Factor Mimetics and Rebalancing Agents for Hemophilia

Policy Number: CS2025D0047A
Effective Date: June 1, 2025

Instructions for Use

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Commercial Policy
None

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	None
Kansas	None
Louisiana	None
Mississippi	None
North Carolina	None
Ohio	None
Pennsylvania	Refer to the state's Medicaid clinical policy
Virginia	None

Coverage Rationale

This policy refers to the following products:

Product	Brand Name
Bispecific factor IXa- and factor X-directed antibody	Hemlibra® (emicizumab-kxwh)
Tissue factor pathway inhibitor (TFPI) antagonist	Alhemo® (concizumab-mtci)
	Hympavzi™ (marstacimab-hncq)

Hemophilia A (i.e., Factor VIII Deficiency, Classical Hemophilia)

Concizumab-mtci (Alhemo) is medically necessary when all of the following criteria are met (note that concizumab-mtci (Alhemo) is a self-injectable medication that should be obtained under the member's pharmacy benefit unless the following criteria are met):

- For **initial therapy**:
  - Diagnosis of hemophilia A; **and**

- Patient is 12 years of age or older; **and**
- Patient has developed high-titer factor VIII inhibitors [≥ 5 Bethesda units (BU)]; **and**
- Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
- **One** of the following:
  - Patient cannot self-inject and does not have a caretaker who can be trained to administer Alhemo; **or**
  - Patient is receiving Alhemo from a contracted hemophilia treatment center

  and
- Alhemo is dosed according to U.S. Food and Drug Administration labeled dosing; **and**
- Authorization is for no more than 12 months

- For **continuation of therapy**:
  - Patient has previously been treated with Alhemo; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Documentation of positive clinical response to Alhemo therapy; **and**
  - **One** of the following:
    - Patient cannot self-inject and does not have a caretaker who can be trained to administer Alhemo; **or**
    - Patient is receiving Alhemo from a contracted hemophilia treatment center

    and
  - Alhemo is dosed according to U.S. Food and Drug Administration labeled dosing; **and**
  - Authorization is for no more than 12 months

Emicizumab-kxwh [Hemlibra] is medically necessary when all of the following criteria are met (note that emicizumab-kxwh [Hemlibra] is a self-injectable medication that should be obtained under the member's pharmacy benefit unless the following criteria are met):

- For **initial therapy**:
  - **One** of the following:
    - **All** of the following:
      - Diagnosis of severe hemophilia A; **and**
      - Documentation of endogenous factor VIII level less than 1% of normal factor VIII (< 0.01 i.u./mL); **and**
      - Prescriber attestation that the patient is not to receive extended half-life factor VIII replacement products (e.g., Adynovate, Afstyla, Altuviiio, Eloctate, Jivi) for the treatment of breakthrough bleeding episodes

      or
    - **All** of the following:
      - **One** of the following:
        - **Both** of the following:
          - Diagnosis of moderate hemophilia A; **and**
          - Documentation of endogenous factor VIII level ≥ 1% < 5% (greater than or equal to 0.01 i.u./mL to less than 0.05 i.u./mL)

          or
        - **Both** of the following:
          - Diagnosis of mild hemophilia A; **and**
          - Documentation of endogenous factor VIII level ≥ 5% (greater than 0.05 i.u./mL)

        and
      - Submission of medical records (e.g., chart notes, laboratory values) documenting a failure to meet clinical goals (e.g., continuation of spontaneous bleeds, inability to achieve appropriate trough level, previous history of inhibitors) after a trial of prophylactic factor VIII replacement products; **and**
      - Prescriber attestation that the patient is not to receive extended half-life factor VIII replacement products (e.g., Adynovate, Afstyla, Altuviiio, Eloctate, Jivi) for the treatment of breakthrough bleeding episodes

      or
    - **Both** of the following:
      - Diagnosis of hemophilia A; **and**
      - Patient has developed high-titer factor VIII inhibitors [≥ 5 Bethesda units (BU)]

    and
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - **One** of the following:
    - Patient is less than 7 years of age; **or**
    - Patient is 7 years of age or older and cannot self-inject and does not have a caretaker who can be trained to administer Hemlibra; **or**
    - Patient is receiving Hemlibra from a contracted hemophilia treatment center

    and
  - Hemlibra is dosed according to U.S. Food and Drug Administration labeled dosing; **and**

- Authorization is for no more than 12 months
- For **continuation of therapy**:
  - Patient has previously been treated with Hemlibra; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Documentation of positive clinical response to Hemlibra therapy; **and**
  - Prescriber attestation that the patient is not to receive extended half-life factor VIII replacement products (e.g., Adynovate, Afstyla, Altuviiio, Eloctate, Jivi) for the treatment of breakthrough bleeding episodes; **and**
  - **One** of the following:
    - Patient is less than 7 years of age; **or**
    - Patient is 7 years of age or older and cannot self-inject and does not have a caretaker who can be trained to administer Hemlibra; **or**
    - Patient is receiving Hemlibra from a contracted hemophilia treatment center

    and
  - Hemlibra is dosed according to U.S. Food and Drug Administration labeled dosing; **and**
  - Authorization is for no more than 12 months

Marstacimab-hncq [Hympavzi] is medically necessary when all of the following criteria are met (note that marstacimab-hncq [Hympavzi] is a self-injectable medication that should be obtained under the member's pharmacy benefit unless the following criteria are met):

- For **initial therapy**:
  - **One** of the following:
    - **All** of the following:
      - Diagnosis of severe hemophilia A; **and**
      - Documentation of endogenous factor VIII level less than 1% of normal factor VIII (< 0.01 i.u./mL); **and**
      - Prescriber attestation that the patient is not to receive extended half-life factor VIII replacement products (e.g., Adynovate, Afstyla, Altuviiio, Eloctate, Jivi) for the treatment of breakthrough bleeding episodes

      or
    - **All** of the following:
      - **One** of the following:
        - **Both** of the following:
          - Diagnosis of moderate hemophilia A; **and**
          - Documentation of endogenous factor VIII level ≥ 1% < 5% (greater than or equal to 0.01 i.u./mL to less than 0.05 i.u./mL)

          or
        - **Both** of the following:
          - Diagnosis of mild hemophilia A; **and**
          - Documentation of endogenous factor VIII level ≥ 5% (greater than 0.05 i.u./mL)

        and
      - Submission of medical records (e.g., chart notes, laboratory values) documenting a failure to meet clinical goals (e.g., continuation of spontaneous bleeds, inability to achieve appropriate trough level, previous history of inhibitors) after a trial of prophylactic factor VIII replacement products; **and**
      - Prescriber attestation that the patient is not to receive extended half-life factor VIII replacement products (e.g., Adynovate, Afstyla, Altuviiio, Eloctate, Jivi) for the treatment of breakthrough bleeding episodes

    and
  - Patient is 12 years of age or older; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Patient does not have a history of inhibitors to factor VIII; **and**
  - **One** of the following:
    - Patient cannot self-inject and does not have a caretaker who can be trained to administer Hympavzi; **or**
    - Patient is receiving Hympavzi from a contracted hemophilia treatment center

    and
  - Hympavzi is dosed according to U.S. Food and Drug Administration labeled dosing; **and**
  - Authorization is for no more than 12 months
- For **continuation of therapy**:
  - Patient has previously been treated with Hympavzi; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Documentation of positive clinical response to Hympavzi therapy; **and**
  - Prescriber attestation that the patient is not to receive extended half-life factor VIII replacement products (e.g., Adynovate, Afstyla, Altuviiio, Eloctate, Jivi) for the treatment of breakthrough bleeding episodes; **and**
  - **One** of the following:

- Patient cannot self-inject and does not have a caretaker who can be trained to administer Hympavzi; **or**
- Patient is receiving Hympavzi from a contracted hemophilia treatment center

and

- Hympavzi is dosed according to U.S. Food and Drug Administration labeled dosing; **and**
- Authorization is for no more than 12 months

Hemophilia B (i.e., Congenital Factor IX Deficiency, Christmas Disease)

Concizumab-mtci [Alhemo] is medically necessary when all of the following criteria are met (note that concizumab-mtci [Alhemo] is a self-injectable medication that should be obtained under the member's pharmacy benefit unless the following criteria are met):

- For **initial therapy**:
  - Diagnosis of hemophilia B; **and**
  - Patient is 12 years of age or older; **and**
  - Patient has developed high-titer factor IX inhibitors [≥ 5 Bethesda units (BU)]; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - **One** of the following:
    - Patient cannot self-inject and does not have a caretaker who can be trained to administer Alhemo; **or**
    - Patient is receiving Alhemo from a contracted hemophilia treatment center

    and
  - Alhemo is dosed according to U.S. Food and Drug Administration labeled dosing; **and**
  - Authorization is for no more than 12 months
- For **continuation of therapy**:
  - Patient has previously been treated with Alhemo; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Documentation of positive clinical response to Alhemo therapy; **and**
  - **One** of the following:
    - Patient cannot self-inject and does not have a caretaker who can be trained to administer Alhemo; **or**
    - Patient is receiving Alhemo from a contracted hemophilia treatment center

    and
  - Alhemo is dosed according to U.S. Food and Drug Administration labeled dosing; **and**
  - Authorization is for no more than 12 months

Marstacimab-hncq [Hympavzi] is medically necessary when all of the following criteria are met (note that marstacimab-hncq [Hympavzi] is a self-injectable medication that should be obtained under the member's pharmacy benefit unless the following criteria are met):

- For **initial therapy**:
  - **One** of the following:
    - **All** of the following:
      - Diagnosis of severe hemophilia B; **and**
      - Documentation of endogenous factor IX level less than 1% of normal factor IX (< 0.01 i.u./mL); **and**
      - Prescriber attestation that the patient is not to receive extended half-life factor IX replacement products (e.g., Alprolix, Idelvion) for the treatment of breakthrough bleeding episodes

      or
    - **All** of the following:
      - **One** of the following:
        - **Both** of the following:
          - Diagnosis of moderate hemophilia B; **and**
          - Documentation of endogenous factor IX level ≥ 1% < 5% (greater than or equal to 0.01 i.u./mL to less than 0.05 i.u./mL)

          or
        - **Both** of the following:
          - Diagnosis of mild hemophilia B; **and**
          - Documentation of endogenous factor IX level ≥ 5% (greater than or equal to 0.05 i.u./mL)

        and
      - Submission of medical records (e.g., chart notes, laboratory values) documenting a failure to meet clinical goals (e.g., continuation of spontaneous bleeds, inability to achieve appropriate trough level, previous history of inhibitors) after a trial of prophylactic factor IX replacement products; **and**
      - Prescriber attestation that the patient is not to receive extended half-life factor IX replacement products (e.g., Alprolix, Idelvion) for the treatment of breakthrough bleeding episodes

and
  - Patient is 12 years of age or older; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Patient does not have a history of inhibitors to factor IX; **and**
  - **One** of the following:
    - Patient cannot self-inject and does not have a caretaker who can be trained to administer Hympavzi; **or**
    - Patient is receiving Hympavzi from a contracted hemophilia treatment center

    and
  - Hympavzi is dosed according to U.S. Food and Drug Administration labeled dosing; **and**
  - Authorization is for no more than 12 months
- For **continuation of therapy**:
  - Patient has previously been treated with Hympavzi; **and**
  - Prescribed for the prevention of bleeding episodes (i.e., routine prophylaxis); **and**
  - Documentation of positive clinical response to Hympavzi therapy; **and**
  - Prescriber attestation that the patient is not to receive extended half-life factor IX replacement products (e.g., Alprolix, Idelvion) for the treatment of breakthrough bleeding episodes; **and**
  - **One** of the following:
    - Patient cannot self-inject and does not have a caretaker who can be trained to administer Hympavzi; **or**
    - Patient is receiving Hympavzi from a contracted hemophilia treatment center

    and
  - Hympavzi is dosed according to U.S. Food and Drug Administration labeled dosing; **and**
  - Authorization is for no more than 12 months

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
C9304	Injection, marstacimab-hncq, 0.5 mg
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics
J7170	Injection, emicizumab-kxwh, 0.5 mg

Diagnosis Code	Description
D66	Hereditary factor VIII deficiency
D67	Hereditary factor IX deficiency

Background

Alhemo (concizumab-mtci) is a monoclonal antibody antagonist of endogenous 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.

Hemlibra (emicizumab-kxwh) is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure binding factor IXa and factor X. It bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis.

Hympavzi (marstacimab hncq) is a human monoclonal IgG1 antibody directed against the Kunitz domain 2 (K2) of tissue factor pathway inhibitor (TFPI) to neutralize TFPI activity and enhance coagulation. TFPI is the primary inhibitor of the

extrinsic coagulation cascade and negatively regulates thrombin generation within the extrinsic pathway of coagulation by inactivating the protease functions of FXa/FVIIa/TF complex. TFPI binds to and inhibits the factor Xa active site via its second Kunitz inhibitor domain (K2).

Clinical Evidence

Factor Mimetics for Hemophilia A

Mahlangu et al. evaluated the use of emicizumab in persons who have hemophilia A without factor VIII inhibitors as prophylactic therapy in a phase 3, multicenter trial.[2] The authors randomly assigned patients aged 12 years or older who had been receiving episodic treatment with factor VIII to receive a subcutaneous maintenance dose of emicizumab of 1.5 mg per kilogram of body weight per week (group A) or 3.0 mg per kilogram every 2 weeks (group B) or no prophylaxis (group C). The primary end point was the difference in rates of treated bleeding between patient groups. Participants who had been receiving factor VIII prophylaxis received emicizumab at a maintenance dose of 1.5 mg per kilogram per week (group D). For patients who participated in the noninterventional study, intraindividual studies were performed. One hundred fifty-two patients enrolled in the study. The annualized bleeding rate was 1.5 events (95% confidence interval [CI], 0.9 to 2.5) in group A and 1.3 events (95% CI, 0.8 to 2.3) in group B, as compared with 38.2 events (95% CI, 22.9 to 63.8) in group C; thus, the rate was 96% lower in group A and 97% lower in group B ($p < 0.001$ for both comparisons). A total of 56% of the participants in group A and 60% of those in group B had no treated bleeding events, as compared with those in group C, who all had treated bleeding events. In the intraindividual comparison involving 48 participants, emicizumab prophylaxis resulted in an annualized bleeding rate that was 68% lower than the rate with previous factor VIII prophylaxis ($p < 0.001$). The most frequent adverse event was low-grade injection-site reaction. There were no thrombotic or thrombotic microangiopathy events, development of antidrug antibodies, or new development of factor VIII inhibitors. The authors conclude that prophylaxis with emicizumab led to a significantly lower bleeding rate than no prophylaxis among persons with hemophilia A without inhibitors; more than half the participants who received prophylaxis had no treated bleeding events. In an intraindividual comparison, emicizumab therapy led to a significantly lower bleeding rate than previous factor VIII prophylaxis.

Rebalancing Agents for Hemophilia A and B

The efficacy of Alhemo (concizumab-mtci) was established in an open-label study in 91 adult and 42 adolescent male patients with hemophilia A or B with inhibitors who have been prescribed, or require, treatment with bypassing agents. The study included 52 patients previously treated on-demand, were randomized to no prophylaxis (arm 1: on demand treatment with bypassing agents) or Alhemo prophylaxis (arm 2). The estimated mean annualized bleeding rate (ABR) was 1.7 (95%CI: 1.01, 2.87) for patients on Alhemo prophylaxis and 11.8 (95%CI: 7.03; 19.86) for patients on no prophylaxis. A ratio of the ABR was estimated to 0.14 ($p < 0.001$), corresponding to a reduction in ABR of 86% for patients on Alhemo prophylaxis compared to no prophylaxis. Warnings and precautions for Alhemo include thromboembolic events and hypersensitivity reactions. The most common adverse reactions (≥ 5%) with Alhemo use were injection site reactions and urticaria.

The efficacy of Hympavzi (marstacimab-hncq) was established in the BASIS study, an open-label, two-phase study in 116 adult and pediatric patients (aged 12 years and older and ≥ 35 kg) with severe hemophilia A without FVIII inhibitors or severe hemophilia B without FIX inhibitors. Following screening, patients entered a 6-month observation phase and were enrolled in two cohorts based on the factor replacement treatment they were receiving prior to study entry: on-demand or routine prophylaxis. Patients who completed the observation phase were to receive 12 months of Hympavzi. The efficacy of Hympavzi for each cohort was based upon the annualized bleeding rate (ABR) of treated bleeds during treatment with Hympavzi compared to ABR during the observational phase. In the cohort of patients receiving on-demand factor-based therapy, the ABR was 38.00 during the observational 6-month period vs. 3.18 with Hympavzi prophylaxis treatment during the 12-month active treatment period (ratio 0.084, 95% CI: 0.059, 0.119; $p < 0.0001$). Hympavzi prophylaxis demonstrated superiority over on-demand factor-based therapy in incidences of treated bleeds. In the cohort of patients receiving routine factor-based prophylaxis, the ABR was 7.85 during the observational 6-month period vs. 5.08 with Hympavzi prophylaxis treatment during the 12-month active treatment period (difference -2.77, 95% CI: -5.37, -0.16). Hympavzi prophylaxis demonstrated non-inferiority to routine prophylactic factor-based therapy as measured by ABR of treated bleeds. The most common adverse reactions (≥ 3%) with Hympavzi use were injection site reaction, headache, and pruritus.

Professional Societies

In October 2024, the National Hemophilia Foundation (NHF) released updated hemophilia treatment guidelines entitled Medical and Scientific Advisory Council (MASAC) Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders #290. A summary of the NHF recommendations for physicians treating patients with hemophilia A and B are as follows:

Treatment of Patients With Hemophilia A		
Recombinant Factor VIII Concentrates	Advate	Treatment of choice in hemophilia A
	Kogenate FS	
	Kovaltry	
	NovoEight	
	Nuwiq	
	Recombinate	
	Xyntha	
Prolonged Half-Life Recombinant Factor VIII Concentrate	Adynovate	
	Afstyla	
	Altuviiio	
	Eloctate	
	Esperoct	
	Jivi	
Plasma-Derived Factor VIII Concentrates	Hemofil M	Recommended
Plasma-Derived Factor VIII/von Willebrand Factor	Alphanate	Recommended
	Humate-P	
	Koate-DVI	
Humanized Bispecific FIXa- and FX-Directed Monoclonal Antibody	Hemlibra	Recommended
Cryoprecipitate	Cryoprecipitate	Not recommended except in life- and limb-threatening emergencies when no factor VIII concentrate is available
Desmopressin	DDAVP Injection	Recommended for use in mild hemophilia A. Children < 2 years of age and patients with mild hemophilia A in whom desmopressin does not provide adequate Factor VIII levels should be treated with either recombinant or plasma-derived FVIII concentrates. Use with caution in pregnant women during labor and delivery

Treatment of Patients with Hemophilia B		
Recombinant Factor IX Concentrate	BeneFIX	Treatment of choice in hemophilia B
	Ixinity	
	Rixubis	
Prolonged Half-Life Recombinant Factor IX Concentrate	Alprolix	
	Idelvion	
	Rebinyn	
Plasma-Derived Factor IX Concentrates	AlphaNine SD	Recommended

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Alhemo (concizumab-mtci) 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, or hemophilia B (congenital factor IX deficiency) with FIX inhibitors.

Hemlibra (emicizumab-kxwh) is a bispecific factor IXa- and factor X-directed antibody and is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

Hympavzi (marstacimab-hncq) 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) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.

References

1. Alhemo® [package insert]. Plainsboro, NJ: Novo Nordisk Inc., December 2024.
2. Hemlibra® [package insert]. South San Francisco, CA: Genentech, Inc., January 2024.
3. Hympavzi™ [package insert]. New York, NY: Pfizer Inc., October 2024.
4. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018; 379:811-22.
5. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. MASAC Document #290. October 2, 2024.
6. Matsushita T, Shapiro A, Abraham A, et al. Phase 3 Trial of Concizumab in Hemophilia with Inhibitors. N Engl J Med. 2023;389(9):783-794. doi:10.1056/NEJMoa2216455.

Policy History/Revision Information

Date	Summary of Changes
06/01/2025	• New Medical Benefit Drug Policy

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.