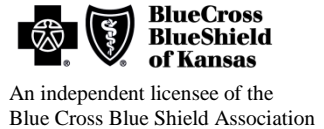


# Medical Policy



## Title: Hemlibra® (emicizumab-kxwh)

➤ **Prime Therapeutics will review Prior Authorization requests**

**Prior Authorization Form:**

<https://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6608KS-HEML.pdf>

**Link to Drug List (Formulary):**

<https://www.bcbsks.com/drugs/ shtml>

### Professional

Original Effective Date: July 1, 2018  
Revision Date(s): July 1, 2018;  
August 24, 2018  
Current Effective Date: August 24, 2018

### Institutional

Original Effective Date: July 1, 2018  
Revision Date(s): July 1, 2018;  
August 24, 2018  
Current Effective Date: August 24, 2018

**State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).**

**The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.**

**The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.**

**If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.**

### DESCRIPTION

The intent of the Hemlibra Prior Authorization (PA) with Quantity Limit (QL) program is to appropriately select patients for treatment according to product labeling and/or clinical studies and/or clinical practice guidelines and according to dosing recommended in product labeling. The PA program will consider emicizumab-kxwh appropriate for patients needing prophylaxis therapy with a diagnosis of Hemophilia A with inhibitors to factor VIII, the requested agent is prescribed by a specialist or the prescriber has consulted with a specialist, and when the patient has an inhibitor level of 5 BU or has tried either ITT or a bypassing agent. If the patient is using activated prothrombin complex

concentrate (aPCC) as on demand therapy – the patient will be monitored for thrombotic microangiopathy and thromboembolism. The patient's weight must be provided and the dose is within FDA labeled dosing. Hemlibra will not be approved for patients who have a contraindication to the requested agent and for those patients whose prescriber has not discussed the need to maintain a treatment log for bleeds.

### Target Agents

- **Hemlibra®** (emicizumab-kxwh)

### FDA Approved Indications and Dosage<sup>1</sup>

Agent	Indication	Dosing
Hemlibra® (emicizumab-kxwh)	<ul style="list-style-type: none"> <li>• 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</li> </ul>	<ul style="list-style-type: none"> <li>• 3mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly</li> </ul>

## POLICY

### Prior Authorization and Quantity Limit Criteria for Approval

#### Initial Evaluation

**Hemlibra® (emicizumab-kxwh) will be approved for use when ALL of the following are met:**

1. The patient has a diagnosis of hemophilia A with documented Factor VIII inhibitors  
**AND**
2. The requested agent is prescribed for prophylactic use  
**AND**
3. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or has consulted with a specialist in the area of the patient's diagnosis  
**AND**
4. ONE of the following:
  - A. The patient's inhibitor level is  $\geq 5$  BU  
**OR**
  - B. The patient has tried and had an inadequate response to Immune Tolerance Therapy (ITT) [Immune Tolerance Induction (ITI)]  
**OR**
  - C. The patient is using a bypassing agent (Feiba, NovoSeven) for on-demand treatment and is not adequately controlled  
**OR**

- D. The patient using a bypassing agent for prophylaxis and had an inadequate response  
**OR**
- E. The patient is using more than 5 doses per week of a bypassing agent  
**OR**
- F. The patient has a documented intolerance, FDA labeled contraindication or hypersensitivity to a bypassing agent  
**AND**
- 5. If the patient is using a Factor VIII product (e.g., Advate, Adynovate, Eloctate, Nuwiq, Recombinate, Xyntha) or a bypassing agent (e.g., Feiba, NovoSeven) for prophylaxis treatment, the prophylaxis with the Factor VIII product or bypassing agent will be discontinued (on-demand treatment is acceptable to continue)  
**AND**
- 6. If the patient is receiving Feiba [activated prothrombin complex concentrate (aPCC)] for breakthrough bleeds, BOTH of the following:
  - A. The patient will be monitored for thrombotic microangiopathy and thromboembolism  
**AND**
  - B. The prescriber has counseled the patient on the maximum dosages of Feiba to be used (i.e., no more than 100 u/kg/24 hours)  
**AND**
- 7. ONE of the following:
  - A. The prescriber has discussed with the patient that a treatment log, documenting at least 6 months of bleeds prior to starting the requested agent, and which includes **ALL** of the following must be maintained and a copy will be submitted (via prescriber or pharmacy) for renewal purposes
    - i. Date of the bleed  
**AND**
    - ii. The treatment used (include the brand name and number of units administered)  
**AND**
    - iii. The number of doses required to treat the bleed  
**OR**
  - B. If there is no historical treatment log, the prescriber has discussed with the patient that a treatment log for bleeds which includes **ALL** of the following must be maintained and a copy will be submitted (via prescriber or pharmacy) for renewal purposes
    - i. Date of the bleed  
**AND**
    - ii. The treatment used (include the brand name, and number of units administered)  
**AND**
    - iii. The number of doses required to treat the bleed  
**AND**

8. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent  
**AND**
9. The prescriber has provided the patient's weight  
**AND**
10. The requested dose is within the FDA labeled dosing based on the patient's weight  
**AND**
11. ONE of the following:
  - A. The patient is requesting induction therapy and maintenance therapy and the requested quantity for maintenance therapy is NOT greater than the allowed quantity (see Hemlibra Weight-Based Approvable Quantities chart)  
**OR**
  - B. The patient is requesting maintenance therapy only and the requested quantity is NOT greater than the allowed quantity (see the Hemlibra Weight-Based Approvable Quantities chart)

**Length of Approval:** 6 months

### **Renewal Evaluation**

1. The patient has been previously approved for the requested agent through the Prime Therapeutics Prior Authorization process  
**AND**
2. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or has consulted with a specialist in the area of the patient's diagnosis  
**AND**
3. The prescriber has provided a copy of the patient's treatment logs for bleeds that includes ALL of the following:
  - A. Date of bleed  
**AND**
  - B. The treatment used (include the brand name and number of units administered)  
**AND**
  - C. The number of doses required to treat the bleed  
**AND**
4. ONE of the following:
  - A. The patient has shown clinical benefit since starting the requested agent (i.e., less breakthrough bleeds as documented in the treatment log)  
**OR**
  - B. The prescriber has submitted documentation supporting the continued use of the requested agent  
**AND**

5. If the patient is receiving Febia [activated prothrombin complex concentrate (aPCC)] for breakthrough bleeds, the patient will be monitored for thrombotic microangiopathy and thromboembolism  
**AND**
6. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent  
**AND**
7. The prescriber has provided the patient's weight  
**AND**
8. The requested dose is within the FDA labeled dosing based on the patient's weight  
**AND**
9. The requested quantity for maintenance therapy is NOT greater than the allowed quantity (see the Hemlibra Weight-Based Approvable Quantities chart)

**Length of approval:** 12 months

Agent	Contraindication(s)
Hemlibra	None

### Hemlibra Weight-Based Approvable Quantities

Weight (lb)	Weight (kg)	30 mg/1 mL vials	60 mg/0.4 mL vials	105 mg/0.7 mL vials	150 mg/1 mL vials
≤ 44	≤ 20	4 mL (4 vials) per 28 days	0	0	0
> 44 and ≤ 88	> 20 and ≤ 40	0	1.6 mL (4 vials) per 28 days	0	0
> 88 and ≤ 154	> 40 and ≤ 70	0	0	2.8 mL (4 vials) per 28 days	0
> 154 and ≤ 220	> 70 and ≤ 100	0	0	0	4 mL (4 vials) per 28 days
> 220 and ≤ 242	> 100 and ≤ 110	0	1.6 mL (4 vials) per 28 days	2.8 mL (4 vials) per 28 days	0
> 242 and ≤ 264	> 110 and ≤ 120	0	0	5.6 mL (8 vials) per 28 days	0
> 264 and ≤ 286	> 120 and ≤ 130	0	0	5.6 mL (8 vials) per 28 days	0
> 286 and ≤ 330	> 130 and ≤ 150	0	0	2.8 mL (4 vials) per 28 days	4 mL (4 vials) per 28 days
>330 and ≤ 440	> 150 and ≤ 200	0	0	0	8 mL (8 vials) per 28 days
> 440	> 200	Use any combination of 3 vials of 60 mg, 105 mg, or 150 mg vials to reach dose of 1.5 mg/kg			

- The 60 mg, 105 mg and/or 150 mg vials are the same concentration (150 mg/mL) and may be combined for dosing
- The 30 mg vials (30 mg/mL) should NOT be combined with the 60 mg, 105 mg and/or 150 mg vials

## **RATIONALE**

Hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) with a prevalence of approximately 1 in 5,000 births.<sup>2</sup>

Within the hemophilia A population, inhibitors to Factor VIII develop in approximately 15–30% of patients. Development of inhibitors usually occurs shortly after replacement therapy has been initiated. These inhibitors are antibodies (primarily IgG) directed against the specific deficient factor.<sup>11</sup> Patients with inhibitors are at increased risk for difficult-to-control bleeding and complications; therefore, bleed prevention or reduction is of crucial importance.<sup>2-4</sup> Repeated bleeding leads to inflammation, erosion, arthritis, and high rates of disability.<sup>3</sup>

The current World Hemophilia Federation Guidelines for the Management of Hemophilia state that treatment of patients with inhibitors depends on several factors including the titer of the inhibitor, records of clinical response to product, and site and nature of the bleed. Patients with a low responding inhibitor or those with a high responding inhibitor but low titer may be treated with factor product at a much higher dose. With an inhibitor level  $\geq 5$  BU, the likelihood that specific factor replacement will be effective in overwhelming the inhibitor without ultra-high dose continuous infusion therapy and alternative agents include bypassing agents such as recombinant factor VIIa and activated prothrombin complex concentrate (aPCC) is extremely low.<sup>10</sup> For high-titer inhibitors, the Medical and Scientific Advisory Council (MASAC) recommends immune tolerance induction as the best option for inhibitor eradication or, depending on type of inhibitor (low or high-responding), current titer of inhibitor, location of the bleed, and previous response, bypassing agents could be used.<sup>8</sup>

The Institute for Clinical and Economic Review (ICER) states that patients with low levels of inhibitors who bleed can often be treated with higher doses of factor VIII, while these with high levels of inhibitors are treated with bypassing agents such as activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII. Treating prophylactically with bypassing agents can generate very high costs and even with bypassing agent prophylaxis, many patients continue to have frequent episodes of bleeding.<sup>12</sup>

In some patients, inhibitors can be eradicated by inducing immune tolerance (ITI) with high and continual doses of factor VIII, which is also expensive but allows for prophylactic and on-demand therapy with factor VIII alone when successful. ITI is typically attempted when patients first develop factor VIII inhibitors, which occurs very early in the course of therapy with factor VIII. ICER suggests using Hemlibra for patients who will not be treated with ITI or for whom ITI has been unsuccessful. The consensus is divided on whether ITI should be initiated when a patient develops inhibitors to factor VIII or if Hemlibra could potentially obviate the need for ITI due to the expected decrease over time of the inhibitors in the absence of treatment with factor VIII. Some patients who are receiving ITI continue to have frequent bleeding while ITI is being attempted. Currently, these patients may receive prophylaxis with bypassing agents, but Hemlibra could potentially be used for prophylaxis during ITI.<sup>12</sup>

The National Hemophilia Foundation states that keeping an accurate treatment log is an essential part of managing bleeding disorders and should include the following information for bleeding episodes: 1) date and time of the bleed 2) location and severity of the bleed 3) how quickly the bleed was treated 4) the treatment used with brand name, expiration date, lot number, and

number of units administered noted 5) additional steps taken to manage the bleed, and 6) level of pain.<sup>6</sup>

### **Efficacy<sup>1, 6</sup>**

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 is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Emicizumab bridges activated factor IX and factor X to restore the function of activated factor VIII. The efficacy of Hemlibra for routine prophylaxis in patients with hemophilia A with FVIII inhibitors was evaluated in 2 clinical trials.

The Haven 1 study (NCT02622321):<sup>1</sup>

This was a randomized phase 3, multicenter, open label trial that enrolled 109 adult and adolescent males (ages 12-75 and weighing > 40kg) with hemophilia A with FVIII inhibitors who previously received either episodic (on-demand) or prophylactic treatment with bypassing agents (rFVIIa and/or aPCC). The patients were randomized into 4 arms. Patients who received on-demand treatment with bypassing agents prior to the study entry were randomized 2:1 into arms A and B respectively. Arm A patients received prophylactic emicizumab. The active comparator arm B patients did not receive emicizumab prophylaxis. Arm C was an experimental arm and enrolled patients who received prophylactic bypassing agents prior to the study entry. Arm D was for patients that used on-demand or prophylactic therapy with bypassing agents but were unable to enroll in arms A through C. After at least 24 weeks on-study, the patients in Arm B had the opportunity to switch to emicizumab prophylaxis. All Arms continued to receive episodic bypassing agent therapy to treat breakthrough bleeds.

The primary outcome measure of the Haven 1 study was the Annualized Bleed Rate (ABR) for Treated Bleeds (Arms A and B). Secondary outcome measures included ABR for various other bleeds including all Bleeds (treated or untreated), all joint bleeds, targeted joint bleeds and spontaneous bleeds. The ABR for treated bleeds was 2.9 in the emicizumab group vs 23.3 in the no prophylaxis group resulting in 87% reduction in ABR (95%CI p<0.0001). Secondary outcomes had similar results (80-92% reduction all with 95%CI and p <0.0001).

The Haven 2 trial (NCT02795767):<sup>1</sup>

This was a non-randomized, single-arm, multicenter, open-label, in pediatric males (ages <12, or ages 12-17 weighing <40 kg) with hemophilia A with FVIII inhibitors. The patients received emicizumab 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter.

The primary outcome measure was efficacy of weekly emicizumab prophylaxis, including the efficacy of weekly emicizumab compared with previous episodic (on-demand) and prophylactic bypassing agent, measured by ABR. An interim analysis of 23 patients was used for FDA approval in this population. The ABR for all treated bleeds was 0.2 (95% CI). The intra-patient analysis comparing emicizumab to previous therapy showed a 99% reduction in bleed rate (previous ABR while on bypassing agents was 17.2 and 0.2 after emicizumab prophylaxis) in the 13 patients in this group. Since the time from FDA approval to now, this study has expanded and currently has 3 arms. Arm A consists of patients using 1.5 mg/kg every week. Arm B consists of patients using

3 mg/kg every 2 weeks. Arm C consists of patients using 6mg/kg every 4 weeks. At this time, the expansion is ongoing and no data is reported.

**Safety<sup>1</sup>**

Due to the increased coagulation potential with emicizumab, if the patient is using a bypassing agent as prophylactic use, it is recommended to discontinue prophylactic use of bypassing agents the day before starting emicizumab. On-demand use of bypassing agents can be continued with caution based on black box warning.

Hemlibra has no limitations of use but the prescribing information contains a black box warning concerning thrombotic microangiopathy and thromboembolism when given with activated prothrombin complex concentrate (aPCC). If these agents must be used together, the patient should be monitored for the development of thrombotic microangiopathy and/or thromboembolism. If one of these events occurs, aPCC therapy should be discontinued and Hemlibra therapy should be interrupted and the event managed as clinically indicated. Consider the benefits and risks of resuming Hemlibra prophylaxis following complete resolution of the event on a case-by-case basis.

Do not use different vials of different concentrations of Hemlibra when combining vials to administer prescribed dose. The 60 mg, 105 mg, and/or 150 mg vials are the same concentration (150 mg/mL) and may be combined for dosing. The 30 mg vials (30 mg/mL) should not be combined with the 60 mg, 105 mg, and 150 mg vials.

The use of any therapeutic protein carries the potential for immunogenicity.<sup>1</sup> There has been a report of at least one patient in the ongoing HAVEN 2 clinical trial that developed an anti-emicizumab antibody and experienced loss of efficacy with Hemlibra resulting in discontinuation of the drug and the decision was made to resume therapy with the patient’s previous (before using Hemlibra) regimen.<sup>13</sup> There are no current available assays in the United States for determination of anti-drug antibodies directed against emicizumab. The Medical and Scientific Advisory Council (MASAC) recommends that if a patient and provider have suspicion of an anti-drug antibody outside of the ongoing clinical trial program, they should contact the manufacturer for guidance on subsequent evaluation.<sup>13</sup>

<b>REVISIONS</b>	
07-01-2018	Policy published July 1, 2018. Policy effective July 1, 2018. Policy added to the bcbsks.com web site.
08-24-2018	In Policy section: <div style="border: 1px solid black; padding: 5px;">                     Summary of revisions:                     <ul style="list-style-type: none"> <li>• Re-organized prophylaxis on factor VIII or bypassing agent to its own bullet point due to confusion</li> <li>• Removed requirement that if patient is on ITT that ITT will be discontinued due to ICER update</li> <li>• Updated Weight Based Approvable Quantities to include both mL and number of vials</li> </ul> </div> Initial Evolution <ul style="list-style-type: none"> <li>▪ Removed "If the patient is using a Factor VIII product for prophylaxis treatment, the prophylaxis with the Factor product will be discontinued (on-demand treatment is acceptable to continue)", "If the patient is using a bypassing agent (e.g., Feiba, NovoSeven) for prophylaxis treatment, the prophylaxis with the bypassing agent will be</li> </ul>



<b>REVISIONS</b>	
	<p>discontinued (on-demand treatment with a bypassing agent is acceptable to continue)" and "Prophylaxis with the bypassing agent will be discontinued before starting the requested agent (on-demand treatment with bypassing agent is acceptable to continue) to read in Item 5 "If the patient is using a Factor VIII product (e.g., Advate, Adynovate, Eloctate, Nuwiq, Recombinate, Xyntha) or a bypassing agent (e.g., Feiba, NovoSeven) for prophylaxis treatment, the prophylaxis with the Factor VIII product or bypassing agent will be discontinued (on-demand treatment is acceptable to continue)"</p> <ul style="list-style-type: none"> <li>▪ Removed "ITT will be discontinued before starting the requested agent"</li> <li>▪ In Item 7 A and 7 B removed "Location and severity of the bleed" and "How quickly the bleed was treated".</li> <li>▪ In Item 7 A ii and 7 B ii removed "expiration date, lot number" to read "The treatment used (include the brand name and number of units administered)"</li> <li>▪ In Item 11 A added "patient is requesting induction therapy and maintenance therapy and the", "for maintenance therapy", and "(see Hemlibra Weight-Based Approvable Quantities chart)" to read "The patient is requesting induction therapy and maintenance therapy and the requested quantity (dose) for maintenance therapy is NOT greater than the program allowed quantity (see Hemlibra Weight-Based Approvable Quantities chart)"</li> <li>▪ In Item 11 B added "patient is requesting maintenance therapy only and the" "NOT" and "(see the Hemlibra Weight-Based Approvable Quantities chart)" to read "The patient is requesting maintenance therapy only and the requested quantity is NOT greater than the allowed quantity (see the Hemlibra Weight-Based Approvable Quantities chart)"</li> <li>▪ Removed "The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit"</li> </ul> <p><u>Renewal Evaluation</u></p> <ul style="list-style-type: none"> <li>▪ In Item 3 removed "Location and severity of the bleed" and "How quickly the bleed was treated".</li> <li>▪ In Item 3 B removed "expiration date, lot number" to read "The treatment used (include the brand name and number of units administered)"</li> <li>▪ In Item 9 added "for maintenance therapy" and "(see the Hemlibra Weight-Based Approvable Quantities chart)" to read "The requested quantity for maintenance therapy is NOT greater than the allowed quantity (see the Hemlibra Weight-Based Approvable Quantities chart)"</li> <li>▪ Removed "BOTH of the following:                             <ul style="list-style-type: none"> <li>i. The requested quantity (dose) is greater than the program quantity limit AND</li> <li>ii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit"</li> </ul> </li> <li>▪ Updated the Hemlibra Weight-Based Approvable Quantities chart.</li> <li>▪ Removed the Quantity Limit chart.</li> </ul>
	Rationale section updated
	References updated

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