites. For every injection, select a new injection site at least 5 centimetres away from where you last injected.



Check your pen 1

Check pen label
Look at the name and colour to make sure you have the correct medicine.

Inspect medicine

Pull off the pen cap and check that Alhemo in the pen window is a clear to slightly unclear and colourless to slightly yellow solution. Transparent to white particles of protein are acceptable. If Alhemo looks discoloured do not use the pen.

Check expiry date
Check the expiry date on the pen label to make sure it has not passed. If the expiry date has passed, do not use the pen.

If your pen is cold
You can inject Alhemo right from the refrigerator or let it reach room temperature before you inject. You can warm the pen in the palms of your hands. Do not use any other heating sources.

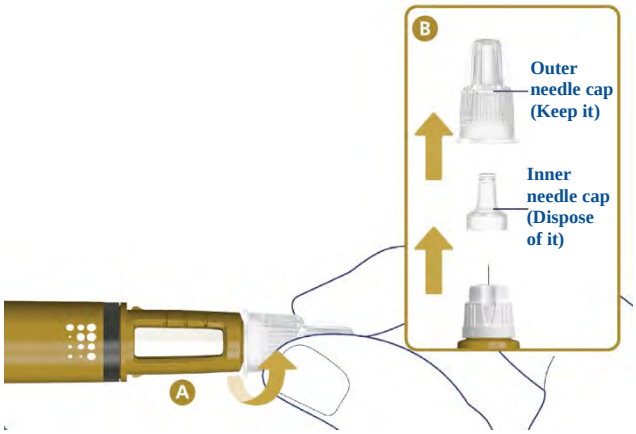
Attach a new needle 2

Take a new needle and tear off the paper tab.

- Push the needle straight onto your pen. Turn until it is on tight. See A.
- Pull off the outer needle cap and keep it. See B.
- Pull off the inner needle cap and dispose of it. See B.

Never use a bent or damaged needle.

Use only needles recommended by your doctor or nurse. This pen is designed to be used with NovoFine Plus 32G x 4 mm or NovoFine 32G x 4 mm injection needles. If you use needles longer than 4 mm, talk to your doctor or nurse about how to perform your injection.

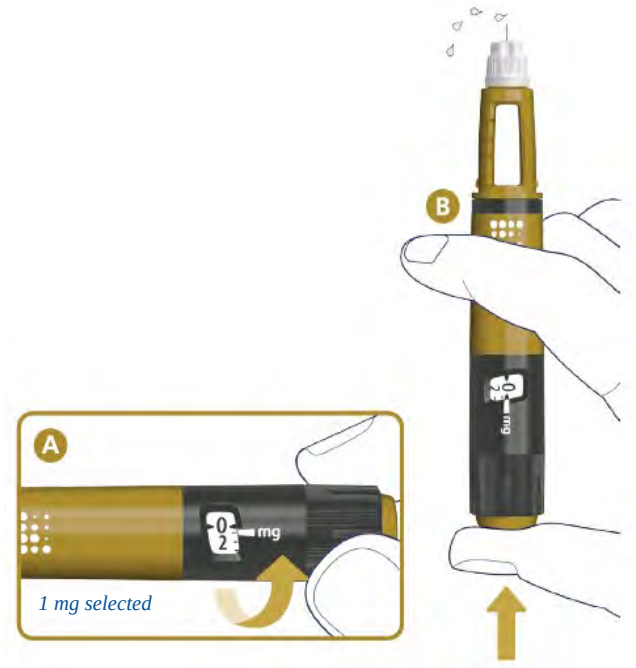


Test the flow 3

A drop of Alhemo may appear at the needle tip, but you should still test the Alhemo flow before **each injection** to avoid underdosing:

a. Turn the dose selector one marking to select 1 mg. See A in the Figure below. Hold the pen with the needle pointing upwards.
b. Press the dose button. See B.
c. Watch for a stream of Alhemo leaving the needle tip. See B.

If no stream appears, go to *Troubleshooting if no stream appears when testing the flow.*



Select your dose 4

Turn the dose selector to select your prescribed dose.

Confirm that you have selected the correct dose.

You can adjust your dose by turning the dose selector in either direction.

If you need a larger dose than you can dial, you must inject yourself multiple times to get your full dose. For more information, see step 6.

The pen contains 150 mg of Alhemo.

The pen can deliver a maximum of 80 mg in one injection.

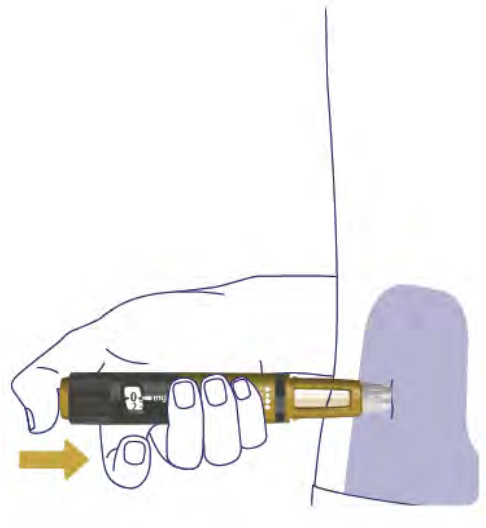
Example 24 mg

Inject your dose **5**

Read through steps a. to e. before you start injecting.
This is to make sure you get your full dose.

a. Select the injection site. See *Where on my body should I inject my dose?*
b. Insert the needle straight into your stomach (abdomen) or thigh at a 90°angle.
c. Press and hold the dose button down until the dose counter returns to **<0>**.
d. While the needle is still in your skin, **count slowly to 6, after the dose counter has returned to <0>.**
e. Retract the needle from your skin.

The pen clicks during dosing and you might also hear or feel a click when the dose counter returns to **<0>**.

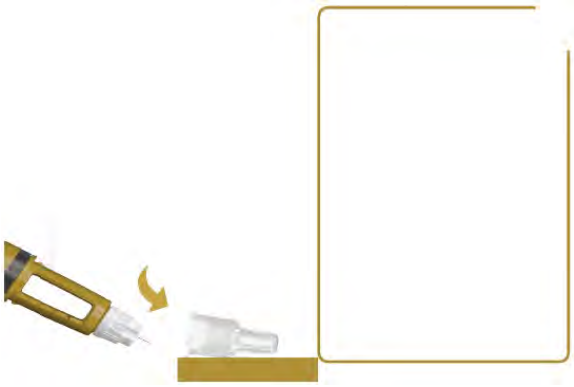


Remove the needle **6**

Remove the needle from your pen after each injection by inserting the needle tip into the outer needle cap without touching the needle or the cap.

When the needle is covered, carefully push the outer needle cap completely on. Unscrew the needle. Do not touch the back end of the needle.

Dispose of the needle as instructed by your doctor, nurse, pharmacist or local authorities.



Do you need a larger dose than you can dial?
If you need a larger dose than you can dial, you must inject yourself more than once to get your full dose. Repeat steps 1 to 6 until you have received your full dose. When you have received your full dose go to step 7.

- Use a new needle for each injection.
- Test the Alhemo flow before each injection.
- Accurately calculate how much to inject in each injection to receive your full dose.

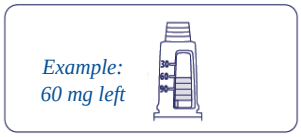
After your dose **7**

Put the pen cap back on your pen to protect Alhemo from light.

Now your pen is ready for storage until you need it next time.

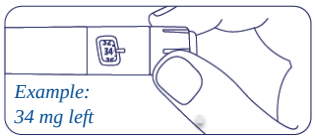
After first use do not use your pen for more than 28 days.

How much Alhemo is left in your pen?
The pen scale shows approximately how much Alhemo is left in your pen.



If you want to see more accurately how much Alhemo is left in your pen, turn the dose selector until it stops. The dose pointer will line up with the number of milligrams left in the pen. The number shown on the dose counter is the number of milligrams left in your pen.

If the dose counter shows 80, there are 80 mg or more left in the pen. The example below shows 34 mg of Alhemo left in the pen.



Troubleshooting if no stream appears when testing the flow (step 3)

- If no stream appears, repeat step 3 up to six times until you see a stream.
- If still no stream appears, prepare a new needle (step 2) and test again (step 3).
- If still no stream appears after using a new needle, do not use the pen. Use a new pen.

Storage
See section 5 “How to store Alhemo” on the reverse side of this leaflet.

Take good care of your pen
Treat your pen with care. Rough handling or misuse may cause inaccurate dosing. If this happens you might not get the intended effect of this medicine.

Do not expose your pen to dust, dirt or liquid.

Do not wash, soak or lubricate your pen. If necessary, clean it with mild detergent on a moistened cloth.

Keep your pen out of sight and reach of others, especially children.

Disposing of Alhemo pens, needles and packaging material
When your pen is empty you must dispose of it according to your local regulations.

You cannot refill your pen.

To reduce the risk of a needle stick, dispose of used needles immediately as instructed by your doctor, nurse, pharmacist or local authorities.

[Text for the front page of the folded leaflet]
Package leaflet and Instructions for use

Package leaflet: Information for the user

Alhemo 300 mg/3 mL solution for injection in pre-filled pen
concizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alhemo is and what it is used for

What Alhemo is

Alhemo contains the active substance concizumab, which belongs to a group of medicines called ‘monoclonal antibodies’. Concizumab is a protein that recognises and binds to a target in the blood involved in the coagulation process.

What Alhemo is used for

Alhemo is used to prevent or reduce the frequency of bleeds in adults and adolescents from 12 years with:
- haemophilia A with inhibitors.
- haemophilia B with inhibitors.

Haemophilia A is inborn blood clotting factor VIII deficiency and haemophilia B is inborn blood clotting factor IX deficiency.

How Alhemo works

Concizumab blocks a natural factor in your blood that prevents blood from clotting. This factor is called tissue factor pathway inhibitor. This blocking makes the clotting of your blood more effective and therefore helps prevent or reduces bleeds when you are lacking a clotting factor.

Alhemo acts independently of factor VIII and factor IX and independently of inhibitors to these.

2. What you need to know before you use Alhemo

Do not use Alhemo
- If you are allergic to concizumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Allergic reactions
There is a risk that you may experience an allergic reaction. Stop the treatment and contact your doctor if you have symptoms of allergic reactions such as rash, redness, hives and itching. You could also experience symptoms of severe allergic reactions such as:
- Itching on large areas of skin
- Redness and/or swelling of lips, tongue, face or hands
- Difficulty in swallowing
- Shortness of breath
- Wheezing
- Tightness of the chest
- Pale and cold skin
- Fast heartbeat
- Dizziness due to low blood pressure.

Stop using Alhemo and immediately seek emergency help if you have symptoms of severe allergic reactions.

Blood clots
Blood clots can form anywhere in the body.

Stop using Alhemo and contact your doctor immediately, if you have symptoms of blood clots such as:
- Swelling, warmth, pain, or redness of the skin – these could be symptoms of a blood clot in your legs or arms.
- Feeling short of breath, severe chest pain – these could be symptoms of blood clots in your heart or lungs.
- Headache, feeling confused, trouble with speech or movement, numbness in face, eye pain or swelling, or problems with your vision – these could be symptoms of a blood clot in your brain or eyes.
- Sudden pain in stomach or lumbar area – these could be symptoms of blood clots in your gut or kidneys.

Children and adolescents

Alhemo is not recommended for children under 12 years with haemophilia A with inhibitors or haemophilia B with inhibitors.

Other medicines and Alhemo

Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

Use a highly effective method of contraception during treatment with Alhemo and for 7 weeks after your last injection. Talk to your doctor about the type of contraceptive to use.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines

Alhemo is unlikely to affect your ability to drive or use machines.

Alhemo contains sodium and polysorbates

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

This medicine contains 0.25 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Alhemo

See the detailed **Instructions for use** on the other side of this leaflet before using your Alhemo pre-filled pen. Ask your doctor if you need to use alternative injection techniques, e.g. lean patients and adolescents may need to inject into a loosely held fold of skin to avoid injecting too deep (into the muscle).

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

Management of breakthrough bleeds

Before you start using Alhemo talk with your doctor about how to handle a potential bleed.

The recommended dose for adults and adolescents is
- Starting dose on day 1: 1 mg per kg body weight.
- From day 2 until the maintenance dose is set: 0.20 mg per kg body weight once daily.
- Individual maintenance dose as decided by the doctor: 0.15, 0.20 or 0.25 mg per kg body weight once daily.

Alhemo is injected under the skin of your abdomen or thigh and can be used any time of the day.

If you use more Alhemo than you should

Contact your doctor immediately.

If you forget to use Alhemo

Alhemo can be used any time of the day.
One or more missed doses of Alhemo affects how well the medicine works. It is important to take Alhemo every day.

If you miss your daily dose of Alhemo:

If you miss a dose during the first 4 weeks of treatment, contact your doctor to discuss how to resume.

If you miss a dose after dose maintenance setting:
- If you missed 1 daily dose, resume your daily dose.
- If you missed 2 to 6 daily doses, take your daily dose twice (as two separate injections each corresponding to a daily dose), and then continue taking your daily dose the next day.
- If you missed 7 or more daily doses, contact your doctor right away as you will need to receive a new loading dose before continuing your daily dose the next day.

If you are in doubt, contact your doctor.

If you stop using Alhemo

You may no longer be protected against bleeding. Do not stop using Alhemo without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Alhemo and immediately contact your doctor if you have any symptoms of **severe allergic reactions or symptoms of blood clots.** See "Warnings and precautions" in section 2.

Other side effects
Very common: may affect more than 1 in 10 people
- Injection site reactions such as redness, bleeding, itching, hives, swelling, pain, numbness.

Common: may affect up to 1 in 10 people
- Allergic reaction

Uncommon: may affect up to 1 in 100 people
- Blood clots

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Alhemo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and carton after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice that the solution is discoloured.

Before use
- Store unused Alhemo pens at 2 °C - 8 °C in a refrigerator.
- Store your new, unused pen with the pen cap on.
- When stored in the refrigerator, do not store the pen directly next to the cooling element.
- Do not use Alhemo if it has been frozen or stored at temperatures above 30 °C.

After first use
- Store the Alhemo pen you are currently using without a needle attached for up to 28 days (4 weeks), either:
  - In the refrigerator at 2 °C - 8 °C.
    Do not store the pen directly next to the cooling element. Do not use Alhemo if it has been frozen.

  or
  - At room temperatures below 30 °C.
    Discard the pen if it has been stored above 30 °C. Do not store the pen in direct sunlight.
- Store your in-use Alhemo pen with the pen cap on.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Alhemo contains

- The active substance is concizumab.
  One millilitre Alhemo 300 mg/3 mL contains 100 mg concizumab.
- The other ingredients are L-Arginine hydrochloride, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment) and water for injections. See also section 2 “Alhemo contains sodium and polysorbates”.

What Alhemo looks like and contents of the pack

Alhemo is a clear to slightly unclear and colourless to slightly yellow solution for injection in pre-filled disposable pen. Transparent to white particles of protein are acceptable.

Alhemo 300 mg/3 mL is available as a unit pack containing 1 pre-filled pen.

Needles for injection are not included.

Marketing Authorisation Holder and Manufacturer

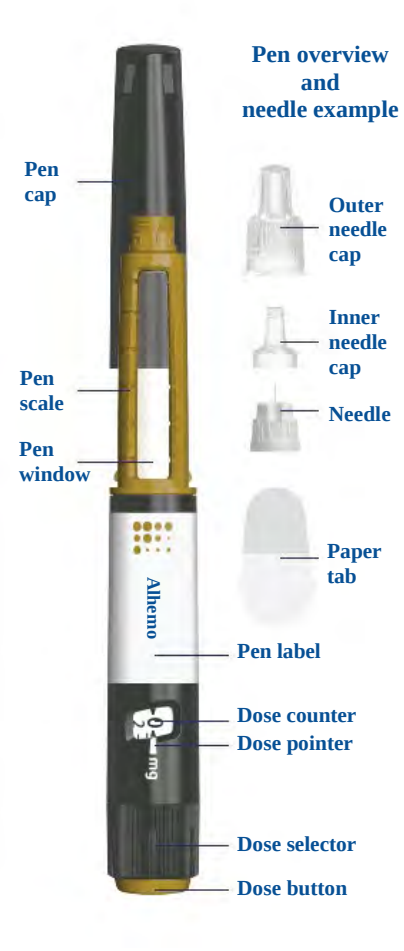
Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
Denmark

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Instructions for use
Alhemo 300 mg/3 mL solution for injection in pre-filled pen
concizumab



What is in this package?

- 1 Alhemo pre-filled pen
- Package leaflet

Needles are not included.

Read the instructions and make sure you have received training from your doctor or nurse before you use the pen.

Follow the instructions from your doctor or nurse on how to use Alhemo and how often you should inject Alhemo.

The pen is pre-filled with 300 mg of Alhemo for subcutaneous use only (injection in the skin). The pen contains several doses of Alhemo.

The pen can deliver a maximum of 80 mg in one injection. The interval on the dose counter is 1 mg. If you need more than 80 mg, you need to inject multiple times.

⚠ Information for safety

The pen is for single patient use only and must not be shared. Sharing your pen or needles may lead to infection and transmission of disease.

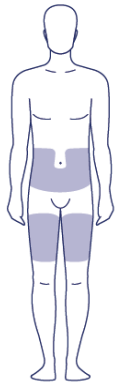
Always use a new needle for each injection. Do not re-use needles as this may lead to needle blockage, infection and incorrect dosing.

The needle is covered by two caps. You must remove both caps. If you forget to remove both caps, you will not inject any solution.

Where on my body should I inject my dose?

You can inject in the skin of:
- your stomach (abdomen) OR
- your thigh.

Inject at a 90°angle. The grey areas on the picture to the right show the injection sites. For every injection, select a new injection site at least 5 centimetres away from where you last injected.



Check your pen **1**

Check pen label
Look at the name and colour to make sure you have the correct medicine.

Inspect medicine

Pull off the pen cap and check that Alhemo in the pen window is a clear to slightly unclear and colourless to slightly yellow solution. Transparent to white particles of protein are acceptable. If Alhemo looks discoloured do not use the pen.

Check expiry date
Check the expiry date on the pen label to make sure it has not passed. If the expiry date has passed, do not use the pen.

If your pen is cold
You can inject Alhemo right from the refrigerator or let it reach room temperature before you inject. You can warm the pen in the palms of your hands. Do not use any other heating sources.

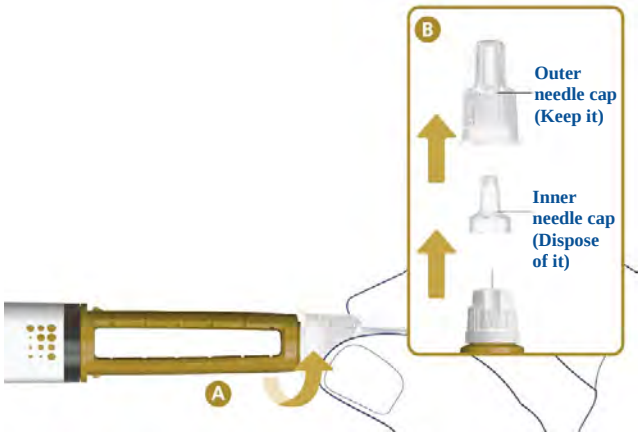
Attach a new needle **2**

Take a new needle and tear off the paper tab.

- Push the needle straight onto your pen. Turn until it is on tight. See A.
- Pull off the outer needle cap and keep it. See B.
- Pull off the inner needle cap and dispose of it. See B.

Never use a bent or damaged needle.

Use only needles recommended by your doctor or nurse. This pen is designed to be used with NovoFine Plus 32G x 4 mm or NovoFine 32G x 4 mm injection needles. If you use needles longer than 4 mm, talk to your doctor or nurse about how to perform your injection.

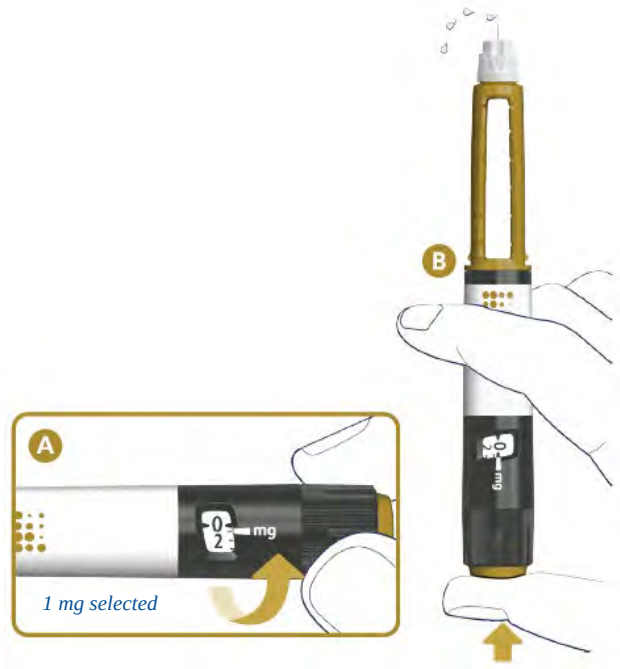


Test the flow 3

A drop of Alhemo may appear at the needle tip, but you should still test the Alhemo flow before **each injection** to avoid underdosing:

a. Turn the dose selector one marking to select 1 mg. See A in the Figure below. Hold the pen with the needle pointing upwards.
b. Press the dose button. See B.
c. Watch for a stream of Alhemo leaving the needle tip. See B.

If no stream appears, go to *Troubleshooting if no stream appears when testing the flow.*



Select your dose 4

Turn the dose selector to select your prescribed dose.

Confirm that you have selected the correct dose.

You can adjust your dose by turning the dose selector in either direction.

If you need a larger dose than you can dial, you must inject yourself multiple times to get your full dose. For more information, see step 6.

The pen contains 300 mg of Alhemo.

The pen can deliver a maximum of 80 mg in one injection.

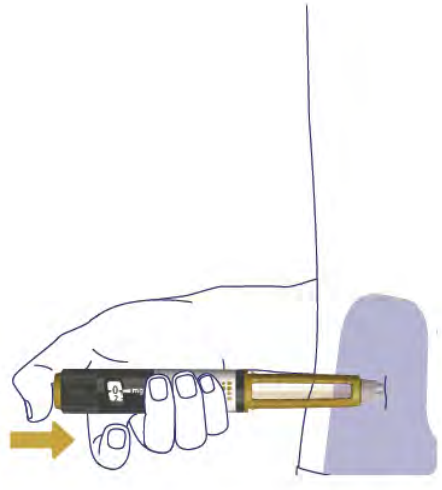
Example 24 mg

Inject your dose **5**

Read through steps a. to e. before you start injecting.
This is to make sure you get your full dose.

a. Select the injection site. See *Where on my body should I inject my dose?*
b. Insert the needle straight into your stomach (abdomen) or thigh at a 90°angle.
c. Press and hold the dose button down until the dose counter returns to **<0>**.
d. While the needle is still in your skin, **count slowly to 6, after the dose counter has returned to <0>.**
e. Retract the needle from your skin.

The pen clicks during dosing and you might also hear or feel a click when the dose counter returns to **<0>**.

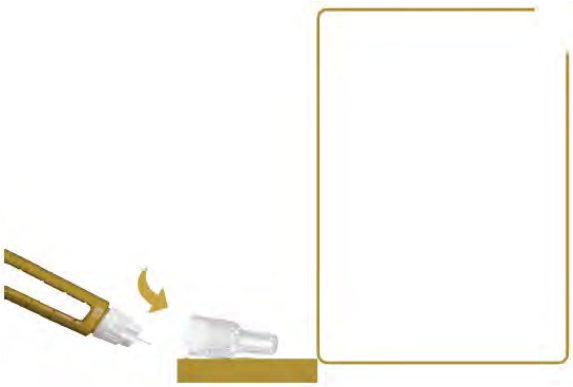


Remove the needle **6**

Remove the needle from your pen after each injection by inserting the needle tip into the outer needle cap without touching the needle or the cap.

When the needle is covered, carefully push the outer needle cap completely on. Unscrew the needle. Do not touch the back end of the needle.

Dispose of the needle as instructed by your doctor, nurse, pharmacist or local authorities.



Do you need a larger dose than you can dial?
If you need a larger dose than you can dial, you must inject yourself more than once to get your full dose. Repeat steps 1 to 6 until you have received your full dose. When you have received your full dose go to step 7.

- Use a new needle for each injection.
- Test the Alhemo flow before each injection.
- Accurately calculate how much to inject in each injection to receive your full dose.

After your dose **7**

Put the pen cap back on your pen to protect Alhemo from light.

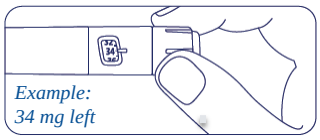
Now your pen is ready for storage until you need it next time.

After first use do not use your pen for more than 28 days.

How much Alhemo is left in your pen?
The pen scale shows approximately how much Alhemo is left in your pen.

If you want to see more accurately how much Alhemo is left in your pen, turn the dose selector until it stops. The dose pointer will line up with the number of milligrams left in the pen. The number shown on the dose counter is the number of milligrams left in your pen.

If the dose counter shows 80, there are 80 mg or more left in the pen. The example below shows 34 mg of Alhemo left in the pen.



Troubleshooting if no stream appears when testing the flow (step 3)

- If no stream appears, repeat step 3 up to six times until you see a stream.
- If still no stream appears, prepare a new needle (step 2) and test again (step 3).
- If still no stream appears after using a new needle, do not use the pen. Use a new pen.

Storage
See section 5 “How to store Alhemo” the reverse side of this leaflet.

Take good care of your pen
Treat your pen with care. Rough handling or misuse may cause inaccurate dosing. If this happens you might not get the intended effect of this medicine.

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Do not wash, soak or lubricate your pen. If necessary, clean it with mild detergent on a moistened cloth.

Keep your pen out of sight and reach of others, especially children.

Disposing of Alhemo pens, needles and packaging material
When your pen is empty you must dispose of it according to your local regulations.

You cannot refill your pen.

To reduce the risk of a needle stick, dispose of used needles immediately as instructed by your doctor, nurse, pharmacist or local authorities.

[Text for the front page of the folded leaflet]
Package leaflet and Instructions for use