emicizumab (Hemlibra®)

Medicare Advantage Medical Policy # 092
Original Effective Date: 05/01/2025
Current Effective Date: 05/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider emicizumab (Hemlibra®)‡ for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for emicizumab (Hemlibra) will be considered when the following criteria are met:

Initial

- Patient has a diagnosis of hemophilia A (congenital factor VIII deficiency); AND
- Patient has at least ONE of the following indications for routine prophylaxis:
    - Severe hemophilia with less than 1% of normal factor (less than 0.01 IU/mL); OR
    - Documented history of one or more episodes of spontaneous bleeding into joints; AND
- Hemlibra will NOT be used in combination with activated prothrombin complex concentrate (aPCC); AND
- The requested dose is no higher or more frequent than 3 milligrams per kilogram body weight (mg/kg) once weekly for the first 4 weeks followed by a cumulative monthly dose no higher than 6 mg/kg for subsequent weeks.

Continuation

- Patient has a diagnosis of hemophilia A (congenital factor VIII deficiency); AND
- Patient has responded to Hemlibra as evidenced by a decrease in bleeding episodes or a decrease in utilization of factor products or bypassing agents compared to baseline; AND
- Hemlibra will NOT be used in combination with activated prothrombin complex concentrate (aPCC); AND
- The cumulative requested dose does NOT exceed 6 mg/kg per month.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of emicizumab (Hemlibra) when the patient does not have severe hemophilia with less than 1% of normal factor, a history of a spontaneous joint bleed, or in combination with aPCC to be **not medically necessary.****
Based on review of available data, the Health Plan considers the continued use of emicizumab (Hemlibra) when the patient has not demonstrated a decrease in bleeding episodes or a decrease in utilization of factor products while on therapy to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers emicizumab (Hemlibra) when patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Hemlibra is a bispecific factor IXa and factor X-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency). The recommended dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks followed by a cumulative monthly dose of 6 mg/kg. The maintenance dose can be divided into 1.5 mg/kg every week, 3 mg/kg every two weeks, or 6 mg/kg every 4 weeks. Hemlibra carries a boxed warning for thrombotic microangiopathy and thromboembolism which has been reported when on average a cumulative amount of > 100 units/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving Hemlibra prophylaxis. Benefits and risks must be considered if aPCC must be used in a patient receiving Hemlibra prophylaxis.

Hemophilia A is a bleeding disorder that is caused by a deficiency or dysfunction in clotting factor VIII, a protein that enables blood to clot. Because the disorder is transmitted on the X-chromosome, it primarily affects males while females are asymptomatic or mildly affected carriers. The incidence of hemophilia is one in every 5,000 males born in the United States, approximately 80% of whom have hemophilia A. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas (e.g., muscles, central nervous system, gastrointestinal). Bleeding in the joints (hemarthrosis) is the main sign of hemophilia in older children and adults. In newborns and toddlers, bleeding in the head, bleeding from circumcision, and bleeding in the oral cavity are more common. The bleeding manifestations can lead to substantial morbidity, as well as mortality, if not properly treated.

Disease severity is usually defined by plasma levels of factor VIII and has been classified as follows:

- Severe: levels less than 1% of normal
- Moderate: levels 1-5% of normal
- Mild: levels > 5% to 40% of normal

Approximately 25-30% of patients with hemophilia A have severe disease which is defined as factor VIII activity level < 1%. The main treatment strategy for hemophilia A is factor VIII replacement therapy in which administration of the deficient clotting factor is given to achieve adequate hemostasis. Depending on individual patient characteristics such as disease severity and number of bleeds, hemophilia patients may receive prophylactic factor VIII replacement therapy or only receive treatment in response to a bleed ("on demand therapy"). The 2012 World Federation of Hemophilia guideline recommends primary prophylaxis for individuals who are at a high risk of bleeding based on severe factor deficiency (i.e. factor activity level < 1%) and secondary prophylaxis for individuals who have had more than one bleeding episode. However, these guidelines note that there are many considerations that determine the decision to initiate prophylaxis and this decision should be made in conjunction with the patient. Many different factor VIII replacement therapies are FDA-approved.

After administration of factor VIII replacement therapies, some patients may develop an immune response known as a factor VIII inhibitor. These inhibitors are antibodies directed against the deficient factor and are more common among patients with more severe disease. Inhibitors occur in approximately 30% of patients with hemophilia A, usually after the first 20 to 30 days of exposure to factor VIII replacement. The inhibitor interferes with the efficacy of the replacement products used for hemophilia A and can lead to bleeding, morbidity, decreased quality of life, and mortality. An inhibitor should be suspected if a bleeding event is not efficiently controlled by usual doses of factor VIII replacement therapy or if breakthrough bleeding increases while receiving routine prophylaxis. Inhibitors are generally classified as high-titer ($\geq$ 5 Bethesda units) or low titer (< 5 Bethesda Units). Low-titer inhibitors can usually be overcome by using supratherapeutic doses of factor VIII replacement therapy and are usually transient. High-titer inhibitors can be permanent if not eradicated. Bleeding episodes in patients with high-titer inhibitors are often managed with bypassing agents (such as FEIBA® and NovoSeven®)‡ which generate thrombin by bypassing the specific missing coagulation factor. Immune tolerance therapy may also be used to eradicate inhibitors via frequent and regular exposure to high doses of factor VIII concentrates over several months to years. Successful immune tolerance therapy allows the patient to resume the use of standard factor VIII therapies for prophylaxis and management of bleeding.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Hemlibra was approved in November 2017 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor

VIII deficiency) with factor VIII inhibitors. In October 2018, the label was updated to include patients with hemophilia A without factor VIII inhibitors.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Hemlibra for routine prophylaxis in patients with hemophilia A with factor VIII inhibitors was evaluated in two clinical trials: HAVEN 1 in adult and adolescent patients and HAVEN 2 in pediatric patients.

HAVEN 1 was a randomized, multicenter, open-label trial in 109 adult and adolescent males with hemophilia A with factor VIII inhibitors who previously received either episodic or prophylactic treatment with bypassing agents. Patients were randomized 3:1 based on prior use of prophylactic or on-demand bypassing agents to receive Hemlibra once weekly or no prophylaxis. Hemlibra was dosed at 3 mg/kg once weekly for 4 weeks followed by 1.5 mg/kg weekly for the remainder of the study. Dose up-titration to 3 mg/kg once weekly was allowed after 24 weeks on Hemlibra prophylaxis in case of suboptimal efficacy. During the study, two patients underwent up-titration of their maintenance dose to 3 mg/kg weekly. Efficacy was evaluated based on the annualized bleeding rate (ABR) requiring treatment with coagulation factors among patients previously treated with episodic bypassing agents compared to the ABR of those receiving no prophylaxis. The median ABR in patients receiving Hemlibra was 0 compared to 18.8 in those receiving no prophylaxis. This represents an 87% reduction in bleeds with Hemlibra which is statistically significant ($p < 0.0001$).

The HAVEN 2 study was a single-arm, multicenter, open-label, clinical study in pediatric males (age < 12 years, or 12-17 years who weigh < 40kg) with hemophilia A with factor VIII inhibitors. Patients received Hemlibra prophylaxis at 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter. This study is not yet published, but interim results are available. At the time of the interim analysis, efficacy was evaluated in 23 pediatric patients who were <12 years old and had been receiving weekly Hemlibra prophylaxis for at least 12 weeks. The ABR for these 23 patients was 2.9 (95% CI: 1.8, 4.9). 13 of the patients had participated in a prior non-interventional study and had an ABR of 17.2 (95% CI: 0.1, 0.8). This corresponds to a 99% reduction in bleed rate. On Hemlibra prophylaxis, 84.6% of patients had zero treated bleeds.

The efficacy of Hemlibra for routine prophylaxis in patients with hemophilia A without factor VIII inhibitors was evaluated in two clinical trials in adult and adolescent patients: HAVEN 3 and HAVEN 4.

HAVEN 3 was a randomized, multicenter, open-label trial in 152 adult and adolescent males with hemophilia A without factor VIII inhibitors who previously received either episodic or prophylactic treatment with factor VIII. Patients received Hemlibra prophylaxis, 3 mg/kg once weekly for the first 4 weeks followed by either 1.5 mg/kg once every week (arms A and D), 3 mg/kg once every two weeks (arm B), or no prophylaxis (arm C). Patients in arm C could switch to Hemlibra prophylaxis after completing at least 24 weeks without prophylaxis. For arms A and B, dose up-titration to 3 mg/kg once every week was allowed after 24 weeks on Hemlibra prophylaxis for patients who experienced two or more qualifying bleeds. For arm D patients, dose up-titration was allowed after the second qualifying bleed. During the study, five patients underwent up-titration of their maintenance dose; however, this study was not designed to investigate the 3 mg/kg once every week dosing regimen. Efficacy was evaluated after a minimum of 24 weeks of follow-up based on the bleed rate for bleeds requiring treatment with coagulation factors. The study also evaluated the randomized comparison of arms A and C and arms B and C for the efficacy of Hemlibra prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds. Both the Hemlibra 1.5 mg/kg once weekly dose and the 3 mg/kg every two week dose resulted in a statistically significant reduction in treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds. The annual bleed rate for treated bleeds was 1.5 for the Hemlibra 1.5 mg/kg weekly dose, 1.3 for the Hemlibra 3 mg/kg every 2 week dose, and 38.2 for the no prophylaxis group.

The HAVEN 4 study was a single-arm, multicenter, open-label trial in 41 adult and adolescent males with hemophilia A with or without factor VIII inhibitors who previously received either episodic or prophylactic treatment with factor VIII or bypassing agents. Patients received Hemlibra prophylaxis at 3 mg/kg once weekly for the first 4 weeks followed by 6 mg/kg once every 4 weeks thereafter. Efficacy was evaluated in a subgroup of 36 patients with hemophilia A without factor VIII inhibitors based on the bleed rate for bleeds requiring treatment with coagulation factors. The annual bleed rate of treated bleeds was found to be 2.6 in this group with a median observation time of 25.6 weeks (range 24.1-29.4 weeks). Of note, 52.8% of patients had zero treated bleeds in this time frame.

References

1. Hemlibra [package insert]. Genentech, Inc. San Francisco, CA. October 2024
2. Hemlibra Drug Evaluation. Express Scripts. Updated January 2018
3. UpToDate. Factor VIII and factor IX inhibitors in patients with hemophilia.

Policy History

Original Effective Date: 05/01/2025
Current Effective Date: 05/01/2025
02/18/2025 UM Committee Review. New policy.
Next Scheduled Review Date: 02/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J7170
ICD-10 Diagnosis	D66, D68.00-D68.09, D68.311, Z29.8, Z79.899

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety,

effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.