LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.581

Pharmacologic Treatment of Hemophilia

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Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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 Beqvez, Hemlibra, and Hemgenix may be considered medically necessary.

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

Beqvez (fidanacogene elaparvovec-dzkt)	**Beqvez (fidanacogene elaparvovec-dzkt) may be considered medically necessary for adults when all the following criteria are met:**
	• Individual is aged 18 years and older
	AND
	• Individual was assigned male at birth
	AND
	• Individual has severe or moderately severe hemophilia B as defined by a plasma Factor IX (FIX) activity level of 2% or less
	AND
	• Individual meets ONE of the following:
	  ○ Current or historical life-threatening hemorrhage
	  ○ Repeated, serious spontaneous bleeding episodes
	  ○ Individual is currently receiving FIX prophylaxis
	AND
	• FIX prophylaxis will be discontinued following administration of Beqvez if the individual is currently receiving FIX prophylaxis
	AND
	• 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
	• Individual 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

Drug	Medical Necessity
	• Medication is being prescribed by or in consultation with a hematologist or a prescriber who specialized in hemophilia B **AND** • Individual does not have a history of receiving gene therapy or is under consideration for treatment for another gene therapy for hemophilia B **AND** • Individual is human immunodeficiency virus (HIV) negative or has a controlled HIV infection **AND** • Individual does not have an active hepatitis B or hepatitis C infection **AND** • Individual does not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid

Hemgenix (etranacogene dezaparvovec-drlb)	**Hemgenix (etranacogene dezaparvovec-drlb) may be considered medically necessary for adults when all the following criteria are met:**
	• Individual is aged 18 years and older
	AND
	• Individual was assigned male at birth
	AND
	• Individual has severe or moderately severe hemophilia B as defined by a plasma Factor IX (FIX) activity level of 2% or less
	AND
	• Individual meets ONE of the following:
	  ○ Current or historical life-threatening hemorrhage
	  ○ Repeated, serious spontaneous bleeding episodes
	  ○ Individual is currently receiving FIX prophylaxis
	AND
	• FIX prophylaxis will be discontinued following administration of Hemgenix if the individual is currently receiving FIX prophylaxis
	AND
	• 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

Drug	Medical Necessity
	• Individual 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 specialized in hemophilia B **AND** • Individual does not have a history of receiving gene therapy or is under consideration for treatment for another gene therapy for hemophilia B **AND** • Individual is human immunodeficiency virus (HIV) negative or has a controlled HIV infection **AND** • Individual does not have an active hepatitis B or hepatitis C infection
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 **Note:** High dose aPCC is defined as greater than 100 U/kg/day administered for greater than 24 hours
Roctavian (valoctocogene roxaparvovec-rvox)	**Roctavian (valoctocogene roxaparvovec-rvox) may be considered medically necessary when all of the following criteria are met:** • Individual is aged 18 years and older **AND**

Drug	Medical Necessity
	• Individual was assigned male at birth **AND** • Diagnosis of severe hemophilia A (congenital factor VIII deficiency) with factor VIII activity < 1 IU/dL **AND** • Factor VIII prophylaxis will be discontinued following administration of Roctavian if the individual is currently receiving factor VIII prophylaxis **AND** • Individual does not have pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test **AND** • Individual 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 specialized in hemophilia A **AND** • Individual is human immunodeficiency virus (HIV) negative or has a controlled HIV infection **AND** • Individual 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

Drug	Investigational
• **Beqvez (fidanacogene elaparvovec-dzkt)** • **Hemgenix (etranacogene dezaparvovec-drlb)** • **Roctavian (valoctocogene roxaparvovec-rvox)**	**All other uses of Beqvez (fidanacogene elaparvovec-dzkt), Hemgenix (etranacogene dezaparvovec-drlb), and Roctavian (valoctocogene roxaparvovec-rvox) for conditions not outlined in this policy are considered investigational.**

Drug	Investigational
	Repeat treatment of Beqvez (fidanacogene elaparvovec-dzkt), Hemgenix (etranacogene dezaparvovec-drlb), and Roctavian (valoctocogene roxaparvovec-rvox) is considered investigational.
Hemlibra (emicizumab-kxwh)	**All other uses of Hemlibra (emicizumab-kxwh) for conditions not outlined in this policy are considered investigational.**

Approval	Criteria
Initial authorization	**Beqvez (fidanacogene elaparvovec-dzkt), Hemgenix (etranacogene dezaparvovec-drlb), and Roctavian (valoctocogene roxaparvovec-rvox) may be approved as a one-time infusion.** **Hemlibra (emicizumab-kxwh) can be approved for 1 year.**
Re-authorization criteria	**Repeat treatment of Beqvez (fidanacogene elaparvovec-dzkt), Hemgenix (etranacogene dezaparvovec-drlb), and Roctavian (valoctocogene roxaparvovec-rvox) is considered investigational.** **Future re-authorization of Hemlibra (emicizumab-kxwh) would depend on 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**
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

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
- Hemlibra (emicizumab-kxwh) reauthorization requires chart notes documenting progress, including decreased incidence of bleeding episodes

Coding

Code	Description
HCPCS	
C9172	Injection, fidanacogene elaparvovec-dzkt, per therapeutic dose (Beqvez) (New code effective 10/1/2024)
J1411	Injection, etranacogene dezaparvovec-drlb, per therapeutic dose (Hemgenix)
J1412	Injection, valoctocogene roxaparvovec-rvox, per ml, containing nominal 2 x 1013 vector genomes (Roctavian) (new code effective 1/1/2024)
J3590	Unclassified biologics (used to report Beqvez)
J7170	Injection, emicizumab-kxwh (Hemlibra), 0.5 mg

Related Information

Benefit Application

Hemlibra (emicizumab-kxwh) and may be managed through pharmacy or medical benefits. Beqvez (fidanacogene elaparvovec-dzkt), Hemgenix (etranacogene dezaparvovec-drlb), and Roctavian (valoctogene roxaparvovec-rvox) are managed through the medical benefit.

Consideration of Age

The ages stated in this policy for which Beqvez (fidanacogene elaparvovec-dzkt), Hemlibra (emicizumab-kxwh), Hemgenix (etranacogene dezaparvovec-drlb) and Roctavian (valoctocogene roxaparvovec-rvox) is considered medically necessary is based on the FDA labeling for this drug.

Evidence Review

Description

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.

Beqvez (fidanacogene elaparvovec-dzkt) is an adeno-associated virus (AAV) vector-based gene therapy.

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

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

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.

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 X 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 ≥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.

Beqvez (fidanacogene elaparvovec-dzkt) has an FDA approval based on results from the pivotal Phase 3 BENEGENE-2 study, an open-label, single-arm study that enrolled 45 adult males with moderately severe to severe hemophilia B who completed a minimum of 6 months of routine factor IX (FIX) prophylaxis therapy during the lead-in study. Individuals received a single intravenous (IV) infusion of Beqvez at a dose of 5 × 1011 vector genomes per kilogram (vg/kg) of body weight. The trial demonstrated noninferiority in annualized bleeding rates (ABRs) compared with standard-of-care (SOC) factor IX therapy. Treatment with Beqvez resulted in a mean annualized bleed rate (ABR) of 2.5 in the efficacy evaluation period between Week 12 and data cutoff (median 1.8 years of follow-up), compared to a mean ABR of 4.5 during the lead-in pretreatment period of at least 6 months (median 1.2 years of follow-up). Bleeds were eliminated in 60% of individuals compared to 29% in the SOC prophylaxis arm.

Ongoing and Unpublished Clinical Trials

The HAVEN 2 trial is an ongoing, multicenter, open-label, single-arm, Phase 3 trial which enrolled children 52-week trial.3 At the time of interim analysis, 20 enrolled individuals had received treatment for >12 weeks. All individuals were treated with emicizumab 3 mg/kg SQ for 4 weeks, then 1.5 mg/kg/week. A primary endpoint was not specified. At the time of interim analysis, the mean ABR was 0.4 for treated bleeds, 3.7 for all bleeds, 0.4 for treated spontaneous bleeds, and zero for joint bleeds. No comparison with baseline ABR was provided. A total of 94.7% of individuals experienced zero treated bleeds and 63.2% had no bleeding events of any type at the time of interim analysis. Additional ongoing trials include HAVEN 3 (R, OL, MC, Phase 3, 24-week trial in 145 individuals with hemophilia A without inhibitors assessing ABR), HAVEN 4

(OL, MC, Phase 3 expansion trial in 46 individuals), and the STASEY trial (2-year, OL, MC, Phase 3b trial in 200 individuals with hemophilia A assessing AEs).[3]

The HAVEN 5 trial is an ongoing randomized, open-label, Phase 3 trial being conducted to the compare emicizumab vs no prophylaxis in Asian adults and adolescents with any severity of hemophilia A n=16 (23%) with inhibitors and n=54 (77%) without. Interim results after 24 weeks have been reported but related subgroup results have not.

The HAVEN 6 trial is an ongoing multicenter, open-label, single-arm, Phase 3 trial being conducted to assess the safety, efficacy and PK of emicizumab in individuals with mild or moderate hemophilia A without inhibitors. At interim analysis, 71 individuals had been enrolled, 51 with moderate hemophilia and 20 with mild hemophilia. The overall annualized rate of treated bleeds was 0.8 (95% CI 0.41-1.46) and 80.3% individuals had zero bleeds.

Safety

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 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.

Beqvez was generally well tolerated, with the most common adverse event reported in trials being elevated transaminases. No serious adverse events and no deaths have been reported. No serious adverse reactions were reported in patients treated with Beqvez. There is no Risk Evaluation and Mitigation Strategy (REMS) program for Beqvez. Providers should monitor liver enzymes for hepatotoxicity and monitor FIX activity and inhibitors for treatment efficacy.

Practice Guidelines and Position Statements

The World Federation of Hemophilia (WFH) published updated hemophilia guidelines in 2020. In regard to emicizumab, the guidelines recommend for:

- Individuals receiving emicizumab in whom confirmation of expected emicizumab levels is required, the WFH recommends use of a modified one-stage assay including an additional pre-dilution step of test plasma and assay calibration with specific emicizumab calibrators.
- Determination of FVIII activity in individuals with hemophilia A receiving emicizumab, the WFH recommends use of a chromogenic FVIII assay containing bovine FX.
- Individuals with a suspected neutralizing anti-emicizumab antibody, the WFH recommends measuring emicizumab levels using a modified one-stage assay including an additional pre-dilution step of test plasma and assay calibration with specific emicizumab calibrators.
- Individuals with severe phenotype hemophilia A without inhibitors, prophylaxis with emicizumab will prevent hemarthrosis, spontaneous, and breakthrough bleeding.
- Individuals with moderate/severe hemophilia A or B, especially those who have experienced a life-threatening bleed (e.g., intracranial hemorrhage [ICH]), the WFH recommends prophylaxis with FVIII or FIX concentrates or with a non-factor therapy (e.g., emicizumab for hemophilia A) in order to prevent a recurrent life-threatening bleed. This is particularly important during the first 3-6 months following an ICH as the risk of recurrence is highest during this period.

The guidelines also strongly recommend the use of viral-inactivated plasma-derived or recombinant clotting factor concentrates (CFCs) in preference to cryoprecipitate or fresh frozen plasma. The WFH supports the use of CFCs in preference to cryoprecipitate or FFP due to concerns about quality, safety, and efficacy. However, the WFH recognizes the reality that they are still widely used in countries around the world where they are the only available or affordable treatment options.

Medicare National Coverage

There is no national coverage determination.

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.

References

1. Shima M, Hanabusa H, Taki M, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. New Engl J Med. 2016;374:2044-2053.
2. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. New Engl J Med. 2017;377(9):809-818.
3. Uchida N, Sambe T, Yoneyama K, et al. A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects. Blood. 2016;127(13):1633-1641.
4. Adamkewicz J, Muto A, Soeda T, Suzuki S, Kitazawa T. In vitro thrombin generation testing and in vivo venous stasis model for assessing the pro-coagulant effects of FVIII, emicizumab, rFVIIa, and aPCC. Haemophilia. 2017; 23(Suppl S2):OR37 (abstract).

5. ICER. Institute for Clinical and Economic Review posts draft scoping document to guide review of emicizumab for hemophilia A. Accessed August 5, 2024.
6. Farrugia A, Cassar J, Kimber MC, et al. Treatment for life for severe haemophilia A – a cost-utility model for prophylaxis vs on-demand treatment. Hemophilia. 2013;19(4):e228-e238.
7. Mehta DA, Oladapo AO, Epstein JD, Novack AR, Neufeld EJ, Hay JW. A budget impact model of hemophilia bypassing agent prophylaxis relative to recombinant factor VIIA on-demand. J Manag Care Spec Pharm. 2016;22(2):149-157.
8. GoodRx. Coagulation factors. Accessed August 5. 2024.
9. Clinicaltrials.gov. HAVEN 1 (NCT02622321). Accessed August 5. 2024.
10. Bauer KA. Current challenges in the management of hemophilia. Am J Manag Care. 2015;21:S112-S122.
11. Kempton CL, Meeks SL. Toward optimal therapy for inhibitors in hemophilia. Blood. 2014;124(23):3365-3372.
12. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia, 2020;26(Suppl 6):1-158. Accessed August 5. 2024.
13. Hemlibra (emicizumab-kxwh) prescribing information. Genentech, Inc.; South San Francisco, CA. Revised January 2024.
14. Yang R, Wang S, Wang X, et al. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: a randomized study (HAVEN 5). Res Pract Thromb Haemostat. 2022;6:e12670.
15. Negrier C, Mahlangu J, Lehle M, et al. Emicizumab prophylaxis in persons with mild or moderate hemophilia A: results from the interim analysis of the HAVEN 6 study [abstract].
16. Centers for Disease Control and Prevention. Factor VIII and factor IX. **https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-reports/2022- 03/table-2-factor.html/** Accessed August 5, 2024.
17. Centers for Disease Control and Prevention. Registry Report on Males with Hemophilia 2014-2017: Health insurance coverage. **https://www.cdc.gov/ncbddd/hemophilia/communitycounts/registry-report-males/health-insurance-coverage.html** Accessed August 5, 2024.
18. Centers for Disease Control and Prevention. A new study of hemophilia occurrence finds many more cases in the United States. **https://www.cdc.gov/ncbddd/hemophilia/features/keyfinding-hemophilia-occurrence-US.htm** Accessed August 5, 2024.
19. Gomez E, et al. Etranacogene dezaparvovec (AAV5-Padua hFIX variant, AMT-061), an enhanced vector for gene transfer in adults with severe or moderate-severe hemophilia B: 2.5 year data from a Phase 2b trial [abstract]. Res Pract Thromb Haemost. 2021;5(Suppl 2). **https://abstracts.isth.org/abstract/etranacogene-dezaparvovec-aav5-padua-hfixvariant-amt-061-an-enhanced-vector-for-gene-transfer-in-adults-with-severe-ormoderate-severe-hemophilia-b-2-5-year-data-from-a-phase-2b-trial/** Accessed August 5, 2024.
20. Miesbach W, et al; HOPE-B Investigators. Final analysis from the pivotal Phase 3 HOPE-B gene therapy trial: stable steady-state efficacy and safety of etranacogene dezaparvovec in adults with severe or moderately severe haemophilia B. Paper presented at: 15th Congress for the European Association for Haemophilia and Allied Disorders; February 2–4, 2022. **https://www.uniqure.com/assets/uploads/doc/eahad2022-hope-b-oral-presentation-20220204.pdf** Accessed August 5, 2024.
21. Miesbach W, et al. Five year data confirms stable FIX expression and sustained reductions in bleeding and factor IX use following AMT-060 gene therapy in adults with severe or moderate-severe hemophilia B [abstract]. Res Pract Thromb Haemost. 2021;5(Suppl 2). **https://abstracts.isth.org/abstract/five-year-data-confirms-stable-fix-expression-and-sustained-reductions-in-bleeding-and-factor-ix-use-following-amt-060-gene-therapy-in-adults-with-severe-or-moderate-severe-hemophilia-b/** Accessed August 5, 2024.
22. Miesbach W, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. Blood. 2018;131(9):1022-1031. doi:10.1182/blood-2017-09-804419 National Hemophilia Foundation. Hemophilia A. **https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a** Accessed August 5, 2024.

23. National Hemophilia Foundation. What is an inhibitor? **https://www.hemophilia.org/bleeding-disorders-a-z/overview/inhibitors/what-is-an-inhibitor** Accessed August 5, 2024.
24. Noone D, et al. Prophylactic treatment in people with severe hemophilia B in the US: an analysis of real-world healthcare system costs and clinical outcomes. Blood. 2019;134(suppl 1):2118. doi:10.1182/blood-2019-126576
25. Roctavian (valoctocogene roxaparvovec-rvox). [Prescribing Information]. Novato, CA; BioMarin Pharmaceutical Inc. Revised June 2023.
26. Beqvez (fidanacogene elaparvovec-dzkt). [Prescribing Information]. New York, NY; Pfizer, Inc. Revised April 2024.

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.

Date	Comments
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 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 Hegenix.
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.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to 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.