PDL DRUG REVIEW

Proprietary Name: Alhemo®
Common Name: concizumab
PDL Category: Antihemophilic Agents

Comparable Products	Preferred Drug List Status
Hemlibra	Preferred

Pharmacology/Usage: Concizumab-mtci, the active ingredient of Alhemo®, is a humanized IgG4 monoclonal antibody produced by recombinant DNA technology. It is a monoclonal antibody antagonist of endogenous Tissue Factor Pathway Inhibitor (TFPI). Through the inhibition of TFPI, concizumab-mtci acts to enhance FXa production during the initiation phase of coagulation, which leads to improved thrombin generation and clot formation with the goal of achieving hemostasis in patients with Hemophilia A or B with inhibitors.

The effect of concizumab-mtci is not influenced by the presence of inhibitory antibodies to FVIII or FIX. There is no structural relationship or sequence homology between concizumab-mtci and FVIII or FIX and, as such, treatment with concizumab-mtci does not induce or enhance the development of direct inhibitors to FVIII or FIX.

Indication: For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with:

- Hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors
- Hemophilia B (congenital factor IX deficiency) with FIX inhibitors.

There is no pregnancy category for this medication; however, the risk summary indicates that based on its mechanism of action, Alhemo® may cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Although there are no data on concizumab-mtci, monoclonal antibodies can be actively transported across the placenta, and concizumab-mtci may cause fetal harm. Alhemo® should only be used during pregnancy if the potential benefit for the mother outweighs the potential risk to the fetus. The safety and efficacy of use have not been established in the pediatric population younger than 12 years old.

Dosage Form: Solution for Injection, available as:

- 60mg/1.5ml (40mg/ml) in a single-patient-use prefilled pen.
- 150mg/1.5ml (100mg/ml) in a single-patient-use prefilled pen.
- 300mg/3ml (100mg/ml) in a single-patient-use prefilled pen.

Recommended Dosage: For once-daily administration. Avoid missed doses (refer to the prescribing information for further information on missed doses). Treatment is intended for use under the guidance of a healthcare provider and should be initiated in a non-bleeding state. Alhemo® may be self-administered or administered by a caregiver after appropriate training and reading the Instructions for Use, if a healthcare provider determines that is appropriate. Inject subcutaneously into the abdomen or thigh with rotation of injection site every day. Always use a new needle for each injection. Alhemo® is recommended to be used with NovoFine or NovoFine Plus needles.

The recommended dosing regimen is as follows:

- Day 1: Loading dose of 1mg/kg.
- Day 2: Once-daily dose of 0.2mg/kg until individualization of maintenance dose
    - 4 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.
- 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:
    - Less than 200ng/ml: Adjust to a once-daily dose of 0.25mg/kg.
    - 200 to 4,000ng/ml: Continue once-daily dose of 0.2mg/kg.
    - Greater than 4,000ng/ml: Adjust to a once-daily dose of 0.15mg/kg.
- The calculated dose is rounded off to the nearest injectable dose.

Additional measurements of concizumab-mtci plasma concentration should be taken at routine clinical follow-ups provided the patient has been on the same maintenance dose for 8 weeks of treatment to ensure steady-state plasma concentrations. Maintenance of concizumab-mtci plasma concentration above 200ng/mL is important to decrease the risk of bleeding episodes. If concizumab-mtci plasma concentrations remains below 200ng/mL at two consecutive measurements, the benefits of continued Alhemo® treatment should be assessed versus the potential risk of bleeding events, and alternative therapies if available should be considered.

As Alhemo® is dosed by body weight (mg/kg), it is important to recalculate the dose when patients experience body weight changes.

Dose adjustments are not required in the case of breakthrough bleeds or in the case of minor surgeries. As there is limited experience in the perioperative setting, it is generally recommended to pause Alhemo® at least 4 days prior to major surgery. Alhemo® therapy can be resumed 10-14 days after surgery on the same maintenance dose without a new loading dose, considering the overall clinical picture of the patient. If necessary, consult a physician experienced in surgery of patients with bleeding disorders.

The safety and efficacy of concomitant use of Alhemo® in patients receiving ongoing Immune Tolerance Induction (ITI), a desensitization strategy for the eradication of inhibitors, have not been established, and no data are available. Careful assessment of the potential benefits and risks should be performed if continuation or initiation of Alhemo® during ITI is considered.

Refer to the prescribing information for information on changing to Alhemo® from other hemostatic products, as well as for instructions and dosage modification for bypassing agents for breakthrough bleeding. Treatment with all bypassing agents can be used for breakthrough bleeds, and the dose and duration will depend on the location and severity of the bleed.

Drug Interactions: Take appropriate precautions when treating break-through bleeding events in hemophilia patients receiving Alhemo® prophylaxis and a bypassing agent. For mild and moderate bleeds that require additional treatment with bypassing agents, the lowest approved dose in the approved product labeling is recommended. For severe bleeds, following the dosing instructions provided in the approved labeling for the specific product based on clinical judgment.

Additive and sometimes synergistic increase in thrombin peak as quantified in the thrombin generation assay has been observed in plasma from hemophilia patients who were on prophylactic treatment with concizumab-mtci with concomitant presence of rFVIII, rFIX, or bypassing agents including rFVIIa and activated prothrombin complex concentrate (aPCC).

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Alhemo® prophylaxis) minus reported % incidence for on-demand treatment. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included injection site reactions (18%) and urticaria (6%).

Venous and arterial thromboembolic events were reported in 1.3% of patients in Alhemo® clinical trials. These cases occurred in patients with multiple risk factors for thromboembolism, including the use of high doses or prolonged treatment with factor product or bypassing agent. Inform Alhemo® treated patients of signs and symptoms of thromboembolic events. Monitor patients for thromboembolic events. In case of suspicion of thromboembolic events, discontinue Alhemo ®and start further investigations and management strategies.

Alhemo® is contraindicated in patients with a history of known serious hypersensitivity to Alhemo® or its components or the inactive ingredients. Hypersensitivity reactions have occurred in Alhemo® treated patients. Discontinue Alhemo® if severe hypersensitivity symptoms occur and start medical management.

Increased levels of fibrin D-dimer and increased levels of prothrombin fragment 1.2 were seen in 29 (9.1%) and 18 (5.6%) of patients, respectively. The plasma concentration of concizumab-mtci is positively correlated with fibrin D-dimer and prothrombin fragments 1.2 indicating a hemostatic effect of concizumab-mtci. For patients taking Alhemo®, these coagulation biomarkers may not be reliable predictive markers for clinical decision-making with suspicion of thrombosis such as deep vein thrombosis and pulmonary embolism.

Contraindications: In patients with a history of known serious hypersensitivity to Alhemo® or to the components of the product or any inactive ingredients.

Manufacturer: Novo Nordisk

Analysis: The efficacy of Alhemo® in patients with hemophilia A and B with inhibitors was assessed in the explorer7 trial, a multicenter, open-label, phase 3 trial that assessed the safety and efficacy of Alhemo® for routine prophylaxis in adult (N=91) and adolescent (N=42) male patients with hemophilia A or B with inhibitors who have been prescribed, or are in need of, treatment with bypassing agents. Eptacog alfa (also known as Novoseven®) was the rFVIIa used in this study. Of the subjects included in the trial, the mean age was 29 years (range 12 to 79), while 42 patients were 12 to <18 years of age, 89 patients were 18 to 64 years of age, and 2 patients were ≥65 years of age. In addition, 78 patients were white, 37 patients were Asian, and all were male.

The trial was comprised of 4 arms, two randomized arms and two non-randomized arms:

- Arms 1 and 2: 52 patients (27 HAwl and 25 HBwl), previously treated on-demand, were randomized 1:2 to no prophylaxis (arm 1: on demand treatment with bypassing agents) or Alhemo® prophylaxis (arm 2), with stratification by hemophilia type (HAwl, HBwl) and prior 24-week bleeding rate (<9 or ≥9).
- Arms 3 and 4: 81 additional patients (53 HAwl and 28 HBwl) treated with Alhemo® prophylaxis.

Treatment with Alhemo® included a loading dose of 1mg/kg on the first day and a once-daily dose of 0.2mg/kg starting on the second day. The dose was individualized. Measurement of concizumab-mtci plasma concentration after 4 weeks was used to optimize the daily maintenance dose. In the trial, a total of 108 patients received their individualized dose, 1 patient on 0.15mg/kg, 79 patients on 0.20mg/kg and 28 patients on 0.25mg/kg.

Efficacy was assessed in hemophilia A and B patients with inhibitors when all patients in arms 1 and 2 had completed at least 24 or at least 32 weeks, respectively, by comparing the number of treated bleeding episodes between Alhemo® prophylaxis (arm 2) and no prophylaxis (arm 1). Using a negative binomial model, a ratio of the annualized bleeding rates (ABR) was estimated to 0.14 ($p<0.001$), corresponding to a reduction in ABR of 86% for subjects on Alhemo® prophylaxis compared to no prophylaxis. The estimated mean ABR was 1.7 for patients on Alhemo® prophylaxis (arm 2) and 11.8 for patients on no prophylaxis (arm 1).

Place in Therapy: Alhemo® is a tissue factor pathway inhibitor (TFPI) antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older

with hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and with hemophilia B (congenital factor IX deficiency) with FIX inhibitors. While treatment with all bypassing agents can be used for breakthrough bleeds, high and/or frequent doses of bypassing agents with Alhemo® increases the risk of thromboembolism. The efficacy of Alhemo® in patients with hemophilia A and B with inhibitors was assessed in a multicenter, open-label, phase 3 study. Efficacy was assessed in hemophilia A and B patients with inhibitors when all patients in arms 1 and 2 had completed at least 24 or at least 32 weeks, respectively, by comparing the number of treated bleeding episodes between Alhemo® prophylaxis (arm 2) and no prophylaxis (arm 1). A ratio of the annualized bleeding rates (ABR) was estimated to 0.14 ($p<0.001$) corresponding to a reduction in ABR of 86% for subjects on Alhemo® prophylaxis compared to no prophylaxis. Alhemo® is the second TFPI antagonist FDA approved. Hympavzi® (marstacimab-hncq) is a TFPI antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A without factor VIII inhibitors or hemophilia B without factor IX inhibitors. Alhemo® is the first FDA approved prophylaxis treatment available in a prefilled pen for subcutaneous injection for patients with hemophilia A with inhibitors and hemophilia B with inhibitors.

Summary

There is some evidence at this time in a phase 3 study to suggest that Alhemo® may be more effective than no prophylaxis (on-demand treatment) for the primary endpoint of ABR; however, there is no evidence at this time to support that Alhemo® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Alhemo® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Alhemo® [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2024.
[2] Hympavzi® [package insert]. New York, NY: Pfizer Labs; 2024.