PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Hemlibra Prior Authorization Policy
- Hemlibra® (emicizumab-kxwh subcutaneous injection – Genentech/Roche/Chugai)

REVIEW DATE: 05/18/2022

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. Self-administration is not recommended for children < 7 years of age.

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 (2022).[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 continue Factor VIII prophylaxis in selected patients based on bleeding

history, as well as physical , 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 regarding 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 prescription benefit coverage of Hemlibra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Hemophilia A with Factor VIII Inhibitors.** Approve for 1 year if the patient meets one 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] intravenous infusion), Sevenfact (Factor VIIa [recombinant]-jncw intravenous infusion), and FEIBA (anti-inhibitor coagulant complex intravenous infusion).

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 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] intravenous infusion), Sevenfact (Factor VIIa [recombinant]-jncw intravenous infusion), and FEIBA (anti-inhibitor coagulant complex intravenous infusion).

iv. Prescriber attests that 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; 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 bleeding events.

2. 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] intravenous infusion), Sevenfact (Factor VIIa [recombinant]-jncw intravenous infusion), and FEIBA (anti-inhibitor coagulant complex intravenous infusion).

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] intravenous infusion), Sevenfact (Factor VIIa [recombinant]-jncw intravenous infusion), and FEIBA (anti-inhibitor coagulant complex intravenous infusion).

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.

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® subcutaneous injection [prescribing information]. South San Francisco, CA and Tokyo, Japan: Genentech/Roche and Chugai Pharmaceutical; December 2021.
2. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised March 2022). MASAC Document #272. Adopted on April 27, 2022. Available at: 272_Treatment (hemophilia.org). Accessed on May 14, 2022.
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-Jarre s 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 #268. Adopted on April 27, 2022. Available at: https://www.hemophilia.org/sites/default/files/document/files/268_Emicizumab.pdf. Accessed on May 14, 2022.
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.