Alhemo®
(concinzumab)

Date of Origin: 05/11/2025 **Last Review Date: 02/11/2026** **Effective Date: 05/11/2025**

Dates Reviewed: 05/11/2025; 02/25/2026

Developed By: Medical Criteria Committee

I. Length of Authorization

A. Authorization is valid for 12 months and may be renewed.

II. Dosing Limits

A. Max Units (per dose and over time) [Medical Benefit]:
   a. Load: 230 billable units
   b. Maintenance: 60 billable units daily

III. Initial Evaluation

I. **Concinzumab (Alhemo)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist; **AND**
   C. Medication will not be used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
   D. Concinzumab (Alhemo) will be used as routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
   E. Documentation of the member's weight; **AND**
   F. A diagnosis of one of the following:
      1. **Hemophilia A**; **AND**
         i. Member has had two or more documented episodes of spontaneous bleeding; **AND**
         ii. Clinical documentation of intolerance or contraindication to emicizumab-kxwh (Hemlibra); **OR**
      2. **Hemophilia B**; **AND**
         i. Member has had two or more documented episodes of spontaneous bleeding; **OR**
            a. Member has had an inadequate response to Immune Tolerance Induction (ITI)

I. Concizumab (Alhemo) is considered investigational when used for all other conditions, including but not limited to:
   A. Concizumab (Alhemo) used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
   B. Pediatric patients <12 years of age with hemophilia A or B
   C. Von Willebrand disease

IV. Renewal Evaluation

A. Member has exhibited improvement or stability of disease symptoms (e.g., decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline); **AND**
B. Medication will not be used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
C. Documentation of member's weight; **AND**
D. Documentation of member's concizumab (Alhemo) plasma concentration; **AND**
E. If the previous plasma concentration was under 200 ng/mL, there is now documentation member's concizumab (Alhemo) plasma concentration is greater than or equal to 200 ng/mL

V. Supporting Evidence

A. Concizumab (Alhemo) is a tissue factor pathway inhibitor (TFPI) antagonist FDA-approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with hemophilia A and B with inhibitors. Tissue factor pathway inhibitor (TFPI) is an anticoagulation protein that regulates the extrinsic coagulation cascade by inactivating the protease functions of FXa/FVIIa/TF complex. When TFPI activity is blocked, the extrinsic coagulation cascade continues to work without requiring amplification by FVIII/FIX whose normal plasma levels are reduced in hemophilia.
B. The efficacy and safety of concizumab (Alhemo) has not been studied in a pediatric population less than 12 years of age. Current FDA approval is limited to those 12 years of age and older.
C. Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX) are X-linked inherited coagulation factor deficiencies that result in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for those with hemophilia A and B. The severity of an individual's hemophilia is determined by the amount of clotting factor present. Plasma levels of FVIII or FIX < 40% are indicative of hemophilia; however, hemophilia A and B are classified moderate when factor levels are 1% to < 5%, and severe when factor levels are < 1%. Joint bleeds are the most frequent bleeding experienced by people with hemophilia of all severities (70-80%) which can lead to deformity, arthropathy, and irreversible joint damage leading to decreased mobility. Given the complexities of diagnosis and treatment of hemophilia A and B, supervision of treatment by a hematologist is required.
D. Typical hemophilia therapies include factor replacement with clotting factor concentrates (CFCs). For some patients treated with CFCs, neutralizing antibodies (i.e., inhibitors) develop in response to repeated exposure to exogenous factor products. Inhibitors are most commonly developed in patients with severe hemophilia A (30%). Incidence of inhibitor development in mild and moderate hemophilia A and hemophilia B populations are lower at 5% and 3% respectively. Inhibitors can significantly increase the cost of care and make bleeding episodes more difficult to treat as high doses of CFCs or bypassing agents are needed to circumvent inhibitors.
E. The World Federation of Hemophilia (WFH) guidelines recommend use of agents for both bleeding prophylaxis and control of acute breakthrough bleeds. Therapy recommendations are not sequential but rather cite the need for individualized care considering a patient's bleeding phenotype, joint status, pharmacokinetic profile, and preference. Medications include factor replacement with clotting factor concentrates (CFCs) (i.e., standard half-life (SHLs) for FVIII for hemophilia A and FIX for hemophilia B), long-acting CFCs (i.e., extended half-life (EHLs)), non-factor, and gene therapies. The frequency of injections varies but overall injection burden is high. The WFH split treatment recommendations for hemophilia A with inhibitors (HAwI) and hemophilia B with inhibitors (HBwI)

based on whether the inhibitor is low-responding or high-responding. The WFH recommends FVIII concentrate for hemophilia A patients with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate) for those with high-responding inhibitors. Hemophilia B patients with low-responding FIX inhibitors, use of a FIX-containing product to treat acute bleeds is recommended. Whereas for those with high-responding FIX inhibitors, rFVIIa is preferred. Additionally, HAwI and HBwI patients may undergo immune tolerance induction (ITI) to eradicate the inhibitor and, thus, allow the patient to return to ordinary CFC replacement therapies. The basic approach used by ITI is to give large doses of FVIII for FIX, often daily, for months or years. The relative success rate of ITI can be low and is only guideline recommended for HAwI though it can be used in HBwI. For patients with hemophilia A who develop persistent low responding inhibitors, the WFH suggests that immune tolerance induction ITI be considered. Guidelines have not been updated to include concizumab (Alhemo).

F. There are varying severities of hemophilia A and B depending on the level of factor produced by the patient, these are divided into the following per the International Society on Thrombosis and Hemostasis (ISTH):
    i. Severe: <1% factor activity (<0.01 IU/mL)
    ii. Moderate: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
    iii. Mild: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)
G. There is a lack of strong scientific evidence from randomized controlled trials supporting the efficacy and safety of multiple agents for routine prophylaxis used in combination. Therefore, use of concizumab (Alhemo) in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.] is not allowable per policy. There is a lack of head-to-head trials showing superior safety or efficacy comparing concizumab (Alhemo) to other prophylactic agents for the treatment of hemophilia A or B. Given the known safety, established efficacy, and cost-effectiveness of these therapies, prior prophylaxis with emicizumab-kxwh (Hemlibra) remains the preferred specialty agents by this plan due to efficacy, safety, and cost. Concizumab (Alhemo) is specifically more costly than other agents, despite not having any evidence of improved clinical efficacy or safety.
H. Concizumab (Alhemo) was studied in the explorer7 trial a Phase 3, open-label, study of 133 adolescent and adult participants with hemophilia A or B with documented history of inhibitor (≥ 0.6 BU). However, only arms 1 and 2 (N=52) were included in the primary efficacy analysis. Previous use of on-demand (OD) therapy with a bypassing agent was required prior to enrollment and participants continued bypassing agents as OD throughout the trial. The mean age was 29 years (range 12 to 79), 80 (60%) with hemophilia A and 53 (40%) with hemophilia B. The primary outcome was a reduction of treated bleeding episodes between concizumab (Alhemo) prophylaxis (arm 2) and no prophylaxis (arm 1).
I. The results of the explorer7 clinical trial showed that concizumab (Alhemo) prophylaxis demonstrated statistical superiority over treatment with placebo as measured by a reduction in the annualized bleeding rate (ABR). The estimated mean ABR was 1.7 for patients receiving concizumab (Alhemo) prophylaxis and 11.8 for patients not on prophylaxis. Patient reported outcomes did not significantly differ between arms 1 and 2 with respect to bodily pain and physical functioning scores on the 36-Item Short-Form Health Survey (SF-36v2). Patients receiving concizumab (Alhemo) prophylaxis reported improved HRQoL after 24 weeks compared with those receiving no prophylaxis as determined by an estimated treatment difference of −22.6 (95% CI, −42.5; −2.7) points in the Haem-A-QoL total score.
J. While the explorer7 clinical trial was able to show a reduction in bleeding events as compared to placebo there are remaining limitations and unknowns. Specifically, the small sample size of the

randomized treatment arms, open-label trial design, insufficient long-term safety data, and lack of comparative efficacy data to other prophylactic hemophilia products. Balancing these concerns there is a need for additional therapies for those with HAwI and HBwI. Inhibitors significantly increase the cost of care and have a negative effect on morbidity and mortality as bleeding episodes become more difficult to treat as compared to those without inhibitors. Therefore, the addition of a once daily, subcutaneous, non-factor therapy could be beneficial to those requiring high doses of factor as well as lessening IV injection burden. Thus, the quality of evidence is considered moderate.

K. Concizumab (Alhemo) was not directly compared with prophylaxis with emicizumab-kxwh (Hemlibra) therapy for the treatment of hemophilia A. Balancing long-term safety data, efficacy, and costs of alternative therapies compared to concizumab (Alhemo), treatment with emicizumab-kxwh (Hemlibra), when applicable, is required.
L. For individuals who have had more than one bleeding episode (e.g., two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level. Use of on demand therapy in those with mild-to-moderate disease with less than two instances of spontaneous bleeding is considered clinically appropriate for the management of hemophilia.
M. Per the prescribing information maintenance of concizumab (Alhemo) plasma concentration above 200 ng/mL is important to decrease the risk of bleeding episodes. If concizumab (Alhemo) plasma concentration remains below 200 ng/mL at two consecutive measurements, the benefits of continued Alhemo treatment should be evaluated versus the potential risk of bleeding events, and alternative therapies if available should be considered.
N. The recommended dosing regimen for concizumab (Alhemo) is as follows:
    i. Day 1: Loading dose of 1 mg/kg
    ii. Day 2: Once-daily dose of 0.2 mg/kg until individualization of maintenance dose (see below)
        1. Four weeks after initiation of treatment: For dose optimization measure concizumab-mtci plasma concentration by Concizumab Enzyme-Linked Immunosorbent Assay (ELISA) prior to administration of next scheduled dose. An FDA-authorized test for the measurement of concizumab-mtci concentration in plasma is not currently available.
    iii. Once the concizumab-mtci concentration result is available, individualize the maintenance dose of Alhemo. No later than 8 weeks after initiation of treatment, based on the following concizumab-mtci- plasma concentrations:
        1. Less than 200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg
        2. 200 to 4,000 ng/mL: continue once-daily dose of 0.2 mg/kg
        3. Greater than 4,000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg
    iv. The calculated dose is rounded off to the nearest injectable dose as follows:
        1. 60 mg/1.5 mL (40 mg/mL) in increments of 0.4 mg (brown label)
        2. 150 mg/1.5 mL (100 mg/mL) in increments of 1 mg (gold label)
        3. 300 mg/3 mL (100 mg/mL) in increments of 1 mg (white label)

Investigational or Not Medically Necessary Uses

I. Concizumab (Alhemo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Concizumab (Alhemo) used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]

i. Use of dual therapies for routine prophylaxis have not been evaluated for safety and efficacy.

B. Pediatric patients <12 years of age with hemophilia A or B
   i. Clinical trial data is currently limited to adult and adolescent patients 12 years of age and older.

C. Von Willebrand disease

VI. Dosage/Administration

Indication	Dose
Routine Prophylaxis in Congenital Hemophilia A or Hemophilia B	**Day 1:** • Loading dose of 1 mg/kg subcutaneously **Day 2:** • Once daily dose of 0.2 mg/kg subcutaneously until individualization of maintenance dose **Maintenance:** • Once the concizumab concentration result is available, individualize the maintenance dose no later than 8 weeks after initiation of treatment, based on the following concizumab plasma concentrations: ○ Less than 200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg ○ 200 to 4,000 ng/mL: continue once-daily dose of 0.2 mg/kg ○ Greater than 4,000 ng/mL: adjust to a once-daily dose of 0.15mg/kg
1 billable unit = 0.5 mg	

VII. Billing Code/Availability Information

- Jcode:
  - J7173 – injection, Alhemo, concizumab-mtci, 0.5 mg; 1 billable unit = 0.5 mg
- NDC:
  - Alhemo, concizumab-mtci 300mg/3 mL prefilled pen: 0169-2081-03
  - Alhemo, concizumab-mtci 150/1.5 mL prefilled pen: 0169-2080-15
  - Alhemo, concizumab-mtci 60/1.5 mL prefilled pen: 0169-2084-15

VII. References

1. Alhemo. Package Insert. Novo Nordisk, Inc; July 2025.
2. Overview of the explorer Clinical Development Program for Concizumab. Novo Nordisk. January 13, 2025.
3. Matsushita T, Shapiro A, Abraham A, Angchaisuksiri P, Castaman G, Cepo K, d'Oiron R, Frei-Jones M, Goh AS, Haaning J, Hald Jacobsen S, Mahlangu J, Mathias M, Nogami K, Skovgaard Rasmussen J, Stasyshyn O, Tran H, Vilchevska K, Villarreal

Martinez L, Windyga J, You CW, Zozulya N, Zulfikar B, Jiménez-Yuste V; explorer7 Investigators. Phase 3 Trial of Concizumab in Hemophilia with Inhibitors. N Engl J Med. 2023 Aug 31;389(9):783-794.
4. Tran H, von Mackensen S, Abraham A, Castaman G, Hampton K, Knoebl P, Linari S, Odgaard-Jensen J, Neergaard JS, Stasyshyn O, Thaung Zaw JJ, Zulfikar B, Shapiro A. Concizumab prophylaxis in persons with hemophilia A or B with inhibitors: patient-reported outcome results from the phase 3 explorer7 study. Res Pract Thromb Haemost. 2024 Jun 17;8(4):102476.
5. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Hemophilia. 2020: 26(Suppl 6): 1-158.
6. Meeks SL, Batsuli G. Hemophilia and inhibitors: current treatment options and potential new therapeutic approaches. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):657-662.
7. Novo Nordisk. FDA approves Alhemo® injection as once-daily prophylactic treatment to prevent or reduce the frequency of bleeding episodes for adults and children 12 years of age and older with hemophilia A or B with inhibitors. Novodordisk.com. December 20, 2024. Accessed January 23, 2025. News detailshttps://www.novonordisk-us.com/media/news-archive/news-details.html?id=915084

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D66	Hemophilia A (congenital factor VIII deficiency) with or without FVIII inhibitors
D67	Hemophilia B (congenital factor IX deficiency) with or without FIX inhibitors