PREMERA HMO

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PHARMACY / MEDICAL POLICY – 5.01.581

Pharmacologic Treatment of Hemophilia

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Introduction

When a person bleeds, the body undertakes a series of steps to stop the bleeding. The first step is that blood platelets collect at the site of injury; this sets up a temporary plug. Next, several other proteins — known as clotting factors — work together to create a permanent plug in the damaged area. There are 13 types of clotting factors. Hemophilia is a condition in which clotting factors don't work as they should. A person with hemophilia bleeds easily and the blood takes much longer to clot. Hemophilia A is the most common form, affects clotting factor VIII (factor 8), is usually inherited, and most often affects males. In some cases of hemophilia A, however, the person doesn't inherit the condition. Rather, a genetic change occurs spontaneously which results in hemophilia A. Hemlibra is a drug that can be used to prevent or reduce the number of bleeding episodes in children and adults with hemophilia A. It's used in people who have developed an immune system response against factor VIII, which is known as factor VIII inhibitors. Hemophilia B is another form, affects clotting factor IX (factor 9), is usually inherited, and also most often affects males. Hemgenix is a gene therapy that can be used to prevent or reduce the number of bleeding episodes in adults with hemophilia B. This policy describes when Alhemo, Hemgenix, Hemlibra, Hympavzi, and Roctavian may be considered medically necessary for the treatment of hemophilia.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can

be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity

Alhemo (concizumab-mtci)	**Alhemo (concizumab-mtci) may be considered medically necessary when all the following criteria are met:**
	• The individual is aged 12 years or older
	AND
	• Was assigned male at birth
	AND
	• Meets 1 of the following:
	  ○ Has been diagnosed with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors
	  OR
	  ○ Has been diagnosed with hemophilia B (congenital factor IX deficiency) with or without factor IX inhibitors
	AND
	• Has severe hemophilia A (congenital factor VIII deficiency) with factor VIII activity less than 1% OR moderately severe to severe hemophilia B (congenital factor IX deficiency) with factor IX activity less than or equal to 2%
	AND
	• Will discontinue use of other prophylactic therapies of hemophilia before initiation of Alhemo (concizumab-mtci)
	AND
	• Medication is being prescribed by or in consultation with a hematologist or a prescriber who specializes in hemophilia
	AND
	• Maintenance dose is limited to 0.25 mg/kg daily

Hemgenix (etranacogene dezaparvovec-drlb)	**Hemgenix (etranacogene dezaparvovec-drlb) may be considered medically necessary for adults when all the following criteria are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity

	• Was assigned male at birth
	AND
	• Has severe or moderately severe hemophilia B as defined by a plasma Factor IX (FIX) activity level of 2% or less
	AND
	• Meets 1 of the following:
	  ○ Current or historical life-threatening hemorrhage
	  ○ Repeated, serious spontaneous bleeding episodes
	  ○ Is currently receiving FIX prophylaxis
	AND
	• FIX prophylaxis will be discontinued following administration of Hemgenix if the individual is currently receiving FIX prophylaxis
	AND
	• The individual does not have a history of FIX inhibitors or a positive screen result of 0.6 or greater Bethesda Units (BU) using the Nijmegen-Bethesda assay
	AND
	• Has received a liver health assessment including enzyme testing [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin] AND a hepatic ultrasound and elastography
	AND
	• A hepatologist has assessed the individual if the individual has radiological liver abnormalities or sustained liver enzyme elevations
	AND
	• Medication is being prescribed by or in consultation with a hematologist or a prescriber who specializes in hemophilia B
	AND
	• The individual does not have a history of receiving gene therapy or is under consideration for treatment for another gene therapy for hemophilia B
	AND
	• Is human immunodeficiency virus (HIV) negative or has a controlled HIV infection
	AND
	• Does not have an active hepatitis B or hepatitis C infection

Drug	Medical Necessity
	AND • Prescriber attests to providing clinical outcome information within the appropriate provider portal as requested by the Company plan

Hemlibra (emicizumab-kxwh)	**Hemlibra (emicizumab-kxwh) may be considered medically necessary for adults and pediatric individuals, when all the following criteria are met:**
	• Diagnosis of hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors
	AND
	• Hemlibra is not used concurrently with high dose aPCC
	AND
	• Maintenance dose is limited to 1 of the following:
	  ○ 1.5 mg/kg once weekly
	  ○ 3 mg/kg once every 2 weeks
	  ○ 6 mg/kg once every 4 weeks
	
	Note: High dose aPCC is defined as greater than 100 U/kg/day administered for greater than 24 hours

Hympavzi (marstacimab-hncq)	**Hympavzi (marstacimab-hncq) may be considered medically necessary when all the following criteria are met:**
	• The individual is aged 6 years or older
	AND
	• Meets 1 of the following:
	  ○ Has been diagnosed with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors
	  OR
	  ○ Has been diagnosed with hemophilia B (congenital factor IX deficiency) with or without factor IX inhibitors
	AND
	• Has severe hemophilia A (congenital factor VIII deficiency) with factor VIII activity less than 1% OR moderately severe to severe hemophilia B (congenital factor IX deficiency) with factor IX activity less than or equal to 2%
	AND

Drug	Medical Necessity

	• Will discontinue use of other prophylactic therapies such as factor products or Hemlibra (emicizumab-kxwh)
	AND
	• Medication is being prescribed by or in consultation with a hematologist or a prescriber who specializes in hemophilia
	AND
	• Meets 1 of the following:
	  ○ Maintenance dose is limited to 150 mg weekly
	  OR
	  ○ Maintenance dose is limited to 300 mg weekly when the individual meets ALL of the following:
	  ▪ Dose titration occurs after 6 months of treatment with Hympavzi 150 mg weekly
	  ▪ The individual weighs 50 kg or greater
	  ▪ There is documentation of 2 or more breakthrough bleeds
	AND
	• The quantity is limited to:
	  ○ 75 mg/0.5 ml pen = 4 pens per 28 days
	  ○ 150 mg/ml pen = 8 pens per 28 days

Qfitlia (fitusiran)	**Qfitlia (fitusiran) may be considered medically necessary when all the following criteria are met:**
	• The individual is aged 12 years or older
	AND
	• Was assigned male at birth
	AND
	• Meets 1 of the following:
	  ○ Has been diagnosed with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors
	  OR
	  ○ Has been diagnosed with hemophilia B (congenital factor IX deficiency) with or without factor IX inhibitors
	AND
	• Has severe hemophilia A (congenital factor VIII deficiency) with factor VIII activity less than 1% OR moderately severe to severe hemophilia B (congenital factor IX deficiency) with factor IX activity less than or equal to 2%

Drug	Medical Necessity
	AND • Does not have antithrombin activity less than 60% **AND** • Will discontinue use of other prophylactic therapies of hemophilia before initiation of Qfitlia (fitusiran) **AND** • Medication is being prescribed by or in consultation with a hematologist or a prescriber who specializes in hemophilia **AND** • Maintenance dose is limited to one 50 mg pen or 20 mg vial monthly
Roctavian (valoctocogene roxaparvovec-rvox)	**Roctavian (valoctocogene roxaparvovec-rvox) may be considered medically necessary when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Was assigned male at birth **AND** • Diagnosis of severe hemophilia A (congenital factor VIII deficiency) with factor VIII activity less than 1 IU/dL **AND** • Factor VIII prophylaxis will be discontinued following administration of Roctavian if the individual is currently receiving factor VIII prophylaxis **AND** • The individual does not have pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test **AND** • Has received a liver health assessment including enzyme testing [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin] AND a hepatic ultrasound and elastography **AND** • Medication is being prescribed by or in consultation with a hematologist or a prescriber who specializes in hemophilia A **AND**

Drug	Medical Necessity
	• The individual is human immunodeficiency virus (HIV) negative or has a controlled HIV infection **AND** • Does not have an active hepatitis B or hepatitis C infection **AND** • Documentation is provided demonstrating that the individual received education relating to alcohol abstinence and the use of concomitant medications **AND** • Prescriber attests to providing clinical outcome information within the appropriate provider portal as requested by the Company plan

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**
• **Hemgenix (etranacogene dezaparvovec-drlb)** • **Roctavian (valoctocogene roxaparvovec-rvox)**	**All other uses of Hemgenix (etranacogene dezaparvovec-drlb) and Roctavian (valoctocogene roxaparvovec-rvox) for conditions not outlined in this policy are considered investigational.** **Repeat treatment of Hemgenix (etranacogene dezaparvovec-drlb) and Roctavian (valoctocogene roxaparvovec-rvox) is considered investigational.**
• **Alhemo (concizumab-mtci)** • **Hemlibra (emicizumab-kxwh)** • **Hympavzi (marstacimab-hncq)** • **Qfitlia (fitusiran)**	**All other uses of Alhemo (concizumab-mtci), Hemlibra (emicizumab-kxwh), Hympavzi (marstacimab-hncq), and Qfitlia (fitusiran) for conditions not outlined in this policy are considered investigational.**

Approval	Criteria

Initial authorization	**Hemgenix (etranacogene dezaparvovec-drlb) and Roctavian (valoctocogene roxaparvovec-rvox) may be approved as a one-time infusion.** **Alhemo (concizumab-mtci), Hemlibra (emicizumab-kxwh), Hympavzi (marstacimab-hncq), and Qfitlia (fitusiran) may be approved up to 12 months.**
Re-authorization criteria	**Repeat treatment of Hemgenix (etranacogene dezaparvovec-drlb) and Roctavian (valoctocogene roxaparvovec-rvox) is considered investigational.** **Alhemo (concizumab-mtci), Hemlibra (emicizumab-kxwh), Hympavzi (marstacimab-hncq), and Qfitlia (fitusiran) may be approved up to 12 months as long as there is a positive clinical benefit/response shown at the time of re-authorization where:** • Chart notes documenting decreased incidence of bleeding episodes

Dosage and Quantity Limits	
Treatment	**Dosage and Quantity Limit**
Alhemo (concizumab-mtci)	• 1 mg/kg loading dose, followed by a once-daily dose of 0.2 mg/kg until individualization of maintenance dose based on the Alhemo (concizumab-mtci) 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 0.15 mg/kg
Hemlibra (emicizumab-kxwh)	• 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose of: ○ 1.5 mg/kg once weekly, or ○ 3 mg/kg once every two weeks, or ○ 6 mg/kg once every four weeks
Hympavzi (marstacimab-hncq)	• 300 mg loading dose, followed by a maintenance dose of: ○ 150 mg once weekly, or ○ 300 mg once weekly

Qfitlia (fitusiran)	• Starting dose of 50 mg once every two months. Adjust the dose and/or dosing interval, if needed, to maintain antithrombin activity between 15-35%

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Initial approval requires chart notes documenting the diagnosis and that all criteria are met
- Alhemo (concizumab-mtci), Hemlibra (emicizumab-kxwh), Hympavzi (marstacimab-hncq), and Qfitlia (fitusiran) reauthorization requires chart notes documenting progress, including decreased incidence of bleeding episodes

Coding

Code	Description
HCPCS	
J1411	Injection, etranacogene dezaparvovec-drlb, per therapeutic dose (Hemgenix)
J1412	Injection, valoctocogene roxaparvovec-rvox, per ml, containing nominal 2 x 1013 vector genomes (Roctavian)
J7170	Injection, emicizumab-kxwh (Hemlibra), 0.5 mg
J7172	Injection, marstacimab-hncq (Hympavzi), 0.5 mg
J7173	Injection, concizumab-mtci (Alhemo), 0.5 mg (new code effective 10/01/25)
J7174	Injection, fitusiran (Qfitlia**)**, 0.04 mg (new code effective 10/01/25)

Related Information

Benefit Application

Alhemo (concizumab-mtci), Hemlibra (emicizumab-kxwh), Hympavzi (marstacimab-hncq), and Qfitlia (fitusiran) may be managed through the pharmacy or medical benefit. Hemgenix

(etranacogene dezaparvovec-drlb) and Roctavian (valoctocogene roxaparvovec-rvox) are managed through the medical benefit.

Consideration of Age

The ages stated in this policy for which Alhemo (concizumab-mtci), Hemlibra (emicizumab-kxwh), Hemgenix (etranacogene dezaparvovec-drlb), Hympavzi (marstacimab-hncq), Qfitlia (fitusiran), and Roctavian (valoctocogene roxaparvovec-rvox) are considered medically necessary is based on the FDA labeling for this drug.

Prescriber Attestation

Provider portals are used to capture clinical outcome information for individuals on select high-cost treatments, such as gene and cellular therapies. If an individual meets the medical necessity criteria as defined by this policy and is approved for treatment, the requesting prescriber must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

Evidence Review

Description

Alhemo (concizumab-mtci) is a monoclonal antibody antagonist of endogenous tissue factor pathway inhibitor (TFPI). Through the inhibition of TFPI, Alhemo 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 individuals with hemophilia A or B with inhibitors. The effect of Alhemo is not influenced by the presence of inhibitory antibodies 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. Emicizumab-kxwh has an approximate molecular weight of 145.6 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. Emicizumab-kxwh has no structural relationship or

sequence homology to FVIII and, as such, does not induce or enhance the development of direct inhibitors to FVIII.

Hympavzi (marstacimab-hncq) is an anti-tissue factor pathway inhibitor (anti-TFPI) therapy.

Hemgenix (etranacogene dezaparvovec-drlb) is an adeno-associated virus (AAV) vector-based gene therapy.

Qfitlia (fitusiran) is a double-stranded siRNA that causes degradation of antithrombin (AT) messenger RNA (mRNA) through RNA interference, reducing plasma AT levels.

Roctavian (valoctocogene roxaparvovec-rvox) is an adeno-associated virus (AAV) vector-based gene therapy.

Background

Hemophilia is characterized as genetic mutations leading to deficiency in the factors necessary for coagulation. The most common types of hemophilia are hemophilia A, due to factor VIII deficiency, and hemophilia B, due to factor IX deficiency. The genes causing hemophilia are located on the X chromosome; therefore, most hemophiliacs are male while females are most commonly carriers. The liver produces both factors VIII and IX.

Summary of Evidence

Alhemo (concizumab-mtci) was studied in the EXPLORER 7 clinical trial which was a Phase 3 study designed to evaluate the safety and efficacy of concizumab, a subcutaneous prophylactic treatment for individuals with hemophilia A or B with inhibitors toward factor VIII (FVIII) or factor IX (FIX). The primary endpoint was annualized Bleeding Rate (ABR). The estimated mean ABR in the concizumab prophylaxis group (Group 2) was 1.7 episodes (95% CI, 1.0 to 2.9), compared to 11.8 episodes (95% CI, 7.0 to 19.9) in the no prophylaxis group (Group 1). This represents a significant reduction in bleeding episodes with a rate ratio of 0.14 (95% CI, 0.07 to 0.29; $P<0.001$).

The secondary endpoints was spontaneous bleeding episodes; the mean ABR for spontaneous bleeding episodes was 1.3 in the concizumab group versus 9.4 in the no prophylaxis group. The mean ABR for joint bleeding episodes was 1.4 in the concizumab group versus 9.1 in the no prophylaxis group. The mean ABR for target joint bleeding episodes was 0.1 in the concizumab group versus 1.1 in the no prophylaxis group. The mean ABR for all treated and untreated

bleeding episodes was 4.4 in the concizumab group versus 13.3 in the no prophylaxis group. The results for individual-reported outcomes measured through SF-36v2 Scores, which measured bodily pain and physical functioning scores on the 36-Item Short-Form Health Survey, version 2 (SF-36v2), did not differ significantly between the concizumab and no prophylaxis groups. However, 93% of individuals preferred concizumab to their previous treatment.

Alhemo (concizumab-mtci) was also studied in the Phase 3 EXPLORER 8 trial which included individuals 12 years of age and older with hemophilia A or B without inhibitors. Individuals were randomly assigned 1:2 to receive on-demand FVIII or FIX (no prophylaxis) or concizumab prophylaxis. The study showed a statistically significant reduction in ABR of 79% for hemophilia B individuals (ABR ratio: 0.21; 95% CI: 0.10–0.45; $p<0.0001$) and 86% for hemophilia A individuals (ABR ratio: 0.14; 95% CI: 0.07–0.29; $p<0.0001$). Additionally, notable reductions in the average and median ABRs further reinforced the efficacy of concizumab prophylaxis in reducing bleeds across both individual groups, with an average ABR of 3.1 (1.9-5.0) and a median ABR of 1.6 (0.0-4.8) for hemophilia B individuals, compared to 14.8 (8.1-26.9) and 14.9 (3.3-22.1), respectively, and an average ABR of 2.7 (1.6-4.6) and median ABR of 2.9 (0.0-5.2) for hemophilia A individuals, compared to 19.3 (11.3-33.0) and 19.6 (17.3-30.4), respectively. In the study, the most common adverse reactions reported in ≥5% of individuals randomized to receive concizumab were injection site reactions (7%) and headache (7%).

Hemlibra (emicizumab-kxwh) has been studied in two Phase 3 studies and a Phase 1 study with a trial extension.[1-3] The trials were small and of moderate to fair quality overall. The Phase 1 study was a 12-week, multicenter, open-label, dose escalation trial conducted in Japan. Individuals with severe hemophilia A, with or without inhibitors, and ages 12-59 were eligible for inclusion. Individuals were enrolled into three cohorts with varying doses of emicizumab. No primary endpoint was specified. The study was limited by very small size (n=18), nonrandomized design, and a difference in baseline ABR between cohorts (baseline ABR 15.9-37.9). Additionally, statistical comparisons were not performed. At Week 12, the median ABR decreased by 15.2-28.1 events from baseline across the cohorts. A total of 73% of individuals with inhibitors and 72% of individuals without inhibitors did not have a bleeding event during the trial. A trial extension with 27 months of follow-up in 16 individuals found the range of change in median ABR from baseline was 15.2-31.1 events; eight individuals did not experience any bleeding during the trial extension.[3]

The HAVEN 1 trial was a 24-week, multicenter, multinational, open-label, randomized, Phase 3 trial in 109 individuals ≥12 years of age with hemophilia A and high FVIII inhibitor titers treated with BPAs.[2] Individuals receiving episodic BPAs prior to study enrollment were randomized to emicizumab prophylaxis or no prophylaxis (Groups A and B). Individuals receiving prophylactic BPAs prior to enrollment were enrolled in Group C and received emicizumab prophylaxis. Group

D received prophylactic emicizumab and consisted of all individuals who did not enroll in the study before the closure of Groups A-C. Six or more bleeding events were required in the past 24 weeks for individuals on episodic BPAs prior to enrollment while ≥2 events were required for individuals on prophylactic BPAs. This difference may have led to selection bias. Controversy exists over the primary outcome measure for the HAVEN 1 trial. This was defined as the ABR for Groups A and B in clinicaltrials.gov while it was described as the rate of treated bleeding events in the same groups in the published NEJM article. At 24 weeks, the annualized rate of treated bleeding events significantly decreased with prophylactic emicizumab compared to no prophylaxis (episodic BPA treatment) (2.9 vs 23.3 events, 87% decrease, $p<0.001$ per NEJM, $p<0.0001$ per manufacturer and NEJM supplement). The ABR for all bleeding events significantly decreased with prophylactic emicizumab vs episodic BPA (5.5 vs 28.3 events, 80% decrease, $p<0.0001$). Overall, 62.9% of individuals in Group A, 5.6% in Group B, and 69.4% in Group C had no bleeding events throughout the trial. Secondary endpoints including treated spontaneous bleeding events (1.3 vs 16.8 events, $p<0.0001$) and treated joint bleeds (0.8 vs 6.7, $p=0.0005$) significantly favored emicizumab prophylaxis over episodic BPA.[3] Of individuals in Group C who participated a previous nonintervention study (n=24), interindividual comparisons found bleeding events with prophylactic emicizumab were significantly less than BPA prophylaxis (3.3 vs 15.7 events, 79% decrease, $p<0.001$).[2] Direct clinical trial evidence comparing emicizumab with prophylactic BPAs is lacking. Additionally, all quality of life (QoL) assessments in the trial overall significantly favored emicizumab prophylaxis compared to no prophylaxis.

Hemgenix (etranacogene dezaparvovec-drlb) has been studied in the HOPE-B (NCT03569891) Phase 3, open-label clinical trial in which 54 individuals prospectively completed a lead-in period of at least 6 months with the intent to receive standard-of-care routine congenital factor IX (FIX) prophylaxis. After completing the lead-in period, participants received a single intravenous dose of Hemgenix, and were followed monthly until Month 12, then at 6-month intervals until Year 5. After a single dose of Hemgenix, increases in FIX activity were observed. For the efficacy evaluation, data up to 18 months post treatment were used. Of the 54 individuals, 53 completed at least 18 months of follow-up in the ongoing study. One individual with numerous cardiovascular and urologic risk factors, who was 75 years of age at screening, died of urosepsis and cardiogenic shock at Month 15 post dose (at 77 years of age); this death was considered to be unrelated to treatment. Another individual received around 10% of the intended dose due to an infusion-related hypersensitivity reaction. Individuals were allowed to continue prophylaxis during Months 0 to 6. Two individuals were not able to stop routine prophylaxis after Hemgenix treatment. During Months 7 to 18, an additional individual received prophylaxis from Days 396–534 (approximately 20 weeks). Individuals were not excluded from the trial based on pre-existing neutralizing antibodies to adeno-associated virus 5 (AAV5). Some experts believe that, unlike other adeno-associated virus (AAV) vector–based gene therapies, AAV5-based products

may be effective in up to 95% of individuals with hemophilia B who also carry antibodies to AAV vectors. Results from the HOPE-B trial demonstrated that Hemgenix allowed individuals to produce mean FIX activity of 39% at 6 months and 36.7% at 24 months post infusion. These factor levels correspond to mild hemophilia. Seven to 18 months post infusion, the mean adjusted annualized bleeding rate (ABR) for all bleeds was reduced by 54% compared to the 6-month lead-in period on FIX prophylactic replacement therapy (from 4.1 to 1.9). Among study participants, 74% had bleeds in the lead-in period and 37% had bleeds 7–18 months after Hemgenix treatment. In addition, 94% (51 out of 54) of individuals discontinued the use of prophylaxis and remained free of previous continuous routine prophylaxis therapy. No inhibitors to FIX were reported.

Qfitlia (fitusiran) was evaluated in two different designed randomized, open-label, multicenter, phase 3 trials on male participants aged 12 or older. The results in both trials were similarly observed. The goal of the trials was to evaluate the efficacy and safety of fitusiran as a prophylactic treatment in people with severe hemophilia A and B, regardless of inhibitor status.

The ATLAS – INH trial randomly assigned 57 individuals with severe hemophilia A or B with inhibitors in a 2:1 ratio to receive once a month 80 mg subcutaneous fitusiran prophylaxis or to continue with bypassing agents on demand for 9 months. All eligible participants in the trial are male, aged 12 years or older with severe hemophilia A (FVIII < 1 %) or hemophilia B (FIX < 2%), presence of inhibitory antibodies to FVIII or FIX, Nijmegen-modified Bethesda assay ≥ 0.6 Bethesda units/mL, and at least six bleeding episodes requiring on-demand bypassing agents within 6 months prior to screen. The completion rate was 91.2%. The primary endpoint was mean ABR during the efficacy period. The ATLAS – INH trial showed that fitusiran prophylaxis reduced the mean ABR significantly compared to bypassing agents on-demand: 1.7 (95% CI: 1.0-2.7) vs 18.1 (10.6-30.8), representing a 90.8% reduction ($p < 0.0001$). The secondary endpoint included ABR in treatment and onset periods, spontaneous and joint bleeding rates as well as changes in physical health and quality of life. The secondary endpoint supported the primary findings, with 66% of fitusiran participants having zero treated bleeds, compared to 5% in the bypassing agent group. Also, significant improvements were noted in spontaneous and joint bleed rates, with better control in those with target joint involvement.

Similarly, the ATLAS – A/B trial involved 120 male participants aged ≥ 12 years with severe hemophilia A or B without inhibitors. Participants were randomized in a 2:1 ratio to receive monthly subcutaneous fitusiran prophylaxis (80mg) or on-demand clotting factor concentrates for 9 months. The primary endpoint was the annualized bleeding rate (ABR) during the efficacy period. The ATLAS – A/B demonstrated fitusiran prophylaxis reduced the mean ABR significantly compared to on-demand treatment. Mean ABR was 0.0 (0.0-3.4) in the fitusiran group vs. 21.8 (8.4-41.0) in the on-demand group, with an estimated mean ABR of 3.1 (95% CI: 2.3-4.3) vs 31.0

(21.1-45.5), corresponding to a 90% reduction ($p < 0.0001$). The secondary endpoints consisted of ABR in the treatment and onset periods, annualized spontaneous and joint bleeding rates, and changes in quality of life. The result of secondary endpoints proved that approximately 51% of fitusiran participants had no treated bleeding events, compared to 5% in the on-demand group. Additionally, significant reductions in spontaneous and joint bleeds were observed, indicating substantial efficacy in maintaining hemostatic balance.

Roctavian was studied in a prospective, phase-3, open-label, single-dose, single-arm trial where 134 adult males with severe hemophilia A received a single IV dose of 6×10^{13} vg/kg body weight of Roctavian. These individuals were followed for a period of 5 years. The study included individuals who were previously treated with prophylactic factor VIII replacement therapy excluding emicizumab. The inclusion criteria required that individuals do not have detectable, pre-existing antibodies to AAV5 capsid. The exclusion criteria included active infection, chronic or active hepatitis B or C, HIV, current or prior history of factor VIII inhibitors, stage 3 or 4 liver fibrosis, cirrhosis, abnormal liver function test, history of thrombosis or thrombophilia, serum creatinine $\geq$1.4 mg/dL, and active malignancy.

The primary efficacy endpoint was a non-inferiority (NI) test of the difference in the annualized bleeding rate in the efficacy evaluation period (EEP) following the mean annualized bleeding rate (ABR) following Roctavian administration compared to the baseline.

The mean EEP ABR was 2.6 bleeds/year compared to the mean baseline ABR of 5.4 bleeds/year, with the mean difference in ABR was -2.8 bleeds/year. The NI analysis met the pre-specified NI margin, indicating the effectiveness of Roctavian. Out of all individuals, a total of 1 individual did not response and 6 individuals lost response to Roctavian treatment over a median time of 3.6 years.

The most common adverse events were nausea, fatigue, infusion related reactions, headache, vomiting and abdominal pain.

The FDA approval of Hympavzi is based on results from the pivotal Phase 3 BASIS (NCT03938792) trial, an open-label, multicenter, two-phase study. The trial included 116 adult and pediatric male individuals with either severe hemophilia A or severe hemophilia B, both without inhibitors. Following screening, individuals entered a 6-month observation phase and were enrolled to two cohorts based on the factor replacement treatment they were receiving prior to study entry: on-demand (OD) (n = 33) or routine prophylaxis (RP) (n = 83). Individuals who completed the observation phase received 12 months of Hympavzi treatment, and received a single loading dose of 300 mg, followed by once-weekly dose of 150 mg. Dose escalation to 300 mg was permitted after 180 days of treatment for individuals weighing 50 kg or greater and experiencing 2 or more breakthrough bleeds. Individuals who completed the 12-month BASIS

study were eligible to enroll in an open-label extension study (NCT05145127). The primary efficacy measure for Hympavzi was the annualized bleeding rates (ABRs) of treated bleeds. During the observational phase, the mean ABRs for treated bleeds were 38 in the OD cohort and 7.85 in RP. Following Hympavzi treatment in the active treatment phase, ABRs for treated bleeds were 3.18 in the OD cohort and 5.08 in the RP cohort, reflecting a 92% and 35% reduction, respectively, over a 12-month active treatment period, in individuals with hemophilia A or B without inhibitors. Hympavzi prophylaxis demonstrated superiority over OD factor-based therapy in reducing treated bleeds, spontaneous bleeds, joint bleeds, total bleeds, and target joint bleeds. Additionally, it demonstrated noninferiority to RP factor-based therapy as measured by ABR for treated bleeds and incidences of spontaneous bleeds, joint bleeds, target joint bleeds, and total bleeds.

The efficacy of Hympavzi was established in 48 adults and pediatric individuals (12 years of age and older and ≥35 kg) with severe hemophilia A (FVIII < 1%) with FVIII inhibitors or moderately severe to severe hemophilia B (FIX ≤2%) with FIX inhibitors enrolled in the BASIS study (NCT03938792), open-label, multi-center, two-phase study (observational and treatment phases). Individuals had current or history of high titer inhibitors (≥5 BU/mL) and were in need of treatment with bypassing agents in the last 6 months prior to enrollment. Individuals with previous or current treatment for or history of coronary artery disease, venous or arterial thrombosis or ischemic disease were excluded from the study. Following screening, 51 individuals entered a 6-month observation phase and received either on-demand (N = 48) or routine prophylactic treatment (N = 3) with bypassing agents (rFVIIa or aPCC). Individuals who completed the observation phase were to receive 12 months of HYMPAVZI. Individuals received an initial 300 mg loading dose of HYMPAVZI followed by maintenance doses of 150 mg of HYMPAVZI once weekly for 12 months. Dose escalation to 300 mg of HYMPAVZI once weekly was permitted after 6 months of treatment in individuals weighing ≥50 kg and experiencing 2 or more breakthrough bleeds. Four (7.8%) of 51 individuals underwent dose escalation. The efficacy of HYMPAVZI was based upon the ABR of treated bleeds during treatment with HYMPAVZI compared to ABR during on-demand bypassing agent therapy during the observational phase. The trial showed Hympavzi was superior to on-demand (OD) bypassing agents, with annualized bleeding rate (ABR) reductions of 93% and 19.8%, respectively. The expanded approval for pediatric individuals was based on descriptive analyses of interim data from the BASIS KIDS study, which showed trends of lower ABR in individuals treated with Hympavzi versus historical model-based mean rates in individuals without inhibitors receiving RP (1.8 vs. 3.6) or individuals with inhibitors receiving OD therapy (1.4 vs. 18.9).

Safety

For Alhemo (concizumab-mtci) the most frequently reported adverse events (AEs) with an incidence ≥5% with were injection site reactions and urticaria. Concizumab serious adverse events (SAEs) in the Explorer7 trial documented a total of 5 SAEs that occurred in 3 individuals (16%) with no prophylaxis and 18 SAEs in 14 individuals (11%) with concizumab prophylaxis. Specific SAEs included bleeding-related in 3 individuals and infections in 4 individuals. Other single event fatal causes included pneumonitis in one individual in the no prophylaxis group. Two deaths occurred during the treatment pause (hematoma, gastrointestinal bleeding). One uneventful death occurred during the post-pause (road accident). One death during extension periods caused by COVID-19 complications. Thromboembolic events included renal infarction in one individual in the concizumab prophylaxis group that occurred before the treatment pause. Overall, only three individuals experienced a thromboembolic event that led to the treatment pause.

For Hemlibra the majority of adverse events (AEs) were described as mild to moderate. Common AEs reported in ≥ 5% of individuals from pooled clinical trials were injection-site reactions (22%), headache (15%), arthralgia (15%), pyrexia (6%), and diarrhea (6%). Serious AEs occurred in 0%-8.7% of individuals. Discontinuations due to AEs occurred in three individuals across all clinical trials. Anti-emicizumab antibodies were detected five individuals in Phase 1 trials and were suspected but not identified in two individuals in the HAVEN 1 trial.

Thromboembolic (TE) events are of concern with emicizumab. The HAVEN 1 trial identified three events of thrombotic microangiopathy (TMA) and two TE events (cavernous sinus thrombosis and skin necrosis/superficial thrombophlebitis), all occurring following activated prothrombin complex concentrates (aPCC) administration (>100 U/kg/d) for >1 day. No events occurred with emicizumab alone, recombinant FVIIA (rFVIIa) alone, or aPCC x1 day. No anticoagulation was required for the TE events. The TMA events resolved in two individuals and were considered to be resolving in the third at the time of death from rectal hemorrhage following treatment with aPCC for 4 days. Treatment was restarted in one TE and one TMA individual. Overall, the HAVEN 1 authors considered there to be a potential for substantial risk with the combination of aPCC and emicizumab. This is supported by in vitro and animal evidence showing increased thrombin formation with emicizumab plus aPCC and to a lesser degree with rFVIIa.

For Hemgenix, there is no Risk Evaluation and Mitigation Strategy (REMS) program. Providers should monitor liver enzymes for hepatotoxicity, order liver testing to monitor for hepatocellular carcinogenicity, and monitor FIX activity and inhibitors for treatment efficacy. The prescribing information for Hemgenix notes that individuals who intend to receive treatment are

encouraged to enroll in a study that evaluates the effect of pre-existing anti-AAV5 neutralizing antibodies on the risk of bleeding.

For Qfitlia (fitusiran) the most common adverse events (AEs) with an incidence >10% are viral infection, nasopharyngitis, and bacterial infection.

For Roctavian, there is no Risk Evaluation and Mitigation Strategy (REMS) program. Providers should monitor liver enzymes for hepatotoxicity, factor VIII activity for thromboembolic events, and hepatocellular malignancy for hepatocellular carcinoma.

Hympavzi may increase the risk of thromboembolic complications. It has not been studied in individuals with a history of previous thromboembolic events and treatment with Hympavzi should be interrupted in individuals who have diagnostic findings consistent with thromboembolism.

Practice Guidelines and Position Statements

On December 22, 2022, Institute for Clinical and Economic Review (ICER) published a comparative clinical effectiveness and value of gene therapy for hemophilia B and an update on gene therapy for hemophilia A. The Report concluded the following:

- There is moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit (B+) for etranacogene dezaparvovec-drlb compared with factor IX prophylaxis.
- There is low certainty about the net health benefit (I) for valoctocogene roxaparvovec compared with emicizumab.

The National Hemophilia Foundations (NHF)'s Medical and Scientific Council (MASAC) guidelines were developed before the approval of the 2 gene therapies etranacogene dezaparvovec-drlb and valoctocogene roxaparvovec. In these guidelines and recommendations, the preferred treatment strategy is pharmacologic treatment, and exogenous factor IX (FIX) replacement by intravenous (IV) injection of recombinant FIX or human plasma-derived FIX concentrates is the recommended treatment of choice for individuals with hemophilia B. The NHF guidelines, however, recommend recombinant over plasma-derived FIX concentrates as the preferred option for hemophilia B.

The World Federation for Hemophilia (WFH) guidelines were developed before the approval of the 2 gene therapies etranacogene dezaparvovec-drlb and valoctocogene roxaparvovec. In these guidelines and recommendations, the preferred treatment strategy is pharmacologic treatment, and exogenous FIX replacement by IV injection of recombinant FIX or human plasma-

derived FIX concentrates is the recommended treatment of choice for individuals with hemophilia B.

2019 Update

A literature search from January 1, 2018, through February 28, 2019, did not identify any new evidence that would change the criteria in this policy.

2020 Update

Reviewed Hemlibra prescribing information and conducted a literature search from March 1, 2019, through February 28, 2020. No new evidence was identified that would change the criteria in this policy.

2021 Update

Reviewed Hemlibra prescribing information and the World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia 3rd Edition. Added additional dose frequency for the maintenance dose of 3 mg/kg once every two weeks and 6 mg/kg once every four weeks to the Dosage and Quantity Limit table. Updated policy with new guidelines and position statements from the WFH specific to Hemlibra.

2022 Update

Reviewed Hemlibra prescribing information and conducted a literature search from March 1, 2020 through October 13, 2022. Added information regarding HAVEN 5 and HAVEN 6 to the Ongoing and Unpublished Clinical Trials. No new evidence was identified that would change the criteria in this policy.

2023 Update

Reviewed the prescribing information and conducted a literature search. No new evidence was identified that would change the criteria in this policy. Added criteria for Hemgenix to this

policy. Updated Hemgenix criteria to state that individual meets one of the following: Current or historical life-threatening hemorrhage OR Repeated, serious spontaneous bleeding episodes OR Individual is currently receiving FIX prophylaxis. Removed separate bullet point "Individual is currently receiving FIX prophylaxis". These changes are based on the FDA approval for Hemgenix and P&T committee in February 2023. Added coverage criteria for Roctavian for the treatment of adults with severe hemophilia A without pre-existing antibodies to adeno-associated virus serotype 5.

2024 Update

Reviewed the prescribing information. Added Beqvez (fidanacogene elaparvovec-dzkt) coverage criteria for the treatment of certain individuals with hemophilia B.

2025 Update

Reviewed the prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated the re-authorization duration for Hemlibra (emicizumab-kxwh) to up to 12 months. Added Hympavzi (marstacimab-hncq) coverage criteria for the treatment of certain individuals with hemophilia A or B. Clarified quantity limit for Alhemo (concizumab-mtci), Hemlibra (emicizumab-kxwh), and Hympavzi (marstacimab-hncq). Updated Qfitlia (fitusiran) quantity limit to one 20 mg vial or 50 mg pen monthly. Updated Roctavian (valoctocogene roxaparvovec-rvox) and Hemgenix (etranacogene dezaparvovec-drlb) coverage criteria to require that the prescriber attest to providing clinical outcome information within the appropriate provider portal as requested by the Company plan.

2026 Update

Reviewed the prescribing information for all drugs. Updated Hympavzi (marstacimab-hncq) coverage criteria to clarify the indication is for hemophilia A without factor VIII inhibitors or hemophilia B without factor IX inhibitors. Added the 300 mg weekly maintenance dose limit to Hympavzi coverage criteria with the requirements stating that the individual must meet all of the following: dose titration occurs after 6 months of treatment with the 150 mg weekly maintenance dose, the individual weighs 50 kg or greater, and there is documentation of 2 or

more breakthrough bleeds. Updated the Dosage and Quantity Limit section to include the 300 mg weekly maintenance dose for Hympavzi. Updated the summary of evidence for Hympavzi to include the dosing regimen used in the trial reviewed for its FDA approval. Updated Qfitlia (fitusiran) coverage criteria to clarify the indication is for hemophilia A (congenital factor VIII deficiency) or hemophilia B (congenital factor IX deficiency) with or without factor VIII or IX inhibitors. No new updates were identified for all other drugs in this policy.

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35. Hemgenix (etranacogene dezaparvovec-drlb). Prescribing information. CSL Behring LLC, King of Prussia, PA. Revised November 2022.

History

Date	Comments
02/01/18	New policy, approved January 16, 2018. Add to Prescription Drug section. Considered medically necessary for pediatric and adults with hemophilia A (congenital factor VIII deficiency) when criteria are met.
04/01/18	Interim Review, approved March 20, 2018. Clarified criteria language for Hemlibra, addition of definition of high dose aPCC and added history of anti-FVIII titer. Also added benefit application information.
11/01/18	Interim Review, approved October 9, 2018. Updated per expanded indication approved by FDA 10/3/18 for hemophilia A with or without Anti-Factor VIII.
11/17/18	Coding update, added HCPCS code Q9995 to policy (effective 7/1/18), removed HCPCS code J3490.
01/01/19	Coding update, added new HCPCS code J7170 (new code effective 1/1/19), replacing Q9995.
04/01/19	Annual Review, approved March 19, 2019. Literature search from 1/1/18, No changes.
01/01/20	Coding update, removed HCPCS code Q9995 as it was terminated 1/1/19.
04/01/20	Annual Review, approved March 19, 2020. Reviewed prescribing information and conducted literature search from March 1, 2019, to February 28, 2020. No changes to coverage criteria.
11/01/21	Annual Review, approved October 5, 2021. Added additional dose frequency for the maintenance dose of 3 mg/kg once every two weeks and 6 mg/kg once every four weeks to the Dosage and Quantity Limit table.
12/01/22	Annual Review, approved November 7, 2022. Reviewed prescribing information and conducted literature search from March 1, 2020, to October 13, 2022. No changes to coverage criteria. Changed the wording from "patient" to "individual" throughout the policy for standardization.
05/01/23	Annual Review, approved April 11, 2023. Changed title of medical policy from Hemlibra (emicizumab-kxwh) to Pharmacologic Treatment of Hemophilia. Reviewed Hemlibra prescribing information and conducted a literature search. No new evidence

Date	Comments
	was identified that would change the criteria in this policy. Added criteria for Hemgenix to this policy. Added HCPC code J3590 to report Hemgenix.
06/30/23	Minor correction in the policy introduction. Corrected "Hemlibra is a gene therapy that can be used to prevent, or reduce the number of bleeding episodes in adults with hemophilia B" to Hemgenix is a gene therapy that can be used to prevent or reduce the number of bleeding episodes in adults with hemophilia B".
09/01/23	Interim Review, approved August 8, 2023. Updated Hemgenix criteria to state that individual meets one of the following: Current or historical life-threatening hemorrhage OR Repeated, serious spontaneous bleeding episodes OR Individual is currently receiving FIX prophylaxis. Removed separate bullet point "Individual is currently receiving FIX prophylaxis". These changes are based on the FDA approval for Hemgenix and P&T committee in February 2023.
10/01/23	Interim Review, approved September 12, 2023. Added coverage criteria for Roctavian for the treatment of adults with severe hemophilia A without pre-existing antibodies to adeno-associated virus serotype 5. Added Roctavian to HCPCS code J3590, and added HCPCS code J1411 for Hemgenix.
12/01/23	Interim Review, approved November 14, 2023, effective for dates of service on or after March 7, 2024, following 90-day provider notification. Updated coverage criteria for Hemgenix to require that FIX prophylaxis will be discontinued following administration of Hemgenix and that a hepatologist has assessed the individual if the individual has radiological liver abnormalities or sustained liver enzyme elevations. Updated the coverage criteria for Roctavian to require that FVIII prophylaxis will be discontinued following administration of Roctavian and that documentation is provided demonstrating that the individual received education relating to alcohol abstinence and the use of concomitant medications.
01/01/24	Coding update. Added new HCPCS code J1412.
09/01/24	Annual Review, approved August 13, 2024. Added Beqvez (fidanacogene elaparvovec-dzkt) coverage criteria for the treatment of certain individuals with hemophilia B.
10/01/24	Coding update. Added new HCPCS code C9172.
01/01/25	Coding update. Added new HCPCS code J1414.
03/01/25	Annual Review, approved February 11, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated the re-authorization duration for Hemlibra (emicizumab-kxwh) to up to 12 months. Added Hympavzi (marstacimab-hncq) coverage criteria for the treatment of certain individuals with hemophilia A or B.
04/01/25	Coding update. Added new HCPCS code C9304.
05/01/25	Interim Review, approved April 8, 2025. Added coverage for Alhemo (concizumab-mtci) for the treatment of certain individuals with hemophilia A and hemophilia B who

Date	Comments
	have documented inhibitors. Added coverage for Qfitlia (fitusiran) for the treatment of certain individuals with hemophilia A and hemophilia B. Removed Beqvez (fidanacogene elaparvovec-dzkt) from policy as the manufacturer has discontinued the product.
07/01/25	Coding update. Added new HCPCS code J7172 for Hympavzi due to quarterly code update.
08/01/25	Interim Review, approved July 8, 2025. Clarified quantity limit for Alhemo (concizumab-mtci), Hemlibra (emicizumab-kxwh), and Hympavzi (marstacimab-hncq). Updated Qfitlia (fitusiran) quantity limit to one 20 mg vial or 50 mg pen monthly. Updated Roctavian (valoctocogene roxaparvovec-rvox) and Hemgenix (etranacogene dezaparvovec-drlb) coverage criteria to require that the prescriber attest to providing clinical outcome information within the appropriate provider portal as requested by the Company plan.
10/01/25	Interim Review, approved September 9, 2025. Updated Alhemo (concizumab-mtci) coverage criteria to include coverage for patients with or without factor VIII or factor IX inhibitors. Added new HCPCS codes J7173 & J7174, effective October 1, 2025.
03/01/26	Annual Review, approved February 10, 2026. Updated Hympavzi (marstacimab-hncq) coverage criteria to clarify the indication is for hemophilia A without factor VIII inhibitors or hemophilia B without factor IX inhibitors. Added the 300 mg weekly maintenance dose limit to the Hympavzi coverage criteria. Updated Qfitlia (fitusiran) coverage criteria to clarify the indication is for hemophilia A (congenital factor VIII deficiency) or hemophilia B (congenital factor IX deficiency) with or without factor VIII or IX inhibitors. Removed HCPCS code J3590.
09/01/26	Interim Review, approved August 11, 2026. Updated criteria for Hympavzi (marstacimab-hncq) age requirement from 12 years to 6 years or older, added for individuals with factor VIII or IX inhibitors, and added a quantity limit per 28 days. Updated Qfitlia (fitusiran) criteria removing the requirement for a minimum number of bleeding episodes prior to treatment. Removed reference to non-formulary exception reviews.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

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the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.