

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^{PR}Alhemo™

concizumab injection

Solution for Subcutaneous Injection

15 mg/1.5 mL (10 mg/mL)
60 mg/1.5 mL (40 mg/mL)
150 mg/1.5 mL (100 mg/mL)
300 mg/3 mL (100 mg/mL)

ATC code: B02BX
Antihemorrhagic

Novo Nordisk Canada Inc.
101-2476 Argentia Road
Mississauga, Ontario
L5N 6M1

Date of Initial Authorization:
March 10th, 2023

Date of Revision:
July 26, 2023

Submission Control Number: 267314

RECENT MAJOR LABEL CHANGES

1 INDICATIONS	TBD
---------------	-----

TABLE OF CONTENTS

TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics	4
1.2 Geriatrics	4
2 CONTRAINDICATIONS	4
3 SERIOUS WARNINGS AND PRECAUTIONS	4
4 DOSAGE AND ADMINISTRATION	5
4.1 Dosing Considerations	5
4.2 Recommended Dose and Dosage Adjustment	5
4.4 Administration	7
4.5 Missed Dose	8
5 OVERDOSAGE	8
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	9
7 WARNINGS AND PRECAUTIONS	9
7.1 Special Populations	11
7.1.1 Pregnant Women	11
7.1.2 Breast-feeding	11
7.1.3 Pediatrics	11
7.1.4 Geriatrics	12
8 ADVERSE REACTIONS	12
8.1 Adverse Reaction Overview	12
8.2 Clinical Trial Adverse Reactions	12
8.2.1 Clinical Trial Adverse Reactions – Pediatrics	13
8.3 Less Common Clinical Trial Adverse Reactions	13
9 DRUG INTERACTIONS	13
9.2 Drug Interactions Overview	13
9.3 Drug-Drug Interactions	13
9.4 Drug-Food Interactions	14
9.5 Drug-Herb Interactions	14
9.6 Drug-Laboratory Test Interactions	14
10 CLINICAL PHARMACOLOGY	14
10.1 Mechanism of Action	14
10.2 Pharmacodynamics	14
10.3 Pharmacokinetics	14
11 STORAGE, STABILITY AND DISPOSAL	16
12 SPECIAL HANDLING INSTRUCTIONS	16
PART II: SCIENTIFIC INFORMATION	17

13	PHARMACEUTICAL INFORMATION	17
14	CLINICAL TRIALS	17
	14.1 Clinical Trials by Indication	17
	Hemophilia Patients with Inhibitors	17
	14.3 Immunogenicity	19
15	MICROBIOLOGY	19
16	NON-CLINICAL TOXICOLOGY	20
	PATIENT MEDICATION INFORMATION	21

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

There is limited clinical experience of Alhemo use in patients known to have mild or moderate hemophilia.

1.1 Pediatrics

- **Pediatrics (aged 12 to less than 18 years):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Alhemo in adolescent patients aged 12 to less than 18 years of age has been established; therefore, Health Canada has authorized an indication for adolescent patients aged 12 to less than 18 years. The safety and efficacy of Alhemo has not been established in patients less than 12 years of age.

1.2 Geriatrics

- **Geriatrics (≥ 65 years of age):** Clinical studies did not include a sufficient number of patients aged 65 years and over to determine if the overall benefit-risk profile of Alhemo is favourable in these patients.

2 CONTRAINDICATIONS

Alhemo is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [Dosage Forms, Strengths, Composition and Packaging \[6\]](#).

3 SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions Box

The following serious adverse reactions have been reported in association with Alhemo use:

- **Thromboembolic Events**

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

Patients at high risk for thromboembolic events have been excluded from clinical studies and there should be careful consideration whether the potential benefit of Alhemo treatment outweighs the potential risk of thromboembolic complications in these patients.

Patients who require bypassing agents for mild or moderate breakthrough bleeds should be administered the lowest possible effective dose of these agents to reduce the risk of thromboembolic

events (see [Warnings and Precautions \[7\]](#)).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment should be initiated under the supervision of a health professional experienced in treatment of hemophilia and/or bleeding disorders.
- Prior to initiation of Alhemo, patients should discontinue prophylactic treatment with bypassing agents. Treatment with recombinant activated Factor VII (rFVIIa) should be discontinued at least 12 hours before starting Alhemo and treatment with activated prothrombin complex concentrates (aPCC) should be discontinued at least 48 hours before starting Alhemo.
- Hemophilia A patients with FVIII inhibitors should discontinue emicizumab 6 months before starting treatment with Alhemo.
- Treatment should be initiated in a non-bleeding state.
- Alhemo is intended for patients' self-administration or by a caregiver (e.g. parent) only after proper training by a health professional..
- Intramuscular injections should be avoided and these may occur inadvertently, particularly in lean and younger patients where it is recommended to inject into a loosely-held skin-fold.

4.2 Recommended Dose and Dosage Adjustment

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

- Day 1: a loading dose of 1 mg/kg once.
- Day 2 and until individual maintenance dose setting (see below): once daily dosing of 0.20 mg/kg.
- 4 weeks after initiation of treatment: measurement of concizumab pre-dose plasma concentration by a validated concizumab enzyme-linked immunosorbent assay (ELISA) as determined by an accredited laboratory.
- Once the week 4 concizumab plasma concentration result is available the individual maintenance dose is set 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
200–4000 ng/mL	0.20 mg/kg
>4000 ng/mL	0.15 mg/kg

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

The individual maintenance dose should be established at the earliest convenience (after concizumab plasma concentration week 4 result is available) and no later than 6-8 weeks after

initiation of treatment. The individual maintenance dose should only be determined in patients who adhere to their initial everyday dose. Patients who miss consecutive daily doses during this dose finding phase should inform their health professional so that a new 4 week uninterrupted daily dose period is established before plasma concizumab concentrations are measured.

In hemophilia study NN7415-4311 (explorer7), of the 97 patients who had a week 4 concizumab plasma concentration, 74.2% (n = 72) of patients remained on the 0.2 mg/kg daily dose, 24.7% (n = 24) of patients had their dose increased to 0.25 mg/kg per day, and 1.0% (n = 1) of patients had their dose decreased to 0.15 mg/kg.

For patients with a plasma concizumab concentration > 4000 ng/mL and who required a dose reduction to 0.15 mg/kg, a second concizumab concentration should be considered. Ideally, the second concizumab concentration should be taken 8 weeks after initiation of the lower dose to ensure patients reach steady-state. If the plasma concentration remains above 4000 ng/mL then the benefits of Alhemo should be evaluated versus the potential for an increased risk of thromboembolic events.

Additional concizumab plasma concentration measurements can also be taken after 8 weeks on the same maintenance dose according to the patient's medical condition. For example, this should be considered if a patient experiences an increased bleeding frequency or acquires a comorbidity, which could affect their coagulation system or drug metabolism/excretion.

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

Geriatrics (> 65 years of age)

No dose adjustments (besides individual maintenance dose setting) are recommended in patients ≥65 years of age.

Pediatrics (<12 years of age)

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

Patients with renal and hepatic insufficiency

No dose adjustments (besides individual maintenance dose setting) are required for patients with renal and hepatic impairment (see [Clinical Pharmacology, Pharmacokinetics \[10.3\]](#)). Patients with severe renal impairment (eGFR ≤ 30 mL/min/1.73 m²) and severe hepatic impairment (AST or ALT > 3x ULN combined with total bilirubin > 1.5x ULN) were not included in the clinical trials.

Guidance on the Use of Breakthrough Bleed Treatment

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

Health professionals should discuss with all patients and/or caregivers about the dose and schedule of bypassing agents to use, if required, while receiving Alhemo prophylaxis, including using the lowest possible effective dose to minimize the risk of thromboembolic events for mild and moderate bleeds, which includes a maximum aPCC dose of 100 U/kg within 24 hours. For severe bleeds, it may be necessary to follow the dosing scheme provided in the approved label for a bypassing agent but this should be based on clinical judgement taking into account the

potential for life-threatening thromboembolic events.

Management in the perioperative setting

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

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

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

Immune tolerance induction (ITI)

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

Calculation of dose

The dose (in mg) is calculated as follows:

Patient body weight (kg) x dose (1, 0.15, 0.20 or 0.25 mg/kg) = total amount (mg) of Alhemo to be administered.

The dose is dialled at increments of

- 0.1 mg on the 15 mg/1.5 mL (10 mg/mL) pen (blue),
- 0.4 mg on the 60 mg/1.5 mL (40 mg/mL) pen (brown), and
- 1.0 mg on the 150 mg/1.5 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL) pens (gold).

The health professional should 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.

4.4 Administration

- Alhemo is available in a pre-filled pen designed to be used with NovoFine® 32G TIP ETW or NovoFine® Plus needles with a gauge of 32 and a length of 4 mm. The pen contains multiple doses.
- Administer Alhemo by subcutaneous injection to the abdomen or thigh with rotation of injection site every day. Subcutaneous injections should not be given in areas where the skin is tender, bruised, red or hard, or areas where there are moles, scars, or stretch marks.
- Always use a new needle for each injection.
- Alhemo is a clear to slightly opalescent and colorless to slightly yellow solution. Translucent particles of protein are acceptable. Do not use if the solution is discoloured

or contains solid foreign particles.

- Alhemo may be self-administered or administered by a caregiver after appropriate training by a healthcare provider and after reading the instructions for use.
- Each Alhemo prefilled pen is for use by a single patient. An Alhemo pen must not be shared between patients, even if the needle is changed.
- Intramuscular injections should be avoided and these may occur inadvertently, particularly in lean and younger patients where it is recommended to inject into a loosely-held skin-fold.

4.5 Missed Dose

It is important that each patient adheres to their daily dosing regimen (see Warnings and Precautions [7], General).

Missed Doses Before the Maintenance Dose has been Determined

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

Missed Doses After the Maintenance Dose has been Determined

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

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

For missed doses **due to other reasons** (e.g. surgery), the patient should follow the instructions in the product monograph (see Recommended Dose and Dosage Adjustment [4.2]) or resume the daily maintenance dose as instructed by their health professional.

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

5 OVERDOSAGE

There is limited experience with overdose of Alhemo.

For management of a suspected drug overdose, contact your regional poison control centre.

Patients who receive an accidental overdose should also immediately contact their health professional and be monitored closely.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 3 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Solution for injection in a pre-filled, multi-dose disposable pen 15 mg (10 mg/mL) 60 mg (40 mg/mL) 150 mg (100 mg/mL) 300 mg (100 mg/mL)	L-Arginine HCl L-Histidine Sodium chloride Sucrose Polysorbate 80 Phenol Water for injection Hydrochloric acid Sodium hydroxide

Alhemo is a clear to slightly opalescent and colorless to slightly yellow solution that may contain translucent particles of protein. Alhemo is available in the following presentations:

- 15 mg/1.5 mL (10 mg/mL) in a single-patient-use prefilled pen with a blue colour-coded dose button and cartridge holder
- 60 mg/1.5 mL (40 mg/mL) in a single-patient-use prefilled pen with a brown colour-coded dose button and cartridge holder
- 150 mg/1.5 mL (100 mg/mL) in a single-patient-use prefilled pen with a gold colour-coded dose button and cartridge holder
- 300 mg/3 mL (100 mg/mL) in a single-patient-use prefilled pen with a gold colour-coded dose button and cartridge holder

The pre-filled pen is packed in a carton. Alhemo is available in a pack containing 1 pen. Injection needles are not included.

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

7 WARNINGS AND PRECAUTIONS

See [Serious Warnings And Precautions \[3\]](#).

General

Health professionals should discuss with patients or caregivers at the start of treatment with Alhemo that one or more missed doses of Alhemo may significantly affect the efficacy of the product and the ability to establish a proper maintenance dose. If a patient or caregiver can not follow the every day dosing regimen then alternative treatment options should be considered.

Driving and Operating Machinery

There is no evidence that Alhemo affects one's ability to drive and use machines.

Hematologic

Thromboembolic Events

Serious thromboembolic events (TEEs) reported in association with Alhemo resulted in a pause in clinical development from March to August 2020, and a new dosing regimen based on plasma concizumab concentrations was implemented (see [Dosage and Administration \[4\]](#)).

Patients treated with Alhemo should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events. Patients who experienced thromboembolic events in clinical trials were exposed to additional hemostatic agents in close proximity with administration of Alhemo.

The half-life of bypassing agents and emicizumab should be considered when switching to Alhemo (see [Dosage and Administration \[4\]](#)).

Patients should be advised on how to treat breakthrough bleeds. In the case where other hemostatic agents are required to treat mild or moderate breakthrough bleeds, it is recommended to treat with the lowest possible effective dose (see [Dosage and Administration \[4\]](#)).

Patients were to be excluded from clinical studies if they were at high risk for developing thromboembolic events and there should be careful consideration whether the potential benefit of Alhemo treatment outweighs the potential risk of thromboembolic complications in these patients. Risk factors include a history or family history of TEEs, obesity, arrhythmias, hypertension, diabetes, hypercholesterolaemia, smoking, recent major surgeries, and old age taking into consideration the totality of risk factors for the individual patient. In addition, patients in which tissue factor is overexpressed (e.g. advanced atherosclerotic disease, crush injury, cancer or septicaemia), may have further risks of thromboembolic events or disseminated intravascular coagulation (DIC) with Alhemo treatment.

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

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

Immune

Hypersensitivity Reactions

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

symptoms occur and initiate appropriate treatment.

Immunogenicity

Anti-concizumab antibodies and neutralizing anti-concizumab antibodies have been reported in 25% and 6.5% of patients treated with Alhemo in clinical trials, respectively (see [Clinical Trials, Immunogenicity \[14.3\]](#)). Most patients found to have anti-concizumab antibodies did not experience a change in concizumab plasma concentrations, an increase in bleeding events or any additional safety concerns; however, there were two cases (one in a clinical trial and one in a compassionate use program) where reduction of effectiveness of Alhemo was reported.

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

Reproductive Health: Female and Male Potential

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see [Non-Clinical Toxicology \[16\]](#)). No fertility data are available in humans. Thus, the effect of Alhemo on male and female fertility is unknown.

Contraception

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

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical studies of Alhemo use in pregnant women. Animal reproduction studies have not been conducted with Alhemo as most patients treated with Alhemo are male. It is not known whether Alhemo can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Alhemo should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

7.1.2 Breast-feeding

There is no information regarding the presence of Alhemo in human milk, the effect on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for and any potential adverse effects on the breastfed infant from Alhemo or from the underlying maternal condition.

7.1.3 Pediatrics

Forty-two adolescent patients (aged 12 to less than 18 years) were included in the main NN7415-4311 (explorer7) clinical study to evaluate the safety and efficacy of Alhemo in hemophilia patients with inhibitors. There is limited clinical experience with Alhemo in patients who are less than 12 years of age. (see [Adverse Reactions, Clinical Trial Adverse Reactions \[8.2.1\]](#) and [Clinical Trials, Study Results \[14.2\]](#)).

The safety profile was similar between adolescent and adult patients.

7.1.4 Geriatrics

Clinical studies did not include a sufficient number of patients aged 65 years and over to determine the overall benefit-risk profile of Alhemo in these patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Hemophilia Patients with Inhibitors

Treatment-emergent adverse events (TEAEs) are reported from the main NN7415-4311 (explorer7) clinical study. Patients included in the safety and efficacy analyses were randomized 1:2 to Arm 1 (n = 19) and received on-demand therapy with bypassing agents or to Arm 2 (n = 33) and received Alhemo prophylaxis (see efficacy results in [Clinical Trials \[14\]](#)). Additional nonrandomized patients treated with Alhemo in Arms 3 and 4 of the study were included in the overall Alhemo safety population for a total of 114 hemophilia patients with inhibitors (78 adults and 36 adolescents).

The safety analysis includes events reported in patients receiving Alhemo before a clinical trial treatment pause with a 1.0 mg/kg loading dose on Day 1 followed by a daily 0.25 mg/kg daily dose and events reported in patients treated with the recommended Alhemo dosing regimen after the clinical pause (see [Dosage and Administration \[4\]](#)).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Hemophilia Patients with Inhibitors

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

Common TEAEs ($\geq 5\%$) are reported in Table 4.

Table 4 Treatment-Emergent Adverse Events ($\geq 5\%$) in Hemophilia Patients with Inhibitors Treated with Alhemo from Study NN7415-4311 (explorer7)

System Organ Class	Frequency
AE (preferred term, MedRA)	N = 114
General Disorders and Administration Site Disorders	
Injection site reactions*	22.8%
Pyrexia	5.3%
Infections and Infestations	

Upper respiratory tract infection	7.0%
Investigations	
Prothrombin Fragment 1.2 Increased	6.1%
Fibrin D-dimer Increased	5.3%
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	11.4%
Nervous System Disorders	
Headache	5.3%

*Injection site reactions: Include the preferred terms injection site rash, injection site erythema, injection site urticaria, injection site reaction, injection site bruising, injection site hematoma, injection site swelling, injection site pruritus, injection site hemorrhage, injection site hypoesthesia, injection site induration, and injection site pain.

Injection site reactions

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

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

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

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Hemophilia Patients with Inhibitors

The safety profile of Alhemo was similar between adolescent and adult patients. There is limited clinical data in children below 12 years of age.

8.3 Less Common Clinical Trial Adverse Reactions

Hemophilia Patients with Inhibitors

The following less common but significant clinical trial adverse reactions have been reported in association with Alhemo.

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Studies were conducted to determine if additive and synergistic interactions exist between Alhemo and other hemostatic factors, including activated recombinant FVII (rFVIIa).

9.3 Drug-Drug Interactions

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

Following the treatment pause, new safety measures were introduced recommending the lowest possible effective dose of bypassing agents to treat mild or moderate breakthrough bleeds for patients who are receiving Alhemo to decrease the risk thromboembolic risks. For severe bleeds, this may require the recommended label dose taking into account clinical judgement (see [Dosage and Administration \[4\]](#)).

Hemophilia A patients with FVIII inhibitors were required to discontinue emicizumab for at least 180 days before receiving Alhemo (see [Dosage and Administration \[4\]](#)).

9.4 Drug-Food Interactions

Interactions with food have not been established as Alhemo is administered subcutaneously.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Concizumab is an anti-Tissue Factor Pathway Inhibitor (anti-TFPI) antibody that binds to the Kunitz-2 domain of TFPI and prevents TFPI from binding to activated Factor X (FXa). The reduced TFPI activity by concizumab allows FXa, produced by the activated coagulation Factor VII (FVIIa)/tissue factor (TF) complex, to increase thrombin generation and subsequent clot formation, which aids in achieving hemostasis in hemophilia patients.

10.2 Pharmacodynamics

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

10.3 Pharmacokinetics

Concizumab exhibited non-linear pharmacokinetics with systemic exposure to concizumab, as measured by AUC and C_{max} , increasing in greater than a 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.

Exposure to concizumab was similar between hemophilia A and B patients.

Steady-state concentration was approximately reached at week 4 following once-daily dosing of 0.20 mg/kg with a loading dose of 1 mg/kg on day 1, as estimated by the pharmacokinetic model.

Geometric mean steady-state concizumab concentrations in adolescent and adult hemophilia

patients (≥ 12 years of age) with inhibitors who received the recommended dosing regimen are shown in Table 5.

Table 5 Steady-State concizumab Concentrations During 24-hour Dosing Interval at Week 24 (Study NN7415-4311 [explorer7])

Parameters	All maintenance doses (0.15, 0.20 or 0.25 mg/kg) N=99 ^a
C _{max,ss} (ng/mL), geometric mean (CV%)	1167.1 (128%)
C _{trough,ss} (ng/mL), geometric mean (CV%)	665.4 (221%)
C _{max} / C _{trough} ratio, mean (SD)	2.2 (5.2)

C_{max,ss}, maximum plasma concentration at steady state; C_{trough,ss}, trough plasma concentration at steady state.

^aOn Alhemo dosing regimen.

Absorption

Following a single-dose subcutaneous administration of 0.05 – 3 mg/kg concizumab in healthy subjects and hemophilia patients, the time to maximum plasma concentration of concizumab (t_{max}) was in the range from 8 hours to 99 hours (4.1 days). The bioavailability of concizumab after subcutaneous administration was estimated as 77.7% by population pharmacokinetic modelling.

Distribution

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

Metabolism

The metabolism of concizumab has not been studied. IgG antibodies are mainly catabolized by lysosomal proteolysis and then eliminated from or reused by the body.

Elimination

Both linear and non-linear pathways contribute to the elimination of concizumab. Due to the non-linear elimination, the half-life is dependent on the concizumab concentration. A terminal half-life in healthy subjects and hemophilia patients who received 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). Following multiple subcutaneous injections and based on a population PK analysis, the linear clearance was approximately 0.192 L/day (0.008 L/h), and the estimated half-life at steady-state C_{trough} (665 ng/mL) was approximately 38 hours.

Special Populations and Conditions

- **Pediatrics:** The mean concizumab exposure was slightly lower in adolescents (≥ 12 years) compared to adults.
- **Geriatrics:** Clinical studies of concizumab did not include sufficient numbers of patients aged 65 and over to determine whether there are differences in exposure compared with younger patients.
- **Hepatic Insufficiency:** Dedicated trials have not been conducted on the effect of hepatic impairment on the pharmacokinetics of concizumab. Of the 112 patients treated with concizumab in explorer7, 4 patients had elevated liver enzymes (ALT or AST $\geq 1.5 \times$ ULN). No impact on exposure of concizumab was observed.
- **Renal Insufficiency:** Dedicated trials have not been conducted on the effect of renal

impairment on the pharmacokinetics of concizumab. Of the 112 patients treated with the concizumab dosing regimen in explorer7, 5 patients had eGFR <90 mL/min/1.73m² at the time when the loading dose was administered. No impact on exposure of concizumab was observed.

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

11 STORAGE, STABILITY AND DISPOSAL

Before use: Store in a refrigerator at 2°C to 8°C.

After first use: Store for up to 28 days in a refrigerator at 2°C to 8°C or at room temperature below 30°C. Write the date of first use in the space provided on the carton.

Store unused Alhemo with the cap on and in the original carton to protect from light. Alhemo should not be stored in direct sunlight, and the Alhemo pen should be kept away from direct heat. Do not freeze or store it close to a cooling element in a refrigerator. Do not use Alhemo if it has been frozen or stored at temperatures above 30°C.

Always remove and safely discard the needle after each injection and store the Alhemo prefilled pen without an injection needle attached. Always use a new needle for each injection to prevent contamination.

12 SPECIAL HANDLING INSTRUCTIONS

Patients are advised to read the Instructions for Use very carefully before using Alhemo pen. Instructions for Use of Alhemo pen are provided within the carton.

Alhemo should appear clear to slightly opalescent and colourless to slightly yellow. Translucent particles of protein are acceptable. Do not use if the solution is discoloured or contains solid foreign particles.

The flow of the Alhemo pen should be checked before each injection.

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

The Alhemo pen must not be refilled.

The Alhemo pen is for use by one person only.

Patients are advised to discard injection needles after each injection.

Any waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Alhemo

Chemical name: concizumab

Molecular formula and molecular mass: C₆₄₆₂H₁₀₀₀₄N₁₇₁₂O₂₀₄₆S₄₆ and 149 kDA

Product Characteristics:

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

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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Hemophilia Patients with Inhibitors

Trial Design and Study Demographics

Table 6 Summary of patient demographics for clinical trials in patients with hemophilia A with inhibitors and hemophilia B with inhibitors

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
NN7415-4311 (explorer7)	Randomized, open-label, Phase 3 study with two additional non-randomized arms	Alhemo , subcutaneous, once-daily	Randomized: Arms 1 (no prophylaxis) and 2 (Alhemo prophylaxis): N=52 (27 HAWl and 25 HBwl) Arms 3 and 4 (Alhemo prophyllaxis): N= 81 (53 HAWl and 28 HBwl)	Mean: 28.1 (12-67)	Male

Study NN7415-4311 (explorer7), was a multi-national, multi-centre, open-label, phase 3 trial that investigated the safety and efficacy of Alhemo (concizumab injection) for routine prophylaxis in hemophilia A patients with inhibitors (HAwI) and hemophilia B patients with inhibitors (HBwI) who were 12 years of age and older and weighed at least 25 kg. Patients were randomized 1:2 to receive either on-demand treatment with bypassing agents (Arm 1, n = 19) or daily prophylactic treatment with Alhemo (Arm 2, n = 33). Two additional arms (arms 3 and 4) enrolled non-randomized patients treated with Alhemo who contributed to the overall safety assessment of this anti-TFPI monoclonal antibody (see [Adverse Reactions \[8\]](#)).

Patients were excluded from the study if they had platelets $\leq 100 \times 10^9/L$, fibrinogen below lower normal laboratory value, hepatic impairment (AST and/or ALT $> 3X$ the upper limit of normal [ULN] combined with total bilirubin $> 1.5X$ the ULN), renal impairment (estimated serum creatinine clearance rate ≤ 30 ml/min/1.73 m²), history or high risk of thromboembolic disease, and any systemic inflammatory condition requiring systemic treatment or treatment with emicizumab within 180 days before screening.

The majority of hemophilia patients randomized to arms 1 and 2 had one documented inhibitor of > 0.6 Bethesda units (BU)/mL reported prior to study entry or at screening. Two patients randomized to the control arm did not have documented inhibitors recorded. Patients were stratified by prior 24-week bleeding rate (< 9 or ≥ 9 total bleeds) according to medical records and according to hemophilia type (HAwI, HBwI). The exact number of baseline bleeds per patient in the prior 24 weeks were not known. While the study was open to hemophilia patients of any severity, the vast majority of patients had either severe or moderately severe disease ($\leq 2\%$ FVIII or FIX activity). Demographics and baseline disease characteristics were generally balanced between the two arms (Table 7).

Table 7 Key Demographic and Baseline Characteristic Comparisons for Arms 1 and 2

	On-demand (Arm 1) N = 19 (%)	Alhemo Prophylaxis (Arm 2) N = 33 (%)
Age Group		
Adolescents (12-17 years)	6 (32)	18 (55)
Adults (18-64 years)	12 (63)	15 (46)
Elderly/Very Elderly (65-84 years)	1 (5)	0
Ethnicity		
Hispanic or Latino	1 (5)	3 (9)
No Hispanic or Latino	16 (84)	29 (88)
Not Reported	2 (11)	1 (3)
Race		
American Indian or Alaska Native	1 (5)	1 (3)
Asian	6 (32)	14 (42)
Black or African American	1 (5)	4 (12)
Native Hawaiian or Other Pacific Islander	0	0
White	9 (47)	12 (36)
Not Reported	2 (11)	2 (6)
Classification of haemophilia type		
Hemophilia A	9 (47)	18 (55)

Hemophilia B	10 (53)	15 (46)
--------------	---------	---------

Patients randomized to the Alhemo arm were initially enrolled and treated with 1 mg/kg on the Day 1 and a once-daily dose of 0.25 mg/kg starting on Day 2. However, the study was paused in March 2020 due to thromboembolic events associated with Alhemo. The study resumed in August 2020 with 29 of the 33 patients randomized to Alhemo arm continuing in the study. Following the study pause, patients were treated with the same 1 mg/kg loading dose on Day 1 but now with a lower 0.2 mg/kg daily maintenance dose of Alhemo starting day 2. At or around week 4, patients were required to give blood for determination of their plasma concizumab concentration by a validated ELISA. Patients who had a concizumab concentration between 200 – 4000 ng/mL remained on the 0.20 mg/kg daily dose. For the other patients, the dose was individualized to 0.25 mg/kg or 0.15 mg/kg if concizumab plasma concentration measured after 4 weeks of treatment was <200 ng/mL or >4000 ng/mL, respectively. The efficacy results reported for Alhemo treated patients were based on data obtained after the study pause.

Study Results

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

Table 8 Mean Annualized Bleeding Rate with Alhemo Prophylaxis versus On-demand Treatment in Patients with Hemophilia A with Inhibitors and Hemophilia B with Inhibitors ≥12 Years of Age

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

During the treatment pause, twenty-four patients randomized to Alhemo were followed while receiving on-demand treatment (median exposure of 42.5 weeks). These 24 patients had a mean ABR of 14.7. After the pause, these 24 patients were on Alhemo prophylaxis (median exposure of 44.1 weeks) with an observed mean ABR of 2.3.

14.3 Immunogenicity

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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The cynomolgus monkey was selected for the nonclinical safety assessment based on cross-reactivity of concizumab to monkey TFPI. Concizumab has been administered to male and female cynomolgus monkeys by weekly intravenous injections for up to 26 weeks and by daily subcutaneous injections for up to 52 weeks. Safety pharmacology endpoints (CNS, cardiovascular, respiratory system), fertility endpoints (testicular size, sperm functionality or menstrual cycle duration) and cytokine release evaluations were included in the general toxicology studies.

Across the toxicology studies, pharmacology mediated formation of thrombi was observed in lung, heart and other organs in the animals at higher doses (≥ 1 mg/kg/day), consistent with the risk of thromboembolic events reported in patients treated with Alhemo. In the 52-week toxicology study with subcutaneous administration of 0.5, 1 and 9 mg/kg/day (corresponding to 85, 310 and 4400-fold the human exposure based on AUC_{0-24h}), the NOAEL was observed at 0.5 mg/kg/day.

A number of observed findings were consistent with the expected pharmacology of concizumab (i.e. activation of the coagulation system). These included increases in coagulation markers (i.e. D-dimers and thrombin-anti thrombin) occurring 24 h after the first dose and decreases in fibrinogen starting after repeat dosing. At subcutaneous doses ≥ 3 mg/kg/day (resulting in exposures ≥ 630 -fold the human AUC_{0-24h}) there were slight and occasional prolongations in clotting time parameters (i.e. activated partial thromboplastin time and prothrombin time), and/or a decrease in platelet counts.

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

Genotoxicity: No studies have been performed to establish the genotoxic potential of concizumab.

Reproductive and Developmental Toxicology: No data are available with respect to potential side effects of concizumab on embryofetal development.

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAlhemo™

concizumab injection

Read this carefully before you start taking **Alhemo** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Alhemo**.

Serious Warnings and Precautions

Alhemo may cause the following serious side effects:

- **Blood Clots.** Blood clots (thromboembolic events) have occurred in patients treated with Alhemo.

Tell your healthcare provider if you or a family member have had blood clots in the past.

Stop taking Alhemo and tell your healthcare provider if you have any signs or symptoms of blood clots during treatment with Alhemo, including:

- swelling, pain, or tenderness in one or both legs and arms
- sudden, unexplained chest or upper back pain
- sudden, unexplained stomach or lower back pain
- shortness of breath or difficulty breathing

Discuss with your healthcare provider when you need other treatments to control bleeding while on Alhemo. These other medicines could increase your risks of developing clots and you may be told to take a dose lower than you would normally.

What is Alhemo used for?

Alhemo is a medicine used to treat people with hemophilia A or hemophilia B (bleeding conditions people are born with), which is caused by missing or faulty proteins (factor VIII or factor IX) that prevents blood from clotting normally. It is used for hemophilia A or hemophilia B patients who have developed “factor VIII inhibitors” or “factor IX inhibitors” that prevent replacement factor VIII or factor IX therapies from working properly.

How does Alhemo work?

Alhemo contains the active substance concizumab, which belongs to a group of medicines called ‘monoclonal antibodies’. The monoclonal antibody in Alhemo recognizes a protein (TFPI) that prevents clotting and by binding to this protein concizumab helps to increase clotting and stop bleeding in hemophilia patients.

What are the ingredients in Alhemo?

Medicinal ingredients: concizumab

Non-medicinal ingredients: L-Arginine HCl, L-Histidine, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid/sodium hydroxide (for pH adjustment) and water for injection.

Alhemo comes in the following dosage forms:

Alhemo is a clear to slightly yellow solution for injection in a pre-filled disposable pen containing Alhemo 15 mg (10 mg / mL), 60 mg (40 mg / mL), 150 mg (100 mg / mL), or 300 mg (100 mg / mL) of drug. Clear particles of protein are acceptable. Do not use if the solution is discoloured or contains solid foreign particles.

Each pack contains 1 pre-filled pen. Needles for injection are not included.

Do not use Alhemo if:

- You are allergic to the active substance or any of the other ingredients of this medicine. If you are not sure, talk to your doctor, pharmacist or nurse before using Alhemo.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Alhemo. Talk about any health conditions or problems you may have, including if you:

Before you start using Alhemo, it is very important you talk to your doctor about when and how to use “bypassing agents” while receiving Alhemo, as this may differ from before. Your doctor will also tell you to stop take these medicines for up to 48 hours before your first dose of Alhemo.

Before you start using Alhemo tell your doctor if you have taken emicizumab to treat hemophilia A. You should stop taking emicizumab for at least 180 days before you are given Alhemo.

The following potential serious side effects may occur. Talk to your doctor if you have had allergic reactions in the past or have had a history or family history of developing clots.

Allergic reactions (hypersensitivity reactions)

Allergic reactions have occurred in patients treated with Alhemo. Stop the treatment and contact your healthcare provider in case you have signs or symptoms of an allergic reaction such as rash, redness, hives and itching. You could also experience more severe signs of allergic reactions (e.g., anaphylactic reaction) 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, or dizziness (low blood pressure), which will need immediate medical attention.

If you have any signs of allergic reactions: stop taking Alhemo and seek emergency help right away*Blood clots (thromboembolic events)*

Blood clots have occurred in patients treated Alhemo and these can form anywhere in the body including legs, chest, arms, head, and kidneys.

In case you experience signs or symptoms of blood clots you should stop taking Alhemo and contact your doctor immediately.

Signs and symptoms of blood clots may include:

- swelling, warmth, pain, or redness of the skin – this could be symptoms of a blood clot

- in your legs or arms.
- feeling short of breath, severe chest pain – this could be symptoms of blood clots in your chest (heart and lungs).
- headache, feeling confused, trouble with speech or movement, numbness in your face, eye pain or swelling or problems with your vision – this could be symptoms of a blood clot in your brain or eyes.
- sudden pain in your stomach or lumbar area – this could be symptoms of blood clots in your gut or kidneys.

If you have any signs of blood clots: stop taking Alhemo and seek emergency help right away.

Other warnings you should know about:

Children and Adolescents

Alhemo can be used in adolescents (aged 12 to 18 years of age). The dose in adolescents is also calculated according to body weight and is the same dose as for adults. If you are younger than 12 years of age you should not take Alhemo.

Pregnancy, breast-feeding and fertility

You should use a highly effective method of birth control (contraception) during treatment with Alhemo and for 7 weeks after your last injection of Alhemo. Talk to your doctor about the type of contraceptives 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 or continuing on this medicine.

Immunogenicity

Your body may make proteins (antibodies) that may stop Alhemo from working properly. Contact your healthcare professional if you notice Alhemo has stopped working for you (e.g. increase in bleeds).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Alhemo:

Stop taking other therapies to prevent bleeds before starting Alhemo.

See the detailed Instructions for Use before using your Alhemo pen. Always use this medicine Alhemo exactly as your healthcare provider has told you regarding dose and frequency. Check with your doctor, pharmacist, or nurse if you are not sure.

Alhemo is given by injection under the skin (subcutaneously). Your doctor or nurse will show you and/or your caregiver how to inject Alhemo. Once you and/or your caregiver have been trained, you should be able to inject this medicine at home, by yourself or with the help of a caregiver.

Your healthcare provider will show you and/or your caregiver which areas of the body should be injected with Alhemo. You should give Alhemo under the skin in the stomach, or the thighs.

Ask your doctor if you need to use alternative injection techniques, e.g. lean patients and

children may need to inject into a loosely held fold of skin to avoid injecting too deep (into the muscle).

Each time you or your caregiver gives an injection, use a different area of the body to the one you used before, using one of the recommended places (the stomach or the thighs).

Usual dose:

- Day 1: The dose is 1 milligram for every 1 kilogram you weigh.
- Day 2 and onwards, until your doctor prescribes you your individual maintenance dose: 0.2 milligrams for every 1 kilogram you weigh, injected once a day

Your doctor will measure the levels of concizumab in your blood 4 weeks after you have started treatment, and prescribe your individual maintenance dose as listed below:

- 0.25 milligrams for every 1 kilogram you weigh, injected once a day or,
- 0.20 milligrams for every 1 kilogram you weigh, injected once a day or,
- 0.15 milligrams for every 1 kilogram you weigh, injected once a day.

If you are told to take 0.15 milligrams for every 1 kilogram you weigh, you should have your levels of concizumab taken 8 weeks after you started on this dose to make sure it is safe for you to remain on therapy.

Additional tests to measure concizumab levels in your blood may be necessary. This may be required if you start bleeding more often than you have in the past.

Your dose is dialed at increments of

- 0.1 mg on the 10 mg / mL pen (blue dose button and cartridge holder),
- 0.4 mg on the 40 mg / mL pen (brown dose button and cartridge holder), and
- 1.0 mg on the 100 mg / mL pen (gold dose button and cartridge holder).

Your doctor or nurse will assist you in determining the correct injectable dose on the pen and if this dose needs to be changed. Your doctor should give you the pen that can deliver your daily dose in one injection.

Management of breakthrough bleeds

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

- Talk with your doctor about how to handle a potential bleed while on this therapy.
- Alhemo makes the blood coagulation more effective. Therefore, to avoid dangerous blood clots, the dose of a bypassing agent may be lower than the dose you used prior to starting Alhemo.

Overdose:

- If you use more Alhemo than you should, contact your healthcare professional immediately.

If you think you, or a person you are caring for, have taken too much Alhemo, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

One or more missed doses of Alhemo affects how well the drug works. It is important to take Alhemo every day. If you or your caregiver cannot take or give the drug every day, see if there is a different drug available to treat or prevent your bleeds. If you miss a dose or multiple doses in a row follow the guidelines below:

- One missed daily dose: No additional dose is required. Take your normal dose the next day and do not make up for your missed dose.
- 2 to 6 missed daily doses in a row: Contact your healthcare professional right away. While your normal dose can be resumed, they may instruct you take the daily dose twice, and then continue taking your normal dose the next day. Do not make up for any missed doses.
- Seven or more missed daily doses in a row: Contact your healthcare professional right away. They may advise you to start a new loading dose (1 mg for every kilogram) before you continue with your daily dose the next day. Do not make up for any missed doses.
- Major surgery: Your doctor will tell you to stop taking Alhemo 4 days before your surgery. After your surgery wait at least another 10 days on the advice of your doctor before starting Alhemo at your normal dose. Do not make up for any missed doses.

If you are in doubt about what to do when you miss one or more doses of Alhemo contact your healthcare professional.

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

What are possible side effects from using Alhemo?

These are not all the possible side effects you may have when taking Alhemo. If you experience any side effects not listed here, tell your healthcare professional.

Very common: may affect more than 1 in 10 people

- A reaction in the area where the injection is given (such as redness, bleeding, itching, hives, swelling, pain, numbness)
- Joint pain

Common: may affect up to 1 in 10 people

- Allergic reaction (hypersensitivity reaction)
- Headache
- Fever
- Infections
- Increase in level of blood clotting component (fibrin D dimer)
- Increase in level of blood clotting component (prothrombin fragment 1.2)

Uncommon: may affect up to 1 in 100

- Blood clots (thromboembolisms)
- Itchy skin (pruritus)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Allergic reaction (hypersensitivity reaction): Difficulty in swallowing or breathing; shortness of breath or wheezing; chest tightness; redness and/or swelling of the lips, tongue, face or hands; rash, hives, swollen marks on the skin or itching; pale and cold skin, fast heartbeat, or dizziness (sign of low blood pressure)		✓	✓
Uncommon			
Blood Clots (thromboembolisms) Signs and symptoms of blood clots may include: <ul style="list-style-type: none"> • swelling, warmth, pain, or redness of the skin – this could be symptoms of a blood clot in your legs or arms. • feeling short of breath, severe chest pain – this could be symptoms of blood clots in your chest (heart and lungs). • headache, feeling confused, trouble with speech or movement, numbness in your face, eye pain or swelling or problems with your vision – this could be symptoms of a blood clot in your brain or eyes. • sudden pain in your stomach or lumbar area – this could be symptoms of blood clots in your gut or kidneys. 		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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.

Always store the pen in the original carton to protect from light.

Do not use this medicine if you notice that the solution is discoloured or contains solid foreign particles.

Before use:

- Store unused Alhemo pens at 2-8°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.

Pen in use:

- Store the Alhemo pen you are currently using without a needle attached, either in the refrigerator at 2-8°C or at room temperatures below 30°C for up to 28 days.
 - If stored in the refrigerator, do not store the pen directly next to the cooling element. Do not use Alhemo if it has been frozen.
 - If stored at room temperature, do not use 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.

If you want more information about Alhemo:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website [www.novonordisk.ca], or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

Last Revised July 26, 2023

Alhemo is a trademark of Novo Nordisk Health Care AG and used under license by Novo Nordisk Canada Inc.

NovoFine® 32G TIP ETW, NovoFine® Plus and Novo Nordisk are trademarks of Novo Nordisk A/S and is used under license by Novo Nordisk Canada Inc.

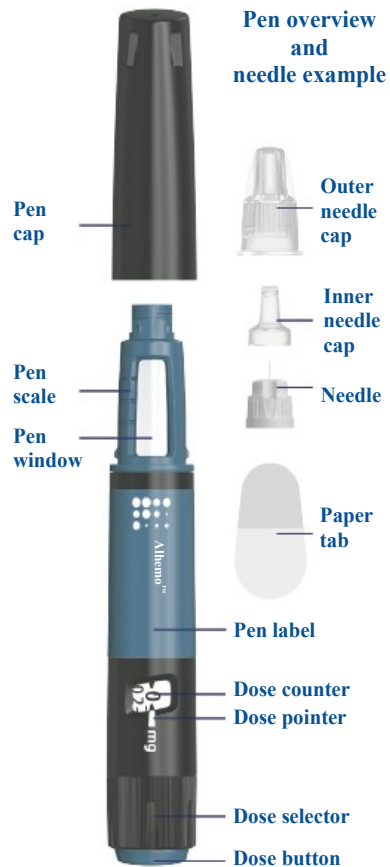
© 2023

Novo Nordisk Canada Inc.

INSTRUCTIONS FOR USE

PrAlhemo™ 15 mg / 1.5 ml (10 mg / ml) solution for injection in pre-filled pen concizumab injection

For subcutaneous administration only



What is in this package?

- 1 Alhemo pen
- Package leaflet

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 administration only. The pen contains multiple 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.

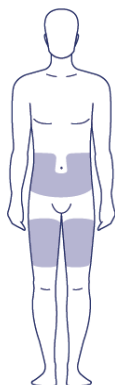
- Needles are not included. Use compatible injection needles of **4 mm in length**. This pen is designed to be used with NovoFine® 32G TIP ETW or NovoFine® Plus 32G x 4 mm injection needles.

Where on my body should I inject my dose?

You can inject in the skin of:

- your stomach (abdomen) OR
- your thigh.

Inject in a 90° (ninety degree) 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 medication.

Check expiration date

Check the expiration date on the pen label to make sure it has not passed (EXP/MM/YYYY). If the expiration date has passed, do not use the pen.

Inspect medication

Pull off the pen cap and check that Alhemo in the pen window is almost clear and colourless to slightly yellow. Clear particles might be seen. If Alhemo looks discoloured, or if solid particles are seen, 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.

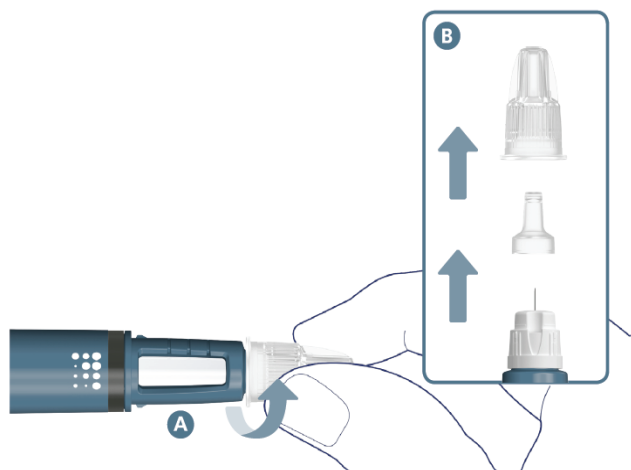
Attach a new needle

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.

Note: Always use a new needle for each injection.



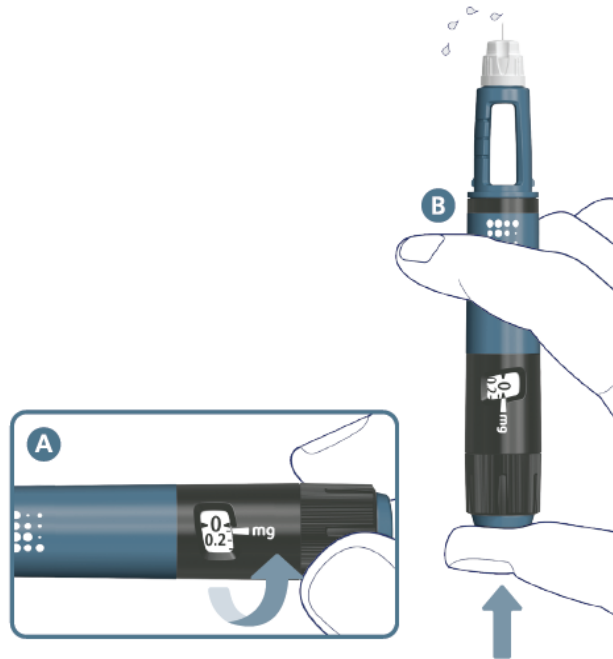
Dial to '0.1' and test the flow

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.
- b. Press the dose button. See B.
- c. Watch 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

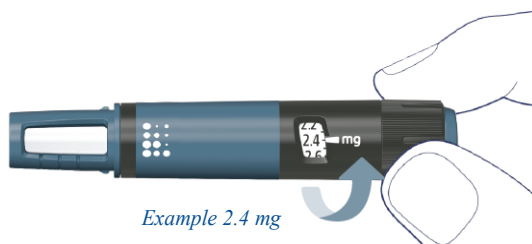
Turn the dose selector to select your prescribed dose.

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.



Inject your dose

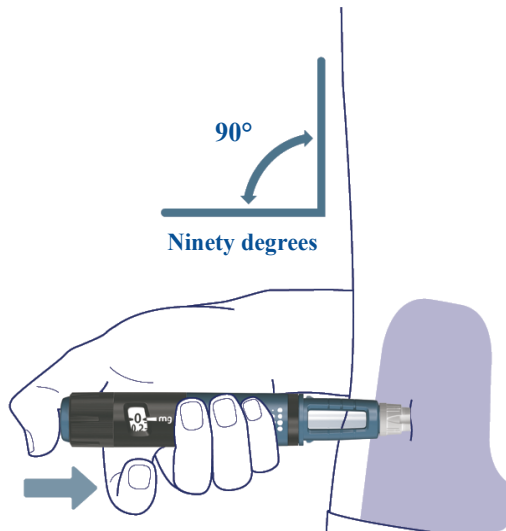
5

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 in a 90° (ninety degree) 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>.

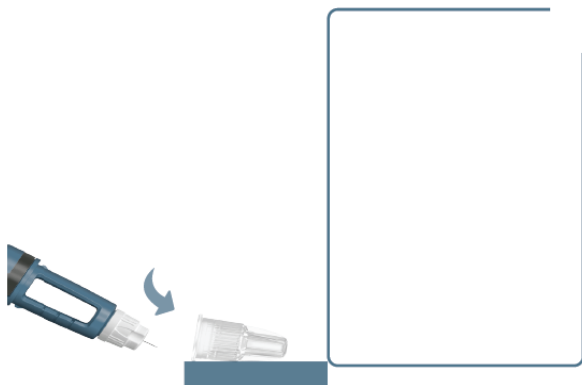


Remove the needle 6

Remove the needle from your pen by leading 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.

Completion 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.



Important information about your pen

- Make sure the pen contains the correct medication.
- Inspect the medication to ensure it is almost clear and colourless to slightly yellow and that no discoloration or solid particles are seen.
- Use a new needle for each injection.
- Pull off both the inner and the outer needle caps before injecting.
- Test the Alhemo flow before each injection.
- Confirm that you have selected the correct dose.
- Insert the needle in the skin of your stomach (abdomen) or thigh in a ninety degree (90°) angle.
- When injecting, make sure the dose counter returns to **<0>** and count slowly to 6 after it has returned to **<0>**.

- If you need a larger dose than you can dial, be accurate when calculating how much to take in each injection.
- Remove the needle from your pen after injection.
- The pen is for single patient use only and must not be shared. Sharing may lead to infection and transmission of disease.
- Follow the instructions from your doctor or nurse on how to use Alhemo and how often you should inject Alhemo.
- After first use do not use your pen for more than 28 days.
- The pen can deliver doses from 0.1 mg to 8 mg in one injection.

Important information about needles

Needles can be used for one injection only.

Do not re-use needles as this may lead to needle blockage, infection and incorrect dosing.

Never share needles with others.

Designed to be used with NovoFine® 32G TIP ETW or NovoFine® Plus 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.

You can use the outer needle cap to remove the needle from your pen. Put the outer needle cap onto the needle and carefully remove the needle.

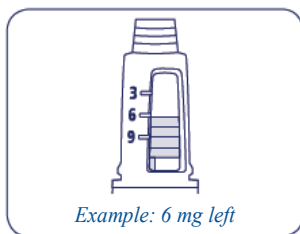
Never use a bent or damaged needle.

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.

How much Alhemo is left in your pen?

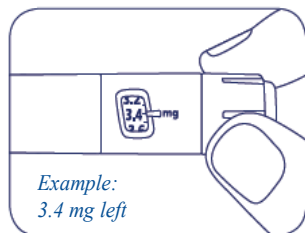
The pen scale shows approximately how much Alhemo is left in your pen.



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 mg left in the pen. The number

shown on the dose counter is the number of mg left in your pen.

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



Storage

See how to store your pen in the *Patient Medication Information* on the reverse side of this leaflet.

Take good care of your pen

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

Do not wash, soak or lubricate your pen. It may be cleaned with a 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.

The packaging material (the carton and leaflet) is recyclable.

INSTRUCTIONS FOR USE

PrAlhemo™ 60 mg / 1.5 ml (40 mg / ml) solution for injection in pre-filled pen concizumab injection

For subcutaneous administration only



What is in this package?

- 1 Alhemo pen
- Package leaflet

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 administration only. The pen contains multiple 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.

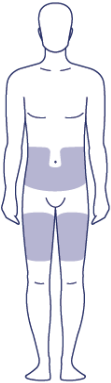
- Needles are not included. Use compatible injection needles of **4 mm in length**. This pen is designed to be used with NovoFine® 32G TIP ETW or NovoFine® Plus 32G x 4 mm injection needles.

Where on my body should I inject my dose?

You can inject in the skin of:

- your stomach (abdomen) OR
- your thigh.

Inject in a 90° (ninety degree) 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 medication.

Check expiration date

Check the expiration date on the pen label to make sure it has not passed (EXP/MM/YYYY). If the expiration date has passed, do not use the pen.

Inspect medication

Pull off the pen cap and check that Alhemo in the pen window is almost clear and colourless to slightly yellow. Clear particles might be seen. If Alhemo looks discoloured, or if solid particles are seen, 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.

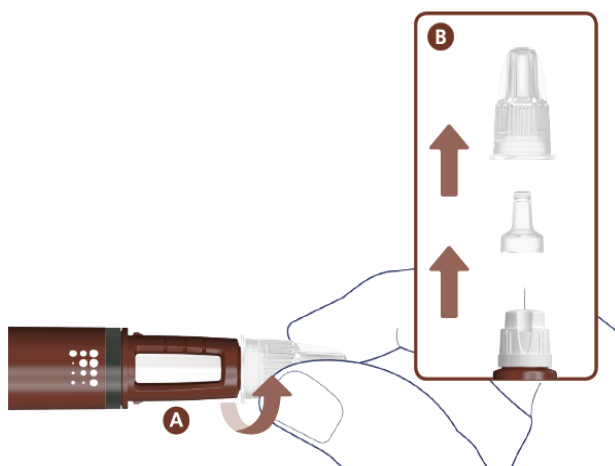
Attach a new needle

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.

Note: Always use a new needle for each injection.



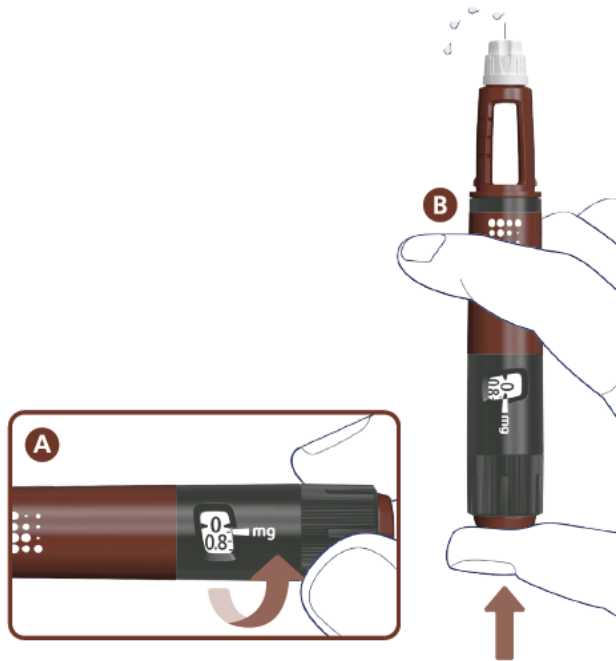
Dial to '0.4' and test the flow

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:

- d. Turn the dose selector one marking to select 0.4 mg. See A.
- e. Press the dose button. See B.
- f. Watch 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

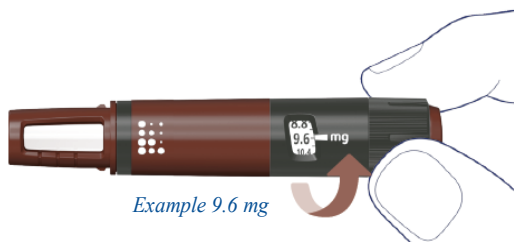
Turn the dose selector to select your prescribed dose.

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.



Inject your dose

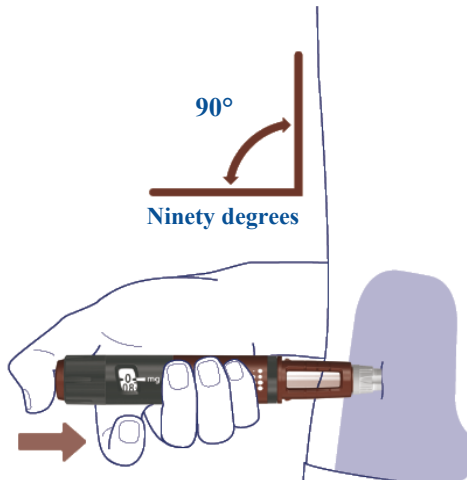
5

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

- f. Select the injection site. See Where on my body should I inject my dose?

- g. Insert the needle straight into your stomach (abdomen) or thigh in a 90° (ninety degree) angle.
- h. Press and hold the dose button down until the dose counter returns to <0>.
- i. While the needle is still in your skin, count slowly to 6, after the dose counter has returned to <0>.
- j. 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>.

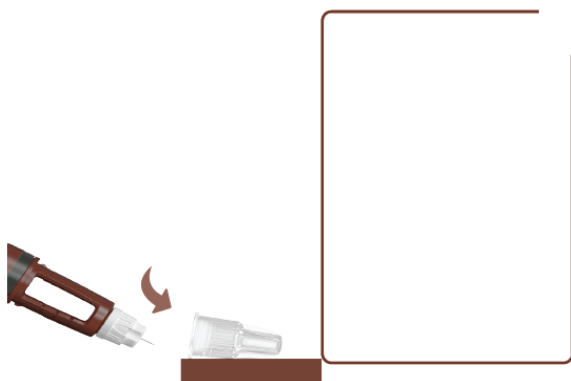


Remove the needle 6

Remove the needle from your pen by leading 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.

Completion 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.



Important information about your pen

- Make sure the pen contains the correct medication.
- Inspect the medication to ensure it is almost clear and colourless to slightly yellow and that no discoloration or solid particles are seen.
- Use a new needle for each injection.
- Pull off both the inner and the outer needle caps before injecting.
- Test the Alhemo flow before each injection.
- Confirm that you have selected the correct dose.
- Insert the needle in the skin of your stomach (abdomen) or thigh in a 90° (ninety degree) angle.
- When injecting, make sure the dose counter returns to <0> and count slowly to 6 after it has returned to <0>.
- If you need a larger dose than you can dial, be accurate when calculating how much to take in each injection.

- Remove the needle from your pen after injection.
- The pen is for single patient use only and must not be shared. Sharing may lead to infection and transmission of disease.
- Follow the instructions from your doctor or nurse on how to use Alhemo and how often you should inject Alhemo.
- After first use do not use your pen for more than 28 days.
- The pen can deliver doses from 0.4 mg to 32 mg in one injection.

Important information about needles

Needles can be used for one injection only.

Do not re-use needles as this may lead to needle blockage, infection and incorrect dosing.

Never share needles with others.

Designed to be used with NovoFine® 32G TIP ETW or NovoFine® Plus 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.

You can use the outer needle cap to remove the needle from your pen. Put the outer needle cap onto the needle and carefully remove the needle.

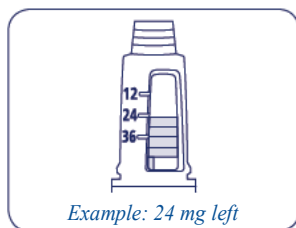
Never use a bent or damaged needle.

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.

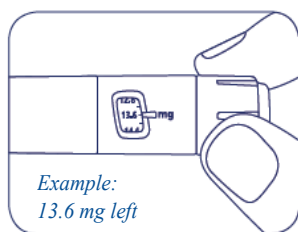
How much Alhemo is left in your pen?

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 mg left in the pen. The number shown on the dose counter is the number of mg left in your pen.

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



Storage

See how to store your pen in the *Patient Medication Information* on the reverse side of this leaflet.

Take good care of your pen

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

Do not wash, soak or lubricate your pen. It may be cleaned with a 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.

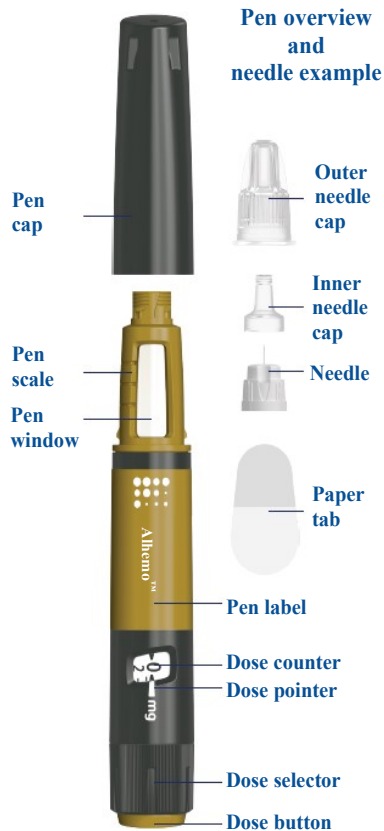
To reduce the risk of a needle stick, dispose of used needles immediately as instructed by your doctor, nurse, pharmacist or local authorities.

The packaging material (the carton and leaflet) is recyclable.

INSTRUCTIONS FOR USE

PrAlhemo™ 150 mg / 1.5 ml (100 mg / ml) solution for injection in pre-filled pen concizumab injection

For subcutaneous administration only



What is in this package?

- 1 Alhemo pen
- Package leaflet

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 administration only. The pen contains multiple 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.

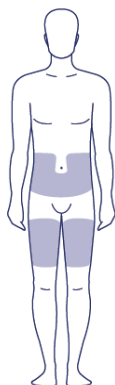
- Needles are not included. Use compatible injection needles of **4 mm in length**. This pen is designed to be used with NovoFine® 32G TIP ETW or NovoFine® Plus 32G x 4 mm injection needles.

Where on my body should I inject my dose?

You can inject in the skin of:

- your stomach (abdomen) OR
- your thigh.

Inject in a 90° (ninety degree) 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 medication.

Check expiration date

Check the expiration date on the pen label to make sure it has not passed (EXP/MM/YYYY). If the expiration date has passed, do not use the pen.

Inspect medication

Pull off the pen cap and check that Alhemo in the pen window is almost clear and colourless to slightly yellow. Clear particles might be seen. If Alhemo looks discoloured, or if solid particles are seen, do not use the pen.

If your pen is cold

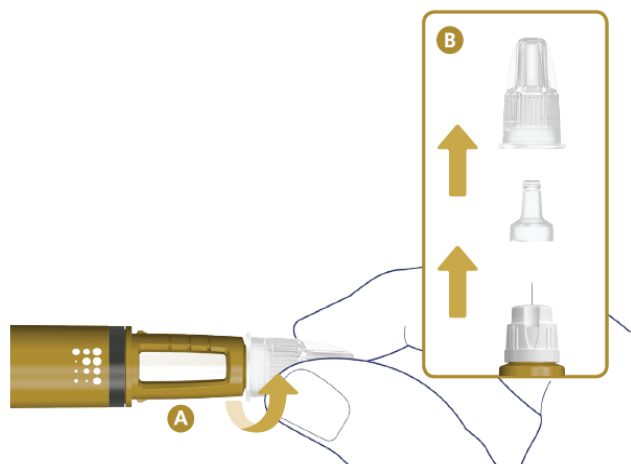
You can inject Alhemo right from the refrigerator or let it reach room temperature before you inject. You can warm the pen in the palms of your hands. Do not use any other heating sources.

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.

Note: Always use a new needle for each injection.



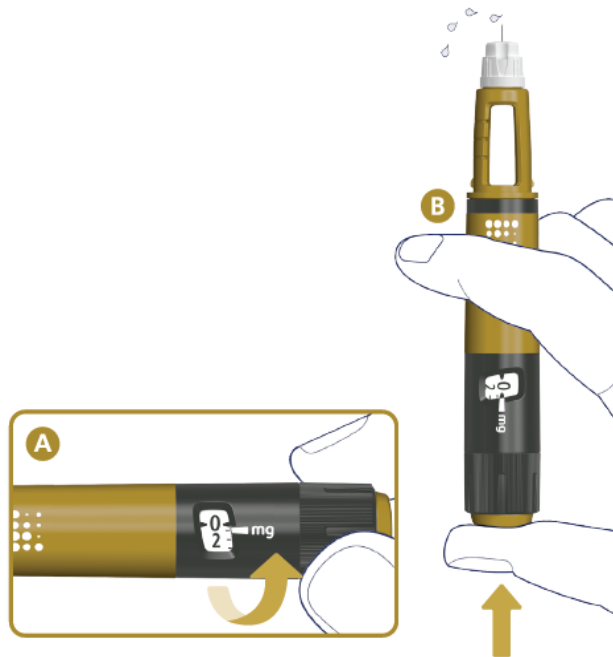
Dial to '1' and test the flow

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:

- g. Turn the dose selector one marking to select 1 mg. See A.
- h. Press the dose button. See B.
- i. Watch 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

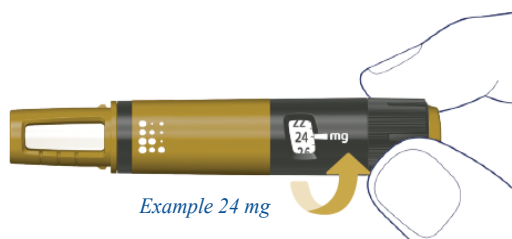
Turn the dose selector to select your prescribed dose.

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.



Inject your dose

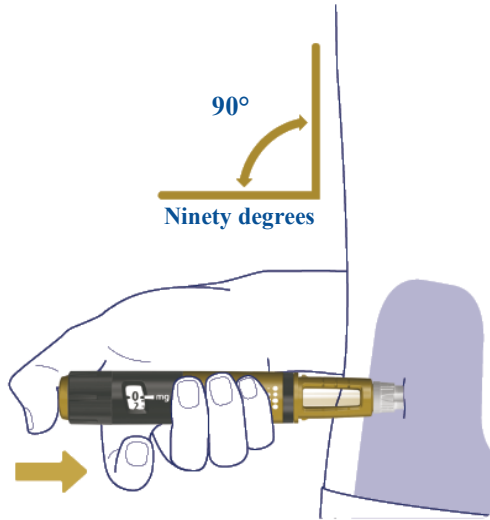
5

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

- k. Select the injection site. See *Where on my body should I inject my dose?*
- l. Insert the needle straight into your stomach (abdomen) or thigh in a 90° (ninety

- degree) angle.
- m. Press and hold the dose button down until the dose counter returns to **<0>**.
 - n. While the needle is still in your skin, count slowly to 6, after the dose counter has returned to **<0>**.
 - o. 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>**.

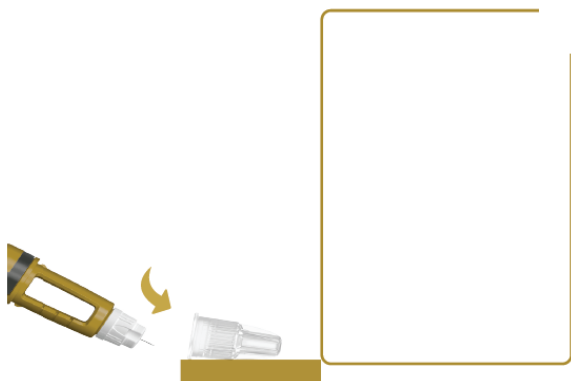


Remove the needle 6

Remove the needle from your pen by leading 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.

Completion

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.



Important information about your pen

- Make sure the pen contains the correct medication.
- Inspect the medication to ensure it is almost clear and colourless to slightly yellow and that no discoloration or solid particles are seen.
- Use a new needle for each injection.
- Pull off both the inner and the outer needle caps before injecting.
- Test the Alhemo flow before each injection.
- Confirm that you have selected the correct dose.
- Insert the needle in the skin of your stomach (abdomen) or thigh in a 90° (ninety degree) angle.
- When injecting, make sure the dose counter returns to <0> and count slowly to 6 after it has returned to <0>.
- If you need a larger dose than you can dial, be accurate when calculating how much to take in each injection.

- Remove the needle from your pen after injection.
- The pen is for single patient use only and must not be shared. Sharing may lead to infection and transmission of disease.
- Follow the instructions from your doctor or nurse on how to use Alhemo and how often you should inject Alhemo.
- After first use do not use your pen for more than 28 days.
- The pen can deliver doses from 1 mg to 80 mg in one injection.

Important information about needles

Needles can be used for one injection only.

Do not re-use needles as this may lead to needle blockage, infection and incorrect dosing.

Never share needles with others.

Designed to be used with NovoFine® 32G TIP ETW or NovoFine® Plus 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.

You can use the outer needle cap to remove the needle from your pen. Put the outer needle cap onto the needle and carefully remove the needle.

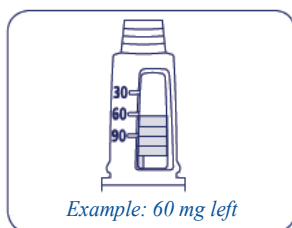
Never use a bent or damaged needle.

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.

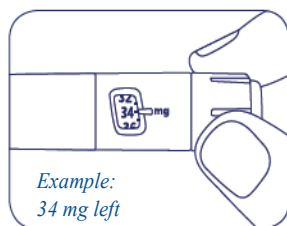
How much Alhemo is left in your pen?

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 mg left in the pen. The number shown on the dose counter is the number of mg left in your pen.

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



Storage

See how to store your pen in the *Patient Medication Information* on the reverse side of this leaflet.

Take good care of your pen

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

Do not wash, soak or lubricate your pen. It may be cleaned with a 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.

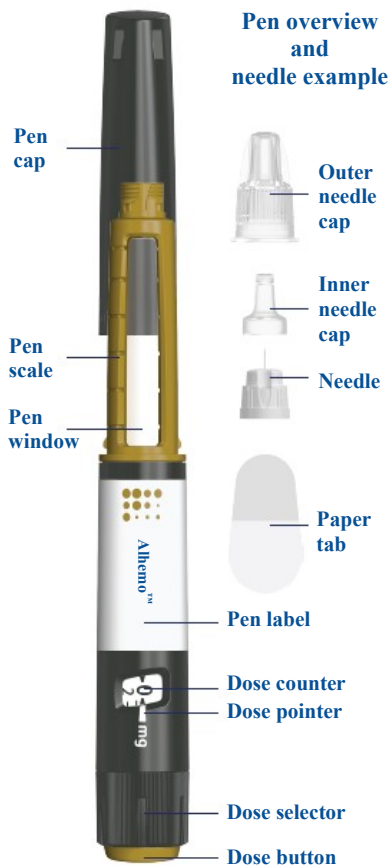
To reduce the risk of a needle stick, dispose of used needles immediately as instructed by your doctor, nurse, pharmacist or local authorities.

The packaging material (the carton and leaflet) is recyclable.

INSTRUCTIONS FOR USE

PrAlhemo™ 300 mg / 3 ml (100 mg / ml) solution for injection in pre-filled pen concizumab injection

For subcutaneous administration only



What is in this package?

- 1 Alhemo pen
- Package leaflet

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 administration only. The pen contains multiple 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.

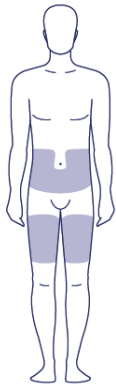
- Needles are not included. Use compatible injection needles of **4 mm in length**. This pen is designed to be used with NovoFine® 32G TIP ETW or NovoFine® Plus 32G x 4 mm injection needles.

Where on my body should I inject my dose?

You can inject in the skin of:

- your stomach (abdomen) OR
- your thigh.

Inject in a 90° (ninety degree) 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 medication.

Check expiration date

Check the expiration date on the pen label to make sure it has not passed (EXP/MM/YYYY). If the expiration date has passed, do not use the pen.

Inspect medication

Pull off the pen cap and check that Alhemo in the pen window is almost clear and colourless to slightly yellow. Clear particles might be seen. If Alhemo looks discoloured, or if solid particles are seen, 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.

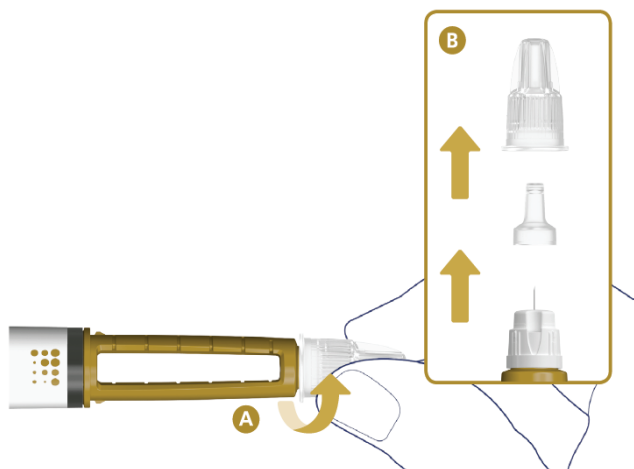
Attach a new needle

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.

Note: Always use a new needle for each injection.



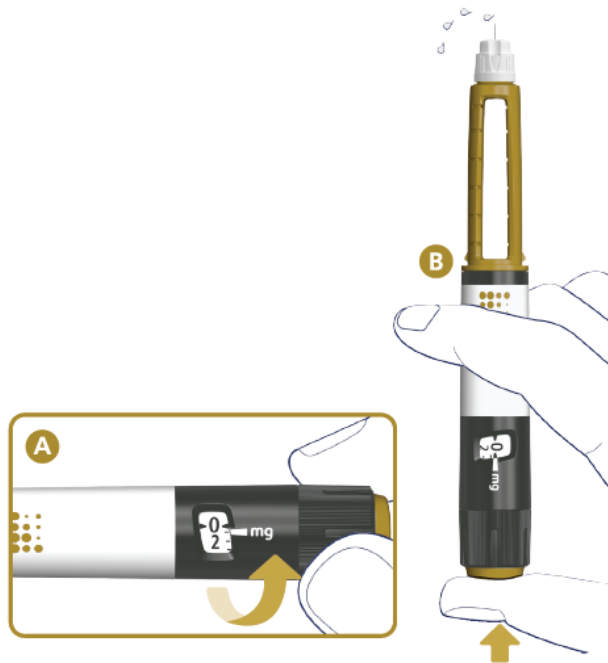
Dial to '1' and test the flow

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:

- Turn the dose selector one marking to select 1 mg. See A.
- Press the dose button. See B.
- Watch 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

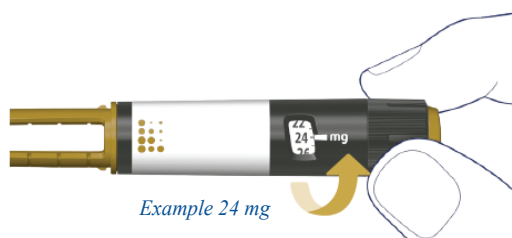
Turn the dose selector to select your prescribed dose.

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.



Inject your dose

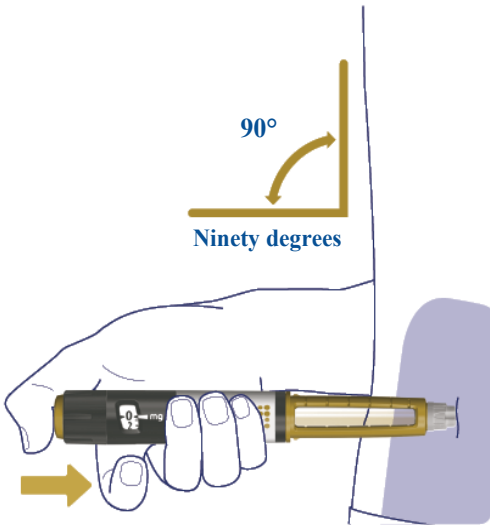
5

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

- p. Select the injection site. See *Where on my body should I inject my dose?*
- q. Insert the needle straight into your stomach (abdomen) or thigh in a 90° (ninety

- degree) angle.
- r. Press and hold the dose button down until the dose counter returns to **<0>**.
 - s. While the needle is still in your skin, count slowly to 6, after the dose counter has returned to **<0>**.
 - t. 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>**.

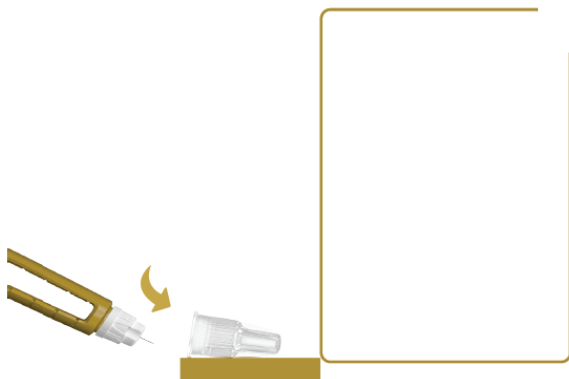


Remove the needle 6

Remove the needle from your pen by leading 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.

Completion

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.



Important information about your pen

- Make sure the pen contains the correct medication.
- Inspect the medication to ensure it is almost clear and colourless to slightly yellow and that no discoloration or solid particles are seen.
- Use a new needle for each injection.
- Pull off both the inner and the outer needle caps before injecting.
- Test the Alhemo flow before each injection.
- Confirm that you have selected the correct dose.
- Insert the needle in the skin of your stomach (abdomen) or thigh in a 90° (ninety degree) angle.
- When injecting, make sure the dose counter returns to <0> and count slowly to 6 after it has returned to <0>.
- If you need a larger dose than you can dial, be accurate when calculating how much to take in each injection.
- Remove the needle from your pen after injection.

- The pen is for single patient use only and must not be shared. Sharing may lead to infection and transmission of disease.
- Follow the instructions from your doctor or nurse on how to use Alhemo and how often you should inject Alhemo.
- After first use do not use your pen for more than 28 days.
- The pen can deliver doses from 1 mg to 80 mg in one injection.

Important information about needles

Needles can be used for one injection only.

Do not re-use needles as this may lead to needle blockage, infection and incorrect dosing.

Never share needles with others.

Designed to be used with NovoFine® 32G TIP ETW or NovoFine® Plus 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.

You can use the outer needle cap to remove the needle from your pen. Put the outer needle cap onto the needle and carefully remove the needle.

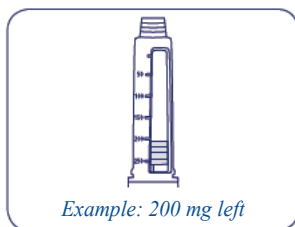
Never use a bent or damaged needle.

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.

How much Alhemo is left in your pen?

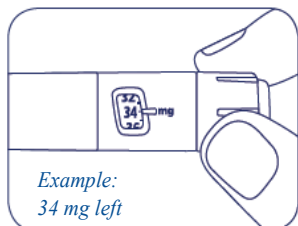
The pen scale shows approximately how much Alhemo is left in your pen.



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 mg left in the pen. The number shown on the dose counter is the number of mg left in your pen.

If the dose counter shows 80, there is 80 mg or more is left in the pen. The example below

shows 34 mg of Alhemo left in the pen.



Storage

See how to store your pen in the *Patient Medication Information* on the reverse side of this leaflet.

Take good care of your pen

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

Do not wash, soak or lubricate your pen. It may be cleaned with a 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.

The packaging material (the carton and leaflet) is recyclable.