Utilization Review Policy 125

POLICY: Hemophilia – Hemlibra® (emicizumab-kxwh injection for subcutaneous use – Genentech)

EFFECTIVE DATE: 1/1/2021
LAST REVISION DATE: 4/21/2021

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

OVERVIEW

Hemlibra, a bispecific Factor IXa- and Factor X-directed antibody, is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients aged newborn and older with **hemophilia A** (congenital factor VIII deficiency) with or without factor VIII inhibitors.[1]

Hemlibra is recommended to be given as a loading dose by subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose given either once weekly, once every 2 weeks, or once every 4 weeks.[1] Discontinue prophylactic use of bypassing medications the day before starting Hemlibra. The prophylactic use of Factor VIII products may be continued during the first week of Hemlibra prophylaxis. If appropriate, a patient may self-inject Hemlibra.

Disease Overview

Hemophilia A is an X-linked bleeding disorder caused by a deficiency in Factor VIII.[2-4] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. Sometimes the disorder is caused by a spontaneous genetic mutation. Males primarily have the disorder and most times females are asymptomatic carriers. 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). Hemarthrosis is the main sign of hemophilia in older children and adults. In newborns and toddlers, bleeding in the head (intracranial hemorrhage and extracranial hemorrhage), bleeding from circumcision, and 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 the plasma levels of Factor VIII and have been classified as follows: severe (levels less than 1% of normal [normal plasma levels are 50 to 100 U/dL]), moderate (levels 1% to 5% of normal), and mild (levels > 5%); phenotypic expression may also vary. Approximately 25% to 30% of patients with hemophilia A have severe deficiency whereas 3% to 13% of patients have moderate to mild deficiency. Diagnoses can be substantially delayed, especially in patients with mild disease, as bleeding may not clinically occur. Higher doses than that typically used for these uses of standard half-life products can be given if the patient develops an inhibitor, which develop in approximately 25% of patients.[5] Products that contains Factor VIII, which are given intravenously, are utilized as well as agents such as Hemlibra.[2-4]

Guidelines

Various guidelines discuss Hemlibra.[2,6,7]

- **National Hemophilia Foundation (NHF):** Two documents from the NHF Medical and Scientific Advisory Council (MASAC) provide recommendations regarding Hemlibra (2020).[2,6] In general, Hemlibra has been shown to prevent or reduce the occurrence of bleeding in patients with hemophilia A in adults, adolescent, children and infants, both with and without inhibitors. Subcutaneous administration at more prolonged dosing intervals is viewed as having advantages for some patients compared with intravenous administration of Factor VIII products.[2] Factor VIII prophylaxis continuation during the week after initiation of Hemlibra is a reasonable approach.[6]

However, because Hemlibra steady-state levels are not achieved until after four weekly doses, it may be reasonable to continued Factor VIII prophylaxis in selected patients based on bleeding history, as well as physical history, until they are ready to initiate maintenance dosing. Factor VIII products may be used for breakthrough bleeding events. Data are limited regarding the use of Hemlibra prophylaxis during immune tolerance induction. The MOTIVATE study is exploring use of Hemlibra prophylaxis in patients in immune tolerance induction. Limited data are available in patients with mild to moderate hemophilia A. HAVEN 6 is a trial underway to evaluate Hemlibra in patients with mild or moderate hemophilia A without Factor VIII inhibitors.

- **World Federation of Hemophilia (WFH):** Guidelines from the WFH for hemophilia (2020) feature Hemlibra in a variety of clinical scenarios.[7] It is noted that the subcutaneous administration permits patients to initiate prophylaxis at a very young age. Other key benefits include its long half-life, high efficacy in bleed prevention, and reduction in bleeding episodes in patients with or without inhibitors.

Safety

Hemlibra has a Boxed Warning regarding thrombotic microangiopathy and thromboembolism.[1] Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was given for 24 hours or more to patients receiving Hemlibra prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events when aPCC is given. Discontinue prophylactic use of bypassing agents the day before starting Hemlibra.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Hemlibra. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed for the duration noted below if the patient continues to meet the criteria and dosing for the indication provided. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with Hemlibra as well as the monitoring required for adverse events and long-term efficacy, approval requires Hemlibra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Hemlibra is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. Hemophilia A with Factor VIII Inhibitors. Approve for 1 year if the patient meets the following (A or B):

A) Initial Therapy. Approve if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

i. Patient is using Hemlibra for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; AND

ii. Patient meets one of the following (a or b):

a) Patient has had a positive Factor VIII inhibitor titer greater than 5 Bethesda Units; OR

b) Patient has had a positive Factor VIII inhibitor titer less than or equal to 5 Bethesda Units and meets one of the following [(1) or (2)]:

(1) Patient has had an anamnestic response (current or past) to Factor VIII product dosing; OR
(2) Patient experienced an inadequate clinical response (current or past) to increased Factor VIII product dosing; AND

iii. Prescriber attests that the patient will not be undergoing immune tolerance induction therapy while receiving Hemlibra; AND
iv. Prescriber attests the following regarding use of bypassing agents (a and b):
a) If the patient is currently receiving a bypassing agent for prophylaxis, the bypassing agent therapy will be discontinued the day prior to initiation of Hemlibra; AND
b) Prophylactic use of bypassing agents will not occur while using Hemlibra; AND
Note: Use of bypassing agents for the treatment of breakthrough bleeding is permitted. Examples of bypassing agents include NovoSeven RT (coagulation Factor VIIa [recombinant] for intravenous use), Sevenfact (Factor VIIa [recombinant]-jncw for intravenous infusion), and FEIBA (anti-inhibitor coagulant complex for intravenous use).
v. Prescriber attests the following regarding Factor VIII products (a and b):
a) If the patient is currently receiving a Factor VIII product for prophylactic use, the Factor VIII product will be discontinued within the initial 4-week loading dose period with Hemlibra; AND
b) Prophylactic use of Factor VIII products will not occur while using Hemlibra; AND
Note: Use of Factor VIII products for the treatment of breakthrough bleeding is permitted.
vi. Medication is prescribed by or in consultation with a hemophilia specialist; OR

B) Patient is Currently Receiving Hemlibra. Approve if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
i. Patient is using Hemlibra for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; AND
ii. Prescriber attests that the patient will not be undergoing immune tolerance induction therapy while receiving Hemlibra; AND
iii. Prescriber attests that prophylactic use of bypassing agent will not occur while using Hemlibra; AND
Note: Use of bypassing agents for the treatment of breakthrough bleeding is permitted. Examples of bypassing agents include NovoSeven RT (coagulation Factor VIIa [recombinant] for intravenous use), Sevenfact (Factor VIIa [recombinant]-jncw for intravenous infusion), and FEIBA (anti-inhibitor coagulant complex for intravenous use).
iv. Prescriber attests that prophylactic use of Factor VIII product will not occur while using Hemlibra; AND
Note: Use of Factor VIII products for the treatment of breakthrough bleeding is permitted.
v. Medication is prescribed by or in consultation with a hemophilia specialist; AND
vi. Patient experienced a beneficial response to therapy according to the prescriber.
Note: Examples of a beneficial response to therapy include a reduction in bleeding events, in the severity of bleeding episodes, in the number of bleeding events that required treatment, and/or in the number of spontaneous bleeds.

Dosing. Approve the following dosing regimens (A and B):
A) Loading dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks; AND
B) The patient is receiving one of the following maintenance doses (i, ii, or iii):
i. 1.5 mg/kg by subcutaneous injection once every week, OR
ii. 3 mg/kg SC by subcutaneous injection once every 2 weeks; OR
iii. 6 mg/kg SC by subcutaneous injection once every 4 weeks.

1. Hemophilia A without Factor VIII Inhibitors. Approve for 1 year if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets the following criteria (i, ii, iii, iv, and v):
- **i.** Patient is using Hemlibra for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; AND
- **ii.** Patient meets one of the following criteria (a or b):
  - **a)** Patient has severe to moderate severe disease as defined by pretreatment Factor VIII levels ≤ 2% of normal; OR
  - **b)** Patient has moderate to mild disease as defined by pretreatment Factor VIII levels greater than 2% to less than 40% of normal and meets one of the following criteria [(1), (2), or (3)]:
    - **(1)** Patient has experienced a severe, traumatic, or spontaneous bleeding episode as determined by the prescriber; OR
      Note: An example is a bleed involving the central nervous system.
    - **(2)** Patient has hemophilia-related joint damage, has experienced a joint bleed, or has a specific joint that is subject to recurrent bleeding (presence of a target joint); OR
    - **(3)** Patient is in a perioperative situation and/or has an additional clinical scenario regarding bleeding/bleeding risk in which the prescriber determines the use of Hemlibra is warranted.
      Note: Examples include iliopsoas bleeding or severe epistaxis.
- **iii.** Prescriber attests that prophylactic use of bypassing agent will not occur while using Hemlibra; AND
  Note: Examples of bypassing agents include NovoSeven RT (coagulation Factor VIIa [recombinant] for intravenous use), Sevenfact (Factor VIIa [recombinant]-jncw for intravenous infusion), and FEIBA® (anti-inhibitor coagulant complex for intravenous use).
- **iv.** Prescriber attests the following regarding Factor VIII products (a and b):
  - **a)** If receiving a Factor VIII product for prophylactic use, therapy will be discontinued within the initial 4-week loading dose period with Hemlibra; AND
  - **b)** Prophylactic use of Factor VIII products will not occur while using Hemlibra; AND
    Note: Use of Factor VIII products for the treatment of breakthrough bleeding is permitted.
- **v.** Medication is prescribed by or in consultation with a hemophilia specialist; OR

B) Patient is Currently Receiving Hemlibra. Approve if the patient meets the following criteria (i, ii, iii, iv, and v):
- **i.** Patient is using Hemlibra for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; AND
- **ii.** Prescriber attests that prophylactic use of bypassing agent will not occur while using Hemlibra; AND
  Note: Examples of bypassing agents include NovoSeven RT (coagulation Factor VIIa [recombinant] for intravenous use), Sevenfact (Factor VIIa [recombinant]-jncw for intravenous infusion), and FEIBA (anti-inhibitor coagulant complex for intravenous use).
- **iii.** Prescriber attests that prophylactic use of Factor VIII product will not occur while using Hemlibra; AND
  Note: Use of Factor VIII products for the treatment of breakthrough bleeding is permitted.
- **iv.** Medication is prescribed by or in consultation with a hemophilia specialist; AND
- **v.** Patient experienced a beneficial response to therapy according to the prescriber.
  Note: Examples of a beneficial response include a reduction in bleeding events, in the severity of bleeding episodes, in the number of bleeding events that required treatment, and/or in the number of spontaneous bleeding events.

Dosing. Approve the following dosing regimens (A and B):

A) Loading dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks; AND

B) Patient is receiving one of the following maintenance doses (i, ii, or iii):
- **i.** 1.5 mg/kg by subcutaneous injection once every week, OR

ii. 3 mg/kg by subcutaneous injection once every 2 weeks; OR
iii. 6 mg/kg by subcutaneous injection once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hemlibra is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Hemlibra® injection for subcutaneous use [prescribing information]. South San Francisco, CA and Tokyo, Japan: Genentech/Roche and Chugai Pharmaceutical; June 2020.
2. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised August 2020). MASAC Document #263. Adopted on September 3, 2020. Available at: https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-263-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-other-bleeding-disorders. Accessed on April 19, 2021.
3. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments and its complications. *Lancet*. 2016;388(10040):187-197.
4. Berntorp E, Shapiro. Modern haemophilia care. *Lancet*. 2012;379:1447-1456.
5. Valentino LA, Kempton CL, Kruse-Jarres R, et al, on behalf of the International Immune Tolerance Induction Study Investigators. US guidelines for immune tolerance induction in patients with haemophilia a and inhibitors. *Haemophilia*. 2015;21(5):559-567.
6. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations on the use and management of emicizumab-kxwh (Hemlibra®) for hemophilia A with and without inhibitors. MASAC Document #258. Adopted on March 16, 2020. Available at: https://www.hemophilia.org/sites/default/files/document/files/258_emicizumab.pdf. Accessed on April 18, 2021.
7. Srivastava A, Santagostino E, Dougall A, et al, on behalf of the WFH guidelines for the management of hemophilia panelists and co-authors. WFH guidelines for the management of hemophilia, 3rd edition. *Hemophilia*. 2020;26(Suppl 6):1-158. Available at: WFH Guidelines for the Management of Hemophilia, 3rd edition (wiley.com). Accessed on April 19, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/30/2019
Early Annual Revision	No criteria changes.	10/02/2019
Annual Revision	No criteria changes.	12/02/2020

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Previous criteria required that the patient be using Hemlibra for routine prophylaxis and that the medication is prescribed by or in consultation with a hemophilia specialist. This criteria was retained but now the indications are divided into patients with Factor VIII inhibitors and without Factor VIII inhibitors as well as if the patient is using Hemlibra for initial therapy or if the patient is currently receiving Hemlibra. Other changes per the revised indications are as follows: **Hemophilia A with Factor VIII Inhibitors:** The phrase "with Factor VIII inhibitors" was added to this indication. For both initial therapy and for patients currently receiving Hemlibra, the requirement that the patient be using Hemlibra for routine prophylaxis had the phrase added "to prevent or reduce the frequency of bleeding episodes". Also, the prescriber must attest that the patient will not be undergoing immune tolerance induction therapy while receiving Hemlibra. Additionally, the prescriber must attest that prophylactic use of bypassing agents will not occur while receiving Hemlibra. Examples of bypassing agents were added in a Note; it is also addressed in this section that use of bypassing agents for the treatment of breakthrough bleeding is permitted. The prescriber must attest that prophylactic use of Factor VIII products will not occur while using Hemlibra; it was clarified in a Note that use of Factor VIII products for the treatment of breakthrough bleeding is permitted. For initial therapy only, the patient must have had a positive Factor VIII inhibitor titer greater than 5 Bethesda Units or the patient has had a positive Factor VIII inhibitor titer less than or equal to 5 Bethesda Units and either has had an anamnestic response (current or past) to Factor VIII product dosing or has experienced an inadequate clinical response (current or past) to increased Factor VIII product dosing. Regarding the use of bypassing agents, the prescriber must attest that if the patient is currently receiving a bypassing agent for prophylaxis, the bypassing agent therapy will be discontinued the day prior to initiation of Hemlibra. Regarding Factor VIII products, the prescriber must attest that if the patient is currently receiving a Factor VIII product for prophylactic use, the Factor VIII product will be discontinued within the initial 4-week loading dose period with Hemlibra. For patients currently receiving Hemlibra, the requirement was added that the patient has had a response to therapy according to the prescriber with examples added in a Note. **Hemophilia A without Factor VIII Inhibitors**: The phrase "without Factor VIII inhibitors" was added to this indication. For both initial therapy and for patients currently receiving Hemlibra, the requirement that the patient be using Hemlibra for routine prophylaxis had the phrase added "to prevent or reduce the frequency of bleeding episodes". Additionally, the prescriber must attest that prophylactic use of bypassing agents will not occur while receiving Hemlibra; examples of prophylactic agents were added in a Note. The prescriber must attest that prophylactic use of Factor VIII products will not occur while using Hemlibra; it was clarified in a Note that use of Factor VIII products for the treatment of breakthrough bleeding is permitted. For initial therapy only, the patient must have either severe to moderate severe disease (defined by pretreatment Factor VIII levels ≤ 2% of normal) OR the patient has moderate to mild disease as defined by pretreatment Factor VIII levels greater than 2% to < 40% of normal. Patients with moderate to mild disease must also meet one of the following requirements: 1) patient has experienced a severe, traumatic or spontaneous bleeding episode as determined by the prescriber and an example was added in a Note; 2) patient has hemophilia-related joint damage, has experienced a joint bleed, or has a specific joint that is subject to recurrent bleeding (presence of a target joint); or 3) patient is in a perioperative situation and/or has an additional clinical scenario regarding bleeding/bleeding risk in which the prescriber determines the use of Hemlibra is warranted with examples added in a Note. Additionally, if the patient is receiving Factor VIII product for prophylactic use, the prescriber must attest that therapy will be discontinued within the initial 4-week loading dose period with Hemlibra. For patients currently receiving Hemlibra, the requirement was added that the patient has experienced a beneficial response to therapy according to the prescriber with examples added in a Note.	04/21/2021