emicizumab (Hemlibra®)

Policy # 00614
Original Effective Date: 04/18/2018
Current Effective Date: 04/18/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), 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 Company may consider emicizumab (Hemlibra®)‡ for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A and factor VIII inhibitors to be **eligible for coverage.**

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

Initial authorization

- The patient has a diagnosis of hemophilia A (congenital factor VIII deficiency); AND
- The patient has a confirmed presence of high-titer factor VIII inhibitors (i.e. factor VIII inhibitor titer of ≥5 Bethesda units per milliliter [mL]); 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 1.5 mg/kg weekly for subsequent weeks.

Re-authorization

- The patient has a diagnosis of hemophilia A (congenital factor VIII deficiency); AND
- The patient has a confirmed presence of high-titer factor VIII inhibitors (i.e. factor VIII inhibitor titer of ≥5 Bethesda units per mL); AND
- The 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
  *(Note: This criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- The requested dose is no higher or more frequent 1.5 mg/kg per week.

When Services Are Considered Not Medically Necessary
The 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 is considered to be **not medically necessary.****

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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 Company 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) with factor VIII inhibitors. The recommended dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks followed by 1.5 mg/kg weekly.

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. 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”). 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 (≥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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal 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 ($p<0.0001$).

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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.

References

1. Hemlibra [package insert]. Genentech, Inc. San Francisco, CA. Nov 2017
2. Hemlibra Drug Evaluation. Express Scripts. Updated January 2018
3. UpToDate. Vactor VIII and factor IX inhibitors in patients with hemophilia. Accessed March 2018.

Policy History

Original Effective Date: 04/18/2018
Current Effective Date: 04/18/2018
04/05/2018 Medical Policy Committee review
04/18/2018 Medical Policy Implementation Committee approval. New policy.
08/30/2018 Coding update
Next Scheduled Review Date: 04/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 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.

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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

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CPT	No codes
HCPCS	C9399, J3490, J3590 Code added effective 07/1/2018: Q9995
ICD-10 Diagnosis	D66, D68.11

*****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 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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.