

Alhemo®

Category:

Best Product for Orphan/Rare Diseases

Company Name:

Novo Nordisk

Product/Solution Name:

Alhemo®

Compound/Tech Name:

concizumab-mtci

Trade Name:

Alhemo®

Corporate Name:

Novo Nordisk

Date of Approval:

2024-12-20

Indications:

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
- hemophilia B (congenital factor IX deficiency) with FIX inhibitors

Therapeutic Areas:

Hemophilia, Rare Bleeding Disorders

General Information File Document upload:

Background information and need for drug / device:

Alhemo®: Responding to the Needs of Underserved Hemophilia Patients

Bringing the treatment of hemophilia B with inhibitors into the modern era

There are two main types of hemophilia: hemophilia A (insufficient levels of clotting factor VIII) and hemophilia B (insufficient factor IX). Remarkable progress has been achieved in treating both forms with the introduction of factor replacement therapy. Factor replacement therapy is administered intravenously (IV), and advancements in technology over the years have decreased the frequency with which the product needs to be administered. The development of these therapies made at-home prophylactic treatment possible, allowing patients to transition from reactively treating bleeds to preventing serious and sometimes life-threatening bleeding episodes from occurring in the first place.

However, a major complication of this prophylaxis treatment approach for some patients is the development of inhibitors, antibodies that neutralize the effectiveness of the factor replacement therapy. For decades, the only treatment option available to these patients was the use of bypassing agents such as recombinant factor VIIa or activated prothrombin complex concentrate (aPCC). These products are primarily used in an on-demand setting, so the patient is not preventing bleeds but treating them when they occur, which leads to long-term pain and joint damage. In 2018, the hemophilia A with inhibitor community benefitted from the FDA approval of subcutaneous prophylactic treatment, replacing a lifelong dependency on painful IV infusions with a long-acting treatment administered with subcutaneous injections.

But despite these significant advances for other hemophilia communities, the hemophilia B with inhibitor (HBWI) community continued to have no subcutaneous or truly effective prophylactic options. Painful IV treatment of bleeds could only limit the damage of bleeding episodes once they occur. Those treated with on-demand therapy experienced an average annual bleeding rate (ABR) of approximately 18-more than one major bleed per month. These patients lived with the fear that a life-threatening bleed could strike at any time. They were often in and out of the hospital. Because of the constant bleeding episodes, their joints would become increasingly deformed. Many were confined to wheelchairs, with others unable to attend school or work regularly. A normal life was unattainable.

The accumulated disease burden associated with HBWI took an enormous emotional toll on these patients and their families. Living with HBWI meant having to cope with

frequent unpredictable bouts of acute distress punctuated by an evolving sense of hopelessness.

All of this changed with the approval of Alhemo® (concizumab-mtci) in 2024.

The story of Alhemo® is the story of extending the promise of modern hemophilia treatment to a subgroup of patients that for many years had been left behind.

Background File Document upload:

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History of the development of the solution/product:

Nearly 35 years ago, the hemophilia treatment landscape began to change. The Swedish hematologist Dr. Ulla Hedner pioneered the first-ever medicine for patients with inhibitors. Her ensuing partnership with Novo Nordisk led to the introduction of rFVIIa (NovoSeven RT®), an innovative and life-saving medicine for patients with inhibitors, catalyzing a robust hemophilia-focused R&D organization within Novo Nordisk. Utilizing rFVIIa as a probe led to a breakthrough in the understanding of the coagulation cascade that identified tissue factor pathway inhibitor (TFPI) as a key regulator of coagulation and possible target for correcting deficiencies in hemostasis. Early pioneering in vitro and in vivo studies suggested that the inhibition of TFPI could restore coagulation in hemophilia blood and plasma. Blocking TFPI generates enough TF/ FVIIa-mediated Factor Xa (FXa) to restore hemostasis.

Specifically blocking the binding of FXa to the second Kunitz-type protease inhibitor (KPI) domain, KPI-2, of TFPI prevents binding to both FXa and FVIIa/TF and, by this dual mechanism, fully abolishes TFPI inhibition of the coagulation cascade. This leads to increased thrombin generation.

A high-affinity monoclonal antibody (mAb) neutralizing TFPI by binding to the KPI-2 domain (concizumab; Alhemo®) was generated, and an extensive pre-clinical proof of concept was performed. Concizumab demonstrated that TFPI neutralization promotes thrombin generation and fibrin clot formation in hemophilia plasma and whole blood. Furthermore, concizumab dose-dependently shortened bleeding time in a hemophilic rabbit model, confirming the biological hypothesis that TFPI inhibition would restore hemostasis.

Concizumab has since undergone multiple clinical trials, resulting in significant publications in high-ranking journals.

Phase 1 trials, initiated in the early 2010s, evaluated the safety profile and pharmacokinetics of concizumab. Clinical proof of concept and dosing was established

through two multiple-dose, open-label, randomized controlled phase 2 trials in patients >12 years with hemophilia A and B with and without inhibitors.

The pivotal study for the current indication of Alhemo® was a randomized prospective, multicenter, open-label phase 3a trial comparing Alhemo® prophylaxis (ppx) to no prophylaxis. It assessed the safety and efficacy of Alhemo® in patients with hemophilia A or B with inhibitors (HAWI or HBWI respectively), including 91 adults (58 HAWI/33 HBWI) and 42 adolescents (22 HAWI/20 HBWI). Of these patients 52 were randomized to receive Alhemo® ppx or standard on-demand treatment of bleeding episodes with bypassing agents. The primary endpoint was the number of treated spontaneous and traumatic bleeding episodes in these randomized patients. The remaining 81 patients received concizumab ppx to collect supportive efficacy and safety data.

A reduction in annualized bleeding rate (ABR) of 86% for patients on Alhemo® ppx (1.7 ABR) was observed compared to no ppx use (11.8). The percentage reduction is based on the estimated ABR ratio for treated spontaneous and traumatic bleeds between Alhemo® ppx and no ppx, which was 0.14 ($P < 0.001$).

The safety and tolerability profile of Alhemo® includes data from 5 controlled clinical trials with a total of 320 male patients with HA or HB with or without inhibitors and Alhemo® exposition for a total of 411 exposure years.

Development File Document upload:

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[Phase3publication.pdf](#)

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

For the first time, HBWI patients have a safe, effective, and patient-centered prophylactic treatment option. Now, HBWI patients can live a more robust life, not only without fear of life-threatening bleeds and compounding disability, but also with the ability to participate more fully in activities with the protection and convenience Alhemo® provides.

Alhemo® isn't just an additional therapy option. It truly is a new chapter in hemophilia care.

A novel mechanism of action:

Alhemo® is a first-in-class subcutaneously administered therapy that acts as a TFPI

(tissue factor pathway inhibitor) antagonist. It is designed to restore thrombin generation in patients with hemophilia B who have developed inhibitors without stimulating further inhibitor formation. Thanks to its targeted mechanism, Alhemo® offers fast onset and achieves steady-state levels quickly. Alhemo® delivers predictable hemostatic balance, ensuring reliable bleed protection. Importantly, its effects can be fine-tuned using a validated ELISA, allowing for individualized dosing based on patient needs. Now, HBwl patients have the possibility of seeing their ABR reduced to as low as 0.

Redefining the treatment experience:

Beyond its clinical efficacy, Alhemo® radically reimagines the treatment experience for HBwl patients. Unlike traditional IV therapies that demand repeated venous access, Alhemo® is delivered via the first-ever subcutaneous pen injector developed for this patient group.

This shift away from IV infusions carries numerous benefits:

Vein preservation: Subcutaneous (SQ) administration helps protect long-term vascular health, an especially critical need for patients with a history of frequent infusions.

Ease of use: The pen utilizes Novo Nordisk's proven delivery system, featuring an ultra-thin 32G 4mm NovoFine Plus needle. The result is a near pain free user-friendly experience.

Positive patient feedback: In usability studies, 98% of patients rated the pen as "easy" or "very easy" to use, and 88% preferred it over their previous injection methods.

Ready when needed: Alhemo® is portable and room temperature stable, requires no mixing, and comes in a low-injection-volume format-delivering unmatched convenience and autonomy.

Elevating Quality of Life:

As anticipated, a transformative prophylactic treatment option in a meticulously designed, first-in-class injector device delivered meaningful quality of life improvements for the highly burdened HBwl population. In clinical trials, patients on Alhemo® prophylaxis reported a significant reduction in treatment burden-as measured with the Hemophilia Treatment Experience Measure- and most patients preferred Alhemo® over their previous treatment according to the Hemophilia Patient Preference Questionnaire.

Most importantly, there was significant improvement in general health, vitality, role-emotional and mental health in the 36-item short-form health survey.

No one left behind:

The evolution of hemophilia treatment has brought remarkable progress, but until recently, that progress largely bypassed patients with hemophilia B with inhibitors. With Alhemo®, Novo Nordisk extends the benefits of modern therapeutic innovation to this underserved subgroup. This pioneering therapy addresses long-standing clinical and emotional burdens, offering life-changing protection, renewed confidence, and improved quality of life. In doing so, Alhemo® ensures that the promise of a better future includes everyone-truly, no one left behind.

Innovation File Document upload:

[AlhemopenDiagram.pdf](#)
[concizumabdevicepreferencestudy.pdf](#)

Please provide appropriate references (PubMed, Abstract, Website):

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