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HEMOPHILIA A PROPHYLAXIS WITH HEMLIBRA

Drug Regimen Review Center

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Introduction

Patients with hemophilia A have a deficiency in the clotting factor VIII (FVIII), a protein essential for maintaining hemostasis. With this disease, patients may experience prolonged or excessive bleeding induced by trauma or surgery. Spontaneous bleeding often re-occurs within joints, causing arthropathy, decreased range of motion, and reduced quality of life—most common in severe disease. Replacement FVIII products are used for both prophylaxis and episodic management of bleeds. A prophylaxis treatment approach for the prevention of bleeding is optimal, especially for patients with severe disease when started early in life, since this reduces the risk of joint damage.

Treatment of the disease becomes substantially more complicated when a patient develops an inhibitor (ie, neutralizing antibody) to the FVIII product, which can render FVIII prophylaxis therapy ineffective. The Food and Drug Administration (FDA) granted a priority review for emicizumab-kxwh (Hemlibra) since there are limited therapies available for patients with FVIII inhibitors. Emicizumab-kxwh (referred to as emicizumab from here on) is a bispecific factor IXa- and factor X-directed antibody that mimics the function of activated FVIII. It is approved for routine prophylaxis in patients with hemophilia who have developed FVIII inhibitors. The purpose of this report is to review the appropriate use of emicizumab and factors that can influence efficacy and safety outcomes.

Methodology

A literature search for systematic reviews addressing the efficacy and safety of medications for the management of hemophilia A patients with inhibitors was conducted in the Cochrane Library. Information regarding emicizumab was searched in OvidMedline, Embase, the FDA website, the ClinicalTrials.gov website, and various treatment guidelines pertaining to the management of hemophilia A. Relevant information from the *Utah Medicaid Pharmacy and Therapeutics Committee Drug Class Review: Factor VIII Replacement Products Indicated for Hemophilia A* report, dated July 2018, prepared by the University of Utah's Drug Regimen Review Center, was incorporated into this document. Search strategies for the literature databases are provided in **Appendix A**.

Hemophilia A Overview

Congenital hemophilia A is an X-linked, recessive, lifelong bleeding disorder.¹ About 99% of the hemophilia A population is male,² and the occurrence of hemophilia A is about 1 out of every 5,000 male births in the United States (US).¹ Although rare, females may also be diagnosed with hemophilia A, but they are most often asymptomatic carriers of the disease.¹ Bleeding manifestations in patients with hemophilia A are generally dependent on the degree of factor FVIII deficiency.³ About 60% of patients diagnosed with hemophilia A have severe disease, defined as a FVIII activity level below 1% of normal.⁴ Patients are diagnosed at a young age, usually in the first month of life for severe hemophilia, and by 36 months of age for mild hemophilia. About two-thirds of cases have a known family history.^{1,5} **Table 1** describes the classification of hemophilia severity endorsed by the International Society on Thrombosis and Haemostasis.³

Table 1. Hemophilia A Severity Classification^{3,6}

Severity	Clotting Factor Activity Level (plasma concentration)	Percentage breakdown of the hemophilia A population ⁴
Mild	5 to <40% of normal (5-40 IU/dL)	About 25% of cases
Moderate	1 to <5% of normal (1-5 IU/dL)	About 15% of cases
Severe	<1% of normal (<1 IU/dL)	About 60% of cases

In patients with hemophilia A, bleeding episodes can be induced by trauma or surgery.¹ Recurrent, spontaneous bleeding into joints and soft tissues is common in patients with severe FVIII deficiency.⁶ The majority of patients with severe hemophilia A experience as many as 20 to 30 bleeding episodes a year, with most episodes localized to joints, primarily the ankles, knees, and elbows.^{7,8} Joints that have repetitive bleeding (ie, 3 or more spontaneous bleeds within a consecutive 6 month period) are called target joints.³

Quality of life is diminished as the long-term effects of recurrent bleeds manifest as chronic joint disease, decreased range of motion, chronic pain, and disability. Disease progression can lead to the patient needing a radiosynovectomy, joint fusion, or joint replacement.^{5,9} Other complications include seizures and paralysis if bleeding occurs in the brain, or death due to unstoppable bleeding or bleeding into a vital organ.¹⁰

Substitution therapy with replacement factor VIII products is the cornerstone of hemophilia A management. Treatment regimens with FVIII products aim to not only prevent and treat potentially life-threatening bleeds on an episodic basis, but also include routine prophylaxis to prevent bleeds and the development of arthropathy.¹¹⁻¹³ Several hemophilia organizations including National Hemophilia foundation Medical and Scientific Advisory Council (MASAC) and the World Federation of Hemophilia recommend routine prophylaxis therapy (continued exposure to FVIII) as the most optimal approach for persons with severe hemophilia.^{6,14} The 2010 United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) guideline recommends that prophylaxis with FVIII should be initiated, ideally before the second joint bleed, for children with severe hemophilia and continued at least until reaching physical maturity.¹⁵

While it is unclear when to stop prophylaxis,^{6,14} continuation is generally tailored to the patient's bleeding frequency and preferences. The UKHCDO recommends re-evaluating the prophylaxis regimen every 6 months, and adjusting dosages based on the frequency of breakthrough bleeds.¹⁵ Continuation of prophylaxis is recommended if the patient experiences any of the following while not receiving prophylaxis: (a) hemarthrosis, (b) bleeding episodes that negatively impact the patient's mobility or ability to work, or (c) recurrence of intracranial hemorrhage.¹⁵ Overall, decisions regarding the treatment strategy and dose modifications as the patient ages are determined on an individual basis, based on the patient's bleeding phenotype, venous access, response to therapy, co-morbidities, and patient/caregiver preferences.

The prophylactic use of replacement FVIII products requires intravenous administration, usually multiple times per week. Intravenous infusion of hemostatic products are commonly performed in the home by the patient or caregiver for prophylaxis or the management of mild episodic bleeding. A comprehensive Hemophilia Treatment Center (HTC) can offer the best care and education for patients who must learn aseptic infusion techniques and medication storage requirements.¹⁶ The HTC can be contacted upon an episodic bleed for consultation regarding the appropriate dosing strategy to resolve bleeding. Life- or limb-threatening bleeding usually requires in-patient management.¹⁷

Inhibitors to Replacement FVIII Products

The most challenging aspect of replacement FVIII therapy is the development of inhibitors (ie, neutralizing antibodies) to the replacement factor product. Inhibitors can diminish the effectiveness of the replacement factors and ultimately render a product ineffective at the usual dose.¹⁸ The development of inhibitors limits treatment options available for a patient and increases therapy costs.^{1,19-21} The incidence of inhibitors is between 20% to 35% for patients with severe disease and 3% to 13% for patients with mild-to-moderate disease.²² Previously untreated patients (PUPs) with severe disease are of particular interest since inhibitor development is high, approximately 30%, in the early stages of prophylaxis therapy (less than 50 exposure days to exogenous FVIII).^{23,24} Testing for inhibitors is performed regularly during therapy, especially during prophylaxis initiation, when switching between FVIII products, after intensive therapy, and when the patient's response to therapy is suboptimal.²⁵

If the FVIII activity does not rise as expected upon administration of the factor, an inhibitor should be suspected and investigated using the Nijmegen Bethesda inhibitor assay.³ A positive inhibitor titer result that is less than 5 Bethesda units (BU) per milliliter is classified as a low-titer inhibitor; patients are described as "low responders."²⁶ A positive inhibitor titer result of greater than 5 BU/mL is classified as a high-titer inhibitor; patients are described as "high responders."²⁶ The National Hemophilia Foundation summarizes that the use of a FVIII replacement therapy for high-responding patients may only resolve bleeding if the inhibitor titer is 10 BU/mL or less; whereas, low-responding patients can usually be managed using higher and more frequent doses of a FVIII product to overcome the inhibitor.²⁶

Acquired Hemophilia A

Another form of FVIII hemophilia is an acquired autoimmune disorder caused by the development of autoantibodies that inactivate FVIII. It mostly occurs in the elderly, but is also associated with pregnancy, malignancy, other autoimmune disorders (ie, rheumatoid arthritis), or may be triggered by an allergic reaction to a medication.²⁷ Acquired hemophilia manifests with extensive cutaneous purpura, gastrointestinal bleeding, and muscle bleeding.^{27,28} This condition will not be a focus of this review since emicizumab is only indicated for congenital hemophilia A. Moreover, the treatment approach for this condition is different compared to congenital hemophilia, as other non-overlapping treatment guidelines and approved medications apply.

Hemlibra (emicizumab-kxwh)

Emicizumab was developed as a substitute for missing FVIII in patients with hemophilia A and FVIII inhibitors. Its molecular structure differs from FVIII enough such that no interaction between emicizumab and the patient's FVIII inhibitor is expected; nor does emicizumab induce the patient's FVIII-inhibitor titer.^{2,29} Emicizumab is a monoclonal, modified immunoglobulin G4 (IgG4), antibody that dually binds to factor IXa and factor X, thereby facilitating factor X activation; this is the normal function of activated factor VIII.^{2,29} Factor X activation allows for the continued functioning of the clotting factor pathway in absence of FVIII.²⁹

Emicizumab was approved by the FDA in November of 2017. It is indicated for routine prophylaxis, to prevent or reduce bleeding episodes, in adult and pediatric patients with hemophilia A who have developed inhibitors to FVIII therapy.²⁹ There is no requirement for a specific disease severity per the FDA-approved product labeling. Emicizumab is administered as a subcutaneous injection, initiated at 3 mg/kg once weekly for 4 weeks, followed by 1.5 mg/kg once weekly thereafter.²⁹ It is available in 2 concentrations. The 150 mg/mL concentration comes in 3 different volumes.

- **30 mg/mL:** 1 mL vial (containing 30 mg)
- **150 mg/mL:** 0.4 mL vial (containing 60 mg); 0.7 mL vial (containing 105 mg); and 1 mL vial (containing 150 mg)

The mean steady-state trough plasma concentration is 52.8 ± 13.5 $\mu\text{g/mL}$ and the mean elimination half-life is 27.8 ± 8 days.²⁹ The long half-life must be considered as some residual drug effects, including the potential for laboratory-test interactions, may persist to 6 months after the last dose. The pharmacokinetics of emicizumab were unaffected by age (3 to 75 years), presence of FVIII-inhibitor, or mild to moderate hepatic impairment (defined as total bilirubin 1 to ≤ 3 times the upper limit of normal).²⁹

Table 2 provides selected product information from the FDA-approved product labeling.

Table 2. Hemlibra Product Information, Indication, and Dosing²⁹

Dosage Form and Storage	Emicizumab-kxwh: subcutaneous injection <ul style="list-style-type: none">▪ Modified immunoglobulin G4 (IgG4) antibody produced in a Chinese hamster ovary cell line▪ Refrigerate (36 to 46°F); the total combined time out of refrigeration (at up to 86°F) should not exceed 7 days
FDA Approved Indication	<ul style="list-style-type: none">▪ For <u>routine prophylaxis</u> in adults and pediatric patients with Hemophilia A and factor VIII inhibitors, to prevent or reduce bleeding frequency episodes
Dosage and Administration	Dose: 3 mg/kg via subcutaneous injection once weekly for the first 4 weeks, then 1.5 mg/kg once weekly thereafter <ul style="list-style-type: none">▪ Do not combine vials of different concentrations (ie, the 30 mg/mL vial with a 150 mg/mL vial) when mixing contents to administer the prescribed dose

Table 2. Hemlibra Product Information, Indication, and Dosing²⁹

	<ul style="list-style-type: none"> ▪ If employing prophylactic therapy with bypassing agents (eg, activated prothrombin complex concentrate or activated factor VII) prior to initiating emicizumab, the patient must discontinue the bypassing agent prophylaxis the day before starting emicizumab ▪ Patients may learn self-injection techniques under the guidance of a healthcare provider; however, self-injection is not recommended for patients younger than 7 years of age per product label ▪ Must rotate injection sites (upper outer arms, thighs, or any quadrant of abdomen)
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I. Place in Therapy

Table 3 provides a list of the additional products indicated for patients with hemophilia A who have developed inhibitors to FVIII. In addition to emicizumab, the activated prothrombin complex concentrate, Feiba, is the only other agent with an approved indication for routine prophylaxis in patients with hemophilia A and FVIII inhibitors.

Table 3. Additional Products Indicated for Patients with Hemophilia A and FVIII Inhibitors^{30,31}

BRAND NAME <i>Other names</i> (Approval date)	Indications
FEIBA <i>Anti-Inhibitor Coagulant Complex, Human; Activated Prothrombin Complex Concentrate (aPCC)</i> (1986)	Indicated for Hemophilia A and B patients with inhibitors <ul style="list-style-type: none"> • To control and prevent bleeding episodes • For perioperative management • <u>For routine prophylaxis to prevent or reduce the frequency of bleeding episodes</u>
NOVOSEVEN RT <i>Coagulation Factor VIIa, Recombinant; Activated Factor VII (rFVIIa)</i> (1999)	Indicated for adults and children with (1) hemophilia A or B and who have inhibitors, (2) congenital Factor VII (FVII) deficiency, or (3) Glanzmann’s thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets <ul style="list-style-type: none"> • <u>For treatment of bleeding episodes</u> • <u>For perioperative management</u> Indicated for adults with acquired hemophilia <ul style="list-style-type: none"> • For treatment of bleeding episodes • For perioperative management

Decisions regarding the appropriate treatment regimen for managing a patient with an inhibitor depends on several factors including the inhibitor titer, the presence of an active bleed, and prior response to inhibitor mitigation. Treatment regimens may include immune tolerance induction (ITI), bypassing agents (eg, recombinant activated FVII and activated prothrombin complex concentrate), or the use of the monoclonal antibody, emicizumab.³²

Immune tolerance induction consists of administering significantly higher than standard doses of a clotting factor (usually the factor product that the patient developed an inhibitor to) in order to induce tolerance and neutralize the inhibitor.²⁵ MASAC states that

“[f]or high-titer inhibitors, immune tolerance induction (ITI) is the best option for inhibitor eradication.”³² There are a number of protocols that have been used for ITI. In addition to various dosages of FVIII, protocols may employ immunosuppressants or prophylaxis with bypassing agents.¹⁸ Patient attributes correlated with ITI success include a lower pre-ITI inhibitor titer (<10 Bethesda units [BU]), a lower historical peak inhibitor titer (<200 BU), and a lower peak inhibitor titer while on ITI.³³ It is estimated that approximately 20% to 40% of patients fail ITI,² and about 12% of those who are successful with ITI relapse within 1 year.²⁵

Bypassing agents (Feiba [aPCC] and NovoSeven [rFVIIa]) are employed for the control and prevention of bleeds, including routine prophylaxis, in patients with inhibitors; however, each option may be cumbersome for patients to use long-term. Feiba is indicated for routine prophylaxis, administered every-other-day and requires a slow infusion by 2 units per kg body weight per minute.³⁰ Feiba may also increase the inhibitor titer since it contains low amounts of FVIII.³⁰ NovoSeven is not approved for routine prophylaxis, but is used off-label for prophylaxis with a once-daily administration frequency.^{34,35} Valentino et al, explained that patient response to bypassing agents is unpredictable and response to the same product can vary between each bleeding episode.⁷ In a 2018 MASAC recommendation document the authors list bypassing agents and emicizumab as options for the management of patients with inhibitors, without specifying preference for one product over another with respect to routine prophylactic therapy.³²

Treatment regimen examples for patients with inhibitors are listed below and represented in **Schematic 1**, however, are not limited to this set:

- a) Immune tolerance induction (ITI) to eradicate the inhibitor (typically for patients with a high-titer inhibitor), with or without bypassing agents used for routine prophylaxis, and with bypassing agents used for on-demand treatment of bleeds
- b) Bypassing agents used for prophylaxis of bleeds and for on-demand treatment of bleeds; some patients with a low inhibitor titer may be able to be managed with high doses of FVIII for episodic bleeds
- c) Emicizumab used for prophylaxis of bleeds plus bypassing agents used for on-demand treatment of bleeds

Schematic 1. Possible Treatment Regimens				
	Regimen Components			
	ITI	BPA for rPhx	EMI for rPhx	BPA for OdT
a)	✓	✓		✓
a)	✓			✓
b)		✓		✓
c)			✓	✓

Abbreviations: BPA, bypassing agent; EMI, emicizumab; FVIII, factor VIII; ITI, immune tolerance induction; rPhx, routine prophylaxis to prevent bleeding; OdT, on-demand therapy for bleeding episode

Table 4 provides an overview of treatment guidelines regarding the management of inhibitors in hemophilia A, published in the last 5 years.

Table 4. Guideline Recommendations for Managing Patients with Inhibitors

Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation

MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders (April 2018; Document #253)³²

- “For high-titer inhibitors: ITI is the best option for inhibitor eradication.”
- Feiba, NovoSeven RT, and Hemlibra are treatment options for the treatment patients with inhibitors. The guideline highlights that the choice of product depends on the type of inhibitor, the patient’s inhibitor titer, the location of bleeding, and previous response to these products.

MASAC Guidelines for Emergency Department Management of Individuals with Hemophilia and Other Bleeding Disorders (September 2017; Document #252)³⁶

For patients with inhibitors (antibodies to FVIII or IX) presenting in a life- or limb-threatening bleed:

“...the safest immediate action is to prescribe recombinant factor VIIa (rFVIIa) at a dose of 90 mcg/kg or activated prothrombin complex concentrates (FEIBA) at 75-100 units/kg.”

MASAC Recommendation on Administration of Inhibitor Bypassing Agents in the Home for Patients with Hemophilia and Inhibitors (June, 2015; Document #233)³⁴

- MASAC notes that ITI may take up to three years or more to restore the utility of factor products and recommends that during this time patients with inhibitors should have an on-hand supply of bypassing agents in the home to treat or prevent bleeds.

MASAC Recommendation Regarding Prophylaxis with Bypassing Agents in Patients with Hemophilia and High Titer Inhibitors (October 2013; Document #220)

- Prophylaxis with bypassing agents (eg, NovoSeven, and FEIBA) should be considered in patients with hemophilia and inhibitors.

US Guidelines for immune tolerance induction in patients with haemophilia A and inhibitors (2015)¹⁸

Patients with severe hemophilia A who are recommended to undergo ITI are as follows:

- Children with persistent inhibitors >5 BU/mL, a peak historical inhibitor titer of <200 BU/mL, and with other predictors of better outcomes (Grade 1A)
- Children with persistent inhibitors >5 BU/mL and a peak historical inhibitor titer of >200 BU/mL (regardless of good-outcome predictors) (Grade 1A); however, higher doses are needed and there should be consideration given to initiating ITI with a VWF-containing product (Grade 2C)
- Adults with persistent inhibitors >5 BU/mL (Grade 2C), particularly those with frequent bleeding or a poor response to bypass therapy (Grade 1C)

Deciding which product should be used for ITI:

- Authors state that there is insufficient evidence regarding which FVIII agent should be used for ITI, as there is conflicting evidence available

Regarding the role of bypassing agent prophylaxis:

- In patients who bleed frequently and with an inhibitor titer >5 BU/mL, before initiating ITI, consider bypassing agents for prophylaxis, (Grade 1A)
- In patients who bleed frequently during ITI, consider concomitant bypassing agent prophylaxis until the inhibitor titer is <1 BU/mL (Grade 2C)

Note: The grading system followed the Delphi-like process used by the American College of Chest Physicians³⁷

Table 4. Guideline Recommendations for Managing Patients with Inhibitors

UKCDO Guideline: Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (2012)²⁵

- “Immune toleration induction is recommended for patients with severe hemophilia A and a persistent inhibitor that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII (Grade 1B).”
- A trial of on-demand bypassing agent therapy should be employed before considered ITI for patients with mild or moderate hemophilia A with an inhibitor (Grade 1C).

Treatment of bleeding

- “Bleeds may be managed with large doses of FVIII/IX in low responders and FEIBA or rFVIIa in high responders. FVIII can be considered for major bleeds in high responding patients with low-titre antibodies. For low-responding patients with low-titre inhibitors it is better to increase the frequency of FVIII/FIX infusions rather than increase the dose (Grade 2C).”

Prophylaxis for patients with inhibitors

- “Prophylaxis with a bypassing agent should be considered in young children after the first haemarthrosis to reduce the risk of arthropathy.”
- “If prophylaxis is required in patients awaiting ITI, rFVIIa should be used.”
- “The choice of product for prophylaxis should be considered on an individual basis, taking into account previous response to treatment, logistics of administration and cost.”

World Federation of Hemophilia: Guidelines for the Management of Hemophilia (2013)³⁸

- Eradication of inhibitors is possible with immune tolerance induction; however, the optimal dosing regimen is unclear. Patients with high-titer inhibitors should discontinue FVIII products for a period of time prior to ITI initiation to first let the titer level fall.

Treatment of bleeding in patients with inhibitors— Product selection should be based on inhibitor titer, any past record of response to previously tried products/regimens, and the location and severity of bleed.

- **Patients with a low-responding inhibitor (titer <5 BU/ml)** : an adequate clinical response may be achieved by using higher and/or more frequent dose of FVIII, in order to neutralize the inhibitor and stop bleeding
- **Patients with a history of a high-responding inhibitor (titer > 5 BU/ml) but with a current low titer:** there may be a treatment opportunity window with high/frequent doses of FVIII when an adequate clinical response may be achieved before the inhibitor titer rises to high levels (usually within the initial 3 to 5 days of re-initiation of FVIII).
- **Patients with a titer > 5 BU:** ultra-high dose continuous infusion therapy may be used or other alternative agents such as recombinant factor VIIa and prothrombin complex concentrates; therapy must be individualized since patient may respond better to one agent other another.

Nordic Hemophilia Guidelines, 2015^{35,39}

ITI

- Children with a low-responding inhibitor should undergo ITI.
- Adults with a persistent low-responding inhibitor should be offered ITI, especially if bleeds are not successfully treated with on demand FVIII.
- Children with a high-responding inhibitor, and without bleedings may wait to initiate ITI until decline of the inhibitor to below 10 BU/mL.
- Patients with high-responding inhibitors should be offered ITI.

Treatment of bleeding

- Replacement factor should be used as the first option for patients with a current low inhibitor titer to manage acute bleeding. Bleeding with a current high titer must be treated with bypassing agents.

Prevention of bleeding

- Consider prophylaxis with rFVIIa (90 µg/kg) once daily or aPCC (50 IU/kg) every other day for patients with severe and/or frequent bleeds.

Abbreviations: aPCC, activated prothrombin complex concentrate; ITI, immune tolerance induction, FVIII, factor VIII; FIX; factor IX; rFVIIa, recombinant factor VIIa

Cochrane Reviews

Two Cochrane reviews have been published with the objective of comparing the efficacy of different regimens used to manage hemophilia patients with inhibitors. Neither of these publications involved comparisons with the newer agent, emicizumab.

- a) There are a number of protocols that have been used for ITI. Protocol components include FVIII and various combinations that may include an immunosuppressant or prophylaxis with a bypassing agent. A 2014 Cochrane review included RCTs comparing any ITI regimen (with or without bypassing agents), or comparing ITI (any regimen with or without bypassing agents) versus a bypassing-agent-only regimen.⁴⁰ A single study meeting the inclusion criteria was identified. There was no difference between high- versus low-dose ITI protocols (200 IU/kg/day versus 50 IU/kg/3 times weekly) with respect to the percentage of patients achieving tolerance after a maximum of 33 months; however, the time to a negative titer was significantly shorter in the high-dose arm.³³ There was no RCT evidence comparing outcomes between ITI (any regimen) versus a bypassing-agent-only regimen used for prophylaxis or on-demand.⁴⁰
- b) The 2017 Cochrane review assessed the efficacy (bleeding rate reduction) of prophylactic therapy using bypassing-agents (rFVIIa or aPCC) for the treatment of patients with hemophilia and inhibitors.⁴¹ Four RCTs were included: 2 comparing aPCC for prophylaxis versus on-demand use, and 2 comparing high-dose versus low-dose rFVIIa regimens for prophylaxis. The authors concluded that while prophylaxis with bypassing agents may effectively reduce bleeding in patients with inhibitors compared to on-demand therapy, “there is a lack of evidence for the superiority of one agent over the other or for the optimal dosage regimen.”⁴¹

II. Efficacy

For the adult and adolescent population ≥ 12 years old, the efficacy of emicizumab prophylaxis was demonstrated in an open-label, phase 3, trial (HAVEN1) that took place in 14 countries.⁴² Randomized patients (N=53) had mild (4%), moderate (4%), or severe (92%) hemophilia A with a history of a high-titer FVIII inhibitor who received episodic treatment with bypassing agents prior to study entry. Patients were stratified based on the number of bleeds experienced in the prior 24 weeks (<9 vs. ≥ 9). The study was designed to compare bleeding rates between each study arm: emicizumab prophylaxis compared to no prophylaxis for at least 24 weeks. Patients in both arms were allowed on-demand treatment with bypassing agents, rFVIIa preferentially, for episodic bleeds.⁴² The primary endpoint was the annualized bleed rate (ABR) for treated bleeds. A treated bleed was defined as a bleed that was directly followed by a medication that was reported to be for the management of the bleed (excluding bleeds due to surgery/procedures) and spaced out from a potential previous bleed of the same type/location by at least 72 hours. Table 1 of **Appendix B** provides further study-design details.

The ABR for the primary endpoint of the emicizumab arm was 2.9, compared to 23.3 with no prophylaxis (ABR risk ratio 0.13, $p < 0.001$).⁴² This translates to an 87% reduction in treated bleeds with emicizumab. Moreover, 22 of 35 patients (63%) on emicizumab prophylaxis had zero treated bleeds, compared to 1 of 18 patients (6%) in the control arm.^{2,42} Differences in ABR were consistently significant and in favor of emicizumab for certain subgroups (eg, bleeding-rate strata, age groups [<18 , ≥ 18 , and <65], race, and for patients entering the study with the presence of a target joint).⁴² Health-related quality of life, health status, and bleeding-related secondary endpoints, including all bleeds (treated or not treated), spontaneous bleeds, treated joint bleeds, and treated target joint bleeds, were all significantly reduced in the treatment arm compared to control.⁴²

In the HAVEN1 study there was also an intra-patient analysis conducted with a non-randomized group (N=24) of patients who were previously receiving prophylaxis with bypassing agents prior to study entry, who then switched to emicizumab prophylaxis.⁴² Their baseline ABR while on bypassing-agent prophylaxis (15.7 events) was significantly reduced to 3.3 events with emicizumab prophylaxis.⁴²

A non-randomized, single-arm trial (HAVEN2) in children is underway.⁴³ Interim results presented to the FDA as part of the drug-application showed a low rate of treated bleeds in children < 12 years of age who had at least 12 weeks of emicizumab therapy: ABR was 0.2 for treated bleeds (95% CI 0.06, 0.62; N=23).^{2,44} Compared to patients' baseline prior to study entry, patients experienced a significant reduction in treated bleeds with emicizumab (based on 13 patients <12 years of age with at least 12 weeks of emicizumab prophylaxis). At the May 2017 cutoff analysis, 57 patients with hemophilia A and FVIII inhibitors had been treated with emicizumab (median observation time of 9 weeks) and 95% of these patients had zero treated bleeds. For the group of patients with at least 12 weeks of treatment (N=23), 87% of these patients had zero treated bleeds.^{2,44}

Regarding other ongoing phase 3 studies, the drug sponsor is investigating alternative maintenance dosing regimens for emicizumab prophylaxis with an every second or forth

week administration frequency and emicizumab efficacy/safety in other populations (eg, patients *without* inhibitors with hemophilia A).⁴³

III. Safety

The most common adverse reactions cited in the product labeling, with an incidence of at least 10%, include injection site reactions, headache, and arthralgia.²⁹ Adverse reactions occurring at an incidence between 5 and 10% included pyrexia, diarrhea, and myalgia.²⁹

Patients must be monitored for thrombotic microangiopathy and thromboembolism (a black box warning for the product) especially if patients begin receiving activated prothrombin complex concentrate (aPCC) for on-demand bleeding management concomitantly with emicizumab prophylaxis at a cumulative dose that exceeds 100 U of aPCC/kg/24 hours.²⁹ In addition, there is a labeled warning concerning the potential for hypercoagulability with emicizumab combined with rFVIIa or FVIII, based on preclinical studies.²⁹

In clinical studies presented to the FDA, the overall proportion of patients receiving emicizumab who developed anti-emicizumab antibodies was 2.8%.² A post-marketing commitment is in effect in which the FDA requires the drug sponsor to develop and validate an assay to measure anti-emicizumab antibodies and their neutralizing capacity on emicizumab (follow-up reports are due to the FDA in 2019).²

The continuation phase of the HAVEN1 study allowed patients who received 24 weeks of emicizumab prophylaxis to either continue on 1.5 mg/kg/week, or increase to 3 mg/kg/week if they had experienced at least two clinically significant bleeds in the past 24 weeks while on the 1.5 mg/kg/week maintenance dose.² Two patients had the dose increased in the HAVEN1 study.²⁹ The FDA product review notes that overall “...dose up-titration resulted in fewer bleeds and no significant safety issues.”² In the supplement for the published HAVEN1 study, authors discuss patient 1121 whose emicizumab plasma concentration consistently declined during the 24 weeks of therapy with 1.5 mg/kg/week. Following up-titration of the patient’s dose to 3.0 mg/kg/week, the plasma concentration remained lower than anticipated at week 33. Specific information regarding the second patient who had a maintenance dose up-titration is not reported.

Table 5 provides a summary of the labeled warnings and concerns regarding special populations.

Table 5. Safety Concerns for Emicizumab²⁹

Special Populations ^a	<p><i>Pregnancy/Lactation</i>- no human or animal model information is available to determine whether the use of emicizumab may negatively affect fetal development. It is unknown whether emicizumab is excreted into human milk. Women of childbearing potential are recommended to use contraception.</p> <p>The pharmacokinetics of emicizumab were unaffected by age (3 to 75 years), factor VIII inhibitor status, mild to moderate hepatic impairment (total bilirubin 1x to ≤ 3x the upper limit of normal), or race (Caucasian, Black, or Asian).</p>
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Table 5. Safety Concerns for Emicizumab²⁹

	<ul style="list-style-type: none"> The FDA product summary review notes that “[n]o patients with moderate or severe renal impairment were enrolled in clinical studies,” and that renal impairment is not expected to affect emicizumab pharmacokinetics.²
Warnings ^a	<p>Black-box Warning: Thrombotic microangiopathy and thromboembolism is associated with concomitant use of emicizumab with activated prothrombin complex concentrate at >100U of aPCC/kg/day.</p> <p>Drug Interactions: Preclinical studies suggest a potential for hypercoagulability with emicizumab combined with rFVIIa or FVIII. No other drug-drug interaction studies have been conducted.</p> <p>Laboratory Coagulation Test Interference: Intrinsic pathway clotting-based laboratory tests are to be avoided while on emicizumab (should not be used to measure emicizumab activity, FVIII inhibitor titer, or used to determine dosing for factor replacement or anti-coagulation):</p> <ul style="list-style-type: none"> activated clotting time (ACT) activated partial thromboplastin time (aPTT) or coagulation tests based on aPTT (eg, one stage aPTT-based single-factor assays, aPTT-based Activated Protein C Resistance Bethesda assays (clotting-based) for factor VIII inhibitor titers <p>Laboratory test options that are unaffected by emicizumab are listed in the package insert.</p>

^a Additional information can be found in the product’s prescribing information
 Abbreviations: aPCC, activated prothrombin complex concentrate; aPTT, activated partial thromboplastin time; FVIII, factor VIII; rFVIIa, recombinant activated factor VII

Medicaid Utilization Data

Less than 5 patients have received emicizumab in the last year; all had diagnosis coding indicating congenital hemophilia A.

Table 6. Hemlibra (emicizumab) Utilization; ACO + FFS, 2017 to August 15, 2018

Claim (patient) counts	Query for ICD10 diagnosis codes (2860, D66) ^a among emicizumab-receiving patients
6 (<5)	Patients had at least one of the above ICD10 diagnosis codes

^a ICD10 Codes: 2860, Congenital Factor VIII Disorder; D66, Hereditary Factor VIII Deficiency

Potential Prior Authorization Criteria and Discussion Topics

Indication requirements

- Documentation of congenital Hemophilia A diagnosis
- Documentation of a history of a high-titer FVIII inhibitor— this was an eligibility criteria in the pivotal trials
 - Ongoing phase 3 trials may provide evidence to support an indication extension to additional populations (eg, patients without inhibitors).
 - Note that low-responding inhibitors may be transient.^{3,5,45,46}
- Prescribed for routine prophylaxis, not on-demand therapy

Use with other hemostatic products

- Concomitant use of FVIII products while on emicizumab may be limited
 - Use of FVIII products or immune tolerance induction while on emicizumab has not been adequately studied to determine the safety. Moreover, there is potential for adverse reactions based on the hypercoagulability warning mentioned in the package insert addressing emicizumab combined with FVIII.²⁹
- Prophylaxis therapy of bypassing agents should be discontinued 24 hours before starting emicizumab. Nonetheless, patients may require on-demand use of bypassing agents to manage episodic bleeding before or during treatment with emicizumab.

Dosage

- The current FDA-approved dosing is 3 mg/kg via subcutaneous injection once weekly for the first 4 weeks, then 1.5 mg/kg once weekly thereafter.
 - The clinical trial section of the product labeling notes that patients were allowed to up-titrate the maintenance dose to 3 mg/kg/week after 24 weeks of emicizumab prophylaxis for cases with inadequate response. Nonetheless, patient adherence should be considered prior to up-titration, in addition to the possible presence of anti-emicizumab antibodies.
 - Other dosing regimens are being studied by the drug sponsor (eg, with an every second or fourth week administration frequency for emicizumab)
- May consider requiring the prescriber to specify any of the following: the prescribed dose in mg/kg/week, patient's weight, total quantity of drug needed per dose, and the quantity and strength of each vial planned to be used to achieve the least amount of waste.

Summary

Hemlibra is an additional treatment option for patients with congenital hemophilia A who have developed inhibitors to replacement FVIII products. The medication is approved for routine prophylaxis therapy with weekly subcutaneous dosing. Other administration frequencies are currently being studied by the drug sponsor. Planned post-marketing studies include an evaluation of how anti-emicizumab antibodies affect emicizumab. Potential prescribing criteria have been outlined while taking into consideration the limited treatment options available for this population and the scenarios for which safety has not yet been fully elucidated.

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Appendix A: Database Searches

Table 1. Database Searches

Cochrane Library for Cochrane Reviews_ July 20th, 2018

1. Search fields (title, abstract, keywords): (factor or VIII or FVIII) and inhibitor* and (hemophilia or haemophilia); Results 10 Cochrane reviews
2. Search fields (all): emicizumab; Results 0 Cochrane reviews

OvidMedline_ July 20th, 2018

1 emicizumab.mp. 36

OvidMedline _ August 6th 2018

- 1 Antibodies, Bispecific/ (1850)
- 2 Hemophilia A/ (19455)
- 3 Autoantibodies/ (63233)
- 4 Antibodies, Monoclonal, Humanized/ (32273)
- 5 (emicizumab or hemlibra).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (38)
- 6 1 and 2 and 3 (0)
- 7 1 and 2 (18)
- 8 2 and 3 and 4 (0)
- 9 2 and 4 (23)
- 10 5 or 7 or 9 (56)**

Embase _ July 20th 2018

1. 'emicizumab':ti,ab,kw 79

Embase _ August 6th 2018

#12 #10 OR #11 51

#11 #7 AND #9 39

#10 #7 AND #8 13

#9 ('clinical study'/mj OR 'clinical trial'/mj OR 'controlled clinical trial'/mj OR 'controlled study'/mj OR 'major clinical study'/mj OR 'randomized controlled trial'/mj OR 'control group'/mj OR

((clinical OR randomi* OR controlled OR multicentre OR multicenter OR 'multi centre' OR 'multi center') NEAR/3 (study OR trial)):ti,ab) OR placebo:ab,ti OR 'head to head':ti,ab) AND [english]/lim 897,406

#8 ('systematic review*:jt OR 'meta analysis'/mj OR 'systematic review'/mj OR ((systematic NEAR/3 review):ti) OR 'meta analys*':ti,ab,kw OR metaanalys*':ti,ab,kw OR ((overview NEAR/4 (review OR reviews)):ti)) NOT ('conference abstract'/it OR 'conference review'/it) AND [english]/lim 190,464

#7 #1 OR #2 OR #6 902

#6 #3 AND #4 AND #5 856

#5 'monoclonal antibody'/exp 485,439

#4 inhibitor* OR antibod* 3,138,785

#3 'hemophilia a'/exp 21,147

#2 'emicizumab'/exp 139

#1 emicizumab:ti,ab,kw OR hemlibra:ti,ab,kw 81

ClinicalTrials.gov

1. Condition or disease field: 'hemophilia'

2. Other terms field: 'HAVEN'

3. Limits: Phase 3 or 4 trial

4. 1 and 2 and 3 5

Appendix B

Table 1. Pivotal Clinical Trial Study Design

HAVEN1, phase 3, Randomized, open-label, trial⁴⁷

Included patients with the following:

- congenital hemophilia A of any severity, with a history of a high inhibitor titer (≥ 5 BU) who were at least 40 kg
- with documentation of treatment with episodic (for ≥ 6 bleeds) or prophylactic (for ≥ 2 bleeds) therapy with bypassing agents for ≥ 24 weeks prior to study entry
- platelet count $\geq 100,000/\mu\text{L}$; hemoglobin ≥ 8 g/dL (4.97 mmol/L), total bilirubin ≤ 1.5 times the upper limit of normal (ULN), both AST and ALT ≤ 3 times ULN, and serum creatinine ≤ 2.5 times ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min

Excluded patients with cirrhosis, inherited or acquired bleeding disorder other than hemophilia A, patients receiving or planning to receive immune tolerance induction therapy or prophylaxis with factor VIII (FVIII), participants with treatment within the last 12 months for thromboembolic disease

Primary endpoint:

- *Arm A versus Arm B (randomized groups); difference in the rate of treated bleeding events over 24 weeks*
 - A treated bleed was defined as a bleed that is directly followed by a hemophilia medication, reported to be a “treatment for bleed”, irrespective of the time between the treatment and the preceding bleed, however, excluding bleeds due to surgery/procedure

Secondary endpoints

- *Arm A versus Arm B (randomized groups): all bleeds; treated joint bleeds; treated spontaneous bleeds; treated target joint bleeds; Haem-A-QoL physical health subscale at 24 weeks; Haem-A-QoL total score at 24 weeks; EQ-5D-5L visual analog scale at 24 weeks; EQ-5D-5L Index utility score at 24 weeks.*
- *Arm A (intra-individual comparison): all bleeds and treated bleeds.*
- *Arm C (intra-individual comparison, non-randomized): for all bleeds and treated bleeds.*

Study Arms:

- All arms could receive bypassing agents on-demand for episodic/breakthrough bleeds
- *Arms selected to receive emicizumab prophylaxis were dosed as 3.0 mg/kg weekly for 4 weeks, then 1.5 mg/kg weekly thereafter. After 24 weeks on emicizumab prophylaxis patients could then continue on 1.5 mg/kg or increase to 3 mg/kg if they had had at least two clinically significant bleeds in the past 24 weeks while on the 1.5 mg/kg maintenance dose.*

Randomized Groups

Arm A (n=35): Emicizumab prophylaxis (Patients were previously on episodic bypassing treatment)

Arm B (n=18): no prophylaxis (Patients were previously on episodic bypassing treatment); after 24 weeks patients could then receive emicizumab prophylaxis

Non-randomized groups

Arm C: Emicizumab prophylaxis (Patients previously on prophylaxis with bypassing agents)

Arm D: Emicizumab prophylaxis (Patients unable to enroll in arm A, B, or C)

Monitoring: assessment frequency

- *Bleeding episodes and medication management: documented at the time of a bleeding event or medication use or at least once every 8 days*
- *Health-related quality of life: every 4 weeks*
- *Health status: at the time of a bleeding event and every 4 weeks*

Table 1. Pivotal Clinical Trial Study Design

HAVEN2, phase 3, non-randomized, open-label, trial²

Note: the completed study has not yet been published; information below was extracted from the FDA product review report

Included patients with the following:

- congenital hemophilia A of any severity, with a high inhibitor titer (≥ 5 BU)
- patients < 12 years, patients 12 to 17 years old weighing less than 40 kg
 - For patients >2 years old,
 - must have documentation of either treatment with episodic (for ≥ 3 bleeds in last 24 weeks) or prophylactic (eg, for ≥ 2 bleeds prior to therapy or 1 life-threatening bleed) therapy with bypassing agents
 - or unable to undergo CVAD placement
 - For patients < 2 years old,
 - eligibility must be determined by investigator based on high unmet medical need
- platelet count $\geq 100,000/\mu\text{L}$; hemoglobin ≥ 8 g/dL, total bilirubin ≤ 1.5 times the age adapted upper limit of normal (ULN), both AST and ALT ≤ 3 times ULN, and serum creatinine ≤ 1.5 times ULN or creatinine clearance $> 70\text{ml}/\text{min}/1.73\text{m}^2$

Excluded patients receiving immune tolerance induction therapy or prophylaxis with factor VIII (FVIII), participants with history of thromboembolic disease

Study endpoints: annualized bleeding rates for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds. The study was also designed to be able to conduct an intra-patient comparison for efficacy and health-related quality of life on the treatment versus the patient's baseline.

Abbreviations: BPAs, bypassing agents; EQ-5D-5L, the five-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire [EQ-5D-5L] visual-analogue scale and index utility score; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; ITI, immune tolerance induction; ULN, upper limit of normal

Related Reimbursement Codes

List of potential coding from the drug sponsor website

- <https://www.genentech-access.com/hcp/brands/hemlibra/learn-about-our-services/reimbursement.html>

ICD-10 Codes:

- 2860 Congenital Factor VIII Disorder
- D66 Hereditary Factor VIII Deficiency
- R760 Raised Antibody Titer