



NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

**MASAC Update on the Approval and Availability of the New Treatment:
Emicizumab (Hemlibra), for Persons with Hemophilia A
with Inhibitors to Factor VIII:
*Interim Guidance on Acute Bleed Management and Use of Laboratory Assays***

Approved by the Medical and Scientific Advisory Committee (MASAC) of the National Hemophilia Foundation (NHF) on November 24, 2017

On November 16, 2017, the US Food and Drug Administration approved emicizumab-kxwh (Hemlibra, Roche). Emicizumab is a recombinant, humanized, bispecific immunoglobulin G4 monoclonal antibody that mimics the cofactor function of activated factor VIII (FVIIIa) by bridging activated factor IX (factor IXa) and factor X. It is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A with inhibitors to factor VIII (FVIII). Weekly 3 mg/kg subcutaneous loading dose x 4 followed by subcutaneous once weekly dosing at 1.5 mg/kg has demonstrated significant reduction in annualized bleeding rates in persons of all ages with congenital hemophilia A with inhibitors.

Clinical Summary

The safety and efficacy of this novel treatment has been investigated in two global clinical trials in infants through adults. The results from the adult and adolescent (age ≥ 12 years old) clinical trial (HAVEN 1) demonstrated an 87% reduction in treated bleeds in patients treated with emicizumab weekly compared to subjects who remained on on-demand therapy with bypassing agents and a 79% reduction in treated bleeds in patients who were previously on prophylaxis with bypassing agents. In addition, patients on emicizumab reported improvement in hemophilia-related symptoms (painful swellings and joint pain) and physical functioning (pain with movement and difficulty walking) compared to patients who did not receive prophylactic treatment. There were 5 serious treatment-related adverse events that occurred during this pivotal trial. These included thromboembolism as well as thrombotic microangiopathy (TMA). There was also a fatal hemorrhagic event that was deemed unrelated to emicizumab treatment. These events have been detailed comprehensively in the recent publication and its appendices of the HAVEN 1 results in the New England Journal of Medicine (Oldenburg, 2017)¹. All of the adverse events occurred in the context of management of breakthrough bleeding events with bypassing agents. Notably, all 5 episodes occurred in patients who had treated bleeds with activated prothrombin complex concentrate (aPCC, FEIBA, Shire) at cumulative doses that were ≥ 100 U/kg/day and for ≥ 24 hours. Although some of these patients who suffered these adverse events had also administered recombinant factor VIIa (rFVIIa, NovoSeven, Novo Nordisk), 37

subjects treated 140 bleeding episodes exclusively with rFVIIa while on emicizumab prophylaxis with no incidence of thromboembolism or TMA². Risk mitigation recommendations were generated based on the insights from these adverse events with a satisfactory safety profile after their implementation and adherence to the guidance in the approximately 180 patients with FVIII inhibitors treated within the emicizumab development program.

The interim results from a pediatric (<12 years old) clinical trial (HAVEN 2), that includes 23 boys with severe hemophilia A and inhibitors on once weekly prophylaxis with emicizumab showed that 87% of the subjects did not have any treated bleeding episodes. This trial included the risk mitigation recommendations derived from the HAVEN 1 experience, and there have been no episodes of thromboembolism or TMA within the pediatric clinical trial.

Implication of a unique mechanism of action on management of bleeding events and utilization of laboratory assays

Although emicizumab has demonstrated efficacy when administered as prophylactic therapy in hemophilia A with inhibitors, it is a fundamentally different protein than FVIII. Factor VIII is not activated upon infusion, requires activation as part of physiologic hemostasis, and is subject to physiologic regulation through activity decay and proteolytic inactivation. Emicizumab does not require any activation and does not have any known inactivation mechanism. In addition, its mechanism of action is mediated directly by the presence of factor IXa and factor X. In addition, FVIII, including extended half-life versions, is generally cleared from the plasma within 48 hr to 5 days, whereas emicizumab may persist for months after cessation of dosing.

Accordingly, these differences have important implications for enhanced procoagulant activity with concomitant use of bypassing agents, especially with aPCC which increase the amount of factor IXa and factor X in plasma. Emicizumab also affects many routine clot-based assays that have commonly been used to assay FVIII activity and measure FVIII inhibitor titers. Both of these issues have been highlighted in the company prescribing information³ as part of the FDA label, including a black box warning on the cumulative dose of and duration of exposure to aPCC that was associated with the thromboembolic and TMA events, and a recommendation to discontinue the use of aPCC and suspend dosing of emicizumab if symptoms occur. The prescribing information also provides details on the coagulation test results that are affected by emicizumab and those tests whose results are unaffected. Recognizing these important implications, MASAC will be issuing guidance in the coming weeks on areas that are not fully addressed in the company prescribing information, based on review of the published data from the clinical trial program and expert consensus from MASAC members and investigators who were part of the clinical trial program.

Interim Guidance

We expect that this therapy will be available for prescribing by providers as early as November 27, 2017. Despite the efficacy in the prevention of bleeding events, clinicians and patients should still expect and be prepared to treat breakthrough

bleeding events in patients on emicizumab prophylaxis. In persons with hemophilia A with inhibitors, treatment likely require concomitant use of alternative hemostatic therapies. Due to the serious adverse events observed in the clinical trial program, we are providing the following interim guidance on management of breakthrough bleeding, surveillance for thromboembolic and TMA events, and recommendations on appropriate use of laboratory assays:

Recommendations on Acute Bleed Management

1. General approach to breakthrough bleeding: We recommend that providers advise their patients who are on emicizumab on when to contact the hemophilia treatment center/provider if they exhibit clinical manifestations of a bleed. Emicizumab is likely to transform the bleeding phenotype of patients to a milder phenotype. Given improved baseline hemostasis in patients on emicizumab prophylaxis, the current paradigm of treating at the first signs and symptoms of bleeding in some cases should change. *Significant and serious or life-threatening bleeding should continue to be treated promptly.* However, there should be additional evaluation of muscle and joint complaints prior to treatment with an additional hemostatic agent. For equivocal signs or symptoms of minor bleeds, the patient should contact their provider before initiating bypass therapy treatment.
2. Caution with dose and duration of bypass therapy:
 - 1) Use of aPCC for breakthrough bleed treatment for patients on Emicizumab should be avoided if possible, and rFVIIa should be the first option used to treat. If aPCC is used, it should be limited to no more than 50 IU/kg administered as an initial dose and not exceed 100 IU/kg/day. Duration of aPCC therapy should also be minimized, as use for more than 1 day, especially with doses above 100 IU/kg/day, were associated with thrombosis and TMA.
 - 2) Caution should also be exercised for patients who are using rFVIIa, with consideration of using no more than 90 mcg/kg as an initial dose.
 - 3) Following initial dosing for an acute bleed, repeated dosing of any BPA should be performed under medical supervision with consideration for verifying severity of bleeds prior to continuing to repeat dosing.
3. Clinical and laboratory monitoring: All patients on emicizumab who have received BPA for breakthrough bleeding for more than 24 hrs should be evaluated for any clinical symptoms suggestive of a thromboembolic event (with a high level of suspicion for atypical sites, e.g. cerebral sinus venous thrombosis). In addition, those receiving aPCC, should have laboratory monitoring to evaluate for evidence of thrombotic microangiopathy (this should include D-dimer, prothrombin fragment F1+2 (if available), platelet count, serum creatinine, LDH and peripheral blood smear analysis to look for schistocytes). Monitoring should continue daily while the patient continues to receive BPA until 48 hours following the last dose of BPA.

Recommendations on Laboratory Assays while on Emicizumab

1. Laboratory monitoring of emicizumab is not required while on routine prophylactic dosing
2. aPTT-based assays, including clot-based FVIII activity assays, should not be performed while on emicizumab, as they will yield misleading results (ie. artifactually shortened aPTT and elevated FVIII activity).
3. Chromogenic FVIII activity assays will only provide an assessment of emicizumab activity if the assay includes all human reagents – these are not widely available but are referenced here for review⁴. Some persons with hemophilia A with inhibitor may still be treated with FVIII concentrates (eg. for acute bleeds or prior to some procedures). A chromogenic FVIII assay that uses bovine reagents may be used to assay FVIII activity in such cases.
4. The clot-based Bethesda assay cannot be utilized to assess FVIII inhibitor levels. The laboratory at the Centers for Disease Control has a bovine-reagent chromogenic-based inhibitor assay that can be used to measure FVIII inhibitor levels. If samples are submitted to the CDC for central laboratory testing, they must be clearly identified that the patient is on emicizumab.

References:

1. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, Santagostino E, Kruse-Jarres R, Negrier C, Kessler C, Valente N, Asikanius E, Levy GG, Windyga J, Shima M. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. *N Engl J Med.* 2017, Aug 31; 377(9):809-818.
2. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, Santagostino E, Kruse-Jarres R, Negrier C, Kessler C, Valente N, Asikanius E, Levy GG, Windyga J, Shima M. Efficacy, Safety and Pharmacokinetics (PK) of Emicizumab (ACE910) Prophylaxis (Px) in Persons with Hemophilia A with Inhibitors (PwHAWI): Randomized, Multicenter, Open-label, Phase 3 Study (HAVEN 1). *Res Pract Thromb Hemost.* 2017, 1(Suppl. 2):3
3. https://www.gene.com/download/pdf/hemlibra_prescribing.pdf
4. <http://www.aniara.com/PROD/A221402-RUO.html>

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